Organ and Tissue Transplantation
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Contemporary Liver Transplantation

The Successful Liver Transplant Program

Springer

Organ and Tissue Transplantation

Series Editor
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Jefferson Transplant Institute
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Kimmel Cancer Center – Jefferson Liver Tumor Center
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Cataldo Doria
Editor

Contemporary Liver Transplantation

The Successful Liver Transplant Program

With 150 Figures and 93 Tables

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To my patients and their families

Foreword

The first liver transplant performed in a human was done in 1963. In half a century, liver transplantation has evolved dramatically. In the USA, we went from 1 to over 150 liver transplant centers that offer this highly specialized treatment for patients needing transplantation. We have become the most scrutinized field in medicine: transplantation is the only specialty with multiple regulatory agencies overseeing the outcomes of the different centers on a yearly basis. Our results in terms of patient and graft survival are publicly available in the SRTR web page; this is not true for any other subspecialty in medicine. When a transplant center does not perform as expected, a mechanism is in place to enroll that transplant center in a remedy program, which can theoretically lead to termination of such a center by federal programs charged of securing very high standard of quality across the country. There is no other field in medicine where clinical management, discoveries, and organizational issues have changed this fast in such a short period of time. In the past 5–10 years, hospitals have tried to organize their services in service lines rather than silos. However, transplantation has been the quintessence of multidisciplinarity since the very beginning. We have been working in a service line model since inception; therefore, transplantation can be used as a model for other disciplines to emulate while they are modernizing their structural organization. This book is a comprehensive review of the most crucial and provocative aspects of liver transplantation. It is a unique source of information and guidance for the current generation of transplant professionals that evolved from being pure clinicians into savvy administrators, knowledgeable in every regulatory aspect governing transplantation.

Cataldo Doria

Preface

The purpose of this book is to prepare transplant professionals to be successful in an era when being good clinicians and surgeons is no longer enough to achieve excellence. A single liver transplant necessitates the effort of a large group of health care providers of different disciplines. This book addresses the need and the questions of everyone involved: surgeons, hepatologists, anesthesiologists, palliative care specialists, immunologists, infectious disease specialists, physiatrists, radiologists, scientists, transplant coordinators, financial specialists, administrators, and attorneys. It also provides access to information generally not available in other books written on the same topic, such as palliative care, integrated medicine, and quality indicators of a successful liver transplant program, just to name a few. The book contains chapters covering every single aspect of the surgical operation in the donors (live and cadaver: whole and split), as well as the recipients of liver transplant. The preoperative work-up, as well as the postoperative immunosuppression management, and the treatment of recurrent diseases are addressed in every single detail. Whole chapters are dedicated to controversial issues like transplantation in patients diagnosed with NASH and transplantation for patients diagnosed with HCC beyond Milan criteria. Dedicated chapters on HCV, HCC, FHF, and NASH will make this book a unique resource for any health care provider part of a multidisciplinary liver transplant team. The book goes beyond the analysis of the formal medical and surgical aspects of liver transplantation and introduces deep knowledge on key aspects of contemporary transplant programs, such as palliative care, pregnancy, liver transplantation as a medical home, the multiple requirements of regulatory agencies ruling transplantation, quality measurements for transplant programs, finance, liability, and the administration of an effective transplant program. The book is organized in 9 sections focusing on each key aspect of liver transplantation. The progression through the different sections is logical and offers the opportunity to analyze clinical as well as basic science and organizational issues that pertain specifically to liver transplantation. This book analyzes and reviews medical as well as surgical issues related to liver transplantation in all its forms. Differently from previously published books in this field, we dissect the organizational issues that are vital for the good performance of transplant programs. We introduce concepts like integrated medicine, stem cell transplantation, and diet that are complementary to and supportive of liver transplantation. This book is the first of its kind in terms of the 360-degree analysis of liver transplantation. It is a unique

resource for trainees as well as leaders in transplantation because it addresses, in detail, all of the most crucial aspects of liver transplantation. This book allows the reader to become a better clinician: purposely not all liver diseases will be discussed in this book. Only the ones that are more difficult to treat or are more controversial in approaching will be dealt with. By discussing topics like palliative care and integrated medicine, it will open new avenues for clinicians to improve the outcome of their programs. By introducing important topics like the ones in the special topics section, it will offer the reader the knowledge needed to become more competitive in an era when liver transplant programs are flourishing without a parallel increase in organ donation. For the first time, a book on liver transplantation will address the most crucial organizational issues that when cared for properly lead to excellence.

Cataldo Doria

Acknowledgments

I would like to acknowledge all my colleagues who worked tirelessly to make this book a reality.

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About the Editor

Cataldo Doria graduated magna cum laude from the University of Perugia–Italy in 1990, where he was also resident in surgery from 1990 to 1995. He completed a research fellowship in small bowel transplantation at the University of Pittsburgh Transplantation Institute and a clinical fellowship in multiorgan transplantation at the Thomas E. Starzl Transplantation Institute of the University of Pittsburgh. Dr. Doria is a Ph.D. in Surgery Biotechnology and Transplant Immunology, and an M.B.A.

Cataldo Doria, M.D., Ph.D., M.B.A., is Professor of Surgery at Sidney Kimmel Medical College at Thomas Jefferson University in Philadelphia, PA. Dr. Doria is the inaugural Nicoletti Family Professor of Transplant Surgery at Sidney Kimmel Medical College, Thomas Jefferson University Hospital. He is also the Director of the Jefferson Transplant Institute, the Director of the Division of Transplantation, and the Surgical-Director of the Jefferson Kimmel Cancer Center – Liver Tumor Center at the same institution. Dr. Doria is the Chairman of the Quality Assurance Performance Improvement Committee of the Jefferson Transplant Institute at Thomas Jefferson University Hospital. He is a multiorgan transplant surgeon who has extensive expertise in cadaveric and living related liver and kidney transplant, pancreas transplant, small-bowel transplant, as well as hepatobiliary and robotic surgery.

Prior to Jefferson, Dr. Doria was at the Mediterranean Institute for Transplantation and Advanced Specialized Therapies (IsMeTT-UPMC Italy) – a partnership between the University of Pittsburgh Medical Center and the Italian National Government – where he served as Chief of Abdominal Organ Transplant. He also served as Assistant Professor of Surgery at the

University of Pittsburgh School of Medicine and at the Thomas E. Starzl Transplantation Institute, Children's Hospital of Pittsburgh, and the US Department of Veterans Affairs Medical Center of Pittsburgh, PA.

His research interest focuses primarily on solid organ transplantation. Dr. Doria's biography has been listed in Who's Who in Medicine and Healthcare, Who's Who in Finance and Industry, Who's Who in Science and Engineering, and Who's Who in America. Dr. Doria, in year 2005, has been named Honorary President of the Italian Association for Organ Donation of the Province of Taranto – Italy. In 2008 Dr. Doria was named "surgeon of the year" by the Mid-Atlantic Division of the American Liver Foundation. In 2009, Dr. Doria was the recipient of the Career Achievement Award by the International Association "Pugliesi nel Mondo." In 2010, he was awarded with the seal of the University of Foggia, Italy. In 2012, Dr. Doria was named Knight of the Italian Republic by the President of the Italian Republic. In 2016, Dr. Doria was named Chairman, Board of Directors, American Liver Foundation, Mid-Atlantic Division. He authored over 269 scientific publications. Dr. Doria is a member of numerous professional and scientific societies where across the years he has covered several official positions. Most importantly, he has been, for the past 10 years, the leader of one of the most successful transplant institute in North America.

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Part I

Historical Perspective

History of Liver and Other Splanchnic Organ Transplantation

1

Thomas E. Starzl

Contents

Abstract

In the late 1950s, transplant models were developed in dogs for all of the intra-abdominal organs (Fig. 1). The most fruitful of these efforts involved the liver (Table 1) (Starzl TE (1969a) In: Starzl TE (ed) Experience in hepatic transplantation. WB Saunders, Philadelphia). In addition to its direct clinical application, the research in liver transplantation yielded new information about the metabolic interrelations of the intra-abdominal viscera in disease and health; a more profound understanding of the mechanisms of organ alloengraftment; and the addition of new nontransplant procedures to the treatment armamentarium against gastrointestinal diseases.

Keywords

Orthotopic liver transplantation • Venous-venous by pass • FK506 • Organ procurement

The Liver Models

Auxiliary Liver Transplantation – In 1955, C. Stuart Welch of Albany, New York, described the insertion of an auxiliary liver into the right paravertebral gutter of nonimmunosuppressed dogs (Welch 1955; Goodrich et al. 1956) (Table 1). The allograft hepatic artery was revascularized from the aorta or iliac artery, and the portal flow was restored by rerouting the high-volume systemic venous return of the host inferior vena cava into the graft portal vein

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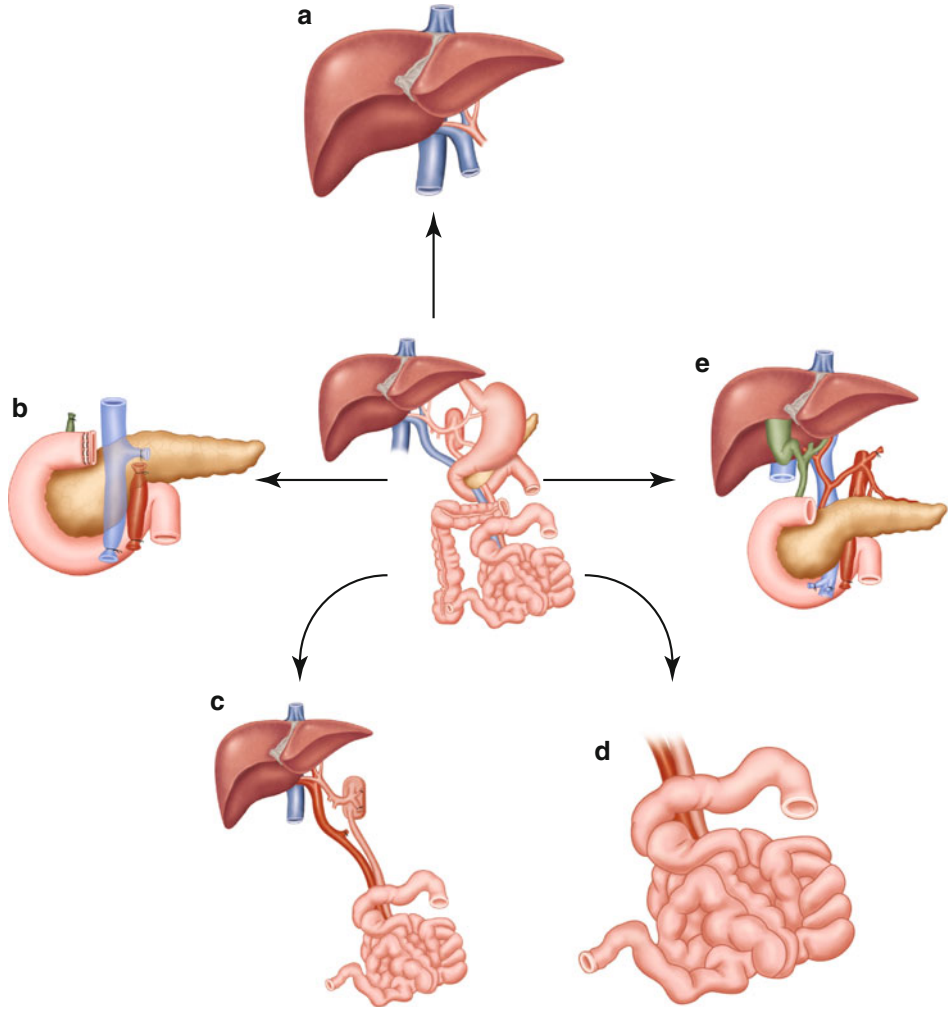

Fig. 1 The complex of intraabdominal viscera that has been transplanted as a unit (*center*) or as its separate components: *a*, liver; *b*, pancreas; *c*, liver and intestine; *d*, intestine; and *e*, liver and pancreas (From Starzl et al. 1993a)

(Fig. 2a). The grafts underwent rapid shrinkage. It was not discovered until a decade later that factors other than rejection contributed to this acute atrophy (see later section "The Pancreas Factor").

Orthotopic Liver Transplantation – Liver replacement (Fig. 2b) was first attempted in dogs in Milan, Italy, by Professor Vittorio Staudacher in 1952. His original report in the Italian journal *La Riforma Medica* was rescued from obscurity 60 years later by the scholarship of Ron Busuttil and still-surviving members of Staudacher's original research team (Busuttil et al. 2012). None of Staudacher's dogs survived operation. Neither this work nor any other mention of liver replacement can be found in Woodruff's massive compendium of the entire field of transplantation published in 1959 (Woodruff 1960). By this time, however, important independent investigations of liver replacement (orthotopic transplantation) had been completed in dogs. The studies began in the summer of 1958 at Northwestern University in Chicago (Starzl et al. 1960, 1961) and at the Peter Bent Brigham Hospital in Boston (Moore et al. 1959, 1960; McBride et al. 1962).

The Boston effort under the direction of Francis D. Moore was a natural extension of an

Table 1 Historical milestones of liver transplantation

Year	Description	Citation
1955	First article in the literature on auxiliary liver transplantation	(From Welch 1955)
1956	First article on orthotopic liver transplantation (Vittorio Staudacher)	(From Busuttil 2012)
1958–1960	Formal research programs on liver replacement at Harvard and Northwestern	(From Starzl 1960; Moore 1960)
1960	Multivisceral transplantation described, the forerunner of composite grafts	(From Starzl 1960, 1962, 1991a)
1963	Development of the azathioprine-prednisone cocktail (kidneys first than livers)	(From Starzl 1963a, 1964, 1969)
1963	First human liver transplantation trial (University of Colorado)	(From Starzl 1963c)
1964	Confirmation of the portal venous blood hepatropic effect; defined the problem of auxiliary liver transplantation	(From Starzl 1964; Marchioro 1965)
1963–1966	Improvements in preservation, in situ and ex vivo	(From Brettschneider 1968a; Marchioro 1963)
1966	Introduction of antilymphocyte globulin (ALG) (kidneys, then livers)	(From Starzl 1967)
1967	First long survival of human liver recipients (1967–1968), treated with azathioprine prednisone, and antilymphocyte globulin	(From Starzl 1968)
1973–1976	Principal portal venous hepatotropic substance identified as insulin	(From Starzl 1973, 1976)
1976	Improved liver preservation (5–8 h) permitting long-distance procurement	(From Wall 1977; Benichou 1977)
1979	Systematic use of arterial and venous grafts for vascular reconstruction	(From Starzl 1979c)
1979	Cyclosporine introduced for kidneys and liver	(From Calne 1979)
1980	Cyclosporine-steroid cocktail introduced for kidneys	(From Starzl 1980)
1980	Cyclosporine-steroid cocktail introduced for livers	(From Starzl 1980, 1981)
1983	Pump-driven venovenous bypass without anticoagulation	(From Denmark 1983; Shaw 1984; Griffith 1985)
1984	Standardization multiple organ procurement techniques	(From Starzl 1984, 1987)
1987	University of Wisconsin (UW) solution for improved preservation	(From Jamieson 1988; Kalayoglu 1988; Todo 1989)
1989	FK-506-steroid immunosuppression	(From Starzl 1989b)
1992	Discovery of chimerism as explanation of hepatic tolerogenicity	(From Starzl 1992, 1993b, c, 1996, 2015)
1992–2014	Maturation of liver transplantation into category of "conventional treatment"	(From Starzl 1989d, e)

immunologically oriented commitment to organ transplantation at the Brigham that was focused primarily on the kidney (Moore 1964). In contrast, the Northwestern initiative stemmed from questions about the functional interrelationships of the pancreas and the liver (Meyer and Starzl 1959a, b; Starzl 1992a). These ultimately led to a new field called hepatotrophic physiology (Starzl et al. 1973, 1983). To facilitate the metabolic investigations, a new technique of total hepatectomy was developed (Starzl et al. 1959). In July 1958, the second step of inserting an allograft into the vacated hepatic fossa was taken. From the outset, there was evidence that portal venous blood had superior liver-supporting qualities relative to systemic venous blood (Starzl et al. 1960, 1961). However, almost 20 years passed before the principal portal hepatotrophic factor was shown to be insulin.

Despite the absence of effective immunosuppression at that time, a solid basis for the future clinical use of orthotopic liver transplantation was laid throughout 1958 and 1959. At the April 1960 meeting of the American Surgical Association, Moore reported 31 canine experiments with 7 survivors of 4–12 days (Moore et al. 1960). In a published discussion of this paper, Starzl described his experience with more than 80 canine

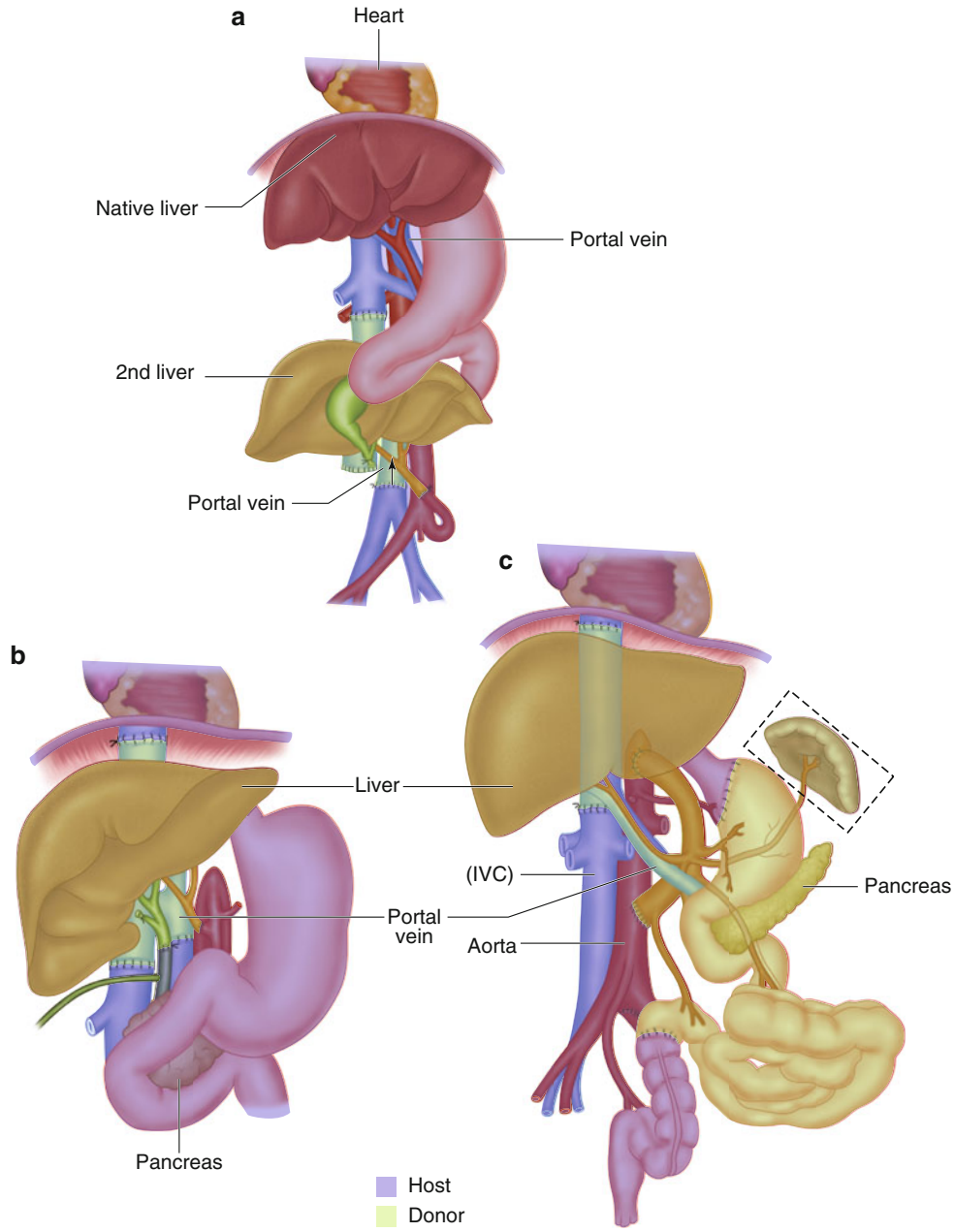

Fig. 2 Three early approaches to liver transplantation. (**a**) Welch's auxiliary liver transplantation in a dog. (**b**) Complete liver replacement in dogs. The fact that the recipient was a dog rather than a human was identifiable only by the multiple lobar appearance of the canine liver. (**c**) Organs (*green*) of a multivisceral graft in dogs or humans. Illustration by Jon Coulter, M.A., C.M.I.

liver transplantations at Northwestern University (Starzl 1960); 18 of these animals had lived 4 to 20-1/2 days (Starzl et al 1960, 1961). In both the Boston and Chicago series, rejection was present after 5–6 days and was usually the principal explanation for death. A few years later, Groth et al. (1968) demonstrated that a drastic reduction in hepatic blood flow was an integral part of the

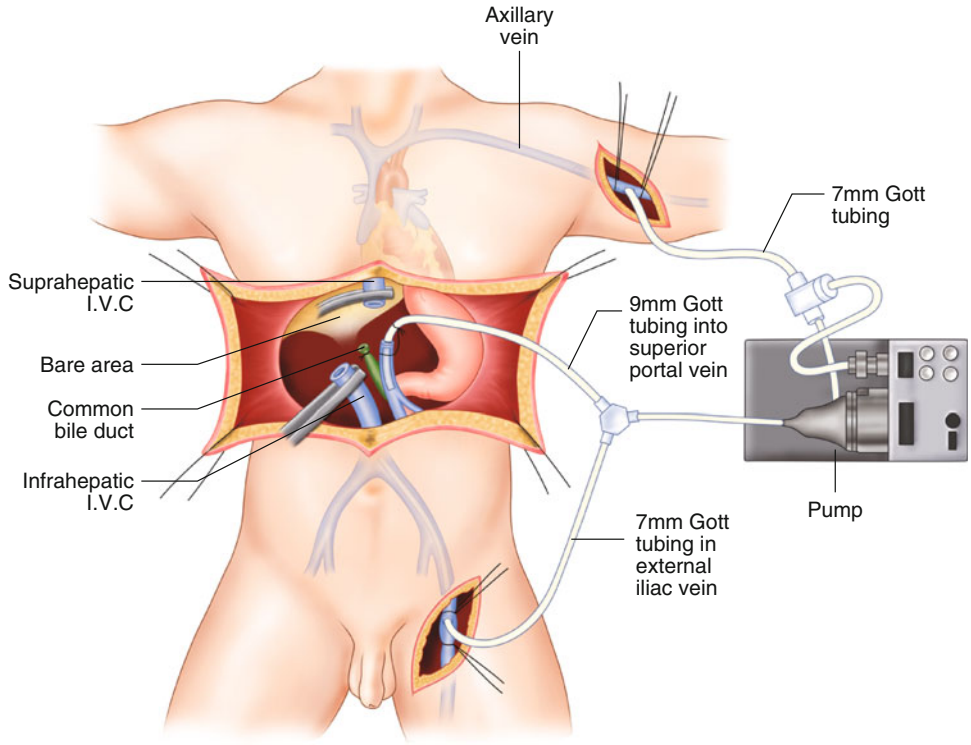

Fig. 3 Pump-driven venovenous bypass, which allows decompression of the splanchnic and systemic venous beds without the need for heparinization

rejection process. The consequent ischemia made the liver a target for infection (Brettschneider et al. 1968b; Starzl 1969b).

Preservation of the transplanted liver was accomplished in experiments with intraportal infusion of chilled electrolyte solutions in much the same way as is practiced clinically today (Starzl et al. 1960, 1961). Improved infusates in the succeeding years (Wall et al. 1977; Benichou et al. 1977) eventually replaced the original lactated Ringer's and saline solutions. Until 1987, however, the safe preservation time for human hepatic allografts was only 5–6 h. Since then, the University of Wisconsin solution (Jamieson et al. 1988) and other solutions have permitted reliable and safe refrigeration of human livers for 18–24 h (Kalayoglu et al. 1988; Todo et al. 1989).

In dogs, survival during recipient hepatectomy and installation of the transplanted liver (Starzl et al. 1960; Moore et al. 1960) required the use of external venous bypasses that passively redirected blood from the occluded splanchnic and systemic venous beds to the superior vena cava. Such venous decompression was later shown to be expendable in dogs submitted to common bile duct ligation several weeks in advance of liver replacement. The obvious safety factor was the development of venous collaterals secondary to the biliary obstruction through which the blocked portal blood could be decompressed (Picache et al. 1970).

It ultimately was recognized that venovenous bypasses were not absolutely essential in most human liver recipients who had chronic liver disease provided the transplants were done by experienced surgeons (Starzl et al. 1982). Nevertheless, the introduction of pump-driven venovenous bypasses in the 1980s (Fig. 3), first with (Starzl et al. 1982; Cutropia et al. 1972) and then without (Denmark et al. 1983; Shaw et al. 1984; Griffith et al. 1985) anticoagulation, made human liver transplantation a less stressful

operation and placed it well within the grasp of most competent general and vascular surgeons (Starzl et al. 1989d, e).

Intestine-Only Model

Alexis Carrel (later working with C.C. Guthrie) was the first to describe canine intestinal transplantation (Carrel 1902). Three quarters of a century passed before Richard Lillehei and his coworkers replaced almost the entire small intestine in unmodified dogs after immersing the graft in iced saline for preservation (Lillehei et al. 1959). The clinical application of intestinal transplantation languished even after it was demonstrated in Toronto (Craddock et al. 1983), London (Ontario) (Grant et al. 1988), and Pittsburgh (Diliz-Perez et al. 1984) that the gut could be successfully replaced in animals under long-term immunosuppression. Isolated examples of successful human intestinal transplantation were not accomplished until the late 1980s (Deltz et al. 1986; Ricour et al. 1983; Goulet et al. 1992; Todo et al. 1992).

Liver Plus Intestine Combinations

At the same time as isolated canine liver transplantation was perfected in 1959, the more radical procedure of multiple organ engraftment (including the liver) was shown to be feasible (Starzl and Kaupp 1960; Starzl et al. 1962) (Fig. 2c). This multivisceral allograft was viewed as a grape cluster with a double arterial stem consisting of the celiac axis and superior mesenteric artery (Fig. 1, center). In clinical variations of the operation used nearly 30 years later, the grapes, or individual organs, were removed or retained according to the surgical objectives (Fig. 1, periphery). Both sources of arterial blood were always preserved if possible (Starzl et al. 1991a).

Observations in the original canine multivisceral experiments of 1959 have been verified in human recipients. First, rejection of the organs making up the composite graft is less severe than after transplantation of the individual organs alone (Starzl et al. 1962). In 1969, Calne and colleagues (1969) confirmed and extended this principle in pig experiments showing that kidney and skin grafts were protected from rejection by a cotransplanted liver. The hepatic protective effect also has been confirmed in rats (Kamada 1985) by the Japanese surgeon Naoshi Kamada and by many others. Most recently, Valdivia et al. (1993) demonstrated the cross-species protection of hamster heart and skin xenografts in rats by the simultaneous or prior xenotransplantation of a hamster liver.

The Risk of Graft-Versus-Host Disease

The specter of graft-versus-host disease (GVHD) was raised by the transplantation of multivisceral grafts. The features of GVHD had been described by Billingham and Brent (1956) and Trentin (1956) as early as 1956. However, their observations had been almost exclusively based on bone marrow or splenocyte (not whole organ) transplantation. Histopathological evidence of GVHD was found in canine multivisceral recipients of 1959 (Starzl et al. 1962) but without physiological manifestations.

By 1965, however, it was realized that the classical GVHD defined by Billingham and Brent could be caused either by the liver or by the intestine. In addition, a humoral variety of GVHD was typified by hemolysis, first in canine liver recipients (Starzl et al. 1965) and later in humans (Ramsey et al. 1984). Although GVHD posed an obvious threat to human intestinal or multivisceral recipients, studies by Monchik and Russell (1971) in mice greatly overestimated this risk. The first example of long survival (>6 months) of a functioning human intestinal graft was provided by a multivisceral recipient (Starzl et al. 1989a). The fact that this child had no evidence of GVHD at any post-transplant time provided a strong incentive to move forward with the development of the Pittsburgh Intestinal Transplantation Program.

The Pancreatic and Other Hepatotrophic Factors

Transplantation of the pancreas alone (Houssay 1929; DeJode and Howard 1962; Idezuki et al. 1968; Kelly et al. 1967) will not be considered in these historical notes because this procedure is performed clinically only for endocrine objectives. However, the importance of first-pass delivery of endogenous insulin to the liver is a vital concern in the design of all liver transplant procedures and of all pancreas transplant operations.

Welch's belief that rejection of his auxiliary canine liver grafts (Welch 1955; Goodrich et al. 1956) was the explanation for their rapid atrophy (see earlier) was based on the long-standing belief that the source of portal venous blood was of no importance in the maintenance of "liver health" (Mann 1944; Child et al. 1953; Fisher et al. 1954; Bollman 1961). Although Welch's view could not have been more wrong, he had unwittingly created an experimental model of great power, the principle of which was the coexistence in the same animal of competing livers (Starzl et al. 1964, 1973; Marchioro et al. 1965, 1967).

The competing liver principle was applied in nontransplant models by simply dividing the dog's own liver into two parts, each of which was vascularized with portal venous inflow from different regions of the body (Marchioro et al. 1967; Starzl et al. 1973; Putnam et al. 1976) (Figs. 4 and 5). The key observation was that the liver fragment supplied with normal portal blood (see Fig. 4) flourished while the fragment given equal or greater quantities of substitute venous blood underwent acute atrophy. With a variety of double liver models (Figs. 4 and 5) the source of the hepatotrophic substances were localized first to the upper abdominal viscera and ultimately to the pancreas. Insulin and other hepatotrophic molecules were removed so completely with a single pass through the hepatic sinusoidal bed that little or none was left for the competing fragment. The deprived hepatocytes underwent dramatic atrophy within 4 days (Fig. 6). In crucial experiments, insulin when infused continuously into the tied-off portal vein after portacaval shunt (Fig. 7) prevented most of the atrophy and other adverse consequences to the liver caused by portal blood deprivation (Starzl et al. 1976, 1979a; Francavilla 1991).

Insulin was, in fact, only the first member to be identified of a diverse family of eight molecules, all others of which perfectly mimicked the hepatotrophic effects of insulin (Table 2) (Francavilla et al. 1994a). Although none of these "hepatotrophic factors" enhanced hepatocyte proliferation when infused into intact animals, all eight augmented preexisting hyperplasia. The second of these eight factors to be discovered, then called hepatic stimulatory substance (HSS), was demonstrated in 1979 in a cytosolic extract from regenerating dog livers (Starzl et al. 1979a) and later renamed "augmenter of liver regeneration" (ALR) (Francavilla et al. 1994a).

After a 14-year search for the identity of ALR, its molecular structure and expression in the rat, mouse, and humans were elucidated (Hagiya et al. 1994). The mammalian DNA of ALR has 40–50 % homology with the dual function nuclear gene scERV1 of baker's yeast (*Saccharomyces cerevisiae*) (Giorda et al. 1996). The gene provides part of the mitochondrial respiratory chain of yeast and also plays a critical role in cell replication. In the mouse, knockout of the ERV1 gene during embryogenesis is mutant-lethal. However, a study of mice with liver-specific conditional deletion of ALR showed that this peptide is required for mitochondrial function and for liver-dependent lipid homeostasis (Gandhi et al. 2015).

In addition to the diverse family of eight hepatotrophic factors, two molecules with specific antihepatotrophic qualities were identified (Table 2): transforming growth factor β, and the immunosuppressant rapamycin (Francavilla et al. 1994a). These discoveries expanded hepatotrophic physiology into multiple research areas of metabolism and regenerative medicine. The laboratory research had immediate clinical implications.

With the demonstration that portal diversion severely damages the liver, human portacaval shunt for the treatment of complications of portal hypertension was greatly reduced. However, a

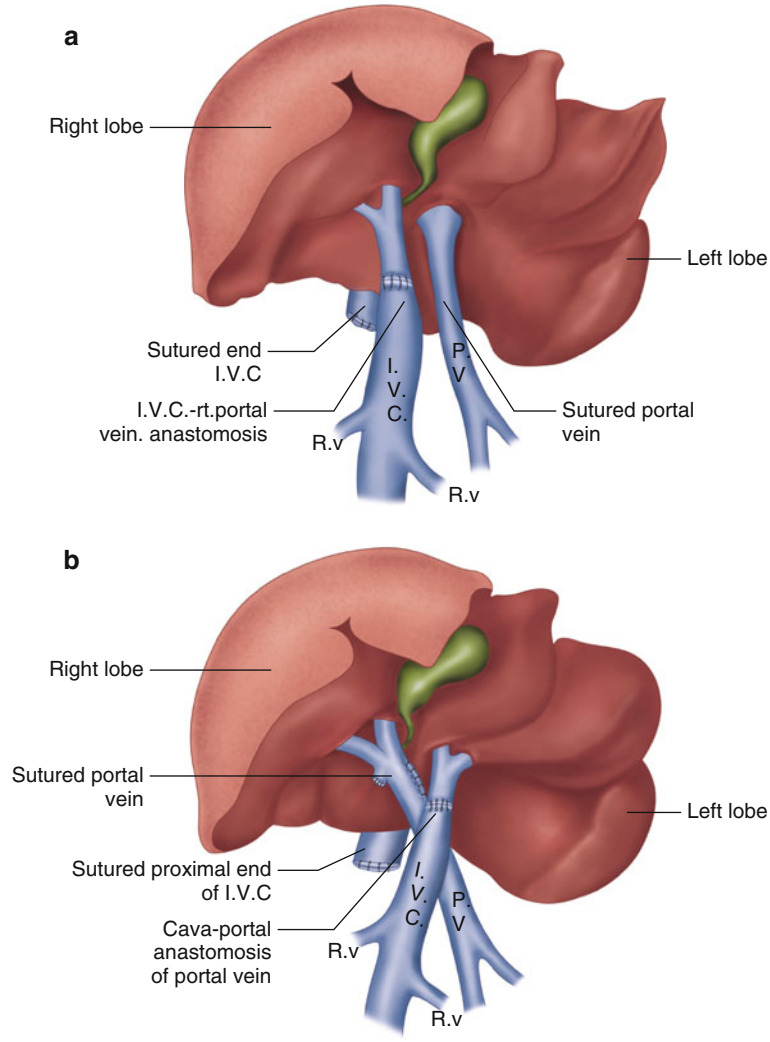

Fig. 4 The operation of partial (split) transposition in dogs. Note that one of the main portal veins *(left in* **a**. *right in* **b***)* retains the natural splanchnic flow and that the other one receives the total input of the suprarenal inferior vena cava. *RV* renal vein (**a** and **b** from Marchioro et al. 1967)

new use emerged. The degraded liver function caused by the procedure was used to palliate human glycogen, cholesterol, or alpha-1-antitrypsin storage diseases. In turn, such palliation identified heritable storage disorders that could be effectively treated with liver replacement (Starzl and Fung 2010).

Another dimension of hepatotrophic physiology was the liver regeneration that follows partial hepatectomy. No matter how much is taken out, the portion of liver that remains is restored to the original size within 3 weeks in humans, and far more rapidly in animals. In transplant-specific studies, it was shown in rodents (Francavilla et al. 1994b), dogs (Kam et al. 1987), and ultimately humans that a "small (or large) for recipient size" liver allograft promptly normalizes its volume to that appropriate for the individual recipient. What initiates this liver regrowth, or alternatively down sizes the liver, and then stops the adjustment at just the right volume has been a question of "hepatotrophic physiology" that has remained enigmatic.

Immunosuppression

After the demonstration by Medawar in 1944 that rejection is an immunological event (Medawar 1944, 1945), the deliberate weakening of the

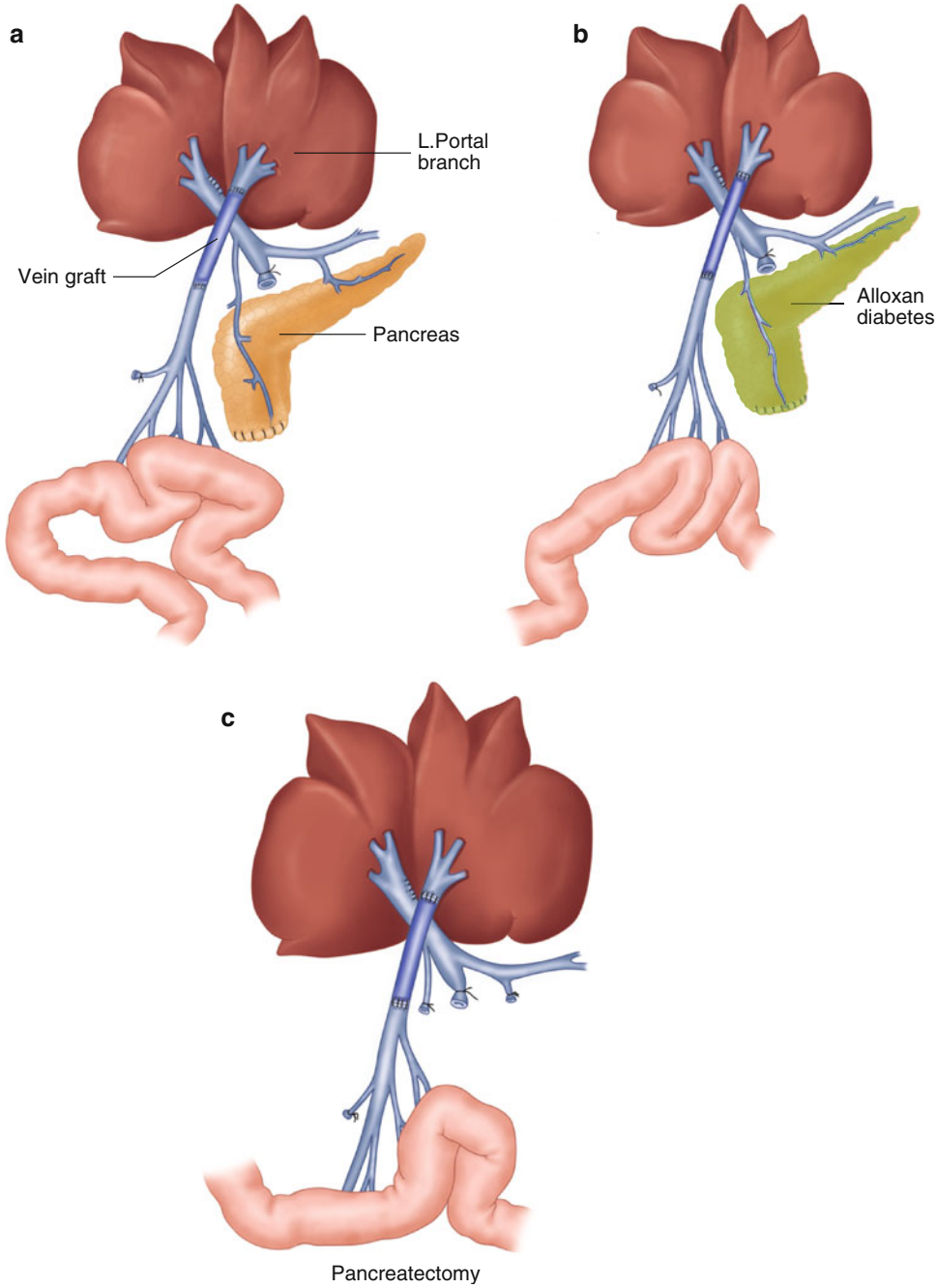

Fig. 5 Splanchnic division experiments. In these dogs. the right liver lobes received venous return from the pancreaticogastroduodenosplenic region. and the left liver lobes received venous blood from the intestines. (**a**). Nondiabetic dogs. (**b**). Alloxan-induced diabetic dogs. (**c**). Dogs with total pancreatectomy (**a**–**c** from Starzl et al. (1975a). By permission of Surgery. Gynecology and Obstetrics)

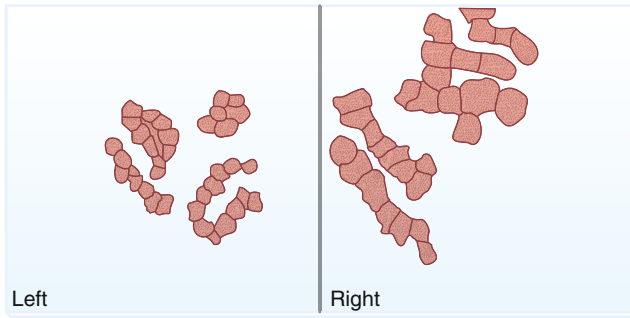

Fig. 6 Hepatocyte shadows traced during histopathological examination of liver biopsy specimens from the experiments shown in Figs. 4 and 5. These tracings were later cut out on standard paper and weighed as an index of hepatocyte size. The lobes with the large hepatic cells received venous blood from the pancreas, stomach, duodenum, and spleen. The relatively shrunken left lobes. with the small hepatocytes. received intestinal blood (From Starzl et al. (1973). By permission of Surgery Gynecology and Obstetrics)

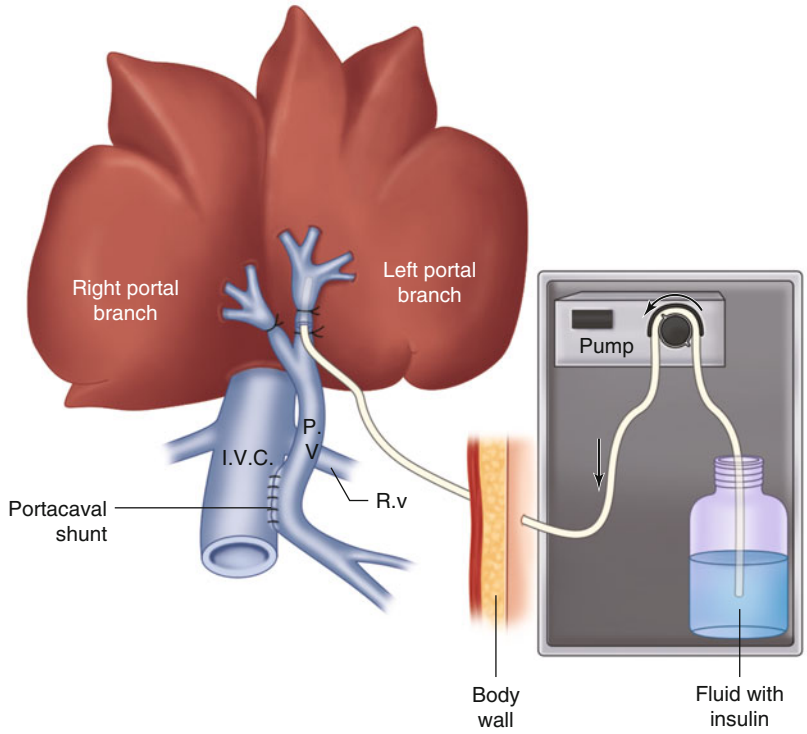

Fig. 7 Experiments in which postoperative infusions of insulin or other candidate hepatotrophic molecules are made into the left portal vein after performance of Eck's fistula (From Starzl et al. (1976), © by The Lancet Ltd, 1976)

immune system was shown to ameliorate the rejection of skin grafts in rodents and renal grafts in dogs. Such immunosuppression was accomplished in animals with total body irradiation (Dempster et al. 1950), adrenal corticosteroids (Billingham et al. 1951; Morgan 1951), and much later the thiopurine compounds 6-mercaptopurine and azathioprine (Meeker et al. 1959; Schwartz and Dameshek 1960; Calne 1960; Zukoski et al. 1960; Calne and Murray 1961). However, the avoidance of rejection with a single modality was rarely achieved without lethal side effects (Murray et al. 1960, 1962, 1963; Woodruff et al. 1963; Goodwin and Martin 1963; Groth 1972; Hamburger et al. 1962; Kuss et al. 1962).

Table 2 Hepatotrophic/anti-hepatotrophic factors (by 1994)

Hepatotrophic
Hormones:
Insulin
"Hepatic Growth Factors:"
Augmenter of liver regeneration (ALR)
Insulin-like growth factor II (IFG-II)
Transforming growth factor α (TGF-α)
Hepatocyte growth factor (HFG)
Immunosuppressants:
Cyclosporine
Tacrolimus
Immunophilins:
FK binding protein$_{12}$ (FKBP$_{12}$)
Anti-hepatotrophic
Growth factors:
Transforming grown factorβ (TGFβ)
Immunosuppressant:
Rapamycin

From: Francavilla et al. (1994a)

This discouraging picture changed dramatically during 1962 and 1963 at the University of Colorado, where the synergism of properly timed azathioprine and prednisone was discovered in animal investigations (Marchioro et al. 1964). When these two drugs were used together in Denver to treat human kidney transplant recipients (Starzl et al. 1963a; Starzl 1964), the results precipitated a revolution in clinical transplantation. The key observations were that organ rejection could usually be reversed with prednisone and then that the amount of drugs required often lessened with time (Starzl et al. 1963a, 1990; Starzl 1964; Hume et al. 1963).

The reversibility of kidney rejection and an apparent but unexplained change in host–graft relationship were eventually verified with all other transplanted organs, beginning with the liver (Starzl et al. 1965; Starzl 1969c). Although immunosuppression has improved, the central therapeutic strategy for whole organ transplantation that had emerged by 1963 (Starzl et al. 1963a; Starzl 1964) has changed very little in over 30 years. The strategy calls for daily treatment with one or two baseline drugs and further immunomodulation with the highly dose-maneuverable adrenocortical steroids (or other secondary or tertiary agents) to whatever level is required to maintain stable graft function. Every organ recipient goes through a trial and potential error algorithmic experience as drug dosages are modified to achieve the desired maintenance levels. The principal baseline drugs used clinically with this format have been azathioprine, cyclosporine, and tacrolimus (Starzl 1964, 1969c, d; Starzl et al. 1963b, 1967, 1971, 1979b, 1980, 1989b, 1990; Hume et al. 1963; Franksson 1984; Strober et al. 1979; Najarian et al. 1982; Calne et al. 1979).

Clinical Liver Transplantation

Phase I: The Failed First Cases – Once the effectiveness of the azathioprine-prednisone cocktail for kidney grafting had been established, a decision was taken at the University of Colorado to move on to the liver (Starzl et al. 1963c; Starzl 1992b). The first recipient was a 3-year-old boy with biliary atresia who had had multiple previous operations. The transplantation could not be completed because of a fatal hemorrhage from venous collaterals and an uncontrollable coagulopathy (prothrombin time infinity, platelet count $<10{,}000/mm^3$). Even for a team that had been fully prepared for technical vicissitudes by hundreds of animal operations, the exsanguination of this child was a terrible shock.

Two more liver transplantations were carried out in the next 4 months. In both, the procedures seemed satisfactory, but the recipients died after 22 and 7 days, respectively (Starzl et al. 1963c; Starzl 1992b). Promotion of coagulation (fresh blood or blood products and E-aminocaproic acid to treat fibrinolysis) had a delayed backfire. During the time when the livers were sewn in, the plastic external bypasses were used to reroute venous blood around the area of the liver in the same way as had been worked out in dogs.

Clots formed in the bypass tubing and passed to the lungs of recipients. Abscesses and other lung damage contributed to or caused delayed death in all four of these patients (Starzl et al. 1963c, 1964). By this time, isolated attempts

Table 3 The first seven attempts of clinical orthotopic liver transplantation

Number	Location	Age (years)	Disease	Survival (days)	Main Cause of Death
1	Denver, (From Starzl et al. 1963c)	3	Extrahepatic bilary atresia	0	Hemorrhage
2	Denver, (From Starzl et al. 1963c)	48	Hepatocellular cancer, cirrhosis	22	Pulmonary emboli, sepsis
3	Denver, (From Starzl et al. 1963c)	68	Duct cell carcinoma	7-1/2	Sepsis, pulmonary emboli, gastrointestinal bleeding
4	Denver, (From Starzl et al. 1964)	52	Hepatocellular cancer, cirrhosis	6-1/2	Pulmonary emboli, hepatic failure, pulmonary edema
5	Boston, (From Moore et al. 1964)	58	Metastatic colon carcinoma	11	Pneumonitis, liver abscesses, hepatic failure
6	Denver, (From Starzl et al. 1964)	29	Hepatocellular cancer, cirrhosis	23	Sepsis, bile peritonitis, hepatic failure
7	Paris, (From Demirleau et al. 1964)	75	Metastatic colon carcinoma	0	Hemorrhage

Fig. 8 Photograph (1968) of a dog whose orthotopic liver transplantation had been carried out in the spring of 1964. The animal, who was treated with azathioprine for only 100 days, died of old age after 112/3 postoperative years. This was the first example of "hepatic tolerogenicity"

at liver replacement made in Boston (Moore et al. 1964) and Paris (Demirleau et al. 1964) had also been unsuccessful (Table 3). A pall-settled over liver transplantation and a self-imposed moratorium followed that lasted more than 3 years.

Pessimism prevailed worldwide. The operation of liver replacement seemed too difficult to allow its practical application. In addition, the methods of preservation were assumed to be inadequate for an organ so seemingly sensitive to ischemic damage. Researchers began to ask whether the available immunosuppression was too primitive to permit success. This possibility was reinforced by the fact that truly long-term survival after liver replacement (i.e., measured in years) had not yet been achieved in experimental animals.

Phase 2: Feasible but Impractical – By the summer of 1967, these deficiencies had been at least partially rectified by 3 more years of laboratory effort. Many long-term canine survivors had been obtained (Starzl et al. 1965), and some dogs had passed the 3-year postoperative mark (Fig. 8). Better immunosuppression with the so-called

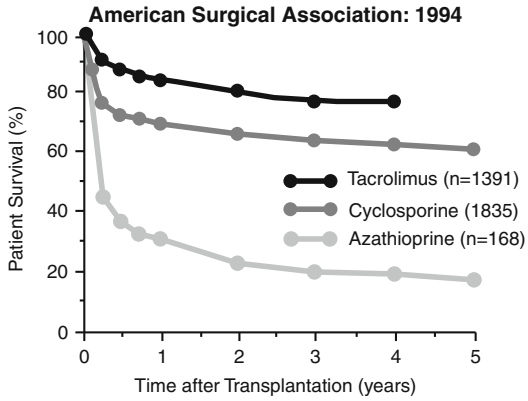

Fig. 9 Patient survival during the successive eras in which the baseline immunosuppressant was azathioprine (*bottom curve*), cyclosporine (*middle*), and tacrolimus (*upper*)

triple-drug therapy was available since the development and first-ever clinical trials of antilymphocyte globulin (ALG). The ALG was prepared from the serum of sensitized horses (Starzl et al. 1967) and used to supplement azathioprine and prednisone in renal recipients. Finally, techniques of organ preservation for as long as a day had been developed (Starzl 1992c; Brettschneider et al. 1968).

On July 23, 1967, a 1-1/2 -year-old child with a huge hepatoma was restored almost immediately from a moribund state to seemingly good health after liver replacement. More cases followed. Most of the attempts made in 1967 and 1968 were initially successful, but all of the patients eventually died. The first long-term survivor succumbed to recurrent cancer after 400 days. The maximum survival of the other six long-surviving liver recipients treated between July 1967 and March 1968 was 2-1/2 years (Starzl et al. 1968, 1982; Starzl 1992d).

For the next 12 years, the I-year mortality rate after liver transplantation never fell below 50 % in cases that were accrued at the University of Colorado at the rate of about 1 per month. The losses were concentrated in the first postoperative months; after this initial period, the life survival curve flattened, leaving a residual group of stable and remarkably healthy survivors (Fig. 9). Of the first 170 patients in the consecutive series that started March 1, 1963, and ended in December 1979, 30 (18 %) lived more than 10 years; 23 remained alive after 13–23 years. All were treated with azathioprine (or the anticancer agent cyclophosphamide), prednisone, and polyclonal antilymphocyte globulin (Starzl et al. 1982).

In the meantime, Roy Calne of Cambridge University in England began clinical trials of liver transplantation on May 23, 1967. As had been experienced earlier, his first patient exsanguinated (Calne and Williams 1968). A few months later, Calne formed a collaboration that endured for more than two decades with the hepatologist Roger Williams at King's College Hospital in London. The extended survival of patients in both the Colorado and Cambridge-London series was a testimonial for liver transplantation. It was asked increasingly on both sides of the Atlantic, however, if such a small dividend could justify the prodigious effort that had brought liver transplantation this far (Starzl 1992e).

Other teams organized in Hannover (Rudolf Pichlmayr 1972), Paris (Henri Bismuth 1974), and Gronigen (Rudi Krom) also reported the nearly miraculous benefits of liver transplantation when this treatment was successful but always with the notation that the mortality rate was too high to allow its practical use. Liver transplantation remained a feasible but impractical operation.

Phase 3: The Cyclosporine and FK506 Eras – The frustration ended when cyclosporine became available for clinical use in 1979 (Calne et al. 1979) and was combined with prednisone or lymphoid depletion in the first of the cyclosporine-based cocktails (Starzl et al. 1980) (Fig. 9). Of the first 12 liver recipients treated with cyclosporine and prednisone in the first 8 months of 1980, 11 lived for more than a year (Starzl et al. 1981), and 7 were still alive more than a dozen years later. As the news was confirmed that a 1-year patient survival rate of at least 70 % was readily achievable, new liver programs proliferated worldwide.

When FK506 was substituted for cyclosporine in 1989 (Starzl et al. 1989b), the 1-year patient and liver graft survival rate rose again in the Pittsburgh experience (Todo et al. 1990) (Fig. 9), an improvement similar to that in a multicenter European trial. By this time, liver transplantation had become the accepted court of last appeal for almost all non-neoplastic liver disease and even for selected patients with otherwise nonresectable hepatic malignancies. The principal limitation of the technology quickly became the small supply of organs to meet the burgeoning need.

Although the ascension of liver transplantation was dominated by improvements in immunosuppression, there were other significant developments including modifications in the details of the operation itself. The incidence of biliary duct complications (obstruction, fistula, and cholangitis), which had been more than 30 % (Starzl et al. 1977), was reduced by the use of choledochocholedochostomy with a T-tube stent or, if this was not feasible, by choledochojejunostomy to a Roux limb (Starzl et al. 1982). Management of coagulopathies was facilitated by the use of the thromboelastogram to follow the minute-to-minute clotting changes in the operating room (Starzl et al. 1963c; Kang et al. 1985). The systematic use of venovenous bypasses without anticoagulation also greatly diminished the occurrence of hemorrhages of nightmare proportions common at one time.

Organ Procurement: Hypothermia and Core Cooling

Although few in number, steps in the development of liver graft procurement and preservation established principles that could be applied to other whole organs. The first was core cooling by infusion of chilled, lactated Ringer's solution into the portal vein (Starzl et al. 1960), a laboratory technique soon modified for use in clinical kidney transplantation (Starzl 1964) and subsequently for other organs.

Today, core cooling is the initial stage in the preservation of all whole organs. However, in contrast to the original method of skeletonization and removal of the individual grafts before infusion of chilled fluids, core cooling is performed by variations of the in situ technique originally developed before the acceptance of brain death conditions. This technique involved continuous hypothermic perfusion of cadaveric kidney and liver donors (Marchioro et al. 1963; Starzl 1969e) (Fig. 10). Ackerman and Snell (1968) and Merkel and colleagues (1972) simplified the in situ cooling of cadaveric kidneys with cold electrolyte solutions infused into the distal aorta without continuous perfusion.

Eventually, in situ cold infusion techniques were perfected that allowed removal of all thoracic and abdominal organs including the liver without jeopardizing any of the individual organs (Starzl et al. 1984) (Fig. 11). Modifications of this procedure were made for unstable donors and even for donors whose hearts had ceased to beat (Starzl et al. 1987). By 1987, multiple organ procurement techniques were interchangeable not only from city to city but from country to country and had become standardized in all parts of the world. Today, after the chilled organs have been removed, subsequent preservation may be by simple refrigeration or by sophisticated methods of continuous perfusion.

Indications for Liver Transplantation

Benign Disease Categories – By 1989, the list of benign diseases treatable by transplantation had become so long (nearly 100) that it was being divided into broad categories (see section "Generic Listing of Liver Diseases Treatable by Liver Transplantation" below) such as cholestatic disorders and those involving the parenchyma (Starzl et al. 1989d, e). Because products of hepatic synthesis permanently retain the original metabolic specificity of the donor after transplantation (Starzl et al. 1989d; Starzl 1992f), the correction of inborn errors by liver transplantation can be expected to endure for the life of the graft. By 1989, 16 liver-based or liver-influenced inborn errors of metabolism had been compiled under the inborn error category of indications (Table 4). The length of the list has been more than doubled since then.

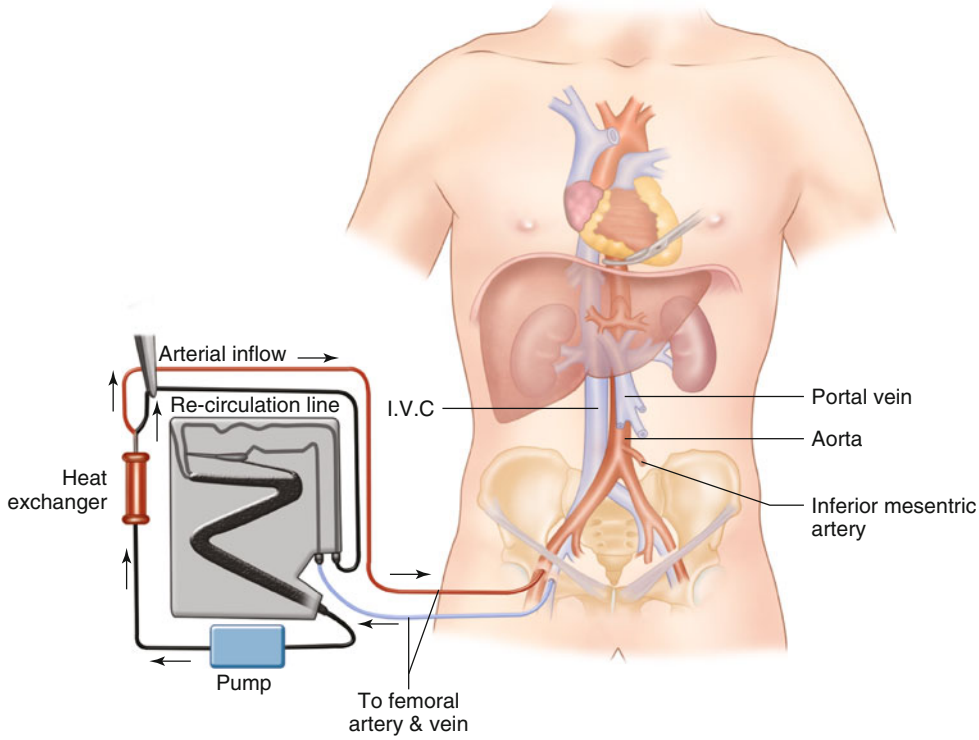

Fig. 10 The first technique of in situ cooling by extracorporeal hypothermic perfusion. The catheters were inserted via the femoral vessels into the aorta and vena cava as soon as possible after death. Temperature control was provided with a heat exchanger. Crossclamping of the thoracic aorta limited perfusion to the lower part of the body. This method of cadaveric organ procurement was used from 1962 to 1969. before the acceptance of brain death. The preliminary stages of this approach provided the basis for subsequent in situ infusion techniques (From Starzl 1964, p. 56)

Generic Listing of Liver Diseases Treatable by Liver Transplantation

Disease

*Parenchymal*Postnecrotic cirrhosis
- Alcoholic cirrhosis
- Acute liver failure
- Budd-Chiari syndrome
- Congenital hepatic fibrosis
- Cystic fibrosis
- Neonatal hepatitis
- Hepatic trauma

Cholestatic
- Biliary atresia
- Primary biliary cirrhosis
- Sclerosing cholangitis
- Secondary biliary cirrhosis
- Familial cholestasis

Inborn Errors of Metabolism

Tumors
- Benign
- Primary malignant
- Metastatic

Trimming the Contraindication List – A number of diseases that once precluded transplantation such as alcoholic cirrhosis are no longer contraindications. Scarring from multiple upper abdominal operations and prior portosystemic shunts have been eliminated as serious adverse factors in major centers. Extensive thrombosis of the portal and superior mesenteric veins, which previously made liver transplantation difficult or impossible, has been almost eliminated as a deterrent to transplantation by the use of vascular grafts (Starzl et al. 1979c; Shaw et al. 1985; Sheil et al. 1987; Tzakis et al. 1989b; Stieber et al. 1991) (Fig. 12). The systematic use of

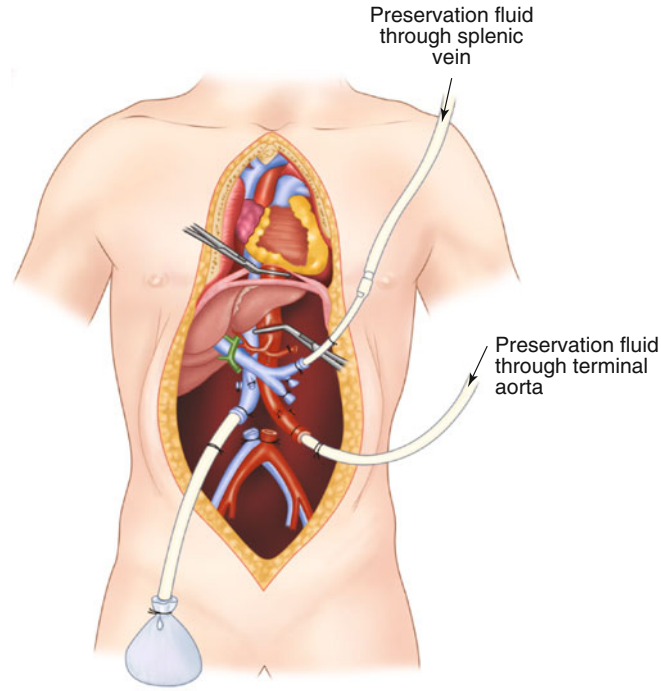

Fig. 11 Principle of in situ cooling used for multiple organ procurement. With limited preliminary dissection of the aorta and great splanchnic veins (in this case the splenic vein), cold infusates can be used to chill organs in situ. In this case, the kidneys and liver were to be removed. Note the aortic crossclamp above the celiac axis (Redrawn from Starzl et al. (1984). By permission of Surgery, Gynecology and Obstetrics)

arterial and venous grafts was introduced at the University of Colorado in the 1970s (Starzl et al. 1979c). Harvesting these life-saving conduits was made an integral component of the cadaveric organ procurement procedure thereafter (Starzl et al. 1984). A particularly useful technique has been the antipancreatic venous jump graft first described by Sheil et al. (1987) in Sydney (Fig. 13).

Similarly, age proscriptions at either the upper or lower range were dropped by the mid-1980s. The shortage of appropriate-sized donors for very small pediatric recipients was greatly ameliorated by the use of liver fragments. The first known reduced liver graft operation was performed in Denver in 1975 (Starzl and Demetris 1990), but it was not reported until long after the landmark descriptions of this technique by Henri Bismuth and Didier Houssin of Paris (1984) and by the team of Rudolf Pichlmayr and Christoph Broelsch et al. of Hanover (1984). In 1989, Lynch and Strong successfully transplanted a portion of the left lobe from a living related donor (Strong et al. 1990), a procedure further refined and popularized by Broelsch during a stint at the University of Chicago (Broelsch et al. 1990). These liver reduction procedures were facilitated by the use of the *piggyback* principle in which the recipient retrohepatic vena cava is kept intact and the suprahepatic venous outflow of the graft is anastomosed to cuffs of the hepatic veins (Tzakis et al. 1989a) (Fig. 14). The piggyback modification was first used in Denver in 1968 in a child with vascular anomalies and was independently described by Calne (Calne and Williams 1968) for the transplantation of a pediatric liver into an adult. Its use was ultimately popularized by Tzakis et al. (1989).

Neoplastic Diseases – The first use of conventional liver transplantation to treat otherwise nonresectable primary or metastatic hepatic cancers resulted in a very high rate of recurrence (Starzl et al. 1989). Nevertheless, its use for this indication is a common practice by many transplantation teams almost invariably in combination with adjuvant chemotherapy or experimental treatment protocols. Certain kinds of neoplasms have a better prognosis than others. A radical

Table 4 Inborn errors of metabolism treated with liver transplantation[a]

Disease	Explanation of disease	Longest survival	Associated liver disease
A_1-ANTITRYPSIN deficiency	Structural abnormality of the protease inhibitor synthesized in the liver	13 years	Cirrhosis
Wilson's disease	Abnormal biliary copper excretion, decreased copper binding to ceruloplasmin, and copper accumulation in tissues; autosomal recessive gene mapped to chromosome 13	16-1/2 years	Cirrhosis
Tyrosinemia	Fumaroylacetoacetate hydrolase deficiency	7-1/2 years	Cirrhosis, hepatoma
Type I glycogen storage disease	Glucose-6-phosphatase deficiency	7 years	Glycogen storage, fibrosis, tumors
Type IV glycogen storage disease	Amylo-1:4, 1:6-transglucosidase (branching enzyme) defect	4-1/2 years	Cirrhosis
Cystic fibrosis	Unknown; pancellular disease, liver often affected	4-1/2 years	Cirrhosis
Niemann-Pick disease	Sphingomyelinase deficiency, sphingomyelin storage	2 years (died)	None
Sea-blue histiocyte syndrome	Unknown, neurovisceral lipochrome storage	7 years	Cirrhosis
Erythropoietic protoporphyria	Hepatic ferrochelatase deficiency, overproduction of protoporphyrin by erythropoietic tissues	1-1/2 years	Cirrhosis
Crigler-Najjar syndrome	Glucuronyl transferase deficiency	4 years	None
Type 1 hyperoxaluria	Peroxisomal alanine : glyoxylate aminotransferase deficiency	8 months	None
Urea cycle enzyme deficiency (three types)	Ornithine carbamoyltransferase deficiency	8 months	None
C protein deficiency	Defective C protein synthesis	2-1/4 years	None
Familial hypercholesterolemia	Low-density lipoprotein receptor deficiency, low-density lipoprotein overproduction	6 years	None
Hemophilia A	Factor VIII deficiency	4 years	Cirrhosis, a complication of blood component therapy
Hemophilia B	Factor IX deficiency	6 months	Cirrhosis, a complication of blood component therapy

From Starzl et al. (1989d, e). Reprinted by permission of *The New England Journal of Medicine*, 1989. Copyright 1989, Massachusetts Medical Society

[a]Most of the patients were in the University of Colorado-University of Pittsburgh series. Follow-up to January 1989

extension of this attempt to increase the resectability is the removal of upper abdominal organs en bloc (liver, pancreas, spleen, stomach, duodenum, proximal jejunum, and right colon) (Fig. 1e); extensive sarcomas and carcinoid tumors that are still regionally confined (Starzl et al. 1989c) are indications. The excised organs are replaced by hepatopancreaticoduodenal grafts or, in some cases, by the liver alone.

Clinical Trials of Intestinal Transplantation in Combination with the Liver or Alone

Composite Grafts – Function of a cadaveric intestine for more than 6 months was not accomplished under any circumstance until 1987. In November of that year, a recipient of a

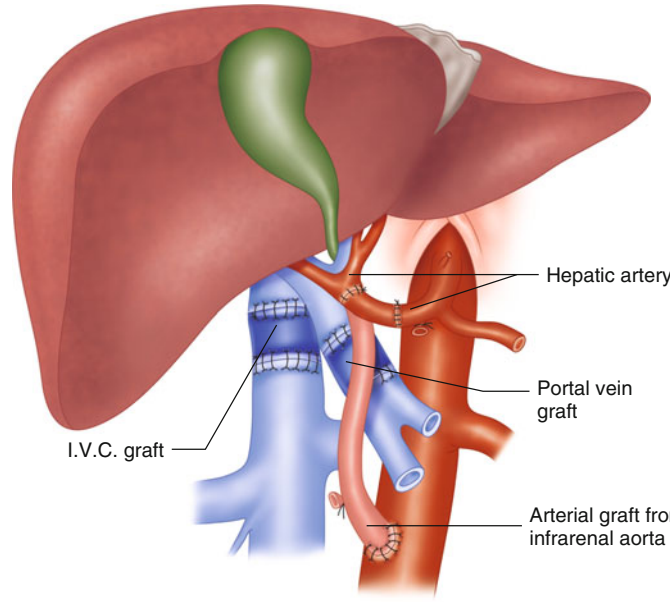

Fig. 12 By 1979, all of the demonstrated grafts had been used clinically. The use of vascular grafts has been life-saving; liver transplantation should never be attempted without an emergency assortment of these grafts (Redrawn from Starzl et al. (1979c), pp. 76–77. By permission of Surgery, Gynecology and Obstetrics)

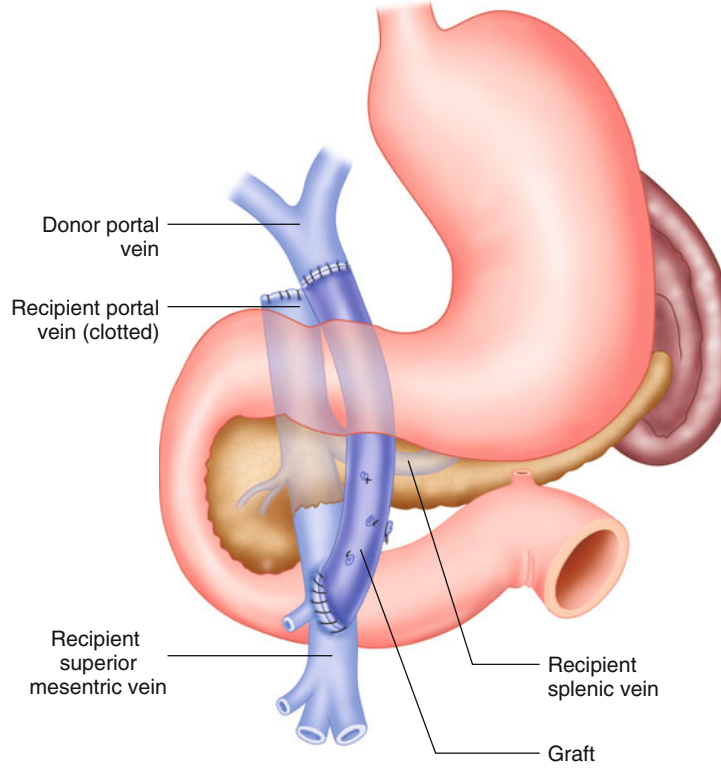

Fig. 13 An antepancreatic route for a vascular graft placed onto the infrarenal abdominal aorta, as originally described by Sheil. The graft is brought to the *right* or *left* of the middle colic vessels, anterior to the pancreas and beneath the pylorus (From Tzakis et al. 1989b)

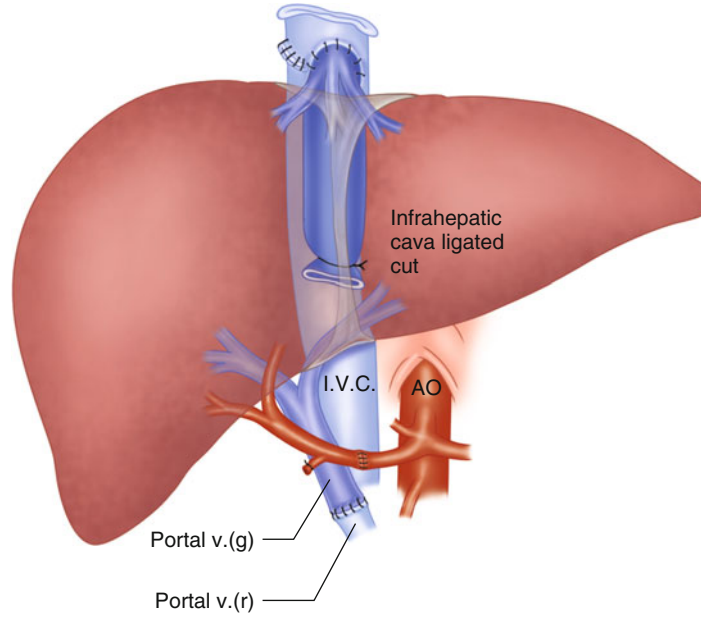

Fig. 14 Transplantation of a liver piggybacked onto an inferior vena cava which is preserved through its length. Note that the suprahepatic vena cava of the homograft is anastomosed to the anterior wall of the recipient vena cava. The retrohepatic vena cava of the homograft is sutured or ligated, leaving a blind sac into which empty numerous hepatic veins (From Tzakis et al. 1989a)

multivisceral graft treated with cyclosporine, prednisone, and the antilymphoid agent OKT3 survived for 192 days before dying of a B-cell lymphoma (Starzl et al. 1989a). By the mid-1990s, several subsequent recipients of the full multivisceral graft had survived more than 2 years under FK506 (Starzl et al. 1993a).

In the early 1990s, a variant procedure in which only the liver and small bowel are retained (see Fig. 1c) was used successfully by Grant and coworkers (1990) of London, Ontario (Canada). This operation has been particularly useful in patients with the short gut syndrome who developed liver failure after prolonged hyperalimentation (Todo et al. 1992). By 1993 and with the use of FK506, 13 (76.5 %) of 17 patients treated in the Pittsburgh series of liver-intestine grafts were alive after 5–31 months (Starzl et al. 1993a). All but one had been liberated from total parenteral nutrition.

Intestinal Transplantation Alone – Some workers in the field believed that the protection to the intestine afforded by the concomitant transplantation of the liver from the same donor (see earlier) was sufficiently great to justify combined liver and intestinal transplantation even when only a technically simpler intestinal transplant was needed. Enthusiasm for this draconian strategy began to fade with the successful transplantation in March 1989 of a cadaveric small intestine by Goulet and colleagues (1992) of Paris and of an ileal segment from a living related donor by Deltz et al. of Kiel, Germany (1990). The French patient was still alive at the beginning of the third millennium. These patients were treated with cyclosporine.

They were isolated straws in the wind. In Pittsburgh, the routine survival of cadaveric intestinal recipients now became possible under immunosuppression with FK506; the results have been better with isolated intestinal transplantation than with either the multivisceral operation or its liver-intestine variant (Todo et al. 1992, 1993; Starzl et al. 1993a). Once FK 506 (tacrolimus) was released by the FDA for general use, the intestinal transplantation field definitively opened.

Metabolic Interactions – Normally, the venous effluent from all nonhepatic splanchnic organs contributes to the portal blood supply, assuring the liver first-pass exposure to the intestinal nutrients and to the so-called portal hepatotrophic substances of which insulin is the most important. Hepatotrophic factors apply to native livers and transplanted ones and should be taken into consideration in planning any intra-abdominal visceral transplantation whether it be

of the liver or intestine alone or one of the multivisceral procedures that alter the portal circulation.

For example, when partial multivisceral grafts such as that of the liver and intestine are used in recipients whose pancreas and other upper abdominal organs are retained, it is preferable to direct the venous effluent from the residual host organs into the portal circulation of the new liver. Similarly, when the intestine is transplanted alone, the ideal route of graft venous return is through the native liver. However, the inability for technical reasons to drain intestinal return into the host liver has not caused severe hepatic complications in a small number of human recipients (Todo et al. 1992).

Conclusion

Throughout the modern history of transplantation, it was not known how grafts were able with the aid of immunosuppression to resist the onslaught of rejection and later merge half forgotten into the host. In 1992, a study of liver, kidney, and other organ recipients who had survived for as long as three decades provided unique insights into the engraftment process. In all studied cases, multilineage donor leukocytes could be demonstrated in the skin lymph nodes, heart, and other tissues of the long-surviving hosts (Starzl et al. 1992, 1993b, c, d, 1996).

These chimeric cells had emigrated from the grafts and then perpetuated themselves for many years. They were present in larger numbers at any given peripheral site in liver recipients than in recipients of other kinds of organs such as the kidney (Starzl et al. 1992, 1993b, c, d, 1996). The large number of these potentially migratory cells in the liver is a possible explanation for the hepatic tolerogenicity that allows the liver to induce its own acceptance more readily than other organs can and in some experimental models undergo engraftment without the aid of immunosuppression. The microchimerism discoveries have necessitated a paradigm shift in many aspects of transplantation immunology (Starzl 2015a; Starzl et al. 2015b).

Cross-References

- ▶ Anesthesia Management of Liver Transplantation
- ▶ Combined Transplantations
- ▶ Donor Operation
- ▶ Immunology of Liver Transplantation
- ▶ Orthotopic Liver Transplantation: Surgical Techniques

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Part II

The Operation

Orthotopic Liver Transplantation: Indications and Contraindications

2

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Abstract

At the beginning of the third millennium, liver transplantation (LT) has turned from dream into a reality. Thomas E. Starzl, who first performed LT in March 1963, and many of his scholars allowed to live one of the most extraordinary adventures of modern medicine. Twenty years later, in 1983, the National Institute of Health Consensus Development Conference concluded that LT was "a promising alternative to current therapy in the management of late phase of several forms of serious liver diseases" and that it had the potential to become a "clinical service" as opposed to an experimental procedure. Half a century later, LT progressed at high speed resulting in a worldwide, curative, treatment of more than 50 different liver as well as liver-based diseases. Today the 250,000 mark has been reached. This chapter gives a detailed overview of all the different aspects of this medical adventure, stressing thereby also the last innovations and forthcoming revolutions to expect.

Keywords

Liver transplantation • Acute liver failure • Chronic liver disease • Viral infection • HBV • HCV infection • Alcoholic liver disease • Autoimmune liver disease • Cholestatic liver disease • Metabolic disease • Familial amyloid polyneuropathy • Oncology • Hepatobiliary oncology • Hepatocellular cancer • Cholangiocellular cancer • Liver metastases • Living donor liver transplantation

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Introduction

The first human liver transplantation (LT) was carried out by Thomas E. Starzl on March 26, 1963, in Denver, Colorado (Starzl et al. 1963). The recipient died due to intraoperative bleeding and liver dysfunction. Eight attempts followed, unfortunately they were also unsuccessful; the longest survival being limited at 23 days. These initial results well reflected the insufficient knowledge about organ procurement and preservation as well as of surgical technique and perioperative care. As a consequence, a voluntary moratorium was observed till 1967. The same team performed the worldwide tenth, this time successful, human LT. The recipient, a 1.5-year infant presenting a biliary atresia complicated with a huge hepatocellular cancer (HCC), died of tumor recurrence 400 days later (Starzl et al. 1968). Following this first short-term success, it took a time span of 20 years in order to make this complex surgical procedure safe. The surgical progress coincided with the introduction in clinical practice in the beginning of the 1980s of a new, selective, immunosuppressive drug, cyclosporine A (CyA). The launch of this drug was the ideal "aid" to definitively transform LT into a clinical service for liver diseased patients as exemplified by the raise of the one-year survival rate from less than 50 % during the period 1976–1979 to more than 75 % during the following 5 years. In June 1983, the National Institute of Health Consensus Development Conference on LT concluded, based on the worldwide experience counting only 540 procedures performed during the period 1963–1983 in the only American (Denver–Pittsburgh) and three European (Groningen, Hannover and Cambridge) centers, that LT was "a promising alternative to current therapy in the management of late phase of several forms of serious liver diseases" and that it had the potential to become a "clinical service" as opposed to an experimental procedure (National Institutes of Health 1983). This potential was recognized only on the condition to restrict the procedure to very well-selected patients complying with ten absolute and five relative contraindications (Table 1). However 6 years later, Starzl wrote that "the conceptual appeal of LT is so great that the procedure may come to mind as a last resort for virtually every patient with lethal hepatic disease" (Starzl et al. 1989). This visionary sentence perfectly synthesized what would happen during the last three decades. Indeed progresses were spectacular leading to an exponential growth of the number of procedures, reaching half a century later, almost the 250,000 mark! All but one of the contraindications to LT forwarded by the Consensus Conference, e.g., active sepsis outside the hepatobiliary system, were wiped away. Today, LT has indeed become "the" curative answer to more than 50 different liver and live-based pathologies (Table 2).

Table 1 Indications and contraindications for liver transplantation identified at the 1983 National Institute of Health Consensus Conference

	Contraindications	
Indications	Absolute	Relative
1. Young patient < 50 years	1. Age > 55 years	1. Age > 50 years
2. No viral infection	2. HBsAg–HBeAg-positive state	2. HBsAg-positive state
3. No alcohol and drug abuse	3. Active alcoholism	3. Intrahepatic or biliary sepsis
4. Ability to accept procedure/ understand its nature	4. Inability to accept procedure or understand its nature or costs	4. Advanced alcoholic liver disease in abstinent alcoholic
5. Ability to accept costs	5. Sepsis outside hepatobiliary system	5. Prior abdominal surgery[a]
6. Normal vessel state	6. Portal vein thrombosis	6. Portal hypertension surgery
7. No CP or renal disease	7. Advanced CP or renal disease	
8. No prior abdominal surgery	8. Severe hypoxemia (right to left shunts)	
9. No infection	9. Metastatic hepato-biliary malignancy	
10. No (advanced) malignancy	10. Primary malignant disease outside hepatobiliary system	

[a]Especially in the right upper quadrant
Abbreviations: CP cardiopulmonary, HB hepatitis B

Table 2 Indications for liver transplantation in 2014

Acute liver failure	Hepatitis A virus Hepatitis B virus Hepatitis D virus Hepatitis E virus Acetaminophen Other drugs Postoperative Posttraumatic Wilson disease Budd–Chiari syndrome Autoimmune hepatitis Cryptogenic Fatty infiltration – acute fatty liver of pregnancy Reye syndrome
Cirrhosis from chronic liver disease	Chronic hepatitis B viral infection Chronic hepatitis C viral infection Chronic hepatitis B and D viral infection Chronic hepatitis E viral infection Cirrhosis viral related (other viruses) Cirrhosis drug related Alcoholic liver disease Autoimmune hepatitis Cryptogenic liver disease Nonalcoholic fatty liver disease
Cholestatic liver diseases	Primary biliary cirrhosis Primary sclerosing cholangitis Caroli disease Secondary biliary cirrhosis Alagille syndrome Byler disease Severe graft-versus-host disease Congenital biliary fibrosis Extrahepatic biliary atresia
Vascular liver disease	Budd–Chiari syndrome Hereditary hemorrhagic telangiectasia Veno-occlusive disease
Metabolic liver diseases	Wilson disease Hereditary hemochromatosis Alpha-1 antitrypsin deficiency Glycogen storage disease I and IV Familial homozygous hypercholesterolemia Tyrosinemia Familial amyloid polyneuropathy Primary hyperoxaluria Protoporphyria Other types of porphyria Crigler–Najjar syndrome Cystic fibrosis Galactosemia Factor VIII (Hemophilia A and B) and V deficiency Thrombophilic disease (e.g., Protein C, S deficiency)
Benign tumor	Hepatic adenoma Adenomatosis Giant hemangioma Focal nodular hyperplasia Nodular regenerative hyperplasia
Malignant tumor	Hepatocellular carcinoma on cirrhosis Hepatocellular carcinoma on non-cirrhotic liver Intrahepatic cholangiocarcinoma Biliary tract carcinoma (Klatskin) Epithelioid hemangioendothelioma Hepatoblastoma NET metastasis Colorectal tumor metastasis[a]
Miscellaneous	Polycystic liver disease Alveolar echinococcosis Cystic echinococcosis Hepatic trauma Schistosomiasis Choledochal cyst Sarcoidosis

[a]Only in pilot studies

This chapter reviews the actual place of LT in the treatment of various liver disease groups and also highlights newer, sometimes controversial, ideas and concepts.

Today's Indications for Liver Transplantation

Chronic Parenchymal Liver Diseases

Alcoholic Disease

Alcoholic liver disease, the first and second most common indication for LT throughout Europe and the USA, remains a controversial indication especially in terms of public attitude toward the responsibility of the patient and his/her environment for a self-inflicted disease. The main problem relates to the risk of relapse, a condition difficult to exclude even when optimal psychological evaluation and follow-up are provided. The 6-month abstinence rule, considered as a "safety belt" in many centers, reveals to be an unreliable selection criterion to justify LT. Alcohol use after LT remains therefore an issue of concern, the exact incidence of which remains poorly

investigated (Mathurin and Ehrhard 2011). Probably, the best positive prognostic parameter is the preserved integration of the potential recipient within his/her familial, professional, and social environment. In this context the role of the general practitioner, knowing usually best these conditions, should be valued in the decision-making process.

Upcoming Features: The social debate about the justification of LT as a treatment of alcoholic liver disease has recently been fueled by the Lille group which proposed to perform LT even in case of severe alcoholic hepatitis not responding to medical therapy (Donckier et al. 2014). The medical treatment, based on glucocorticoid administration, indeed generates poor results as most patients die within 2–6 months. The survival rate only reaches 30 % in patients having a Lille score of $\geq$0.45 at day 7 of such treatment. A prospective study proposing early LT in 26 patients having a Lille score $\geq$0.45 allowed to raise significantly the 6-month survival rate to 77 %; only 11 % of patients presented alcohol abuse after LT (Mathurin et al. 2011).

Despite the fact that LT represents the best therapy for both alcoholic cirrhosis and severe hepatitis refractory to medical therapy, durable abstinence, the mandatory objective needed to link patient compliance and public awareness, can only be obtained by implementing a structured and tight follow-up. Close medical care might have another, neglected, but important "side effect." Indeed as alcoholic liver disease is one of the few diseases that does not recur in the allograft, this patient group represents a unique and "fertile" domain in the research fields of minimization of immunosuppression (IS) and clinical operational tolerance (COT) protocols. Long-term follow-up biopsies in such patients will allow a more precise evaluation of liver biopsies as confounding factors such as viral and autoimmune allograft recurrences will be absent.

Viral Diseases

Hepatitis B-Related Cirrhosis (HBV): Worldwide, HBV infection is still the leading cause, mainly in Eastern countries, of cirrhosis and development of liver cancer despite aggressive vaccination campaigns aiming at disease prevention. The newer antiviral drugs dramatically improved results of both antiviral therapies and LT. Five-year recipient survival rates are now reaching more than 80 %, promoting nowadays HBV-related cirrhosis as one of the best indications for LT on the condition that a lifelong prophylactic therapy using specific anti-HB immunoglobulins (HBIg) is pursued. The introduction of nucleos(t)ide analogs, such as lamivudine, adefovir, and tenofovir, has even allowed to obtain excellent results in case of active viral replication at moment of LT (Samuel et al. 1993). These prophylactic therapies have eliminated the development of cholestatic fibrosis and allowed to reduce the incidence of allograft reinfection beneath 5 % on the condition that close monitoring of anti-HBs antibodies clearing and that immunoglobulins are administered, either intravenously or intramuscularly, lifelong. The drawback of this very efficacious prophylactic treatment is its high cost. A recent meta-analysis, including 1,484 liver recipients, showed that HBIg treatment reduces allograft reinfection in pre-LT HBV DNA-positive patients but did not confer a significant advantage in DNA-negative patients especially when receiving the newer nucleos(t)ide analogs. Combining HBIg and oral antivirals does not seem to improve results (Wang et al. 2014b).

Upcoming Features: Due to the very high costs (6,000–8,000 €/year) and low allograft recurrence after the third post-LT year, several alternative antiviral therapies have been proposed. Shifting to the less costly self-administered subcutaneous HBIg has shown to be safe and effective in an Italian cohort of 135 patients when maintaining anti-HBs levels >100 IU/L (Di Costanzo et al. 2013). Selected recipients can even be safely switched to the less expensive, oral nucleoside analog monotherapy. The Hong Kong group obtained in a cohort of 80 patients, receiving only entecavir, a 98.8 % clearance of post-LT HBV DNA levels and no evidence of mutations at sites able to confer resistance to entecavir (Fung et al. 2011). Recent European guidelines focused on these innovations (European Association for the study of the Liver 2012a).

Finally, besides this "pure viral" point of view, it is of note that HBV patients display low rejection rates which may be partly explained by the interaction of HBIg with dendritic allograft cells.

Hepatitis C-Related Cirrhosis (HCV): Especially in the Mediterranean Basin, HCV-related cirrhosis with or without hepatocellular cancer (HCC) has become the primary indication for LT. Unfortunately, HCV graft reinfection is the rule being responsible for the (more rapid) development of allograft cirrhosis in 30 % of patients and graft loss in 10 % of recipients after 5 years (Charlton 2007). Retransplantation (reLT) is the only option in case of allograft decompensation. The indication for reLT, especially if early, is controversial due to the poor results. A retrospective US multicenter study compared 43 retransplanted HCV patients with 73 non-HCV retransplanted and 156 HCV not retransplanted patients. In the retransplanted groups, 3-year patient survival rates were 49 % versus 55 % in HCV and non-HCV patients, respectively. The most common reasons for not listing for reLT were early recurrent HCV (<6 months) (22 %), fibrosing cholestatic hepatitis (19 %), and renal dysfunction (9 %) (McCashland et al. 2007).

Upcoming Features: Until recently, antiviral therapy combining pegylated interferon and ribavirin represented the unique strategy to avoid allograft reinfection. As this therapy can only be applied fully in about 20 % of the recipients due to its side effects, sustained viral response can only be obtained in 20 % of the recipients. The direct-acting antivirals (DAA) provided new therapeutic options (Gane and Agarwal 2014). The addition of the first-generation NS3/4A protease inhibitors (PI) boceprevir or telaprevir has increased the efficacy of pegylated interferon and ribavirin in patients with chronic HCV genotype 1 infection. In 37 recipients treated with boceprevir ($n = 18$) or telaprevir ($n = 19$), a sustained virologic response was observed after a 12-week treatment in 71 % and 20 % (Coilly et al. 2014). Unfortunately, the application of such triple therapy is hampered by the occurrence of anemia and DAA-IS interaction. Clinical trials including newer classes of DAA targeting different steps of HCV replication, including nucleotide polymerase (NUC-NS5B) inhibitors (sofosbuvir), non-nucleotide polymerase (non-NUC-NS5B) inhibitors (setrobuvir), and NS5A inhibitors (ledipasvir, daclatasvir), have been started. A phase III study combining once-daily oral sofosbuvir–ledipasvir with or without ribavirin reached a 99 % sustained virologic response in the absence of severe adverse events in 865 HCV patients (Afdhal et al. 2014). These extremely encouraging results obtained in naïve as well as in transplant patients will dramatically change the outlook of HCV-infected patients. The indirect consequence will be an enlargement of the scarce allograft pool due to the foreseen reduction of HCV patients in need for LT and the reduced incidence of graft loss and thus need for reLT.

Autoimmune Cirrhosis

In 1950, Waldenström first described a chronic form of hepatitis in young women termed "lupoid hepatitis" because of its association with other autoimmune disease manifestations. This disease was termed in 1965 "autoimmune hepatitis" (AIH); in the 1970s and 1980s, several specific autoantibodies could be identified. T–cell activity directed against hepatocytes leads to interface hepatitis, fibrosis, and finally cirrhosis. AIH is an archetype autoimmune condition, with female preponderance (F/M ratio 7:1), hypergammaglobulinemia, serum autoantibodies, response to corticosteroids, and association with other autoimmune features in 40 % of patients (Carbone and Neuberger 2014). Two distinct AIH subtypes have been identified based on the profile of serum antibodies: type 1 (AIH-1) is associated with antinuclear, anti-smooth muscle, anti-actin, anti-soluble liver antigen, or anti-liver–pancreas antigen antibodies; the less common type 2 (AIH-2) is associated with anti-liver–kidney microsomal antibodies type 1 and type 3 and anti-liver cytosol antibodies type 17. The heterogeneous immunoserology and genetics explain the great variability of the disease expression in relation to race, geographical distribution, and genetic predisposition (Manns and Vogel 2006). Despite the increased risk for infectious complications in the early post-LT period, especially in recipients aged

over 50 years, 5-year patient survival rate post-LT nowadays reaches 80–90 %.

Upcoming Features: Recurrent (auto- or alloimmune) disease, de novo allograft hepatitis, and immunosuppressive therapy post-LT are all matters of debate in this difficult field of LT. Recurrent allograft disease, observed in 12–46 % of the recipients, is treatable in most patients by instauring or increasing steroid therapy. Progress to cirrhosis and graft failure is rather uncommon (Schreuder et al 2011). These patients need careful follow-up as they frequently present different manifestations of their primary disease such as polyarthritis, thyroiditis, and GI tract disease. Although many transplant groups advocate the necessary use of a steroid-based IS in order to avoid allograft recurrence and extrahepatic disease manifestations, LT can be done safely for this condition using a steroid-free IS (Strassburg and Manns 2011).

The "problem" of de novo hepatitis (DNH) after LT should also be addressed in this context as this condition is diagnosed more and more frequently. The real meaning of DNH is not yet fully understood, but it could be that DNH is a manifestation of a frust form of chronic rejection (Sebagh et al. 2013). A recent study focused on the role of atypical anti-liver–kidney microsome antibodies (LKMA) in the development of DNH, showing proteasome and carbonic anhydrase III as their respective autoantigens (Huguet et al. 2007). If diagnosed, careful, pathologic-based, follow-up and careful IS adaptation are required. Maybe the recent findings in relation to impact of donor-specific antibodies (DSA) on outcome in LT will allow to obtain further insights in this condition.

Cholestatic Diseases

Primary Biliary Cirrhosis (**PBC**): LT is the gold standard in the treatment of end-stage liver disease due to PBC. The number of LT for this condition declined during the last decades due to the introduction of an efficacious pharmacological treatment with ursodeoxycholic acid. PBC is an autoimmune liver disease whose two main features are the presence of highly specific antimitochondrial antibodies (AMAs) and lymphocytic cholangitis. The chronic destruction of small to medium caliber intrahepatic bile ducts leads to cholestasis, fibrosis, and biliary cirrhosis (Selmi et al. 2011). Indications for LT are anticipated death in <1 year, impaired quality of life, or intractable disease-specific symptoms such as pruritus. Despite the availability of prognostic models, serum bilirubin level of over 4 mg/dL provides a simple guide to time LT. Five-year patient survival rates reach 85 %. These patients seem to develop more frequently features of chronic rejection, although such changes are similar to recurrent allograft PBC. IS reduction should therefore be done cautiously. Following LT, AMAs usually persist, and histological features of recurrent allograft PBC are seen in about 50 % of the recipients 10 years post-LT (Rowe et al. 2008). Recurrence, which may occur in the presence of normal liver tests, is most often discovered on long-term protocol biopsies. In the medium term, disease recurrence rarely causes clinical problems. During follow-up, osseous complications (bone fractures) and flaring up of several other disease manifestations, such as polyarthritis, scleroderma, and thyroiditis, may compromise quality of life.

Upcoming Features: Still too much elderly women are transplanted presenting with very advanced osseous disease. Such condition may seriously compromise the LT outcome (Guichelaar et al. 2006). An active "osseous" follow-up should be addressed to these patients especially when already presenting severe pre-LT osteoporosis.

Primary Sclerosing Cholangitis (**PSC**): PSC is a chronic, cholestatic autoimmune liver disease leading to inflammation and fibrosis of the macroscopic, intrahepatic and extrahepatic, biliary system. The hallmark of PSC is the alternation of multiple biliary strictures and dilatations on imaging (Maggs and Chapman 2008). PSC is a progressive disease with no proven therapy, whose natural history may lead to the development of decompensated cirrhosis and biliary cancer. In LT series cholangiocellular carcinoma (CCC) has been diagnosed in up to 20 % of patients. Up to 70 % of patients present other major disease manifestations such as

inflammatory bowel disease and vitiligo. Although patient selection and timing for LT are not always easy, serum bilirubin, splenomegaly, development of portal hypertension, and duration of disease are good practical guides for the LT indication. Pre-LT screening with MRI, PET scan, and brush cytology of the biliary tract is indicated in case of dominant strictures in order to exclude CCC. Although early patient and graft survival rates following LT are excellent, the one-year survival reaching 90 %, late outcome is frequently compromised due to allograft recurrence. Ten-year survival rates reach 50 % only, indeed the worst result of LT for benign liver diseases. Diagnosis of recurrent PSC is difficult as morphologic features of recurrent PSC and the frequently observed ischemic-type biliary lesions (ITBL) are similar (Graziadei 2002).

Recurrent PSC affects 20–40 % of the recipients, with higher reLT rates compared to PBC. Because of the enhanced risk of colonic cancer, annual colonoscopy is advised. Many patients however had and many will have complex GI tract surgery consisting of proctocolectomy with ileoanal reservoir because of their inflammatory bowel disease (Bjoro et al 2006). In a study performed in 303 PSC recipients, the only significant risk factor for colectomy was LT itself, while it did not affect the incidence of colorectal cancer (Dvorchik et al. 2002).

Upcoming Features: Some technical issues need to be addressed when transplanting PSC patients. Roux-en-Y hepaticojejunostomy is the preferred option for biliary reconstruction due to the involvement of the extrahepatic bile duct (Welsh and Wigmore 2004). However, the much easier duct-to-duct anastomosis and even choledochoduodenostomy have been reported more recently. A meta-analysis involving 692 patients showed that duct-to-duct anastomosis has very satisfactory results in terms of clinical outcome, graft survival, risk of biliary complications (leaks and strictures), infection, and PSC recurrence (Wells et al. 2013). A recent series of 98 PSC adults, 45 of whom with duct-to-duct and 53 with RY reconstruction, showed more episodes of cholangitis and late-onset non-anastomotic biliary strictures in case of biliodigestive anastomosis (Sutton et al. 2014). In this view choledochoduodenostomy or duct-to-duct reconstruction (in case of macroscopical "normal" recipient bile duct) can be accepted as an alternative technique in case of difficult intra-abdominal conditions.

Secondary Biliary Cirrhosis (SBC): SBC, the end-stage evolution of a prolonged chronic damage such as caused by iatrogenic bile duct injury (mostly following laparoscopic cholecystectomy), graft-versus-host disease following bone marrow transplantation, cystic fibrosis, and status after Kasai operation during infancy because of biliary atresia, is an uncommon (less than 1 %) indication in adult LT. Few series have been published. An Argentinian study reported about 20 patients with end-stage liver disease secondary to biliary injury; four patients died on the waiting list, and 16 were transplanted. All patients had surgical treatment(s) before being considered for a LT. The median time between biliary lesion and liver transplant was 60 months. The 5-year survival reached 75 % (de Santibañes et al. 2008).

Upcoming Features: The message of this experience is that such patients should be referred early to specialist hepatobiliary centers in order to avoid SBC and thus LT.

Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

The term "nonalcoholic fatty liver disease" was first used in the 1980s to describe a slowly progressive disease linked to fat accumulation within liver cells without evident reasons (Ludwig et al. 1980). NAFLD can range from simple steatosis to NASH, a condition leading to fibrosis and cirrhosis due to ongoing inflammation. NAFLD and NASH are associated with obesity and metabolic syndrome. Due to the current obesity epidemic, NASH-related cirrhosis has become the third leading indication for LT in the USA, accounting for up to 11 % of the liver recipients (Younossi et al. 2011). NASH represents the second leading etiology for HCC requiring LT in the USA and is the most rapidly growing indication in LT for liver cancer (Wong et al. 2014). Overall 5-year survival rates of

these patients are similar to other indications. Although the risk for graft failure is lower, these recipients have a higher post-LT mortality due to cardiovascular events or sepsis. Risk factors for NASH such as increased BMI, insulin resistance, and diabetes are moreover worsened because of steroid- and CNI-based IS. Weight control after LT is mandatory in order to avoid allograft steatosis which has been reported in up to 100 % of patients. Adapted diet and physical activity are advised besides various pharmacological interventions using metformin, vitamin E, pioglitazone, statins, ursodeoxycholic acid, pentoxifylline, and orlistat. However, none of them has proved to be effective in reverting liver fibrosis (Khullar et al. 2014).

Upcoming Features: Bariatric surgery has been introduced with a good safety and efficacy profile either before, during, or after LT. A US experience reported about 44 prospectively enrolled patients having a BMI >35 at the moment of wait-list insertion. Thirty-four patients had an "isolated LT"; 21 raised their weight above BMI >35, twelve had post-LT diabetes, seven had steatosis, and three patients died. Seven patients had combined LT–sleeve gastrectomy procedure. There was no death, graft loss, diabetes, nor steatosis. One patient developed a leak from the gastric staple line. All patients had substantial weight reduction (mean BMI 29) (Heimbach et al. 2013). Further investigations are underway to explore specific polymorphisms involved (PNPLA3, IL28) in the development of post-LT NASH in order to define mechanisms and therapies against this pathology.

Hepatobiliary Oncology

Primary Tumors

Hepatocellular Cancer (HCC) in Cirrhotic or Fibrotic Liver: HCC represents the fifth most common malignant tumor worldwide and the third leading cause of cancer-related death. Ninety percent of HCC develop in a diseased liver, 5–10 % in a normal, non-cirrhotic or non-fibrotic liver (NC-HCC). LT is the therapeutic gold standard as it simultaneously removes tumor and underlying (precancerous) disease. The introduction in 1996 of the Milan criteria (MC) (one lesion smaller than 5 cm or up to three lesions smaller than 3 cm, without extrahepatic manifestations or vascular invasion) and the steady improvement of neoadjuvant locoregional therapies (LRT) allow to obtain 5-year disease-free survival rates reaching 85 % (Ciccarelli et al. 2012). These too restrictive MC and the unexpected good results in some recipients outlying the MC on pathologic examination of the total hepatectomy specimen led to the development of many (mostly center based) wider inclusion criteria in the West as well as in the East (i.e., San Francisco, Kyoto, Kyushu, Hangzhou, Toronto, Seoul, and Milan up to seven) (Yao et al. 2001, Mazzaferro et al. 2009). Up to now, only the extended San Francisco criteria have been accepted by the international transplant community. Despite the fact that the Zurich Consensus Conference about HCC and LT reviewed the current practice of LT in HCC patients aiming at streamlining the approach of the transplant community toward HCC, many questions remain unanswered (Clavien et al. 2012).

Upcoming Features: Sound oncologic principles such as "dynamic" morphologic (number and diameter) and biologic tumor criteria (evolution of tumor markers or response to LRT) will be necessary to justifiably extend the inclusion criteria. Combining alpha-fetoprotein (AFP) and/or des-gamma carboxyprothrombin (DCP) (or protein induced by vitamin K absence [PIVKA II]) values and dynamics, inflammatory markers such as neutrophil-to-lymphocyte or platelet-to-lymphocyte ratios and radiological response to LRT based on RECIST criteria (also called downstaging) will be necessary to refine the HCC therapeutic algorithm in order to discriminate between utile and futile LT (Lai and Lerut 2014). Clear identification and definition of cutoff values as well as of downstaging will allow to progress in this field. Living donor liver transplantation (LDLT) represents a unique soil to safely explore the expansion of inclusion criteria for LT. It is also of notice to underline that adaptation of IS (steroid-free IS regimens, introduction of mTor inhibitors) will help to further support this development.

HCC developed in a non-cirrhotic, non-fibrotic liver: Inclusion criteria for LT differ importantly. Despite the dogma that partial liver resection is "the" therapeutic gold standard in these patients, 5-year recurrence rates are very high ranging from 40 % to 70 %. LT might therefore be of value both in the treatment of initially non-resectable HCC or in case of recurrence after resection (Lerut et al. 2011). The ELTR–ELITA analysis, dealing with 62 patients with initially "non-resectable" NC-HCC, confirmed that excellent 5-year disease-free survival rates of 60 % and 48 % can be obtained after primary and salvage LT for intrahepatic recurrence (Mergental et al. 2012). Macrovascular and lymph node invasion, interval of less than 12 months between partial resection and recurrence, are unfavorable factors, in contrast to HCC developed in a cirrhotic liver tumor diameter and MC do not significantly influence outcome. The best results of LT for NC-HCC are achieved in the presence of AFP level <100 ng/mL, number of tumors less than four, and absence of vascular and lymph node involvement (Decaens et al. 2012).

Cholangiocellular Carcinoma (CCC): CCC, a very aggressive primary neoplasm arising from malignant transformation of the biliary epithelium, has been for a long time considered an absolute contraindication to LT (DeOliveira 2014).

Upcoming Features: CCC has evolved from an absolute to a relative contraindication for LT. The Nebraska, Mayo and Dublin transplant teams pioneered a strategy of neoadjuvant radiochemotherapy followed by LT for patients with unresectable hilar CCC; recently the French health authorities even authorized to extend this indication to resectable CCC. The Mayo Clinic protocol is based on a strict, multidisciplinary therapeutic project combining external beam radiation, endo-biliary brachytherapy, and 5-FU chemotherapy. After negative surgical laparoscopic exploration, capecitabine is started until moment of LT. This protocol needs to adapt surgical timing and technique. This protocol is restricted to highly selected patients presenting a tumor <3 cm and absent extrahepatic metastases including negative lymph nodes. Despite the complex algorithm, the high dropout, and the very strict patient selection, 5-year recurrence-free survival rates reached 68 % (Rosen et al. 2010). In the most recent update concerning 199 patients, elevated CA 19–9 (>120 UI/mL), portal vein encasement, and residual tumor on explant pathology were the most significant predictors of CCC recurrence (Darwish Murad et al. 2012).

LT is not yet considered an option to treat intrahepatic CCC. LT is till now only proposed for small tumors developed in a cirrhotic liver. One 1- and 5-year recurrence for mixed HCC–intrahepatic CCC reach 42 % and 65 % (Razumilava and Gores 2014). A recent multicenter study from Spain analyzed 27 and 15 patients with mixed tumors and intrahepatic CCC comparing them with 84 HCC matched controls. Intrahepatic CCC showed worse results with respect to their controls (5-year actuarial survival rates of 51 vs. 93 %), but no differences were observed between mixed tumor patients and HCC controls (78 vs. 86 %) (Sapisochin et al. 2014). These results reflect the aggressiveness of intrahepatic CCC and also raise the question about the "necessity" of pre-LT as well as pre-LRT tumor biopsies. More data on HCC–CCC patients should be obtained, but their absolute exclusion from transplant option is controversial.

Secondary Liver Tumors

Neuroendocrine Liver Metastases (NETLM): LT for unresectable NETLM is another controversial area in the field of LT. A recent review reports about 706 such patients. Five-year survival rate from the time of diagnosis was approximately 70 %. Metastases confined to the liver and not poorly differentiated are favorable candidates for LT; evolution of tumors over 6 months is an unfavorable feature (Fan et al. 2015). The initial French multicenter transplant experience comprising 85 patients reported a 5-year survival rate of 47 %. Factors of poor prognosis were concomitant upper abdominal exenteration and primary tumor in the duodenum or pancreas with accompanying hepatomegaly. Recipients presenting with these unfavorable prognostic factors had significantly worse results (5-year survival rates of

12 vs. 68 %) (Le Treut et al. 2008). Similar results were obtained in the UNOS cohort including 150 patients (Gedaly et al. 2011).

Upcoming Features: Two recent publications indicate that LT will have to be considered in the therapeutic algorithm of NET patients. The Milan group indeed showed that LT can cure 85 % of patients with non-resectable NET metastases when adhering to strict inclusion criteria consisting of low proliferation index (Ki < 5 %), delay between R0 resection of the primary tumor and LT of more than 6 months, tumor location in the portal venous drainage system, adapted IS and neoadjuvant and adjuvant therapies (Mazzaferro et al. 2007). Without any doubt, LT will take a more important place in the treatment of these patients in the near future as LT (Bonaccorsi-Riani et al. 2010).

The large ELTR–ELITA, retrospective, multicentric study including 213 patients transplanted during the period 1982–2009 supports the Milan experience. The 5-year overall and disease-free survival rates for the whole patient cohort reached 52 % and 30 %. Since 2000, 5-year OS increased to 59 % as a result of better selection process (Le Treut et al. 2013). More importantly is the fact that this detailed multivariate analysis identified major resection in addition to LT (or multivisceral resection), poor tumor differentiation, hepatomegaly and age >45 years as poor prognostic factors.

Colorectal Liver Metastases (CRLM): CRLM were considered an absolute contraindication for LT due to the very poor obtained survivals. A review of the earlier ELTR–ELITA experience including 48 patients revealed that near half of these patients died due to non-tumoral causes and that two thirds of patients had heavy IS (Foss et al. 2010).

Upcoming Features: Impressive improvements in chemotherapy, surgical technique (such as repeated surgery and ALPPS procedure), and imaging paved the way for the prospective Norwegian SECA (secondary cancer) study looking at the value of LT in the treatment of unresectable CRLM (Foss and Lerut 2014). The outcomes of 21 SECA-LT patients and 47 non-transplanted unresectable liver-only CRLMs were compared in the NORDIC VII study. Although disease-free survivals were similar, substantial different 5-year actuarial overall survival rates were observed (56 % vs. 9 % in patients starting first-line chemotherapy) (Dueland et al. 2014). The recurrence rate was 100 %, but one third of patients could be rendered disease-free after resection of pulmonary metastases. The historic Vienna and recent Oslo experiences paved the way for larger multicenter studies that will be soon launched (Kappel et al. 2006).

Metabolic (Liver Based) Diseases

Hereditary Hemochromatosis (**HH**): HH, a disorder of iron metabolism leading to iron overload due to reduced hepatic hepcidin secretion, is a rather uncommon indication for LT. These patients have a higher risk to develop cardiac complications and HCC. After LT, hepcidin secretion is normalized, preventing the recurrence of hepatic iron overload (Bardou-Jacquet et al. 2014). These recipients have a higher morbidity and mortality due to a higher incidence of cardiac, diabetic, and infectious complications, cancer recurrence, and post-LT iron reaccumulation.

Wilson Disease (**WD**): This rare inherited autosomal recessive disease of copper metabolism is responsible for systemic copper accumulation that damages especially the liver, brain, cornea, and kidney (European Association for the Study of the Liver 2012b). Such accumulation can be prevented with copper-chelating agents or zinc salts. The progression of systemic complications and hepatic involvement under an adequate long-term therapy is rare. LT may be required in the setting of acute liver failure (ALF), subacute liver disease, and end-stage liver disease, with or without neuropsychiatric manifestation. Adult patients always present in a stage of cirrhosis. WD-related ALF can be stratified according to Nazer index, revised King's College Criteria, and PELD/MELD scores (Devarbhavi et al. 2014). Outcomes after LT for WD are excellent with 5-year survival rates of 86–89 %. Although copper metabolism normalizes in the long run (Arnon et al. 2011a), neuropsychiatric disorders do not recover in half

to one third of patients, and in some patients they may even progress (Medici et al. 2005). Living donation is a safe option for heterozygote carrier relatives.

Hemophilia: Hemophilia is a family of X-liked coagulation disorders most commonly caused by the deficit of factor VIII (F VIII, hemophilia A) or factor IX (F IX, hemophilia B). The most severe forms result in persistent risk of prolonged bleeding. During the last decades, life expectancy of hemophilic patients has been dramatically improved, initially by plasma derivatives, later by recombinant factors. Unfortunately insufficient inactivation processes of human derivatives were responsible for the development of end-stage liver disease due to transmission of HCV and HIV infections (Soucie et al. 2014). Most patients are therefore transplanted because of liver decompensation and/or HCC development. Perioperative evolution can be more complicated due to HIV/HCV coinfection. Coagulopathy usually is not an important matter as the allograft very rapidly corrects the hematologic condition (Horton et al. 2012). Adapted perioperative care allows nowadays to obtain results comparable to those of non-hemophilic patients (Lerut et al. 1995).

Familial Amyloid Polyneuropathy (FAP): FAP is a slow but fatal disease, belonging to a group of systemic disorders caused by an amyloidogenic transthyretin variant. More than 100 genetic variants have been identified explaining the widely variable clinical expression. Patients with a same mutation can even present, an until now unexplained, variation in the clinical presentation. The most frequent mutation is the Val30Met variant. Non-Val30Met variants have a significantly different clinical presentation and outcome. The V30M mutation has an early-onset (between 25–35 years), a more benign course and cardiac involvement in the form of rhythmic disturbances. The NV30M-FAP has a late-onset (> 50 years) presentation, a more rapid evolution with more functional impairment, development of restrictive/mechanical cardiomyopathy and lower survival. Isolated cardiac involvement in African-Americans is invariably associated with the V122I mutation (Zeldenrust 2012). LT eliminates the source of the variant molecule, therefore representing till now the only known curative treatment for this disease. LT was first performed for this pathology in 1990 in Sweden. The FAP World Transplant Registry (Herlenius et al. 2004) collected up to 2,000 LT recipients during the period 1995–2012 done in 77 centers distributed in 19 countries. Today, approximately 120 LT are performed annually worldwide. Patient survival is comparable to the survival with LT performed for other chronic liver disorders. The main causes of death have been cardiac related and septicemia (21 % each) (http://www.fapwtr.org/ 2014). Recent experiences identified time interval between diagnosis and LT and preoperative modified body mass index (mBMI) <700 kg g/L m^2 as poor prognostic factors (Franz et al. 2013).

A major plus of LT for FAP is to transfer their normally functioning liver to another recipient, a procedure better known as sequential or domino LT. This procedure was introduced by Furtado in Coimbra in 1993. According to the Domino Liver Transplantation Registry, from 1999 to December 2012, 1085 domino LT have been performed in 62 hospitals located in 21 countries. Transfer of polyneuropathy by the domino graft has been documented in very rare cases (Tincani et al. 2011). Survival after LT is similar to this obtained in other benign liver disorders. The main causes of recipient death after domino LT were tumor recurrence (24 %) and septicemia (16 %) (http://www.fapwtr.org/ 2014).

Primary Hyperoxaluria (PH): PHs are a group of autosomal recessive disorders of endogenous oxalate overproduction typically developing in childhood. PH type 1 is caused by hepatocellular alanine–glyoxylate aminotransferase deficiency, the more aggressive form. Type 2 is related to glyoxylate reductase/hydroxypyruvate reductase deficiency. The latter type is associated with lower morbidity and mortality. Deposition of calcium oxalate crystals in the kidney, nephrocalcinosis, progressive renal failure, and systemic deposition of oxalate (oxalosis) are the main clinical manifestations of PH1. Different approaches have been proposed for the treatment of this pathology such as isolated renal transplantation, isolated preemptive LT to correct the metabolic defect before the occurrence

of significant renal damage, and finally combined kidney–liver transplantation (CKLT) to correct both problems simultaneously. Isolated renal transplantation offers only a temporary solution as oxalate deposition results in recurrent disease and renal graft failure, with a 3-year renal graft survival of only 17–45 %. Isolated liver transplant is an attractive treatment option, but its timing remains controversial. CKLT, firstly introduced in 1984, has been accepted as the treatment of choice, considerably improving patient and graft survival (Nair et al. 2013). According to the European PH1 transplant registry, 117 patients received CKLT during the period 1984–2004, showing 5-year patient survival rates of 80 % (Jamieson 2005). A recent multicenter study from France analyzed 54 patients with PH1. Ten-year patient survival was similar between the 33 CKLT and 21 KT patient groups (78 % vs. 70 %). Kidney graft survival at 10 years was however much better after CKLT (87 % vs. 13 %, respectively). Recurrence of oxalosis occurred in 11 renal grafts (52 %) of the KT group versus none in CKLT group (Compagnon et al. 2014). Five cases of domino LT in the setting of PH1 have been reported; all rapidly developed dialysis-dependent kidney failure within the first 4 weeks after LT (Saner et al. 2010).

Tyrosinemia Type I (TT1): TT1 is an autosomal recessive metabolic disorder, caused by the deficiency of fumarylacetoacetate hydrolase (FAH), an enzyme involved in the final step of the catabolism of tyrosine and phenylalanine. Its deficiency induces accumulation of toxic metabolites stimulating apoptosis of both hepatocytes and kidney tubular epithelial cells and increasing the risk for HCC development. TT1 has an incidence of about 1:100.000; in specific areas such as Scandinavia and Quebec, its incidence is higher. TT1 can present either in an acute or a chronic form. The acute form occurs within the first months of life and leads to ALF during the first year. Chronic form features are characterized by failure to thrive, hepatomegaly and chronic liver disease, renal tubular dysfunction, rickets, cardiomyopathy, and porphyria-like neurological syndrome (Fagiuoli et al. 2013). The mainstays of TT1 treatment are tyrosine-/phenylalanine-free diet and the use of 2-(2-nitro-4-trifluoromethylbenzoyl)-1-3-cycloexenedione (NTBC), which blocks the second step of tyrosine catabolism. This combination prevents toxic metabolites' accrual and hepatic and renal deterioration, improves nutritional and neurological status, and reduces HCC development cutting the need for LT from 35 % to 12 % (Paradis 1996).

Indications for LT include end-stage liver disease despite medical treatment, unresponsive ALF, poor quality of life, and HCC. The risk of HCC is high in cirrhotic patients with histologically proven dysplastic nodules, so early LT is indicated. Five-year survival rates are currently above 90 % (Arnon et al. 2011b). As heterozygosity does not induce the disease, healthy relatives can be considered as living liver donors. Renal FAH deficiency is not corrected by LT, but renal-sparing properties of NTBC have reduced the rate of CKLT.

Glycogen Storage Disease Type I (GSD I): This autosomal recessive inborn error of carbohydrate metabolism is caused by defects in the glucose-6-phosphate transporter (G6PT)/glucose-6-phosphatase (G6Pase) complex. Deficient activity of G6Pase causes GSD Ia, and deficient activity of G6PT causes GSD Ib. GSD I is a rare disorder with an incidence of 1:100.000, represented in 80 % of the patients by GSD Ia and in 20 % by GSD Ib. Clinical complications include hepato- and nephromegaly, hypoglycemia, hyperlipidemia, hyperuricemia, lactic acidemia, and growth retardation (Rake et al. 2002). Because of the prominent hepatic manifestations in GSD I, LT represents a solution for this pathology. A recent literature review included 58 cases of GSD Ia and 22 cases of GSD Ib transplanted during the period 1982–2012. In the GSD I group, LDLT was performed 16 times, and six patients had CKLT. Main indications for LT were hepatic adenomas/liver abnormalities/focal nodular hyperplasia, poor metabolic control, growth retardation, and renal failure. In the 54 surviving cases, a metabolic control was obtained, and in 13 cases catch-up growth was mentioned. In the GSD Ib group, LT was indicated for poor metabolic control, recurrent infection, and growth retardation. In all 19 survivors metabolic abnormalities were

corrected also, and catch-up growth was reported twice (Boers et al. 2014).

Upcoming Features: More confidence with LT should instigate the LT community to opt for prophylactic transplant procedures. Indeed nowadays the recovery after successful LT of these patients is many times hampered by the already, irreversible, damages caused by the metabolic deficit. The role of LDLT should also be explored as a less expensive and prophylactic treatment of many metabolic diseases (Tsukada et al. 2011). The frequently absent portal hypertension in such conditions makes it possible to implant a smaller (left) liver graft, reducing thereby the donor risk.

FAP patients represent a valuable source of allografts (Inomata et al. 2001). Because of the very low rate of disease transmission, domino livers should be more frequently directed also to younger, non-HCC recipients (Azoulay et al. 2012). Results of LT for FAP will probably improve in the near future due to the introduction in clinical practice of stabilizers of TTR tetramers (tafamidis and diflunisal), and gene therapies to suppress TTR expression (antisense methods and the use of small interfering RNAs) are in progress. These therapies might be useful for the treatment of patients transplanted in an advanced disease stage. Apart from FAP, fibrinogen a-chain amyloidosis, maple syrup urine disease, and hypercholesterolemia represent the only other metabolic diseases in which domino LT should be considered. Primary hyperoxaluria is indeed a contraindication to such LT as all recipients rapidly develop renal failure due to oxalic acid overload (Franchello et al. 2005).

Last but not least, a small number of auxiliary LT have been reported in order to cure metabolic diseases; firm conclusions cannot yet be drawn from these experiences (Trotter and Milliner 2014).

Acute Liver Failure (ALF)

Various, heterogeneous conditions may lead to ALF. ALF has been defined by Trey as a massive necrosis of previously normally functioning liver. The definition of acute and subacute failure relates to the time span between jaundice and encephalopathy of less than two weeks or from two to eight weeks. The main cause of ALF is drug-induced toxicity, mainly in the setting of deliberate ingestion with suicidal intent of acetaminophen. ALF caused by an identified hepatotropic virus accounts for 15–50 % of cases in Europe, with an additional 20 % of cases related to hepatitis of unknown etiology; in these cases viral etiology is frequently presumed. HCV infection is rarely responsible for ALF in Western countries but accounts for a higher proportion of cases in Japan. Hepatitis E infection, commonly observed in the Indian subcontinent, may also lead to ALF particularly in pregnant women. Uncommon nonviral-related causes of ALF are represented by Wilson disease or poisoning after ingestion of the mushroom *Amanita phalloides*.

ALF is a rapidly progressive critical illness with still a high mortality. Complex intensive care protocols and emergency LT represent the strategies to adopt. The most widely used criteria to justify indication for LT are the 1989 and updated 1993 King's College Criteria (O'Grady 2007). A review related to the clinical course of 2095 "ALF adults" admitted at this institution during the period 1973–2008 revealed an improvement of hospital survival from 17 % in 1973–1978 to 62 % in 2004–2008. In non-transplanted patients, survival rose from 17 % to 48 % and in liver recipients ($n = 387$) from 56 % in 1984–88 to 86 % in 2004–2008 (Bernal et al. 2013).

Similarly the ELTR reported 5-year patient and graft survival rates of 68 % and 57 % in 4903 ALF patients transplanted during the period 1988–2009. Despite increased donors age over 60 years from 1.8 % to 21 %, survival further improved during the period 2004–2009. The combination of recipient age >50 and donor age >60 years resulted in the highest mortality/graft loss rates within the first post-LT year (57 %) (Germani et al. 2012).

As the King's College Criteria have a low negative predictive value for non-acetaminophen-induced ALF; a score was needed to better identify indication for LT in patients presenting viral induced ALF. The Clichy group developed

criteria combining age, severe encephalopathy and factor V disorder group developed. Mortality without LT was predicted with a positive predictive value of 82 % and a negative predictive value of 98 %. As several studies reported contradictory data, there is still no agreement about the best selection criteria for LT in these critically ill patients.

The US-based Drug-Induced Liver Injury Network (DILIN) aimed at prospectively collecting all cases of drug-induced liver injuries in order to get a usable overview of all hepatotoxic drugs causing ALF. A recent study prospectively enrolled 839 patients diagnosed with hepatotoxicity due to conventional medications, herbals, and dietary supplements: 45 had injury due to bodybuilding dietary supplements, 85 to other dietary products, and 709 due to different medications. Liver injury from non-body building dietary supplements was most severe with significant differences in unfavorable outcome, death, and transplantation (Navarro et al. 2014). Another study on 660 adults with drug-induced ALF showed that nearly one out of ten patients died or underwent LT within 6 months, and nearly one out of five remaining patients evidenced persistent liver injury at 6 months (Fontana et al. 2014).

Upcoming Features: Artificial liver support devices may represent a possible way to avoid LT in ALF patients. Most of these (costly) devices still have to be considered as "bridge to" rather than a way to avoid LT. A prospective randomized US study analyzed the role of an extracorporeal porcine hepatocyte-based bioartificial liver (BAL) in 171 patients (86 control and 85 BAL). Patients with fulminant/subfulminant hepatic failure and primary nonfunction following LT were included. Thirty-day survival was 71 % versus 62 % for BAL and control groups; excluding primary nonfunction patients resulted in similar survival rates (73 % vs. 59 %). When survival was analyzed accounting for confounding factors, no difference between the 2 groups was observed (Demetriou et al. 2004). Another randomized controlled trial involving 16 French LT centers evaluated the role of albumin dialysis (molecular adsorbent recirculating system, MARS) (Gambro, Lund, Sweden), a "non-cell" artificial liver support device, in 102 patients: 49 patients were randomized to conventional and 53 to MARS and conventional treatment. Sixty-six patients had LT (41 % among paracetamol-induced ALF; 79.4 % among non-paracetamol-induced ALF). The short delay from randomization to LT (medium 16.2 h) precluded however to evaluate efficacy and safety profiles; only 39 MARS patients had at least one session of 5 h or more. Six-month survival was 75.5 % with conventional treatment and 84.9 % with MARS. In patients with paracetamol-related ALF, 6-month survival was 68.4 % with conventional treatment and 85 % with MARS. Adverse events between groups were similar (Saliba et al. 2013). A monocentric Italian study including 45 ALF patients treated with MARS during the period 1999–2008 is worthwhile to mention. Thirty-six patients survived: 21 were bridged to LT, 15 continued their extracorporeal treatment until liver and clinical recovery, and nine patients died before LT due to multiorgan failure. Six prognostic relevant parameters were identified: reduction of lactate, IL-6 and intracranial pressure, systemic vascular resistance index values, Glasgow Coma Scale <9, and number of MARS treatments. Patients with 0–2 risk factors all survived without LT; patients with 5–6 risk factors all died before LT. Patients with improved neurological status, cytokines, lactate, and hemodynamic parameters could "escape" LT (Novelli et al. 2009). The fractionated plasma separation and adsorption system (FPSA) (Prometheus, Fresenius Medical Care) represents another support device. A Turkish study utilized 85 sessions to treat 27 patients (median three treatments/patient) with ALF or acute-on-chronic liver failure. The overall survival was 48.1 % (Sentürk et al. 2010). Four patients (14.8 %) were transplanted, and in nine (33 %) LT could be avoided; the remaining 14 patients were not transplanted because they were judged as inappropriate candidates or because of organ unavailability.

All these well-documented clinical experiences together with the literature review show minimal or even no advantage of extracorporeal devices compared to conventional treatments despite their positive effect on blood toxemia

and encephalopathy. More progress needs to be made and larger, investigator-driven, studies are needed to make firm conclusions. Unfortunately the development of efficacious liver assist devices remains difficult because of the complexity of the liver functions to be replaced and because of the heterogeneity of the ALF patient population.

Although used in a very limited way, auxiliary LT (ALT) represents another possible solution for ALF patients. A European multicenter experience reported about 47 ALT patients transplanted in 12 European centers compared to 384 consecutive patients undergoing LT for ALF in the Eurotransplant area. One-year patient survival was similar between LT and ALT patients (61 % vs. 62 %). However, 65 % of surviving ALT were IS-free within 1 year, compared with none of the patients transplanted by LT (van Hoek et al. 1999). A UK study reported about 13 patients with paracetamol overdose treated with subtotal hepatectomy, auxiliary LT of a whole liver graft, and gradual IS withdrawal after recovery. When compared with directly transplanted ALF patients, actuarial survival was better (69 % vs. 54 %). The eight surviving patients had normal liver function, were IS-free, and had better quality of life compared to seven surviving LT patients (Lodge et al. 2008).

Another UK study including 128 children with ALF reported about 20 cases of ALT. LT technique was somewhat different; results were similar. After native liver partial hepatectomy, 20 grafts (eight right lobes, eight left lateral segments, three left lobes, and one whole liver)were implanted orthotopically. Regeneration of the native liver was observed. Patient survival was 85 % at 1, 5, and 10 years. Of 17 survivors, 14 (82 %) successfully regenerated their native liver, and 11 children (65 % of the survivors) became IS-free (Faraj et al. 2010).

Upcoming Features: The use of alternative LT techniques, based on mere knowledge of split and LDLT, should be applied more frequently as these methods allow in a majority of (merely young) patients to withdraw lifelong IS. Undoubtedly the upcoming wave of regenerative medicine will play an important role in the therapeutic algorithm of ALF (Orlando et al. 2012).

Living Donor Liver Transplantation (LDLT)

The first attempt of an adult-to-child LDLT was done by Raia in Sao Paulo, Brazil, in December 1988 (Raia et al. 1989); the first successful (pediatric) LDLT was done 7 months later by Strong in Sydney, Australia (Strong et al. 1990). European and American programs followed the encouraging results obtained in the early 1990s, but LDLT literally exploded at the same time in Asia. This rapid evolution in the East was explained by the absence of deceased donor LT due to different religious and cultural matters. In November 1993, the first adult-to-adult LDLT was performed by Makuuchi in Tokyo, Japan, implanting a left liver in a women suffering from PBC. In that same year, Tanaka in Kyoto, Japan, first used a right liver in an adolescent. The first adult-to-adult right liver LDLT program was started by Fan in Hong Kong in May 1996 (Lo et al. 1997). LDLT nowadays represents an ethically justified answer to postmortem liver graft shortage even in the West. The worldwide application of LDLT allowed to progressively resolve most technical and ethical challenges. In contrast to the Eastern medical community, the Western one still struggles with the further development of LDLT nurtured by the concerns about morbidity (including abortion of procurement hepatectomy, the need for biliary interventions and even for transplantation of the donor) and, more importantly, mortality of the donor. This surgical procedure is still considered in the Western hemisphere as a too risky surgery to be restricted to very well specified conditions (Miller 2008). The restriction of LDLT to some expert centers will undoubtedly be the answer to this. The Western experience in LDLT remains small compared to the Eastern one. The initial enthusiasm in the 1990s during which 49 US centers performed at least one LDLT has been damped by the first cases of donor mortality reported in 2002 leading to a substantial decline of LDLT activity. The Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) reported about 2,366 cases performed during the period 1998–2007 (Olthoff

et al. 2011). The European experience parallels the US one due to similar unfortunate events. During a first decade of optimism (1991–2001), the ELTR reported 806 LDLT performed in 46 centers in 15 different European countries (Adam et al. 2003). Until December 2009, the number of LDLT has increased to 3622 (3.9 %) on a total of 93.634 transplants performed in 74 centers. In contrast the Eastern experiences are still growing, and many new centers successfully set up LDLT programs. The pioneering experiences from the "big five" Asiatic centers (Tokyo, Kyoto, Hong Kong, Kaohsiung, and Seoul) triggered the development of this field of hepatobiliary surgery (Chen et al. 2003). By the end of 2004, 2,667 patients underwent LDLT in Japan; in June 2005, Lee reported the first 1,000 consecutive LDLT from the Asan Medical Center in Seoul (Hwang et al. 2006), reaching a yearly incidence of 300. The China Liver Transplant Registry reported about 643 LDLT performed in the period 1995–2008, with 588 (91 %) of whom realized during the last 3 years, and finally India took on a leading position in this field. All these data confirm the prominent role of Asia in LDLT and innovative hepatobiliary surgery (Chen et al. 2014).

Despite the fact that the first experience of adult-to-adult LDLT was based on the successful use of a left liver graft, clinical experience rapidly led to a shift from left to right LT in order to avoid graft failure due to the small-for-size syndrome (SFSS). The main problem of the right liver graft function relates to the inadequate drainage of the anterior sector (segments V and VIII) reducing so the functional liver mass to a possible insufficient insufficient one. The venous drainage of the graft has been approached in diverse ways going from the "radical" Hong Kong approach always including the MHV (the "extended right graft") (Fan et al. 2003) via the "radical" Kyoto approach always excluding the MHV (Campsen et al. 2008) to inclusion/exclusion of this vein based on peculiar donor and/or recipient findings such as intraoperative ultrasound findings demonstrating venous interconnections between the anterior and posterior sectors of the graft (allowing to exclude the MHV from the graft) (Sano et al. 2002), anatomy of the MHV, and finally recipient body/graft weight ratio and residual liver volume in the donor to be respected. The Kyoto group includes the MHV in the graft in case of a dominant MHV, a graft-to-recipient weight ratio (GRBWR) of less than 1 %, and a remnant left liver in the recipient beneath 35 % (Kasahara et al. 2005). The Kaohsiung group excludes the MHV from the graft if the donor is bigger than the recipient, if the estimated graft volume by CT volumetry is greater than 50 % of the standard liver volume of the recipient after correction for steatosis, if the right hepatic vein is large, and if segment V and VIII hepatic veins are less than 5 mm in size (de Villa et al. 2003). The ASAN and SNUH Seoul groups in contrast advocate the concept of "standardized right liver graft" implying the reconstruction of all draining segmental veins having a diameter >5 mm with a venous or prosthetic graft (Hwang et al. 2012). Dual liver grafting represents the ultimate approach to overcome SFSS: this method reported in 2000 implies the sequential implantation of two grafts (of different types) allowing to reach a sufficient liver mass. Up to 2007, 226 dual grafts were reported by the Asan group (Song et al. 2010).

Upcoming Features: Due to the reported incidence of morbidity (up to 24 %) and mortality (up to 0.02 %) of LDLT (Cheah et al. 2013), there is a renewed interest for left liver LDLT. This change corresponds to a shift from recipient to donor safety. In 2004, the Shinshu University group reported an 84 % five-year survival in 97 left liver LDLT (Hashikura and Kawasaki 2004). In 2012, the same authors reported a 91 % five-year survival in 42 consecutive adults, this time without the use of inflow modulatory techniques such as splenectomy and portacaval shunting (Ishizaki et al. 2012). The Kyushu University group validated this approach in 200 consecutive adult recipients (Soejima et al. 2012). Five-year patient survival rate reached 78 %; the incidence of SFSS was 20 %. Donor liver tests and length of hospital stay of left liver donors were significantly better than those of right liver donors. Recently this team evaluated the impact of splenectomy in left liver AALDLT: in

154 patients simultaneous splenectomy reduced portal venous pressure from 24 to 19.1 mmHg and postoperative total bilirubin level, and ascites output were lower (Wang et al. 2014a). The Kyoto group investigated donor safety by comparing evolution of post-donation donor liver tests and morbidity between the right ($n = 168$) and left (=140) hemilivers procured during the period 2006 and 2012. Hyperbilirubinemia, coagulopathy and liver tests of left liver donors normalized more rapidly, all findings that correlated with a lower overall complication rate (Iwasaki et al, 2014). It was concluded that the lower limit of the GRBWR can be safely reduced to make better use of the left lobe graft in AALDLT on the condition that portal pressure is modulated. In December 2007, the acceptable limit for GRBWR was set to ≥0.7 % and by April 2009 to ≥0.6 %; the portal pressure control was targeted at <15 mmHg. As a result, the donor complication rate decreased from 13.8 % to 9.3 %, and the survival of the recipients with GRBWR <0.8 % was similar to the one of recipients with a GRBWR ≥0.8 % (Kaido et al. 2014). As a consequence of these results, left liver LDLT has been evaluated also in Western countries. A retrospective analysis of US LDLT performed during the period 1998–2010 showed that 154 (5.4 %) of 2,844 adult LDLT were done using a left liver. Although left liver LDLT decreased donor morbidity and mortality, allograft failure raised and survival decreased (Saidi et al. 2012).

The recent boost in hepatic laparoscopic surgery led to the introduction of this technical innovation in the field of LDLT. After the initial experience reported from Paris (Cherqui et al. 2002), laparoscopic left lobectomy becomes the standard procedure in pediatric LDLT. Recently this approach has been applied successfully to both left and right hepatectomy. No donor deaths have so far be reported (Troisi et al. 2013). In the near future, standardization of these procedures together with modulation of the portal pressure and optimization of hepatic venous outflow reconstruction will help to restimulate the development of LDLT in the Western world.

Split Liver Transplantation (SPLT)

Split LT is an important means of overcoming organ shortages. Division of the donor liver for one adult and one pediatric recipient has almost eliminated the mortality of children waiting for LT. More frequent use of SPLT from postmortem donors would probably almost completely eliminate the need for LDLT in children. Liver splitting can be performed during organ procurement ("in situ" splitting) or during back-table surgery ("ex situ" splitting). A large experience from UK reported that 76 of 80 consecutive pediatric split liver procedures were done "ex situ." Sixteen transplants were performed for ALF and 64 for chronic liver diseases. Three-year patient and graft survival were 88.1 % and 86.1 %. Four patients only required reLT. Vascular and biliary complications occurred in 7.5 % and 8.7 % (Deshpande et al. 2002). A similar US study about 100 consecutive "in situ" splits yielding a left lateral segment and right trisegmental graft generated 105 pediatric and 60 adult grafts, and 25 shared allografts across the USA. Outcomes and incidence of complications were similar when compared to LDLT and LT performed using whole organs performed during the same time period (Yersiz et al. 2003).

Excellent results of SPLT have been reported in children. The acceptance of SPLT in adults is however far from unequivocal mainly due to higher short-term morbidity and also lack of long-term outcome reporting. A US study compared results of 70 right-extended SPLT and 70 whole graft LT. Five-year patient and graft survival rates were 82.6 % and 77.3 % versus 75.6 % and 65.8 %; there were no differences between both groups in terms of short- and long-term morbidity (Wilms et al. 2006).

Upcoming Features: National mandatory split programs can represent a useful tool with the intent to further reduce the number of patients waiting for LT and to reduce the necessity of living donation. An Italian study investigated the opportunity to split livers from pediatric donors (<15 years). Forty-three conventional split liver procedures, 19 of whom from donors weighing ≤40 kg, were done. Matching of organs was based on donor–recipient weight ratio (DRWR) for left

lateral segment and on estimated graft-to-recipient weight ratio (eGRWR) for extended right grafts; no matching was found in three cases. The celiac trunk was included in the left lateral graft in all but one case. Forty left lateral segments were transplanted into 39 children; 39 right grafts were transplanted into 11 children and 28 adults. No differences were observed in terms of complications and survival when comparing grafts from donors weighing more or less than 40 kg. Only donor ICU stay >3 days and use of interposition arterial grafts were associated with an increased risk of graft loss and arterial complications (Cescon et al. 2006).

Another recent Italian multicenter prospective study investigated the potential benefit of SPLT for two adults. Sixty-four patients who received a full-right or a full-left liver were compared to patients receiving a whole graft in a match-control fashion. Split patients showed higher postoperative complication rates (64.1 % grade III–IV Dindo–Clavien classification) and lower 5-year survival rates (63.3 % vs. 83.1 %). The conclusion of this preliminary analysis is that SPLT should be an option for well-selected smaller-sized adults only in experimental clinical studies and in very experienced centers (Aseni et al. 2014).

Another fascinating aspect of SPLT could be its use in hyperimmunized or crossmatch-positive renal patients, the rationale being that the liver graft (ideally from the same donor) protects the kidney by absorption of the harmful HLA antibodies. Seven patients, with broadly reacting HLA antibodies and positive crossmatches, were transplanted with a partial auxiliary liver and a kidney from the same donor, once a living donor was used. Crossmatch turned negative five times, and kidney function remained excellent in the absence of rejection during the follow-up (Olausson et al. 2007).

Combined Transplantation of Liver with Other Organs

Combined Abdominal Transplantation

Combined Kidney–Liver Transplant (CKLT): Renal and hepatic function are often intertwined through both the existence of associated primary organ diseases and hemodynamic interrelationships. Failure of both organs may necessitate CKLT. Several liver diseased patients also present with morphologic renal disease. Examples of this are polycystic disease, HCV infection, amyloidosis, sarcoidosis, hemochromatosis and alcoholic cirrhosis (Davis et al. 2002a). End-stage liver disease may also trigger functional renal failure caused by a major impairment of effective circulating volume secondary to both splanchnic arterial vasodilatation and reduction of cardiac output. This particular condition is called hepatorenal syndrome (HRS) or link. Type 1 HRS is defined by a rapid deterioration of the kidney function and type 2 HRS by refractory ascites with a more moderate and slowly progressive renal failure (Gines and Schrier 2009). HRS together with the other morphologic underlying kidney disorders is present in up to 20 % of liver diseased recipients (Garcia-Tsao et al. 2008). Patients with simultaneous hepatic and renal disease may be candidates for CKLT. Renal failure caused by acute injury or hepatorenal syndrome may be often reversible, so CKLT is not indicated. If kidney function remains disturbed for more than 6–8 weeks, indication for CKLT may be considered depending on the general condition of the patient. The criteria for CKLT have been progressively refined during the last years in order to avoid futile KT. In 2002, the criteria proposed by UNOS were end-stage renal disease, metabolic disease requiring CKLT, acute renal failure with ≥8 weeks of dialysis, and chronic kidney disease with documented glomerular filtration rate or creatinine clearance ≤30 mL/min (Davis et al. 2002b). The MELD-based liver allocation had resulted in a steep increase in the number of simultaneous CKLT. The US consensus conference was set up in 2008 aiming to counteract this evolution. The criteria for CKLT were adapted, and those for KT in patients presenting portal hypertension due to liver diseases not yet requiring LT were also introduced: end-stage renal disease with cirrhosis and symptomatic portal hypertension or hepatic vein wedge pressure gradient ≥10 mmHg; liver failure and chronic kidney disease with glomerular filtration rate or creatinine clearance ≤30 mL/min; acute kidney injury or HRS with creatinine ≥2.0 mg/dL

Table 3 Indications for CKLT in patients on liver transplant wait-list

1. Candidates with persistent AKI for ≥4 weeks with one of the following:
(a) Stage 3 AKI as defined by modified RIFLE, i.e., a threefold increase in SCr from baseline, SCr ≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL or on renal replacement therapy
(b) eGFR ≤35 mL/min (MDRD–6 equation) or GFR ≤25 mL/min (iothalamate clearance)
2. Candidates with CKD* for 3 months with one of the following:
(a) eGFR ≤40 mL/min (MDRD–6 equation) or GFR ≤30 mL/min (iothalamate clearance)
(b) Proteinuria ≥2 g/day
(c) Kidney biopsy showing >30 % global glomerulosclerosis or >30 % interstitial fibrosis
(d) Metabolic disease

Abbreviations: AKI acute kidney injury, *RIFLE* risk injury failure loss end-stage, *sCr* serum creatinine, *MDRD* Modification of Diet in Renal Disease, *CKD* chronic kidney disease, *GFR* glomerular filtration rate

[a]As defined by the National Kidney Foundation

and dialysis ≥8 weeks; and liver failure and chronic kidney disease and biopsy demonstrating >30 % glomerulosclerosis or 30 % fibrosis (Eason et al. 2008).

Upcoming Features: The previously proposed guidelines, despite their ability to improve survival rates in patients with both liver and kidney pathologies, are still troubled by pitfalls such as definition of acute kidney injury, glomerular filtration rate determination, and dialysis criteria (Levitsky et al. 2012). Improvement has been made by the introduction of RIFLE score (risk, injury, failure, loss, end stage) (Ferreira et al. 2010) and Modification of Diet in Renal Disease (MDRD) Study equation (Francoz et al. 2014).

In 2012 a new consensus meeting took place with the intent to critically evaluate published and registry data regarding patient and renal outcomes following LT alone or CKLT and to further modify current guidelines for CKLT (Table 3) (Nadim et al. 2012).

Another important aspect to consider in the context of CKLT is the immunosuppressive handling of these patients. A study from the UNOS database performed on 352 kidney-after-liver transplants versus 1,136 CKLTs confirmed the immunologic protective capacity of the liver allograft if both organs, originating from a same donor, are transplanted simultaneously. Kidneys transplanted following LT had less good outcomes (renal half-life: 6.6 vs. 11.7 years; 3-year rejection-free status: 61 % vs. 79 %) (Simpson et al. 2006). This aspect must be carefully considered when organs are allocated because of the reduced risk of graft loss and immunosuppression exposure. There is surely also a need to adapt and homogenize the IS scheme of CKLT recipients; "liver IS" approach should be preferentially adopted.

Combined Liver–Intestinal (CLIT) and Multivisceral Transplantation (MVT): Intestinal failure is a clinical condition characterized by the inability of the gastrointestinal tract to preserve adequate nutrition and fluid and electrolyte balance or sustain normal growth and body development in children. Different causes for intestinal failure in childhood (necrotizing enterocolitis, intestinal atresia, volvulus, aganglionosis motility disorders and enterocyte abnormalities) and adults (mesenteric ischemia, inflammatory bowel disease, volvulus, tumors) have been treated with variable success using intestinal transplantation (IT) (Abu-Elmagd et al. 2009). In case of intestinal failure, total parenteral nutrition (TPN) still represents the hallmark of treatment. Accepted indications for IT in patients on TPN include loss of major routes of venous access, multiple episodes of catheter-associated life-threatening sepsis, fluid and electrolyte abnormalities despite optimal medical care, and parenteral nutrition-associated cholestatic liver disease. Other indications for IT include diffuse mesenteric thrombosis and benign/low-grade malignant tumors involving the mesenteric root and abdominal catastrophes due to trauma or multiple resections. In 60–70 % of patients, CLIT or MVT is considered. The pathophysiology of liver failure in case of TPN is partly due to triglyceride-rich parenteral nutrition and partly to the exclusive intravenous route for nutrition. In adults, hepatic steatosis and biliary lithiasis and, in children, intrahepatic cholestasis leading to lithiasis are commonly reported. Initial signs of liver involvement by

intestinal failure are hypersplenism and bilirubinemia. High levels are in favor of CLIT/MVT; in case of intermediate values, indication for CLIT/MVT is based on histology and liver function (translated by signs of portal hypertension, encephalopathy, hypoalbuminemia, and coagulation disorders) (Beyer-Berjot et al. 2012).

Liver and small bowel grafts can be transplanted in a composite or non-composite allograft. In the first case, donor pancreas and duodenum are transplanted together with the liver in order to preserve the biliary tract (Bueno et al. 2000). In the non-composite transplant, liver and small bowel are transplanted separately; this approach allows to adjust major donor–recipient size discrepancies and is valuable in case of troubled abdomen.

It has been clearly shown that results of CLIT/MVT fare better than those of isolated IT, a fact explained by the well-documented immunological protective function of the liver (Yin et al. 2009). Despite this, any type of IT remains a challenging endeavor. Outcomes slowly but surely improved during recent years by aiming at less aggressive, tolerogenic, IS therapies. Commonly adopted IS regimens were responsible for a high incidence of both infectious and lymphoproliferative complications, accounting for half of deaths. Acute and chronic rejection, graft-versus-host disease, and posttransplantation lymphoproliferative disorders are also thought to be linked to the mass of lymphoid tissue transplanted with the bowel graft (Wu et al. 2011).

Upcoming Features: Abdominal wall transplantation represents a useful strategy for the closure of the abdomen in patients undergoing IT or CLIT/MVT. Nine such cadaveric abdominal wall composite allograft transplants were reported by the Miami group. The blood supply was based on the inferior epigastric vessels left in continuity with the donor femoral and iliac vessels. Five of six survivors had intact, viable abdominal wall grafts (Levi et al. 2003). Recent experiences suggesting the use of the abdominal rectus fascia as a nonvascularized allograft for abdominal wall closure have been reported (Gondolesi et al. 2009).

Reduced-size grafts have also been proposed in order to overcome difficult abdominal closure. The Birmingham group adopted the use of pretransplant abdominal tissue expanders (1998) combined, en bloc reduced liver and intestinal transplantation (1998) and staged abdominal closure (2001) as strategies reduce complications. Twenty-three of 39 children had reduced CLIT (Gupte et al. 2010) and recently a sequential SPLT followed by isolated IT has also been proposed to solve this problem (Nassar et al. 2014). Further experiences are needed with the intent to define the best strategy to adopt in these patients.

Combined Thoracic Organ–Liver Transplantation

Combined Heart–Liver Transplantation (CHLT): Heart transplantation has become the gold standard therapy for many causes of end-stage heart failures. Sometimes an underlying liver disease is responsible for the heart failure. FAP and hemochromatosis are most commonly connected with this condition. Some patients with heart failure can also develop hepatic failure due to chronic venous congestion. The first successful CHLT was reported in 1984 in a 6-year-old girl with familial hypercholesterolemia and coronary artery disease; she survived 7 years (Starzl et al. 1984). Few series containing more than 20 cases are reported. The Mayo Clinic experience comprises 27 CHLT; four patients also had a CHLuLT. FAP was the main indication (78 %); twelve FAP livers were used for domino LT. Excellent postoperative course was observed, with median duration of mechanical ventilation, intensive care unit and hospital stays of 1, 5.5, and 15 days. Only one patient died within 30 days of CHLT (Barbara et al. 2014). The Philadelphia group reported 26 (0.02 %) CHLT on a total of 1.050 HT. All CHLT were successful and 5-year survival rate 83 %. Only 3 (11 %) patients had a biopsy-proven rejection confirming once more the immunological protecting role of the liver allograft (Atluri et al. 2014). A multicenter US survey covering the period 2007–2013 showed that

CHLT prolonged the wait-list time of 268 liver recipients only without compromising their survival (Goldberg et al. 2014). Another US multicenter study analyzed 97 reported cases of CHLT transplanted during the period 1987–2010; amyloidosis was the most common indication. Liver and cardiac allograft 5 years survivals were 72.8 % and 73.2 %, results which are similar to those obtained in isolated HT or LT (Cannon et al. 2012).

Combined Lung–Liver Transplantation (CLuLT): Few series exist about CLuLT. This type of combined transplantation will without any doubt further expand due to improved care given to patients suffering from cystic fibrosis, α1-antitrypsin deficiency, idiopathic pulmonary fibrosis and portopulmonary hypertension. The Paris experience with 11 children with cystic fibrosis reveals that one patient underwent bilateral lobar lung from a split left lung and a reduced liver, two underwent sequential double CLuLT, four combined heart–lung–liver and four isolated LT. Pulmonary infection was the most common cause of morbidity in patients undergoing lung transplantation; actuarial survival was 64.2 % at 5 years (Couetil et al. 1997). The Hannover group reported 13 consecutive CLuLT done during the period 1999–2003. One, 3, and 5 years patient survival rates were 69 %, 62 %, and 49 % (Grannas et al. 2008). The Houston group reported about eight consecutive CLuLT performed during the period 2009–2012. The need for this combined procedure was based on the low FEV1 of 25.7 %. Overall one-year patient survival was 71.4 %. Early postoperative mortality was mainly due by sepsis (Yi et al. 2014).

Portopulmonary hypertension (POPH) and hepatopulmonary syndrome (HPS) merit particular attention as both are diagnosed in 6 % and 10 % of cirrhotics. Both conditions result from a lack of hepatic clearance of vasoactive substances produced in the splanchnic territory resulting in a functional and/or morphologic remodeling of the pulmonary vasculature leading to elevated pulmonary pressure and right ventricular dysfunction. In HPS, the vasoactive mediators cause intrapulmonary shunts leading many times to severe hypoxia. Medical treatment is not only difficult and invalidating but most of all disappointing. Typically, isolated LT results in the disappearance of HPS within 6 to 12 months. On the opposite, in case of POPH, results of isolated LT are poor with a reported 5-year survival of 28 % (Aldenkortt et al. 2014). Due to the prohibitive mortality of isolated LT, CLuLT potentially including also the heart has been proposed (Krowka et al. 2013). The Houston group reported seven patients with moderate to severe POPH (mean pulmonary arterial pressure $\geq$35 mmHg) treated with LT following pre-LT improvement of their pulmonary pressure with vasodilators. Patient survival rates were 85.7 % after a median follow-up of 7.8 years. Four of six survivors further required oral vasodilator therapy for persistence of their POPH (Khaderi et al. 2014). The management of HPS and especially POPH has to be improved as well as the selection of the potential recipients harboring these pulmonary diseases in order to make CLLuT a more common and secure procedure.

Combined Heart–Lung–Liver Transplantation (CHLuLT): Combined transplantation of the heart, lung, and liver may be indicated in patients with end-stage respiratory failure complicated by advanced liver disease or end-stage liver failure complicated by advanced lung disease. The main indications of this combined surgical approach are represented by cystic fibrosis or POPH refractory to vasodilators. In 1987, the first CHLuLT was performed in Cambridge in a patient with PBC, pulmonary hypertension, and cardiorespiratory failure with encouraging results. The retrospective review of nine patients transplanted showed 1- and 5-year actuarial survival of 56 % and 42 % (Praseedom et al. 2001). The Paris experience comprising four fibrosis pediatric patients showed excellent survival (Couetil et al. 1997). A literature review focusing on combined transplants for POPH revealed only 10 cases, six of whom treated with CLuLT and four with CHLuLT. Two of 6 CLuLT patients died within 24 h of transplantation because of acute right heart failure. CHLuLT seems therefore to be the best approach in case of refractory POPH (Scouras et al. 2011).

Particular Technical Considerations

Cavoportal Hemi-transposition (CPHT): CPHT represents an exceptional technical modality to overcome extensive splanchnic venous thrombosis impossible to solve with other surgical approaches such as anastomosis to a patent splanchnic tributary, portal vein arterialization or reno-portal anastomosis. In this technique, the inflow from inferior caval vein is used to perfuse the portal vein of the allograft. The first human application of CPHT was performed in patients with GSD (Starzl et al. 1973). In 1998, the Miami group reported a series of nine cases done because of diffuse portal vein thrombosis (Tzakis et al. 1998). To date, 107 cases have been reported (Lai et al. 2014). CPHT can be performed either as an end-to-end or an end-to-side anastomosis between inferior caval and portal vein. This procedure carries a mortality rate up to 34 %, mainly due to sepsis and multiple organ failure. Postoperative complications are mainly related to anastomotic thrombosis or stenosis, incompletely resolved portal hypertension, and inferior caval vein congestion. Mild-to-severe renal dysfunction is observed in almost all patients, with hemodialysis required in 12 % of patients. Ascites and variceal bleeding are observed up to 20 % of cases. Splenectomy and gastric devascularization can be of help to solve this complication.

Complex Arterial Reconstruction: Restoration of arterial flow is essential in LT. Compromised arterialization of the allograft is followed by several, many times potentially lethal, complications such bilomas, abscesses, non-anastomotic biliary complications, and graft failure due to extensive necrosis. In some cases, an inadequate flow can be observed due to stenosis, intimal dissection, or anomalies of the hepatic artery and splenic arterial steel. Arcuate ligament syndrome is a probably underestimated cause of stenosis. The nowadays frequently applied pre-LT LRT (especially transarterial chemoembolization) can cause intimal dissection or arteritis in up to 20 % of patients.

The splenic artery (SA) may be very useful help to correctly arterialize the allograft as shown by the Barcelona experience in 23 cases. One- and 3-year patient actuarial survival were 78 % and 72 % (Figueras et al. 1997). Worldwide experiences in patients undergoing LDLT showed similarly satisfactory results (Piskin et al. 2012). The gastroepiploic artery may be another "graft" saver in case of compromised arterial tree.

Use of Aortic Conduit: In case of abnormal hepatic arterial inflow in the recipient, it can be necessary to perform revascularization of the liver allograft by using a transmesocolic iliac arterial interposition graft between infrarenal aorta and allograft artery. An Italian experience with 101 such cases demonstrated a poorer 5-year graft survival when compared with standard re-arterialization (53.4 vs. 69.2 %) and also a higher rate of hepatic artery thrombosis (21.8 % vs. 8.6 %) (Del Gaudio et al. 2005). No good agreement exists in relation to the long-term outcome of this technique The Dallas experience with 149 first LT with aortic conduit showed excellent long-term results comparable with conventional arterialization (5 year, 59 % vs. 67 %; 10 year, 50 % vs. 52 %; 15 year, 33 % vs. 35 %) (Nikitin et al. 2008). In contrast, the Miami reported less favorable long-term results in a series of 267 adult and 81 pediatric LT with aortic conduit. Adults had higher hepatic artery thrombosis rate (4.1 % vs. 0.7 %) and lower 5-year graft survival rates (61 % vs. 70 %) when compared with aortic conduit LT and conventional LT. In children, complications were similar, but the 5-year graft survival rate was significantly impaired in the conduit group (69 % vs. 81 %) (Hibi et al. 2013).

Conclusion

LT revolutionized without any doubt the modern medical practice in the field of liver pathology. Progresses have been spectacular over the last half a century. Several contraindications have been, one after the other, eliminated, and today only extrahepatic active sepsis remains as an absolute contraindication to the procedure. Long-term survival rates are becoming very frequent so the attention of the transplant community must be shifted to the

optimization of the quality of life of the successfully transplanted recipient. More clinical and immunologic research will be needed to make these long-term survivors "immunosuppression-free" (or tolerant), a condition necessary to face the more and more frequently diagnosed renal failure, de novo tumor formation, cardiovascular and infectious events in an ever aging transplant population. Recent developments in immunosuppressive strategies (using minimization approaches) and in combined organ failure care will lead to more frequent combined transplant procedures. Besides the further development of postmortem LT, more frequent implementation of technical variants such as split and living liver donor LT will have to play a more prominent role in order to cope with the ever-growing liver allograft shortage.

Cross-References

- Artificial Liver Treatment: When and Which One?
- Combined Transplantations
- Donor Operation
- Downstaging Hepatocellular Carcinoma for Liver Transplantation
- Fulminant Hepatic Failure: Diagnosis and Management
- HCC: The San Francisco Criteria
- Hepatitis C Virus Infection: A New Era
- Hepatopulmonary Syndrome and Portopulmonary Hypertension
- History of Liver and Other Splanchnic Organ Transplantation
- Immunology of Liver Transplantation
- Infections and Sepsis After Liver Transplantation
- Live Donor Liver Transplant
- Liver Transplantation for HCC: The Milan Criteria
- Minimally Invasive Live Donor Liver Hepatectomy
- NASH: The Ethical Dilemma
- Orthotopic Liver Transplantation: Complications
- Orthotopic Liver Transplantation: Indications and Contraindications
- Orthotopic Liver Transplantation: Surgical Techniques
- Split Liver Transplantation

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Donor Operation

3

Javier Bueno, Matias Ramirez, and José Andrés Molino

Contents

Abstract

An optimal organ procurement technique is crucial to allow adequate post-operative graft function. The guiding principle for this is the avoidance of warm ischemia in all organs. The standard guideline for organ procurement consists of three successive phases: (1) variable dissection of the organs to be used with intact donor circulation, (2) cannulation and in situ cooling by aortic infusion of the different organs with simultaneous exsanguination, and (3) organ removal. The liver is usually retrieved simultaneously with one or more other organs (heart, lungs, pancreas, kidneys, and sometimes the intestine), and there are different methods for procurement of the liver based on the organs that are being retrieved. However, the success of solid-organ transplantation has brought with it increasing waiting lists due to insufficient donation rates and substantial waiting list mortality. To increase the donor pool, the use of "extended criteria" livers, such as those taken from donors in the extremes of age, with steatosis, or with hemodynamic instability and the use of non-heart-beating donors, has become standard. However, these grafts have a higher risk of increased ischemia reperfusion injury that translates to primary graft nonfunction or delayed graft dysfunction. In some of these circumstances, it is usual to perform immediate aortic cannulation and in situ cooling, followed by en bloc recovery of the organs with subsequent division of the vascular structures and preparation on the bench.

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Introduction

Liver procurement using the standard and rapid techniques was first described by Starzl and colleagues in 1984 and 1987, respectively (Starzl et al. 1984, 1987). Later, Nakazato et al. described the "en bloc" total abdominal evisceration procedure (Nakazato et al. 1992). Since then, several modifications have been described that simplify the surgical methods and minimize the risk of damage to the liver allograft (Boggi et al. 2004; Gubernatis 1989; Miller et al. 1988; Starzl et al. 1991).

The liver is usually retrieved simultaneously with one or more other organs (heart, lungs, pancreas, kidneys, and sometimes the intestine). Therefore, several surgeons are usually involved in the whole procedure: heart–lung surgeons, liver surgeons, pancreas surgeons, and urologists. The participating teams are committed to carrying out the surgical strategy without causing jeopardy to any of the individual grafts. The order of organ retrieval starts with the thoracic organs and is followed by liver, pancreas, and kidney procurement. The guiding principle is the avoidance of warm ischemia in all organs. The standard guideline for organ procurement consists of three successive phases: (1) variable dissection of the organs to be used with intact donor circulation, (2) cannulation and in situ cooling by aortic infusion of the different organs with simultaneous exsanguination, and (3) organ removal (Starzl et al. 1984, 1987; Renz and Yersiz 2005).

Some surgeons perform the liver dissection before the perfusion, while others perform the perfusion first, followed by en bloc recovery, and then proceed with the dissection during bench surgery. Each procedure has its advantages and disadvantages. In situ dissection reduces the cold ischemia time, simplifies identification of vascular structures, eliminates unintentional graft rewarming during ex vivo manipulation, and reduces hemorrhage. The different methods to procure the liver are influenced by different variables, which include donor hemodynamic instability, non-heart-beating donors (NHBDs), logistics, and the surgeon's experience, among others. In those circumstances, it is usual to perform immediate aortic cannulation, cross-clamping of the thoracic aorta, and in situ cooling, with en bloc recovery of the kidneys, pancreas, stomach–duodenum, and liver, and its posterior separation with preparation of vascular structures during bench surgery (Boggi et al. 2004; Nakazato et al. 1992). However, in this method, the bench work is time consuming, which causes a prolonged warm ischemia time. In addition, the methods of dissection and cannulation may be different in cases of multiorgan procurement, particularly when the liver is procured simultaneously with the pancreas and/or the intestine. In certain cases, the liver is divided to obtain two grafts for two recipients (split liver). This partition can be in situ in the donor or ex vivo during benchwork.

An optimal procurement technique is crucial in allowing a good post-operative graft function. A suboptimal technique, particularly in marginal donors, aids development of primary or poor graft function. The potential mechanisms for this can be divided into donor-, procurement-, and transplantation-related factors. In the majority of transplant centers, the rate of primary graft nonfunction of the liver allograft is in the range of 2–10 % (Jain et al. 2000; Ploeg et al. 1993; Strasberg et al. 1994). Several studies have demonstrated that donor-related factors, such as extremes of age, steatosis, hemodynamic instability, and high-dose administration of vasopressive drugs, among others, are potential risk factors for primary graft nonfunction or delayed graft function (Busuttil and Tanaka 2003).

Deceased Donors

Deceased donors are classified as heart-beating donors or NHBDs. The heart-beating group includes the classical brain-dead donor, from whom organs are procured while the heart is still beating and the lungs are mechanically ventilated.

Table 1 Non-heart-beating donor categories (Maastricht criteria)

Category	Status	Condition
1	Dead on arrival	Noncontrolled
2	Unsuccessful resuscitation	Noncontrolled
3	Awaiting cardiac arrest	Controlled
4	Cardiac arrest while brain dead	Noncontrolled

The NHBDs develop definitive cardiac arrest, defined as a nonreversible absence of circulation, before organs are procured, resulting in severe ischemic injury. The warm ischemia time is very important for the viability of the organ and post-transplant graft function. It is crucial with NHBDs to cool the organs as soon as possible after cessation of circulation in order to protect them. Several cooling techniques may be used, the simplest of which is to establish intra-aortal cooling after laparotomy.

Because cardiac arrest may occur under very different conditions, four categories of donation after cardiac death or NHBD can be distinguished following the Maastricht criteria (Kootstra et al. 1995, 2002), as shown in Table 1.

Category 1, or "dead on arrival," donors are declared dead outside the hospital prior to their arrival at the emergency department. It is probable that only the kidneys will be recovered from these donors, and the delay in obtaining consent from relatives and legal authorities may lead to an unsuccessful donation. However, immediate intra-aortic cooling could salvage the organs for donation.

Category 2, "unsuccessful resuscitation," donors are maintained with external cardiac massage and artificial ventilation. After consent, the organs are cooled immediately.

Category 3, "awaiting cardiac arrest," includes the group of patients who are going to die from irreversible brain damage but who do not fulfill the criteria for brain death. Organs are procured after intentional withdrawal of ventilatory support and subsequent cardiac arrest in a controlled situation that takes place in the operating room. After cardiac arrest, immediate laparotomy and intra-aortic cooling can preserve abdominal and thoracic organs for transplantation. Under noncontrolled conditions, it is likely that only the kidneys can be obtained.

In category 4, "cardiac arrest while brain dead," patients suffer a cardiac arrest during the process of being declared brain dead or after brain death has been diagnosed but before organs could be retrieved. To prevent the kidneys from being lost in these donors and to establish cooling as soon as possible, a femoral double-balloon triple-lumen cannula to administer cooling preservation solution should be ready for use at the bedside. A liver allograft is seldom retrieved from these donors due to the risk of primary graft nonfunction and severe biliary tract damage.

Donor Preparation and Surgical Fields

To prepare the patient for donation, they are brought to the operating room orotracheally intubated, with the radial or femoral artery and peripheral and central veins canalized. The donor is placed on the operating table in the supine decubitus position with their arms extended; the chest and abdomen are fully covered with povidone and draped. This permits simultaneous interventions.

Donor Surgical Procedure

Dissection with Intact Circulation

Initially, chest and liver surgeons work simultaneously. Following a complete midline incision from the suprasternal notch to the pubis, evaluation of thoracic and abdominal organs is performed, and their viability is confirmed. Some surgeons use a cruciform abdominal incision. It is essential that a full manual and visual exploration is performed to exclude unknown primary or secondary tumors in the abdomen. Ligation of the round ligament and division of the falciform ligament up to the coronary ligament allows the surgeon to analyze the liver for aspect, color, texture, signs of steatosis or ischemia, and visible or palpable lesions. Two anatomical

variations are important in liver transplantation: a right accessory hepatic artery or a total hepatic artery replacement originating from the superior mesenteric artery (SMA), which runs posterior or lateral to the portal vein, and a left accessory hepatic artery originating from the left gastric artery by the gastrohepatic ligament (Abid et al. 2008; Hiatt et al. 1994; Todo et al. 1987). The surgeon will check for both anomalies. First, tactile assessment with the index finger of the posterior aspect of the hepatoduodenal ligament is performed to feel the pulse of the anomalous right hepatic artery (present in around 15 % of total cases). However, despite its existence, the pulse is not always perceivable. Therefore, a principle in liver procurement is to act assuming that a right accessory or replaced hepatic artery is present. Second, the left triangular ligament of the liver is incised to allow exploration of the gastrohepatic ligament for the presence of the left accessory hepatic artery, which is present in between 10 % and 13 % of cases.

The Cattel-Braasch and Kocher maneuvers mobilize the cecum, right colon, duodenum, and small bowel en bloc to the left, allowing exposure of the retroperitoneum and inferior vena cava, renal veins, SMA, and infrarenal aorta down to the iliac bifurcation (Cattel and Braasch 1960). The inferior mesenteric artery is identified and divided between ligatures to facilitate later aortic cannulation. The infrarenal aorta should be dissected from right to left to avoid injury of the vena cava and should be encircled with two umbilical tapes for the eventual insertion of a cannula for preservation solution infusion, with special care taken to avoid damage and bleeding of the lumbar arteries that originate on the posterior aortic wall. In certain cases, a polar renal artery may have its origin in this portion of the aorta and can also be injured. In addition, the inferior mesenteric vein (IMV) is identified in the inframesocolic retroperitoneum, lateral to the ligament of Treitz, and referenced with two ligatures for posterior cannulation and portal perfusion.

The SMA, located above the left renal vein, is identified and encircled. The intestine is then repositioned inside the abdomen to allow exploration and dissection of the hepatic hilum. The common bile duct is localized, mobilized, and transected as far as possible, always below the cystic duct. Then, the common hepatic artery is identified and freed of the surrounding tissues; the origin of the gastroduodenal artery is identified and carefully ligated to avoid intimal dissection or stricture of the common hepatic artery. The common hepatic artery is followed till the origin of the splenic and left gastric arteries, which are encircled. In situations in which either an accessory right or left hepatic artery, or both, are found, those arteries require dissection and individualization until their origin with posterior reconstruction during bench surgery.

The portal vein is beneath the gastroduodenal and common hepatic arteries. The portal vein dissection extends down to the confluence of the splenic and superior mesenteric veins (SMVs), providing another site for further cannulation and venous perfusion. Once the portal vein has been cleaned, no further dissection is required in the liver hilum. The SMV, splenic vein, and IMV can also be used for cannulation and portal vein perfusion (Fig. 1). The choice of vein is based on surgeon preference, the organs procured (avoid the SMV in cases of pancreas retrieval), and unstable donor condition (IMV being the preference in this case).

The last step prior to perfusion and cooling is exposure of the supraceliac aorta, which is cross clamped to prevent the cold preservative solution going to the cephalic part of the body and to the extremities, so that the flush can be concentrated into the abdominal organs. The types of supraceliac aortic cross-clamping are shown in Fig. 2. The most frequent site of aortic cross-clamping is at the level of the diaphragmatic crura (Fig. 2a). The most common technique for its exposure is to retract laterally toward the right of the left lateral segment (the left triangular ligament of the liver has already been sectioned) and for an assistant to retract the esophagus and stomach toward the left to expose the diaphragmatic crura. Next, the diaphragmatic crura is

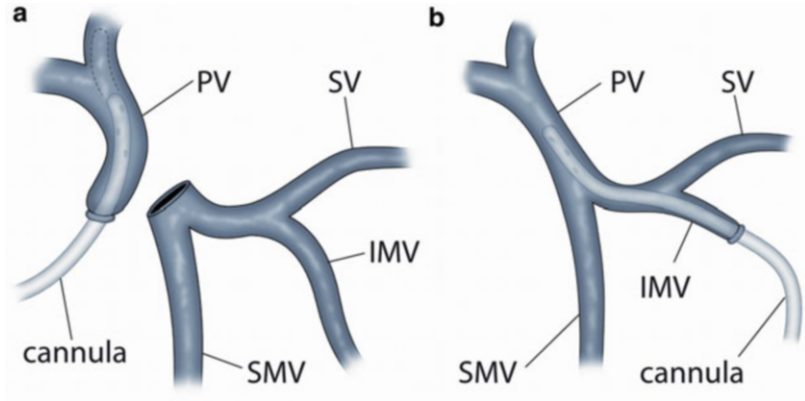

Fig. 1 (**a**) Sites for portal venous system cannulation. Choice of the site is based on surgeon preference, the organs being procured (avoid the superior mesenteric vein in cases of pancreas procurement), and unstable donor condition (for which the inferior mesenteric vein is preferred). When the cannula is inserted in the portal vein, the surgeon must check that the tip of the portal vein cannula is placed in the portal vein trunk and not in one of its branches. (**b**) When the cannula is inserted in the inferior mesenteric vein, the surgeon must be aware that the tip of the cannula is in the portal vein. *IMV* inferior mesenteric vein, *PV* portal vein, *SMV* superior mesenteric vein, *SV* splenic vein

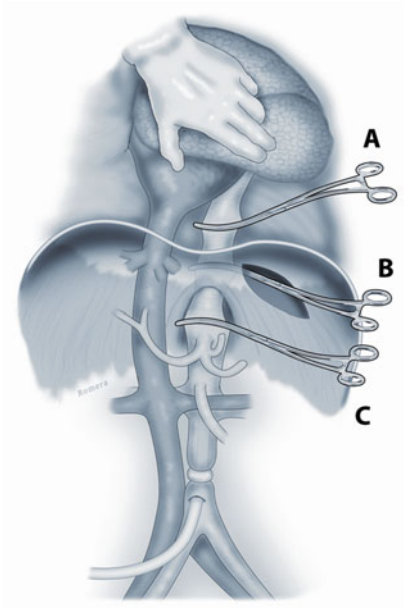

Fig. 2 Sites of supraceliac aortic cross-clamping. (**a**) The most frequent site is at the level of the diaphragmatic crura. (**b**) Another option is to cross-clamp the aorta at the thorax following incision of the left diaphragm. (**c**) In cases in which the thoracic organs are not procured, the easier way to encircle the thoracic aorta is to eviscerate the left lung through the sternotomy

longitudinally sectioned, exposing the preaortic fascia, followed by encirclement of the supraceliac aorta with an umbilical tape to allow cross-clamping later. Intercostal or lumbar branches are ordinarily not encountered in this location. In the case of a replaced or accessory left gastric artery, this maneuver might add undue tension, which can injure the accessory left gastric artery. To avoid such tension, the left lateral segment, gastroesophageal junction, and stomach can be retracted to the right side and the spleen retracted downward to expose the right diaphragmatic crura, followed by aortic encirclement (Desai et al. 2014).

Another option is to perform supraceliac aortic cross-clamping at the thorax (Fig. 2b). The stomach is retracted to the right, the spleen is retracted down, and the posterior abdominal side of the left diaphragm is incised. Following division of the left pulmonary ligament, the thoracic aorta is easily identified. In cases in which the thoracic organs are not retrieved, an easier way to encircle the thoracic aorta is to eviscerate the left lung through the sternotomy (Fig. 2c).

Finally, before cannulation and in situ cooling, the gallbladder is incised and washed out with

saline solution in order to prevent autolysis of the mucosa of the biliary tract.

Cannulation and In Situ Cooling

Following full heparinization of the donor with 350 units/kg of intravenous sodium heparin, the infrarenal aorta and either a portal, splenic, SMV, or IMV cannula are inserted. The tip of the aortic cannula must be introduced with caution below the origin of the renal arteries for adequate perfusion of the intra-abdominal organs (Fig. 2). Where there is severe aortic atherosclerosis, the cannula is inserted in one of the iliac arteries instead of the aorta. Also, for adequate perfusion of the whole liver, it should be confirmed that the tip of a portal vein cannula is placed in the portal vein trunk instead of one of its branches (left or right portal vein) (Fig. 1a). When the cannula is inserted in the IMV, the tip is advanced superiorly approximately 5 cm. To optimize portal perfusion, the surgeon must be certain that the tip of the cannula is in the portal vein and not directed toward the splenic hilum (Fig. 1b).

The cross-clamping and perfusion sequence is initiated by the cardiac/pulmonary team. Immediate cardioplegic, pulmoplegic, and chilled preservation solution is then perfused through the cannulas for the heart, lungs, and abdominal organs. The vena cava is then immediately vented at the junction with the donor right atrium to permit venous drainage of the abdominal organs, avoiding their congestion. In those situations in which the chest cannot be approached through sternotomy (i.e., previous heart surgery) and the thoracic organs are not retrieved, vena cava venting is performed through the right diaphragm, which is incised following retraction of the liver downward with the surgeon's left hand.

The donor heart and lungs are immersed in cold solution. Simultaneously, the encircled supraceliac aorta is cross clamped, and perfusion of the abdominal organs with preservation solution starts through the cannula inserted in the infrarenal aorta (18–22 F) and portal vein, splenic vein, or IMV (12–14 Fr) (Figs. 1 and 2). The abdominal organs are immersed in an ice-slush cold solution. The total amount of preservation solution used is guided by blanching of the organs and when the effluent solution through the vented cava changes to a light color. The liver requires 2–4 L of preservation solution through the aorta and 2 L through the portal system. The organs remain in situ until the cold infusion is completed (Renz and Yersiz 2005; Starzl et al. 1984).

The majority of liver procurement teams still consider portal system cold infusion to be mandatory for liver cooling. However, the method of only cannulation and perfusion through the aorta is also effective (de Ville de Goyet et al. 1994; El-Rassi et al. 2005). In this method, the portal system is perfused after the preservation solution crosses the intestinal circulatory bed via the SMA (which is not ligated) and splenic artery. The author has performed such a technique in more than 200 donors (unpublished data) without deleterious effect and with correct post-transplant graft function. This technical modification requires less dissection and cannulation, making it safer in critically unstable donors. The same technique is performed in cases of retrieval of multivisceral grafts, which include the intestine (Abu-Elmagd et al. 2003).

Organ Removal

During organ removal, the heart and lungs are procured first. When the perfusion of the abdominal organs is finished, the organs are then retrieved: first the liver, then the pancreas, and finally the kidneys.

In those cases in which the liver hilum has not been dissected or a rapid technique is required, mobilization of the colon out of the field will facilitate the organ procurement enormously.

The upper vena cava is transected together with a patch of the right diaphragm around the lumen of the suprahepatic inferior vena cava. The inferior vena cava is divided above the renal veins, leaving a cuff of the vena cava for the kidney allografts. This is followed by portal vein division at the confluence of the splenic vein and the SMV. Finally, the splenic and the left gastric arteries are sectioned. The left gastric artery is preserved when a left accessory hepatic artery is present, and its division will be distal to this branch with ligation of the proximal gastric branches. The celiac artery is dissected until its origin from the aorta and is recovered with a Carrel patch.

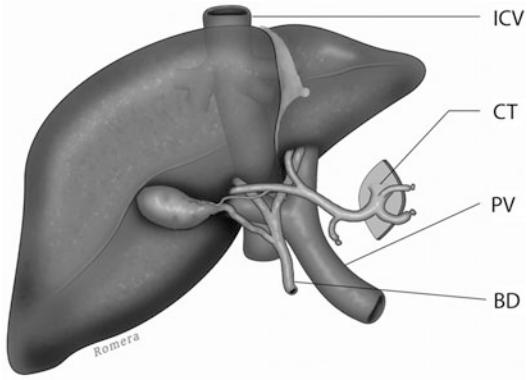

Fig. 3 Liver allograft procurement. The upper vena cava is transected above the suprahepatic veins, and the inferior vena cava is divided above the renal veins. The portal vein division is at the confluence of the splenic vein and the superior mesenteric vein. The celiac artery is dissected till its origin from the aorta and recovered with a Carrel patch. *BD* bile duct, *CT* celiac trunk, *ICV* inferior vena cava, *PV* portal vein

When a rapid technique is being performed, another way to approach the celiac axis is to dissect the SMA above the renal arteries and veins (Fig. 3). To facilitate this step, the axis of the intestine and SMA is placed perpendicular to the aorta. Then, the SMA anterior wall is cleaned from the surrounding tissue and celiac plexus. The aorta is transected (scissor at 45 °) immediately caudal to the origin of the SMA to avoid damage of the renal arteries. A large aortic patch that encompasses both the origins of the celiac artery and SMA is then applied. This maneuver is also useful when an anomalous right hepatic artery is present. To avoid injury of this accessory artery, a length of SMA needs to be preserved with the graft for posterior reconstruction during the benchwork.

Finally, the liver is released of all its attachments to the diaphragm and the right kidney to permit its recovery, concluding the liver allograft procurement. It is then stored in a sterile bag with cold preservation solution until bench surgery is performed.

Following liver procurement, iliac venous and arterial grafts are retrieved and conserved in preservation solution as they may be needed in the recipient operation. In severe atherosclerotic disease, the grafts can be taken from supra-aortic branches.

Bench Surgery

Bench surgery is performed with the liver in a basin with slush ice and preservation solution at a temperature of 4 °C. It consists of a meticulous inspection to identify and repair lesions and preparation and cleaning of the blood vessels from the surrounding tissues to facilitate the anastomosis with the recipient's vessels. The inferior vena cava is released from the diaphragm, via ligation of the phrenic veins, with special care taken to avoid injuries of the suprahepatic veins. The right adrenal vein is ligated to prepare the infrahepatic vena cava. The branches of the portal vein (right gastric and left coronary vein) are tied, and the main portal vein trunk is dissected until its bifurcation into left and right portal veins. This maneuver helps to orient the portal vein reconstruction on the recipient, and it avoids portal kinking, which can result in vein thrombosis. The hepatic artery is cleaned out from the origin of the gastroduodenal artery up to the Carrel patch to facilitate the arterial reconstruction in the recipient. When an anatomic variation is present, the arterial reconstruction should be performed at this time.

Pancreas Procurement

There are several key points in pancreas retrieval when it is performed simultaneously with liver procurement. As the liver and pancreas share the same arterial supply and arterial anomalies are common, good communication between the pancreas and liver procurement teams is necessary. The main technical considerations in combined liver and pancreas procurement are preservation of the arterial blood supply and an adequate length of portal vein for both organs. The head of the pancreas and duodenum have a dual arterial supply: the superior pancreaticoduodenal arcade with its origin from the gastroduodenal artery and the inferior pancreaticoduodenal arcade with its origin from the SMA. The tail and most of the body of the pancreas are supplied by the splenic artery, which is a branch of the celiac axis. Therefore, preservation of both the splenic artery and SMA is

essential for this organ. Venous drainage of the pancreas is by the splenic vein and SMV.

Opening of the lesser sac permits visual and tactile assessment of the pancreas. Pancreases with extensive fibrosis/calcification, intralobular fat, and severe edema should be discarded. Once the liver surgeons have finished the dissection and preparation of the liver allograft, the greater omentum is divided between ligatures along its entire length. A total colectomy before or after cooling of the organs may facilitate pancreas procurement. The spleen, body, and tail of the pancreas require mobilization from its retroperitoneal attachments with ligation and division of the short gastric vessels between the stomach and spleen. The spleen is mobilized by dividing the splenocolic and splenorenal ligaments and diaphragmatic attachments. The stomach is retracted upward and to the right, exposing the lesser sac and anterior surface of the pancreas. The spleen is used as a handle to avoid pancreas manipulation. The duodenum, together with the head of the pancreas, will have already been mobilized with the Kocher maneuver. Following irrigation of the stomach and duodenum with the antibiotic amphotericin and cold povidone–iodine solution through a nasogastric tube, the duodenum is transected just distal to the pylorus with a gastrointestinal anastomosis (GIA) stapler. In the same manner, the proximal jejunum next to the ligament of Treitz is also divided.

The aorta and IMV are used for cannulation and perfusion, with the portal vein and splenic vein remaining intact. The gastroduodenal and splenic artery should never be tied before in situ cooling. Once in situ cooling has been finished, the splenic artery is divided close to the celiac trunk, leaving as much splenic artery length with the pancreas as possible, and is marked with a 6-0 polypropylene suture for its later identification. The gastroduodenal artery is divided and marked in a similar way. The portal vein is transected, leaving 1–2 cm of portal vein on the pancreas side. The left gastric vein is an optimal landmark for portal division.

The root of the small bowel mesentery away from the pancreas is divided after ligation of mesenteric vessels. It can be transected with mass ligature using an umbilical tape or stapling device or with individual ligation of the major branches of the SMVs and SMAs. Finally, the nerve bundles and lymphatic tissue around the SMA are divided, and the SMA is skeletonized down to the aorta. The SMA, with an aortic Carrel patch, will remain with the pancreas rather than the liver. Care should be taken to avoid injury to renal arteries.

The presence of an anomalous right hepatic artery originating from the SMA is a matter of discussion. Pancreas surgeons prefer to divide the anomalous branch before its SMA origin and to leave the SMA and aortic patch with the pancreas allograft. In contrast, liver surgeons prefer to leave the origin of the anomalous right hepatic artery with a patch of SMA and perform its reconstruction during benchwork with the stump of the gastroduodenal artery. If agreement cannot be reached between teams, the rational decision should always be based on liver transplantation being a life-saving procedure.

The pancreas allograft includes the duodenal C, the pancreas itself, and the spleen (as a handle). The arterial reconstruction during benchwork consists of anastomosis of the splenic artery and SMA to a bifurcated iliac or supra-aortic arterial graft. The allograft splenectomy will be performed in the recipient after organ reperfusion.

When the pancreas and small bowel are procured simultaneously for different recipients, the SMA and SMV are transected at the insertion point of the middle colic vessels immediately distal to the uncinate process, allowing enough vascular length for the intestinal allograft without harming pancreatic arterial supply (Abu-Elmagd et al. 2000). The principal concern during this dissection is to avoid injury to the inferior pancreaticoduodenal artery, which originates just proximal to the origin of the middle colic artery and must be left intact with the pancreas. The reason for this is that the superior pancreaticoduodenal artery is the terminal branch of the gastroduodenal artery, which is ligated while removing the liver. The additional loss of the inferior pancreaticoduodenal artery will devascularize the head and part of the uncinate process of the pancreas.

Small Bowel Procurement

The small bowel allograft can be retrieved in isolation, combined with the liver, or as part of a multivisceral allograft (with or without the liver) in cases in which the stomach is included**.** The procurement technique is different based on the organs being retrieved.

In all cases, the first step is the division of the ileum with a GIA stapler near the ileocecal valve, followed by a total colectomy preserving the ileal branches of the ileocolic artery. The sigmoid colon is stapled, and the large bowel and greater omentum are removed in continuity from the field. The small bowel is wrapped, and using upward retraction, the root of the small intestinal mesentery is freed from its retroperitoneal attachments. The mesenteric root, abdominal aorta, and infrahepatic vena cava, including the entry of the renal veins, are further exposed with an extended Kocher maneuver.

Isolated Small Bowel Procurement

Following transection of the pylorus with a GIA stapler, the bile duct and gastroduodenal artery are ligated and divided and the portal vein dissected. After exposure of the SMV at the root of the mesentery, the index finger is passed under the neck of the pancreas, which is ligated and transected. The jejunum is then divided approximately 10 cm from the ligament of Treitz with a GIA stapler. The mesentery at the mesenteric border of the proximal jejunum is ligated and divided. Next, the proximal jejunum and fourth and third portion of the duodenum are reflected gently beneath the mesenteric vessels and to the right. The uncinate process is separated carefully from the SMV by division of the small venous tributary branches, and the SMV is scheletonized until exposure of its confluence with the portal vein and splenic vein. The wrapped intestine is gently lifted, and the origin of the SMA from the aorta is exposed. Once the liver has been prepared for its retrieval, the aorta is cannulated. In addition, the IMV can be cannulated for portal perfusion. After cross-clamping the supraceliac aorta and in situ cooling, the SMV is sectioned at the level of the splenic vein. The origin of the SMA is obtained with a small aortic cuff, using special care to avoid injury of the renal arteries and celiac trunk. The liver is then retrieved, as described earlier. The donor's external iliac artery and vein will be used as interposition grafts between the SMA and SMV of the allograft and the aorta and vena cava or SMV of the recipient, respectively.

Combined Liver and Intestine Procurement

In combined liver and intestine procurement, the entire liver hilum (preserving the biliary system) in continuity with the duodenum and the pancreas is also included in the allograft. The duodenum, spleen, and body and tail of the pancreas are mobilized, as explained in the Pancreas Procurement section. The duodenum is transected just distal to the pylorus with a GIA stapler. The origin of the SMA is dissected from the origin of the aorta. In this case, only cannulation of the aorta is required. After cross-clamping the supraceliac aorta and in situ cooling, the upper vena cava is transected together with a patch of the right diaphragm, and the inferior vena cava is divided above the renal veins. A large aortic patch that encompasses both the origins of the celiac artery and SMA is obtained (Fig. 3). In addition, the thoracic aorta is removed, and this conduit will be anastomosed to the aortic patch during the bench surgery. Another option is to free the proximal aorta in continuity with the celiac trunk including the thoracic aorta. This portion of aorta is prepared for anastomosis to the conduit by closure of the distal abdominal aorta beyond the SMA orifice using a simple running suture or arterial patch. An allograft splenectomy will be performed during bench surgery (Fig. 4).

Multivisceral Procurement

The same technique as used for procurement of a combined liver–intestine graft is applied for multivisceral procurement, the only difference being that the stomach and the left gastric and gastroepiploic arteries are preserved. The junction of the stomach with the esophagus is transected with a stapler device. In this case, only cannulation of the aorta is required.

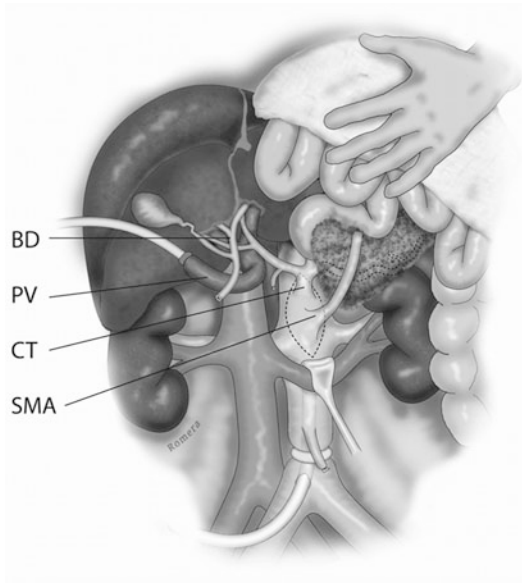

Fig. 4 When a rapid technique is needed, a useful maneuver to approach the celiac axis is to dissect the superior mesenteric artery above the renal arteries and veins. To facilitate this step, the axis of the intestine and superior mesenteric artery is placed perpendicular to the aorta, and the anterior wall of the superior mesenteric artery is cleaned from the celiac plexus. The aorta is transected (scissor at 45 °) immediately caudal to the origin of the superior mesenteric artery to avoid damage to the renal arteries. *BD* bile duct, *CT* celiac trunk, *ICV* inferior vena cava, *PV* portal vein

Kidney Procurement

The kidneys are the last organs to be removed. The procurement is en bloc, without identification of the hilar structures. The first step is mobilization of the ureters following their division distally as close as possible to the bladder. Hemostatics are placed on the tip of each ureter. They are dissected in a cephalad direction with adequate amounts of periureteral tissue left in place to avoid damage of the ureteral blood supply. The distal cava as well as the distal aorta with the cannula in place are divided and separated from the vertebral bodies, sectioning the lumbar arteries from the posterior wall of the aorta. The paraspinal muscles are sectioned and the kidneys mobilized in their lateral and superior aspect, preserving Gerota's fascia and adrenal glands. As the dissection advances, all of the structures (kidney, cava, aorta, and ureter) are lifted to avoid injury to them. The procurement is finished once the vena cava and aorta above the renal vessels are reached. During benchwork, the kidneys are separated, which is started by exposing the posterior surface of the grafts. The aorta is split first in its posterior aspect along its length between the lumbar arteries. The ostias of the renal arteries are identified, as well as the accessory polar arteries. Thereafter, the left renal vein is identified easily and is divided with a small cuff of the vena cava, leaving the entire vena cava with the right kidney.

Conclusion

An efficient procurement technique that ensures optimal preservation of undamaged organs is essential, and an optimal outcome will depend on the surgeons and donor condition. The different techniques used to retrieve the organs depend on multiple variables, such as which and how many organs are procured, type of donor, and hemodynamic instability.

Cross-References

- ▶ Combined Transplantations
- ▶ History of Liver and Other Splanchnic Organ Transplantation
- ▶ Live Donor Liver Transplant
- ▶ Orthotopic Liver Transplantation: Complications
- ▶ Orthotopic Liver Transplantation: Surgical Techniques
- ▶ Split Liver Transplantation

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Orthotopic Liver Transplantation: Surgical Techniques

4

Cataldo Doria, Samuel Goldstein, and Ignazio R. Marino

Contents

Abstract

The authors have chosen to describe the most commonly used surgical techniques for liver transplantation and their variations, namely, the standard technique with and without venous-venous bypass, the piggy-back technique with and without venous-venous bypass, and the Belghiti modification of the piggy-back. In addition to that, two rare forms of liver transplantation will be discussed: the procedures used for situs viscerus inversus and auxiliary liver transplantation.

Keywords

Liver transplantation • Surgical technique • Venous-venous bypass • Bile duct

Introduction

Thomas E. Starzl performed the first orthotopic liver transplantation in 1963 (Starzl 1969). The introduction of venous-venous bypass, complex immunosuppression regimens, and computer imaging contributed to making this procedure widely available in a span of half a century. Figure 1 indicates the textbook hepatic anatomy.

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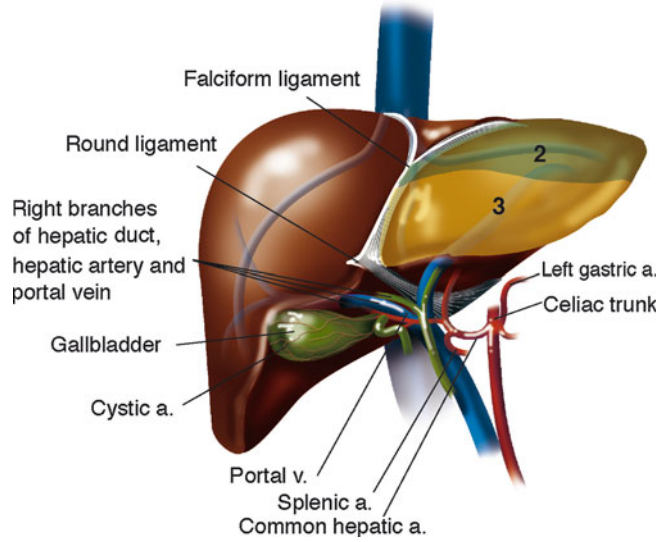
Fig. 1 Liver anatomy



Orthotopic Liver Transplant (OLT): Standard Technique With and Without Venous-Venous Bypass

The standard procedure of orthotopic liver transplant is the preferred surgical method. This technique should be used any time a liver malignancy is growing next to the inferior vena cava (IVC). The standard technique is the simplest of the procedures to perform, and it takes the shortest amount of time. The introduction of the venous-venous bypass has made the training of many surgeons possible and has dramatically decreased the intraoperative mortality experienced during the early days of liver transplantation. Before the introduction of the venous-venous bypass, survival rates were low in the setting of hemodynamic instability (Shaw et al. 1984). Patients were especially vulnerable during the anhepatic phase due to decreased venous return to the heart and hypertension in portal and systemic vessels upon clamping of the IVC and the portal vein (Shaw et al. 1984). The venous-venous bypass shunts blood flow from the portal and caval systems in the lower part of the body into the internal jugular vein, bypassing the inferior vena cava. This shunt provides the surgical team with time to implant the allograft without subjecting the patient to a decreased venous return to the heart during a complete occlusion of the IVC.

The preferred incision of choice is known as the Mercedes-Benz. It consists of a bilateral, subcostal incision with an upper midline extension made with electrocautery. Once the peritoneum is entered, the ascitic fluid, if present, is drained. Specimens are sent for culture and sensitivity studies. The round ligament of the liver is divided between 0 silk ties, and the falciform ligament of the liver is divided with electrocautery. At this stage, the xiphoid process is removed using electrocautery and heavy scissors. Subsequently, the midline peritoneum is tucked to the fascia with interrupted 2/0 silk stitches. This maneuver facilitates reopening of the midline if needed. In fact, by bringing the peritoneum up to the fascia, the intensity of the adhesions is limited in that area. In addition to that, covering the stump of the xiphoid process with peritoneum prevents injuries during the mobilization of the cirrhotic liver and the implantation of the allograft. A wet folded lap is placed on the tip of the spleen to avoid splenic injury caused by the retractor's blades. To provide adequate exposure, the surgeon uses a combination of the self-retaining rib-grip (Stieber) and the Iron Intern retractors. The operation begins with an exploratory laparotomy. This phase is particularly important and aims to rule out possible contraindication to transplantation. Contraindication is most commonly lymph node metastasis from primary liver cancers.

Subsequently, the elements of the hepatic hilum are skeletonized. First, the common bile duct is isolated and transected between 2/0 silk ties. A sample of bile is collected and sent for culture. This is the second and last standard culture obtained during liver transplantation. Patients undergoing liver transplantation are often colonized with bacteria that can cause infection postoperatively under the effect of the immunosuppressive treatment. Therefore, knowing which bacteria, if any, are colonizing the bile duct and the peritoneal cavity can help expedite antibiotic treatment while waiting for the final culture results. Next, the hepatic artery is divided between 2/0 silk ties. It is a good practice for the surgeon to alert the anesthesiologist before the silk is tied off on the artery. This provides the anesthesiologist enough time to draw the last arterial blood sample while the native liver is perfused with systemic blood flow. In fact, the lactate clearing activity of the liver is predominantly controlled by the blood flow coming from the hepatic artery. Lastly, the portal vein is skeletonized. At this stage we proceed to dissect the hepatic artery proximally to 1 cm below the takeoff of the gastroduodenal artery (GDA). The distance of 1 cm generally provides enough room to place a surgical clamp on the common hepatic artery and to rotate the vessels when performing the anastomosis.

At this stage, the access sites for the venous-venous bypass are prepared. The return cannula is placed in the right internal jugular vein by the anesthesia team after induction of general anesthesia and before prepping the surgical field. The IVC cannula is placed percutaneously through the left groin using a Seldinger technique. Although the left groin is preferred, the right groin can be used if needed. Of note, the IVC is accessed through the iliac-femoral vessels. To safely place the portal vein cannula, the portal vein skeletonization is first maximized to obtain the longest possible vessel trunk. Then, a large surgical clamp is applied distally on the portal vein as far as possible in the porta hepatis, while the proximal end of the vessel is clamped between fingers. The portal vein is divided as close as possible to the clamp in the porta hepatis. To facilitate the cannulation of the portal vein, three tonsils are applied on the edge of the vessel to keep it open. The cannula is secured in place by two wet umbilical tapes. Both cannulas are tested and flushed with a heparinized saline solution. The portal and femoral vein cannulas are connected with a Y connector, and the bypass cannula is connected to the patient, as shown in Fig. 2. The bypass is started and the flow is maintained above 1 l per minute. Below this speed, the patient is subject to thrombosis (Shaw et al. 1984). If the volume flow rate slows to below 1 l/min, it may be a sign of hypovolemia or malpositioning of the portal vein cannula. In the first case, administration of fluid boluses can increase the bypass flow rate. At times, low flow results from a cannula facing the wall of one of the vessels, typically at the juncture of the splenic and superior mesenteric veins. To increase the flow in this case, the surgeon must maneuver the cannula away from the wall of the vessel. However, if the flow rate cannot be increased above 1 L/min, the patient is required to go off bypass.

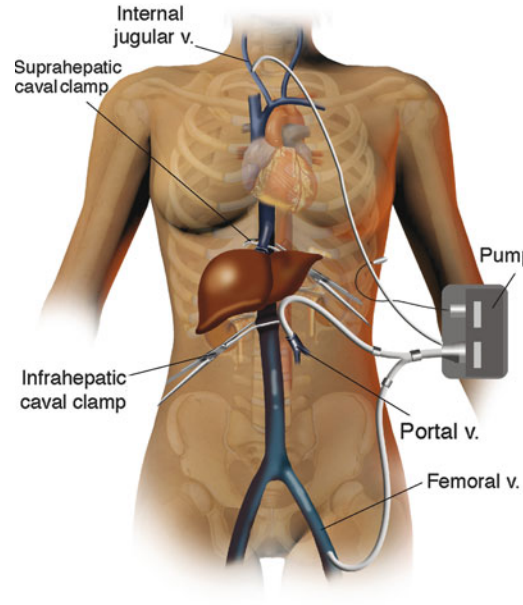


Fig. 2 Venous-venous bypass anatomy

The distal stump of the portal vein is oversewn with Prolene 3/0. The infra-hepatic IVC is skeletonized and cross-clamped with an adult angle

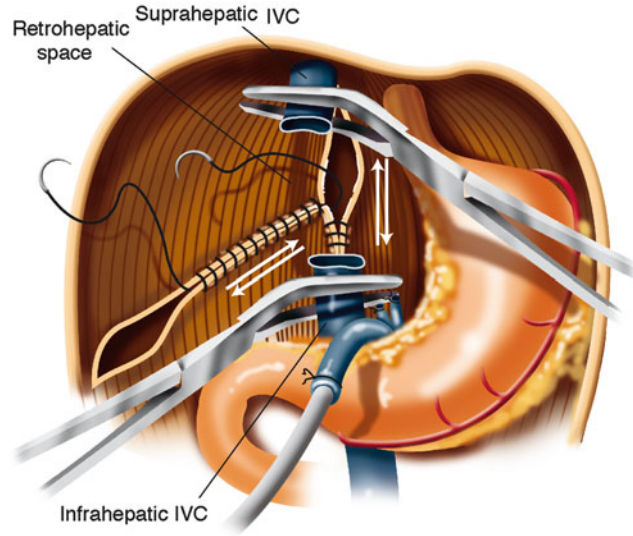


Fig. 3 Bare area hemostasis

Potts clamp. The left triangular ligament is divided with electrocautery, and the gastrohepatic ligament is divided between 2/0 silk ties. The right triangular ligament is divided with electrocautery. The suprahepatic IVC is encircled and clamped with a German clamp. The liver is removed from the field using blunt and sharp dissection. As soon as the native liver is removed from the surgical field, the right adrenal vein is tied off using a 0 silk tie, which is passed around the area where this vessel merges with the IVC. Further hemostasis is obtained in the bare area of the liver by two running 2/0 Prolene sutures: one vertically placed in the IVC area and one from the tip of the right triangular ligament forward as shown in Fig. 3. These two running sutures are not always necessary. At times, proper hemostasis of the bare area can be achieved with argon beam coagulation.

Achieving hemostasis by oversewing the bare area tends to decrease the size of the retro-hepatic area, allowing for transplantation of a smaller liver. This change in size of the right upper quadrant of the abdomen should be kept in mind when using large livers that might not fit the anatomical area. In that case, different hemostatic techniques should be considered.

The cuffs of the supra- and infra-hepatic IVC are prepared, and the new liver is brought into the operative field. It is helpful to position two 4/0 silk sutures on the upper left of the suprahepatic IVC cuff. By pulling these two sutures cranially, a better exposure of the posterior wall of the anastomosis is achieved. The suprahepatic IVC anastomosis is done in an end-to-end fashion using running 3/0 Prolene sutures. Subsequently, the infra-hepatic IVC anastomosis is completed in an end-to-end fashion using running 4/0 Prolene sutures. Once the posterior wall of the infrahepatic IVC anastomosis is completed, the liver is flushed with 1 l of chilled (4 °C) lactated Ringer's (LR) solution. The allograft is flushed through a cannula that was secured in the portal vein at the time of the back-table preparation. The practice of flushing the liver with chilled LR intends to remove as much University of Wisconsin® solution (UW) as possible from the allograft. UW is rich in potassium. If the UW is not removed from the allograft, a load of potassium would reach the right atrium at the time of reperfusion. This process may be responsible for deadly cardiac arrhythmias. At this stage, in preparation for the portal vein anastomosis, the portal cannula of the venous-venous bypass is clamped with a tubing clamp. The portal cannula is removed from the portal vein, and the portal vein is clamped with a pediatric angled Potts clamp. The surgeon should clamp the tip of the portal vein cannula with a large Kocher clamp to prevent air embolism in the case of failure of the tubing clamp. In preparation for the portal vein anastomosis, three wet lap

sponges are placed between the right hemidiaphragm and the dome of the liver. The right arm of the rib-grip retractor is lowered by three complete turns. The combination of these two maneuvers shortens the distance between the donor and recipient's portal vein stumps. This prevents the creation of a long portal vein that could kink and therefore cause vessel thrombosis in the postoperative time. The donor's portal vein is then shortened to a sufficient length to obtain a straight and nonredundant anastomosis. The portal vein anastomosis is completed end-to-end with running 6/0 Prolene sutures. When the running suture is tied, a generous growth factor is left behind so the anastomosis can expand at reperfusion and stenosis can be prevented. The laps are removed from the field and the rib-grip retractor is placed in its original position. There are two ways of proceeding at this time. One way is to perfuse the liver solely with portal blood and to reconstruct the hepatic artery once reasonable hemostasis is achieved. The second option consists of reconstructing all of the vessels before reperfusing the allograft. This second option is the one favored. However, in order to safely proceed with four-vessel reconstruction before reperfusion, the total implantation time cannot exceed 1 h. In addition, reperfusing allografts with portal as well as systemic blood can cause more hemodynamic instability that should be taken in account by the anesthesiology team. The four-vessel technique is completed as follows. The GDA is tied off with two 2/0 silk ties. The use of two separate sutures guarantees better control of this vessel. The common hepatic artery is clamped with a spoon clamp, and the recipient's hepatic artery is opened. A cuff of the recipient's hepatic artery is prepared at the level of the GDA patch. The donor's hepatic artery is shortened and beveled in the opposite direction, and a straight and nonredundant anastomosis is made end-to-end using running 7/0 Prolene sutures. Once the anterior wall of the hepatic artery anastomosis is completed, the anesthesia team is alerted that the allograft will be reperfused in approximately 3 min. This gives the anesthesiologist enough time to prepare the drugs needed to counteract possible hemodynamic instability after reperfusion and to record the last potassium level before reperfusion. At this stage the liver is reperfused. The hepatic artery, the portal vein, the infra-hepatic IVC, and the suprahepatic IVC clamps are removed in sequence. It is possible to keep the suprahepatic IVC clamp on until the liver is fully reperfused. In this case, the liver outflow runs into the bypass machine before reaching the heart rather than going directly into the right atrium. This maneuver prevents a potentially fatal, arrhythmogenic potassium load.

If the patient is stable after packing the operative field, it is suggested to go off bypass. After all cannulas are removed, the blood in the circuit can be recuperated in the cell saver. The next step of the operation is to achieve hemostasis. It is customary to proceed in a clockwise fashion starting from the anterior wall of the suprahepatic IVC, moving toward the medial side wall of the same vessel, to the infra-hepatic IVC on its medial aspect, to the hepatic hilum, and lastly to the lateral walls of the infra- and suprahepatic IVC. There are several areas not mentioned above that are addressed while moving in the clockwise direction, namely, the falciform ligament on both sides (donor and recipient), the left triangular ligament on both sides, the hepatogastric ligament on the recipient's side, and the right triangular ligament on the donor's side. Generally, these areas are addressed with argon beam coagulation. Packing during hemostasis is exceptionally important because pressure alone has been shown to be one of the most effective methods of achieving hemostasis, and because it maintains hemostasis while the anesthesiologist progressively corrects any coagulopathy based on the results of thromboelastography (Kang et al. 1985).

The last step of the operation is the bile duct reconstruction that will be discussed in a separate paragraph.

This same operation can be performed without venous-venous bypass when the degree of portal hypertension is such that cross-clamping the IVC would not cause a significant reduction in the blood flow return to the right heart. Hemodynamic stability in this case can be achieved by maintaining the patient's electrolyte and volume status (Starzl et al. 1968).

Bile Duct Reconstruction

The bile duct continuity can be achieved with several techniques. It is preferential to perform an end-to-end choledochocholedochostomy over a T tube. First, the donor's duct is explored. This is done with a bile duct probe. With this maneuver, the distance between the stump of the donor's duct and the bifurcation in the right and left duct is assessed. Next, cholecystectomy is carried out in an antegrade fashion using electrocautery. The cystic artery is transected to check for good blood flow from the hepatic artery. The cystic artery is then tied off with a 2/0 silk tie when satisfactory pulsating blood flow is identified. The gallbladder is removed from the surgical field. Hemostasis is achieved in the bed of the gallbladder with argon beam coagulation. The cystic duct is then opened flat with electrocautery to avoid possible mucocele formation in the post-operative time. The stump of the bile duct is trimmed by 1 or 2 mm until arterial bleeding is noted from the edge of the duct. The bleeding vessels are always located in the medial and lateral corner of the bile duct stump; hemostasis is achieved with one transfixed stitch per arterial vessel. Different types of stitches can be used, such as 4/0 silk or 6/0 PDS. At this stage, two 4/0 silk stitches are placed on the lateral and medial corner of the donor's bile duct stump. The recipient's duct is opened, explored, and trimmed. Although this anastomosis can be performed with or without a T tube, T tube use is preferred. The T tube gives easy access to the bile duct if a cholangiogram is needed in the postoperative time. Other uses of the T tube include: macroscopic evaluation of the bile characteristics and bile collection for culture in case of postoperative infections. Thick dark bile is considered to be normal. Bile that is light in color, and less dense than normal, is typical in primary non-function or acute cellular rejection. Nine 5/0 PDS sutures are used to complete the anastomosis. Two stitches are placed in the posterior wall, three on each side, and one on the anterior wall. A purse string is placed around the exit site of the T tube. Lastly, the anastomosis is checked for leakage by injecting heparinized saline solution through the T tube first, and air, while the anastomosis is submerged in water, second.

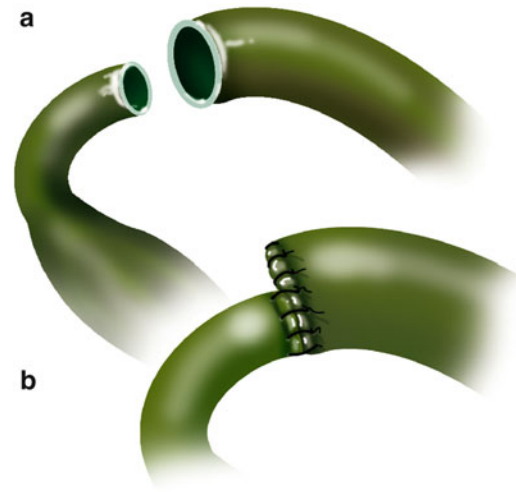


Fig. 4 End-to-end choledococholedochostomy without T tube

In cases of significant size discrepancy between the donor and recipient's ducts, the larger duct is partially sutured closed prior to performing the anastomosis, as displayed in Fig. 4 (Busuttil and Klintlalm 1996). Alternatively, a choledocho-jejunostomy over a Roux-en-Y can be used for the same purpose (Sarmiento 2000). The latter is also indicated for patients with primary sclerosing cholangitis (PSC), a disease that carries an increased risk of malignancies of the bile duct. From a technical standpoint, the Roux-en-Y loop is created in the usual fashion, using a hand-sewn technique in two layers, where the sero-serosa is completed with 4/0 silk interrupted sutures. The inner layer is anastomosed using the Gambee technique with 4/0 PDS. The tip of the afferent loop is oversewn with interrupted 4/0 silk stitches. The Roux loop is placed ante-colic; however, a retrocolic placement is an acceptable choice. The ante-colic option is safer, because although portal hypertension is resolved after reperfusion, enlarged varicosities are spread through the abdominal cavity, including the transverse mesocolon. These varices can be injured when the tunnel in the transverse mesocolon is created. Once the intestine is opened, in the antimesenteric border, the mucosa and the serosa are tucked

together in the four cardinal points using 6/0 PDS. A silastic tube, placed across the anastomosis, is anchored to the intestine with 5/0 chromic; the 9 stitches technique previously described is used to complete the choledochojejunostomy.

Piggy-Back Technique

There are different ways of performing a liver transplantation using the piggy-back technique. The common denominator of the different approaches is that the recipient's caval blood flow to the heart is never more than partially occluded at any time during the surgery. Uninterrupted flow through the IVC affords ample venous blood flow, proper cardiac filling, and hemodynamic stability throughout the procedure (Calne and Williams 1968).

Sir Roy Y. Calne first described the piggy-back technique, but Andreas Tzakis popularized it in 1989 (Tzakis et al. 1989). It is especially indicated in cases when the donor's liver is smaller than the diseased liver (Tzakis et al. 1989). The procedure is identical to the standard technique up until the skeletonization of the hepatic hilum is completed.

Subsequently, the liver is peeled off the IVC. The accessory hepatic veins are divided between 2/0 silk ties, and the accessory hepatic caval stumps are sutured with transfixed 4/0 silk stitches. This is done to prevent the ties from coming off in the postoperative time due to the swings in the central venous pressure (CVP), which are typical during recovery in the intensive care unit (ICU). The right hepatic vein is skeletonized free and clamped both proximally and distally. It is subsequently divided, and the two stumps are oversewn with running 4/0 Prolene sutures. The portal vein is divided between clamps. A German clamp is applied at the common trunk of the left and middle hepatic veins anterior to the vena cava, and the liver is removed from the surgical field using blunt and sharp dissection. Figure 5 demonstrates the left and middle hepatic veins being opened, and the septa separating both veins being cut, creating a common cuff.

The new liver is brought into the field. The anastomosis between the recipient's hepatic venous cuff and the donor's suprahepatic IVC is completed in an end-to-end fashion using 4/0 Prolene sutures. In this case, the upper left of the hepatic veins cuff is kept open by two 4/0 silk stitches while the posterior wall is sewn. Once the posterior wall of this anastomosis is completed, the liver is flushed with 1 l of chilled LR at 4 °C. Subsequently, the allograft's infrahepatic IVC is tied off. The portal vein and hepatic artery anastomoses are performed as in the standard technique. At this stage, the liver is reperfused. The hepatic artery, the portal vein, and the hepatic vein clamps are removed in sequence. In the piggy-back procedure as well, the liver reperfusion can be done with or without hepatic arterial flow. After a few complete rounds of hemostasis, the bile duct reconstruction is completed as previously described. More hemostasis is performed, and the field is washed with several liters of antibiotic solution. Three Jackson-Pratt drainages are place in the abdominal cavity.

Fig. 5 Left and middle hepatic vein division and cuff formation

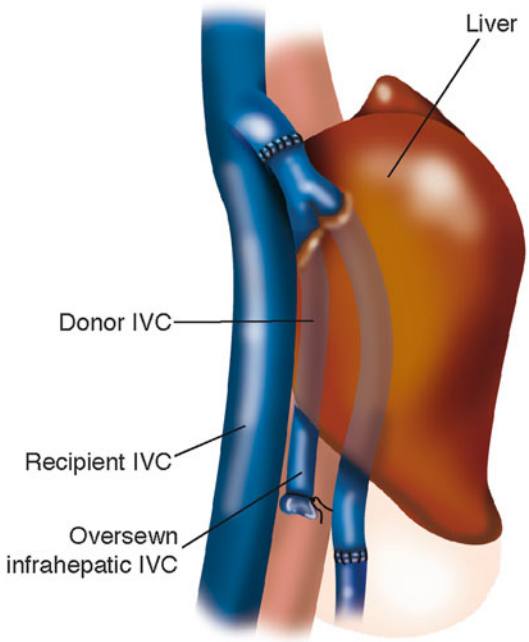


Fig. 6 Anatomy post piggy-back procedure

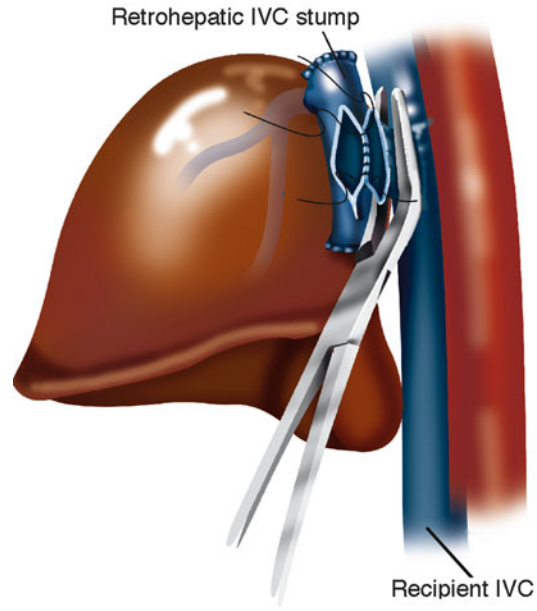


Fig. 7 Belghiti modification of the piggy-back procedure

Since there is no end-to-end infra-hepatic IVC anastomosis, the completed procedure leaves the recipient with a section of the donor's IVC lying anteriorly to the recipient's IVC, as diagrammed in Fig. 6. Within 1 week post-operation, a thrombus is often visible by ultrasound in the section of the donor's IVC sandwiched between the liver and the recipient's IVC. This is common and is not pathologic, as it does not often result in pulmonary embolus (Tzakis et al. 1989). There is no reason to administer anticoagulant medications in this case.

Piggy-Back with Side-to-Side Caval Anastomosis (Also Known as the Belghiti Technique)

Jacques Belghiti described the side-to-side piggy-back technique. Without removal of the retro-hepatic vena cava, and by requiring only one caval anastomosis, Belghiti claimed to reduce the duration of the anhepatic phase (Belghiti et al. 1992). It is the opinion of the authors that this is not the case. Belghiti describes that often, the piggy-back procedure necessitates temporary caval occlusion when creating the common cuff of the left and middle hepatic veins. This assumption is arguable, especially because in the classic piggy-back technique, the common trunk of the middle and left hepatic veins is clamped, a structure that is distant from the IVC. In the Belghiti technique, the IVC is always partially clamped.

In the following paragraph, discussion of the portions of the operation that are not different form the ones previously discussed is omitted.

The IVC is peeled off retro-hepatically by dividing the accessory hepatic veins between 2/0 silk ties. Following this, the left, middle, and right hepatic veins are clamped, divided, and oversewn. The vast majority of the surgeons embracing this technique perform this part of the operation with mechanical staplers, increasing the cost of the operation significantly. The liver is removed from the peritoneal cavity, leaving the full length of the IVC intact.

To perform the cavotomy on the recipient's IVC, a vascular clamp is placed on a section of the IVC "pinching" the vessel' side wall, as exhibited in Fig. 7. This incomplete vascular clamp ensures a constant caval flow throughout

the procedure. This clamp stays on the recipient vessel until the surgeon is prepared to allow portal blood to flow into the IVC. The donor's cavotomy is performed on the back table as well as oversewing of the donor's supra- and infra-hepatic cavas. This ensures that once the caval anastomosis is performed, blood flows from the donor's IVC stump into the recipient's IVC. The donor's liver is then brought into the peritoneal cavity, and a side-to-side caval anastomosis is created, connecting the donor and recipient's retro-hepatic vena cavas. The vessels of the porta hepatis are anastomosed. Once the portal vein anastomosis is complete, both portal and caval clamps are removed. This is, generally speaking, done in sequence while the running suture on the caval anastomosis is not tied off yet, so that the residual air in the anastomosed vessels can vent out of the blood stream. Supposedly, an advantage of this technique is that the anastomosis formed between the donor and recipient's vena cavas is large. This ensures that there will not be outflow obstruction.

Although this procedure technically is feasible, there are several drawbacks. Following this procedure, there tends to be a large amount of scar tissue formation postoperatively surrounding the side-to-side caval anastomosis. In the event that the patient needs a secondary liver transplant, it is difficult to access the suprahepatic IVC to remove the existing liver. Also, due to the nature of the neo-anatomy, if a TIPS procedure is needed, it is difficult to reach the right hepatic vein from the internal jugular vein, because with the new anatomy, a near right angle is formed at the IVC anastomosis.

Liver Transplantation in Situs Viscerus Inversus

Situs inversus (SI) is a rare congenital condition in which the abdominal viscera are located in mirror image positions across the midline compared to situs solitus. The inferior vena cava is located to the left of the abdominal aorta. During normal embryological development, the liver forms a larger right lobe compared to the left lobe due to asymmetric venous outflow (Farmer and Busuttil 1996). In SI, asymmetric hepatic venous outflow does not exist, leading to the formation of a symmetric liver. Other complications, presented in Fig. 8, often coexist with SI including polysplenia, aberrant left hepatic artery, aberrant

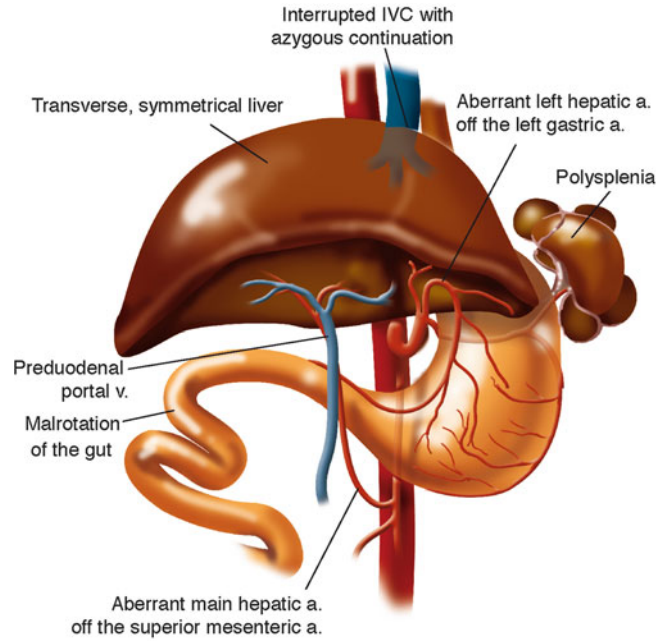


Fig. 8 Common complications with situs inversus

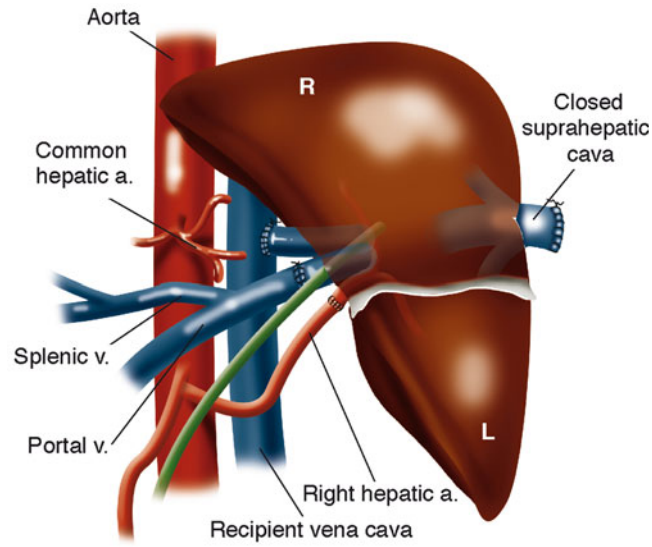


Fig. 9 Situs inversus anastomoses

main hepatic artery, preduodenal portal vein, malrotation of the gut, and interrupted IVC with azygous continuation (Farmer and Busuttil 1996).

Indications for transplant in SI patients are similar to those with SS anatomy. Often, the discovery of SI anatomy occurs during radio-imaging for nonrelevant procedures. There is much debate on how to position the allograft in a patient diagnosed with SI who needs transplantation. If a SS allograft is positioned without rotation in the recipient's upper left quadrant, the large right hepatic lobe lays across the stomach and vertebral column where space is restricted.

Dr. Klintmalm and associates described a case, in 1991, of a liver transplantation into an SI patient (Klintmalm et al. 1993). All vessels and ligaments to the recipient liver are divided, and the retro-hepatic IVC is left intact. The native liver is removed, and the allograft, in preparation for the implantation, is rotated clockwise 90°, as in Fig. 9, with the left lobe pointing into the left iliac fossa and the right lobe sitting in the recipient's hepatic fossa. The donor's suprahepatic vena cava is oversewn. The donor's infra-hepatic vena cava is anastomosed end-to-side to the recipient's left-sided inferior vena cava. The other major vessels are anastomosed end-to-end and blood flow to the allograft is restored. Benefits of this technique are the recipient's stomach is not obstructed by the donor's right lobe, there is no risk of venous outflow obstruction, and the size of the allograft is not an exceedingly important factor (Klintmalm et al. 1993).

Auxiliary Liver Transplantation

Orthotopic liver transplant (OLT) is the treatment of choice for fulminant hepatic failure (FHF) (Bismuth et al. 1995). A suitable alternative is auxiliary liver transplantation, a procedure where the allograft is transplanted either heterotopically or orthotopically in place of a section of the native liver. The allograft is removed after the native liver recovers from the original insult. The main advantage of this procedure is that the patient avoids life-long immunosuppressive treatment once the allograft is removed (Jaeck et al. 2002). The theory behind auxiliary liver transplant is that the implanted allograft will lend the patient hepatic support while the failing liver regenerates. Orthotopic versus heterotopic auxiliary partial liver transplant is debated.

Auxiliary partial orthotopic liver transplantation (APOLT) is completed by removing a section of the failing liver and replacing it with an equal lobe or part of a lobe from a donor. This operation is more commonly done in children using a live donor. Depending on the recipient's size, the left lobe or the left lateral segment is used (Jaeck

et al. 2002). When the left lateral segment is chosen, the donor's operation requires the resection of the left lateral segment with accompanying vessels. The donor's vessels procured with the partial allograft consist of the stumps of the left portal vein, hepatic artery, and hepatic vein. The left bile duct is taken with the allograft.

The allograft's left hepatic vein is anastomosed end-to-end with the recipient's vessel. The donor's hepatic artery is anastomosed, preferably, with the recipient's left hepatic artery. The portal vein and the bile ducts are anastomosed to their corresponding recipient vessels. The anatomy of the recipient right liver is left untouched. The hepatic function offered by the partial allograft provides the failing liver time to heal. Primary non-function of the graft is not statistically different between OLT and APOLT (van Hoek et al. 1999).

Gubernatis et al. explain that hypothetically, portal blood flow should be distributed between the two livers by resistance to flow. Early after transplantation, blood should preferentially flow through the allograft due the high resistance in the diseased liver. Once the diseased liver begins to heal, blood flow shifts back to the healing liver due to resistance in the donor allograft. This increased resistance is the result of rejection, once the immunosuppressive medication is discontinued. Conveniently, the blood flow is preferentially distributed to the healthy liver section (Gubernatis et al. 1991).

Heterotopic auxiliary partial liver transplant is a procedure where the recipient's liver is left intact while a partial donor allograft is implanted into the recipient's subhepatic space as illustrated in Fig. 10. The goal of this procedure is the same as APOLT, but the efficacy is diminished (van Hoek et al. 1999). This operation can be accomplished using a cadaver or a live donor. In preparation for the allograft's implantation when a cadaver donor is used, a section of the allograft is resected so it can be accommodated in a small space. On the back table, the suprahepatic IVC is oversewn. Upon implantation, an end-to-side anastomosis of the donor's infra-hepatic IVC and the recipient's suprarenal IVC is performed. Anastomoses are created between the recipient's celiac axis and the donor's hepatic artery as well as the donor and recipient's portal veins. An end-to-side choledochojejunostomy is performed between the donor's bile duct and the recipient's jejunum. Although the heterotopic implantation of a partial liver should be technically performed as well as APOLT, it does not due to issues such as elevated venous backpressure and inadequate portal perfusion of the donor and recipient's partial livers (Gubernatis et al. 1991).

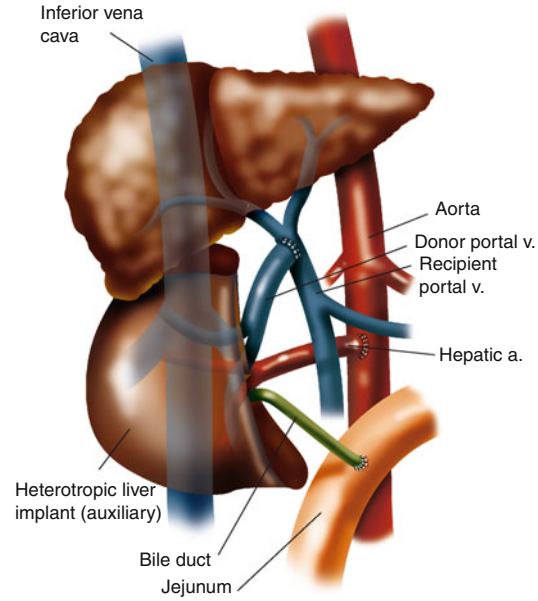


Fig. 10 Heterotopic auxiliary partial liver transplant anastomoses

Conclusion

In a span of 50 years, liver transplantation has evolved dramatically and faster than any other known field in medicine. This is partially due to a better understanding of the physiology of patients with end-stage liver disease and the intraoperative management of these patients. Furthermore, the introduction of the venous-venous bypass and the development of structured training programs have made this procedure a routine. It is unfortunate that we have not observed any growth in transplantation in the past several years despite a continuous increase in the number of patients waiting for a liver transplant. As a consequence of

that, access to liver transplantation is still restricted to less than 150 centers in the entire United States. It should not be forgotten that although routine, when compared with any other field in surgery, liver transplantation is still a procedure left in the hands of a very limited number of extraordinarily talented surgeons committed to serving a group of patients that for the most part fall into the category of the "underprivileged."

All images are courtesy of Paul Schiffmacher, Medical Illustrator for Medical Media Services at Thomas Jefferson University.

Cross-References

- Donor Operation
- History of Liver and Other Splanchnic Organ Transplantation
- Orthotopic Liver Transplantation: Complications
- Orthotopic Liver Transplantation: Indications and Contraindications

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Split Liver Transplantation

5

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Contents

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Abstract

Split liver transplantation (SLT) creates two marginal grafts from one perfect deceased donor liver to save two recipients simultaneously. Since its inception in 1988, SLT has contributed tremendously to decreased mortality on the pediatric liver transplant waiting list. Despite unfavorable survival rates in the early experience of SLT for adults, successful outcomes have been reported by experienced centers, further substantiating the feasibility of this technique. Indeed, various advancements have encouraged more frequent use of this technique to overcome the shortage of donor livers. More than two decades of experience have documented the criteria necessary for SLT to achieve equivalent or superior outcomes to whole liver transplantation. Still, substantial challenges in surgical techniques, allocation, logistics, and ethics persist, and SLT remains underutilized worldwide. This chapter outlines the current state of SLT, focusing on donor and recipient selection, surgical techniques, outcomes, and current and future challenges such as allocation and associated ethical issues.

Keywords

Split liver transplantation • Left lateral segment • Right trisegment • Hemiliver • In situ split • Ex vivo split • Donor selection • Recipient selection • Surgical technique • Graft size • Survival • Ethical issue

Introduction

The shortage of donor livers has led transplant programs to seek innovative ways to increase the number of available organs for liver transplantation. In 1984, Bismuth first reported the use of a reduced-size liver graft in pediatric liver transplantation, using a whole liver graft from a deceased donor to create a small functional graft to fit a pediatric recipient (Bismuth and Houssin 1984). This technique became popular in pediatric liver transplantation with excellent survival rates and significantly decreased pediatric waiting list mortality. When this technique is used, however, the remaining part of the liver mass is discarded. For this reason, the concept of "splitting" a whole liver graft to simultaneously transplant two recipients emerged and subsequently was performed successfully (Pichlmayr et al. 1988; Bismuth et al. 1989; Emond et al. 1990). Unlike reduced-size grafts, split liver transplantation (SLT) was initially characterized by higher mortality and complication rates (Broelsch et al. 1990). However, with the accumulation of experience, improved surgical techniques, and better donor and recipient selection, split grafts have been used more frequently worldwide.

For successful SLT, two functional grafts have to be created from a whole deceased donor liver. Since the first report of SLT in 1988 (Pichlmayr et al. 1988), deceased donor livers have been most commonly split into a smaller left lateral segment (LLS, segments II and III; 15–25 % of the liver) for a child and a larger right trisegment (RTS, segments I, IV, and V–VIII; 75–85 % of the liver) for an adult. The potential for SLT was further expanded to use two hemiliver grafts to transplant two adult recipients: a left lobe (segments I–IV; 30–40 % of the liver) and a right lobe (segments V–VIII; 60–70 % of the liver). While the procedure has shown a great success worldwide and could theoretically double the number of available organs, many challenges have precluded its more widespread use.

Donor Evaluation

Careful donor selection is essential to the success of SLT (Table 1). The upper donor age limit of the bipartition of a liver graft is between 40 and 50 years (Emre and Umman 2011). The donor liver function test ideally should be normal, but can be mildly elevated. When liver enzymes are elevated, as long as they show improvement before organ recovery, the liver can be used for SLT. However, since liver splitting can compromise donor quality, any additional negative factors are discouraged (Feng et al. 2006). High BMI, history of heavy alcohol use, and low platelet counts on donor admission could signal the presence of graft steatosis and fibrosis. Hypernatremia

Table 1 Donor selection criteria in split liver transplantation

Ideal split donor	Donor age < 40–50 years
	Liver function test (normal or mildly elevated)
	Serum sodium level < 160 mEq/L
	No or minimal inotropic support (hemodynamic stability)
	Normal macroscopic and microscopic appearance of the liver
Acceptable split donor	Mild macrosteatosis < 10–20 % in biopsy
	Mild inflammation in biopsy
	Elevated liver enzymes, but improving
	ICU stay before organ recovery > 5 days
	Serum sodium level > 160 mEq/L
	Obese donor (BMI > 30 m^2/kg)

(>160 mEq/L) and the use of inotropic support can be risk factors for a nonfunctioning split graft. Other compounding risk factors should be taken into consideration to determine whether the liver is splittable or not. These include estimated cold ischemia time, length of ICU stay of the donor, recipient MELD score, the degree of portal hypertension, and recipient functional status.

Direct evaluation by the donor team at the time of organ recovery is of utmost importance. If the donor liver does not look normal on visualization, a frozen section biopsy of liver is indicated. Pathological changes such as macrosteatosis, inflammation, fibrosis, and cholestasis are generally considered to be contraindications for splitting. However, if other donor and recipient factors are ideal, mild steatosis (<10–20 % macrosteatosis) or the presence of mild inflammation can be acceptable. Once the decision is made to proceed, the donor team must coordinate the recovery process with the recipient team to minimize cold ischemia time.

Estimation of Graft Size

Split graft size is an important factor in SLT. Splitting at the falciform ligament yields LLS and RTS grafts (Fig. 1, **line A**). The LLS is generally suitable for pediatric recipients. When a small infant is the recipient, graft-to-recipient weight ratio (GRWR: [liver graft weight ÷ recipient body weight] × 100) should not exceed 4–5 % to avoid large-for-size-related complications, such as open abdomen and vascular thrombosis. If this is the case, the LLS split graft has to be further reduced to avoid such problems (Kasahara et al. 2003). The RTS graft size, on the other hand, is in most instances large enough to avoid small-for-size-related graft dysfunction in adult recipients.

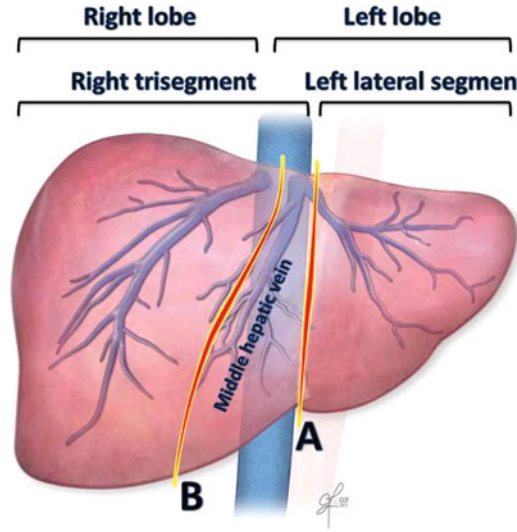

Fig. 1 Graft types used in split liver transplantation. Splitting at the falciform ligament yields left lateral segment and right trisegment grafts (**line A**). In hemiliver splitting for left lobe and right lobe grafts, the liver is split on the right side of the middle hepatic vein (**line B**)

In hemiliver splitting for two adult-sized recipients, the liver is split on the right side of the middle hepatic vein (Fig. 1, **line B**). Determination of graft size is crucial to decide whether splitting is feasible and to minimize the possibility of small-for-size-related graft failure. Although the minimal graft size to meet recipient's metabolic demand in living donor liver transplantation is considered to be as small as a GRWR of 0.6–0.8 %, the minimal ratio remains unknown. SLT appears to require a higher GRWR to compensate for suboptimal graft quality related to longer cold ischemia time and donor hemodynamic instability associated with brain death. Accordingly, a GRWR of 1.0 % seems to be the minimal

requirement in SLT to avoid early graft dysfunction (Lee et al. 2013).

Imaging studies are rarely available in SLT to estimate graft weight and evaluate donor liver anatomy. Therefore, this important surgical information is most often unknown until the time of organ recovery or after a liver is taken out of a deceased donor. Using the donor body surface area, whole liver volume (mL) can be estimated using equations 1072.8 × body surface area (m^2) − 345.7 for Caucasians (Heinemann et al. 1999) and 706.2 × body surface area (m^2) + 2.4 for Asians (Urata et al. 1995). More simply, whole liver weight can be estimated as 2 % of donor body weight (Lee 2010). These estimated values can be divided into standard estimates for lobar distribution (35 % for the left lobe and 65 % for the right lobe) to estimate hemiliver graft size.

Recipient Evaluation

For successful SLT, recipient selection is as important as donor selection. In SLT using the LLS graft for pediatric recipients, graft-recipient size mismatch resulting in large-for-size complications should be avoided. When the recipient is an older child, the LLS graft might not be enough to provide adequate liver mass. In such an instance, the left lobe graft is necessary to achieve a GRWR > 1.0 %. For the RTS graft, recipients can be chosen more liberally, similar to when a whole liver graft is used.

SLT for adults has the potential risk of small-for-size syndrome, particularly with hemiliver grafts. Generally, the best SLT recipients for a hemiliver graft are an adolescent or a small adult with minimal portal hypertension and/or a relatively low MELD score, particularly for the left lobe graft. Although a recipient with a high MELD score can be transplanted with a hemiliver split graft, the data are not available to support the routine use of hemiliver grafts for high-risk recipients (Nadalin et al. 2009; Hashimoto et al. 2014). When a recipient has significant portal hypertension, a larger right lobe graft is preferred in order to lower the risk of small-for-size syndrome. In addition to examining medical history, the severity of portal hypertension can be assessed using a triphasic CT scan or MRI (Aucejo et al. 2008). These imaging studies show the recipient's surgical anatomy and also can show portosystemic shunt, portal vein thrombosis, and stenosis of the celiac trunk, which are important pieces of surgical information. The management of portosystemic shunt is controversial (Ikegami et al. 2013). When recipients have a large spontaneous or surgical portosystemic shunt, the shunt can cause hypoperfusion of a transplanted split graft due to a steal phenomenon. In contrast, it also helps lower portal vein pressure to favorably accept a small partial graft that is damaged by portal hyperperfusion. Accordingly, a case-by-case assessment is important to determine whether to close shunts in recipients.

In addition to thorough donor and recipient selection, appropriate donor-recipient paring is crucial to achieve good outcomes in SLT. In adult SLT, split grafts are generally taken from larger donors and transplanted into smaller recipients. This graft-recipient paring enables the majority of recipients to achieve a GRWR > 1.0 % (Hashimoto et al. 2014), representing a size advantage that helps avoid small-for-size syndrome.

Split Liver Transplantation Under MELD Allocation

The use of split grafts for high-risk recipients is controversial (Nadalin et al. 2009; Hashimoto et al. 2014). Under the philosophy of the "sickest first" MELD allocation, standard criteria donors who are suitable for bipartition are allocated to those recipients with a high MELD score who are generally unsuitable for SLT.

When a splittable donor becomes available, the most important factors determining whether to proceed with SLT are when a whole donor liver is deemed to be too large to fit a primary adult candidate or a small pediatric recipient is on the waiting list. SLT has proven to be a great benefit for pediatric candidates who usually need an LLS graft without compromising survival in adult recipients receiving the RTS graft (Maggi et al. 2015). It is equally important,

however, that small adults who are often bypassed on the waiting list due to size mismatch can have more opportunities by SLT. For these recipients, split grafts can provide enough liver volume to tolerate portal hyperperfusion. The remaining split graft can be used for a candidate with minimal portal hypertension and a lower MELD score. This graft-recipient matching helps achieve excellent survival after SLT under the allocation system where the MELD score regulates transplant priority. However, such ideal matching is difficult to achieve on a routine basis, and this is why many centers underutilize or do not use split grafts, particularly when hemiliver splitting is indicated. According to the Cleveland Clinic experience from April 2004 to June 2012, 137 out of 1089 deceased donors (12.6 %) met the SLT criteria and were identified as suitable for splitting. However, among these splittable donors, only 38 (3.5 %) were used for SLT because suitable recipients were not available.

Sharing Patterns of Major Vessels and Bile Duct in Split Donors

An important technical challenge in SLT is a lack of consensus between transplant centers regarding surgical techniques, particularly sharing patterns of major vessels and bile ducts between two split grafts. The ideal sharing pattern was originally described by Bismuth in 1989 (Bismuth et al. 1989). The principle concept of this technique is to avoid multiple branches to be reconstructed in the recipient operation. Impeccable knowledge of surgical liver anatomy is essential to understand this sharing pattern. The left lobe frequently has a single branch of the portal vein, hepatic duct, and venous outflow that is a common channel of the left and middle hepatic veins, but multiple branches of the hepatic arteries often exist. The right lobe, on the other hand, often has a single right hepatic artery and multiple branches commonly seen in the venous drainage, hepatic duct, and portal vein. According to the sharing pattern by Bismuth, the left lobe retains the celiac trunk, and the right lobe retains the remaining major structures, including the common hepatic duct, main portal vein, and vena cava. Although typically the priority is for the primary recipient to keep necessary structures in the graft allocation, sharing should depend on actual donor anatomy and recipient needs. The final decision should be made with flexibility and agreement by both teams who each take one of the split grafts.

Donor Anatomical Variation

As long as both sides of the split grafts have a complete set of inflow and outflow vessels and biliary drainage, anatomical variations are not considered to be a contraindication to splitting. Recipient surgeons must decide on the division of these vital structures to make the liver graft safely usable in the recipients. The following are relatively common anatomical variants seen in organ recovery:

Hepatic Artery

Arterial variants are commonly seen in split organ recovery. Identification of the origin of the middle hepatic artery (A4: segment IV artery) is crucial. In LLS/RTS splitting, A4 can be the only blood supply to the medial segment of the RTS graft. If A4 arises from the left hepatic artery, it may need to be sacrificed. In the presence of the left accessory hepatic artery arising from the left gastric artery, retaining the celiac trunk with the left-sided graft helps keep the blood supply to all small branches from a single anastomosis. A right replaced hepatic artery from the superior mesenteric artery is the most commonly seen variant in the hepatic artery. In this instance, the artery can be taken with the superior mesenteric artery to be used as a patch for a wider anastomosis.

Portal Vein

Anatomical variants of the portal vein leading to multiple anastomoses or as a contraindication for

splitting are uncommon. Trifurcation of portal branches is most commonly seen in about 20 % of the general population. The right anterior branch can arise from the left portal vein, but it is usually identified in the extrahepatic portion. As long as the left branch of the portal vein is transected distally to the origin of the right branch, this variant is not a contraindication to splitting. When the left-sided graft retains the main portal vein, the right-sided graft can be left with two separate portal vein branches. While not ideal, this situation is not a contraindication to splitting because conducting two portal vein anastomoses with or without a vein graft is feasible. When one of the right portal vein branches arises from the left intrahepatic portal branch, splitting may not be feasible. Such a portal variant is usually accompanied with a biliary anomaly that can be seen with an intraoperative cholangiogram.

Hepatic Vein

Since venous outflow is critical in determining functional graft size, ensuring perfect flow in the hepatic veins is essential in SLT. Most of the time, hepatic venous anatomy is unknown before split organ recovery. Since the left hepatic vein is almost always (92 %) dominant for the left lobe, the left lobe graft retaining both the left and middle hepatic veins usually promises optimal outflow. On the other hand, various anatomical variants are seen in the right and middle hepatic veins. In general, the right anterior segment (segments V and VIII) predominantly drains into the middle hepatic vein that is retained in the left lobe graft in a hemiliver split. Therefore, a significant (>5 mm) venous branches of segments V (V5) and VIII (V8) should be reconstructed with a vein graft to prevent severe graft congestion (refer to section "In Situ Hemiliver Split Technique"). When congestion occurs, the congested area does not fully function, and the amount of functional graft volume can be reduced, which may cause small-for-size syndrome. A significant branch of the inferior right hepatic vein (>5 mm) directly draining into the vena cava exists in 20–40 % of donors. When the vena cava is retained in the left lobe graft, this vein should be preserved and reconstructed in the recipient.

Bile Duct

Intraoperative cholangiogram should be routinely performed in split organ recovery to rule out any anatomical variant that renders the donor unsuitable for splitting, particularly in hemiliver split. For instance, an aberrant right hepatic duct arising from the cystic duct (2–3 %) increases the complexity of recipient surgery. If surgeons are not aware of such variant, it can cause serious complications in the recipient.

Ex Vivo vs. In Situ

Originally the development of SLT started with the ex vivo technique that splits the liver on the back table after conventional whole organ retrieval. The early experiences in the 1990s demonstrated the feasibility of this technique, which was followed by the first report of the in situ technique by Rogiers in 1995, who split the liver in a heart-beating deceased donor (Rogiers et al. 1995). Since then, two decades of experiences have proved that both techniques are equally effective and have been used with continual refinements. Although pros and cons of both techniques have been recognized, the decision whether to use the in situ or ex vivo technique is often made based on logistical issues, hemodynamic stability of the donor, and the surgeon's preference (Table 2).

Since the ex vivo technique does not require extra time before organ retrieval, it offers easier and better coordination with other organ teams. However, this technique potentially causes prolonged cold ischemia to perform the complex back table preparation. During ex vivo splitting, the liver is hardly immersed in cold preservation solution, so that the liver may not be preserved cold enough to prevent graft rewarming injury. Equally important is the risk of substantial bleeding and bile leakages from the cut surface of liver parenchyma. On the other hand, the in situ

Table 2 Comparisons of ex vivo vs. in situ splitting

	Ex vivo	In situ
Organ recovery time	Shorter	Longer
Donor hemodynamics in organ recovery	Same as regular organ recovery	Potentially unstable due to bleeding during splitting
Coordination with other organ teams	Easier	Harder
Cold ischemia	Longer	Shorter
Risk of rewarming injury on back table	Higher	Lower
Post-reperfusion bleeding	Potentially profuse	Minimal

technique requires prolonged time in organ recovery, which is not always possible due to donor hemodynamic instability and logistical challenges with other organ recovery teams. However, the in situ technique promises shorter cold ischemic time and better hemostasis after graft reperfusion.

In Situ Hemiliver Split Technique

Laparotomy and Hilar Dissection

After opening the abdominal cavity, the liver is visually and manually assessed to ensure that it is suitable for splitting. If the liver looks marginal, the liver should be biopsied, or the split procedure can be aborted at this point. Estimated weight of the liver should be notified to recipient teams. The left lobe is mobilized by dividing the left triangular, coronary, and gastrohepatic ligaments. When a left accessory hepatic artery is seen, it must be preserved. The right triangular and coronary ligaments are taken down to mobilize the right lobe. The hepatorenal ligament and bare area of the liver are dissected until the retrohepatic vena cava appears. The hepatocaval ligament does not need to be divided, unless the vena cava is kept with the left lobe graft. Although short hepatic veins of the left lobe are divided to detach the left caudate lobe from the vena cava, this step can be easily and safely done on the back table. Before hilar dissection and parenchymal transection, the supraceliac and infrarenal aortas should be isolated according to standard deceased donor techniques in case the donor becomes unstable.

What need to be done at the hepatic hilum are cholecystectomy, cholangiogram, and anatomical evaluation. After a standard cholecystectomy, the cystic duct is cannulated to perform cholangiogram to rule out anatomical variants that would make it not feasible to perform the split procedure. If cholangiogram is not available in the donor hospital, the common bile duct can be transected to probe the bile duct. The hepatic hilum is examined manually to delineate the arterial anatomy, particularly the location of arterial bifurcation and the presence of the right replaced hepatic artery. The bifurcation of the hepatic artery can be dissected free, but this step also can be safely done on the back table.

Preparation for Liver Hanging Maneuver

The hanging maneuver is used to isolate liver parenchyma from the vena cava and the hepatic hilum on the transection line. This technique facilitates hemostasis by elevating the liver, and more importantly, it guides donor surgeons to divide liver parenchyma straight down to the vena cava. The groove between the right and middle hepatic veins is dissected free to tunnel the tissue between the liver and retrohepatic vena cava. A Kelly clamp is vertically introduced along the anterior surface of the infrahepatic vena cava toward the groove to complete tunneling. After 4–5 cm of gentle blind dissection, the clamp appears at the groove, and an umbilical tape is pulled through this tunnel. An angled clamp is directly introduced into liver parenchyma at 0.5 cm above the bifurcation of the hepatic hilum and passed behind the hepatic hilum through liver parenchyma. The tip of the clamp appears at 0.5 cm below the bifurcation, and the umbilical tape is pulled back through liver parenchyma (Fig. 2). This technique has a minimal risk of major bleeding or bile

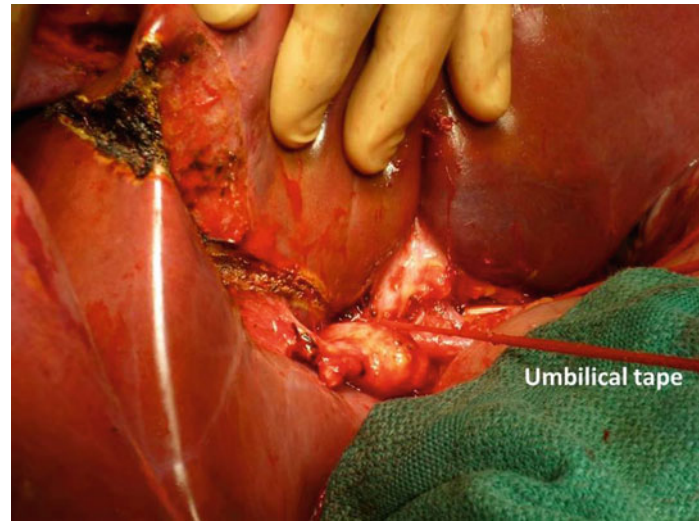

Fig. 2 Hanging maneuver in the in situ split technique. An umbilical tape is seen to isolate liver parenchyma from the vena cava and the hepatic hilum on the transection line

leakage because there are no major vessels or bile ducts in the area of liver parenchyma where the clamp passes through. Introducing a clamp along the cephalad margin of the hepatic hilum may cause serious bleeding or bile leakage if a tip of the clamp migrates into the hilar structures (Hashimoto and Fung 2013).

Parenchymal Transection

A transection line is marked by electrocautery along the Cantlie line. This line can be deepened from 0.5 to 1 cm since there is no important vascular structure or bile duct present. Because the transection line in hemiliver splitting is determined based on the anatomy of the middle hepatic vein, it is not necessary to confirm the demarcation line by a temporary hemihepatic inflow occlusion. Parenchymal transection can be done with any available methods at the donor hospital (clamp-crushing technique, CUSA, etc.). The Pringle maneuver is usually unnecessary. If major bleeding occurs and the donor becomes unstable, the liver surgeon should not hesitate to abort in situ splitting and proceed with cross clamping in coordination with the thoracic team. Then the liver can be split ex vivo after the liver is taken out. During parenchymal transection, small vessels can be cauterized, but larger vessels should be tied or clipped. Once the middle hepatic vein is identified, transection should be continued to stay on the right side of the middle hepatic vein until the V5 is identified. The V5 is tied proximally (on the middle hepatic vein) and clipped distally (on the right lobe side). Parenchymal transection is continued until the V8 is isolated and divided in the same manner. When the liver is split in situ, the degree of graft congestion in the anterior segment can be assessed during parenchymal transection. To prevent bleeding from small branches of the middle hepatic vein, a thin layer of parenchymal tissue should be left over the middle hepatic vein. To complete parenchymal transection, the both ends of the umbilical tape are pulled to give upward traction to facilitate the exposure and hemostasis. The liver is completely separated into the right and left lobes, and the anterior aspect of the retrohepatic vena cava is exposed.

Cross Clamp and Organ Retrieval

After coordinating with the thoracic team, the donor is systemically heparinized, and an infusion cannula is placed into the distal aorta. The supraceliac aorta is cross-clamped, and cold perfusion is initiated. The clips on the V5 and V8 are removed to better flush the anterior segment. The liver is subsequently taken out using the standard technique (Fig. 3). The donor surgeon must

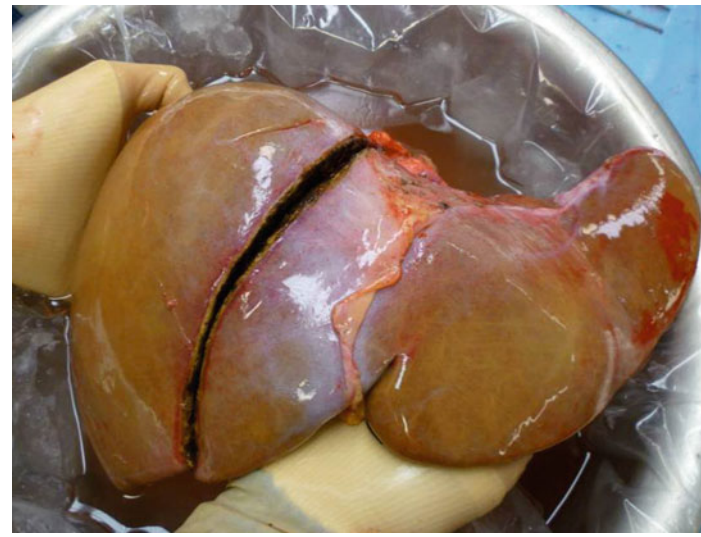

Fig. 3 A liver graft after cold perfusion on the back table. The liver is already split in situ to yield left lobe and right lobe grafts

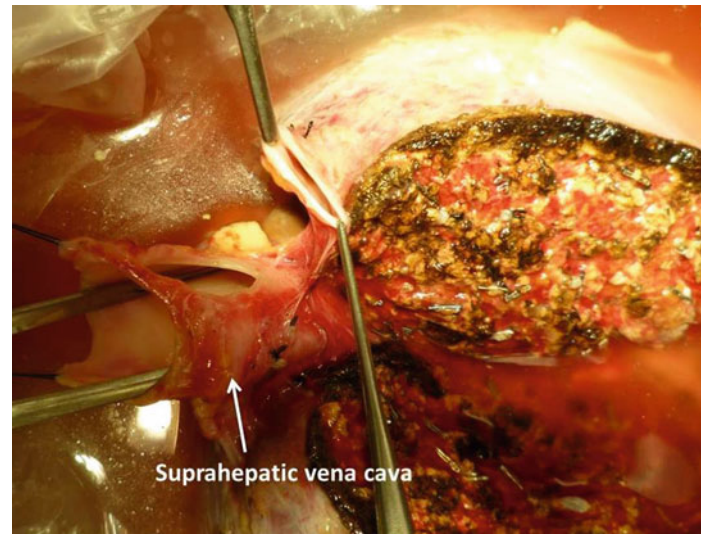

Fig. 4 Preparation of the venous outflow of the left lobe graft. The common channel of the left and middle hepatic veins is transected with a small vena cava patch

retrieve the iliac arteries and veins of good length and quality. When iliac grafts need to be shared with other organ teams, extra vessels must be taken from the carotid artery, subclavian artery/vein, internal jugular vein, and innominate vein.

Back Table Preparation to Separate Vessels and Bile Duct

The liver is placed in a basin and perfused through the main portal vein with cold preservation solution. After the standard preparation of the vena cava, the common channel of the left and middle hepatic veins is transected with a small vena cava patch (Fig. 4). This technique ensures a good outflow of the left lobe without the need for a venoplasty, which is commonly needed in living donor liver transplantation. Short hepatic veins left undivided in situ are divided to detach the left caudate lobe from the vena cava. The main portal vein is dissected free all the way to its bifurcation. The left branch of the portal vein is dissected and transected 2–3 mm from the

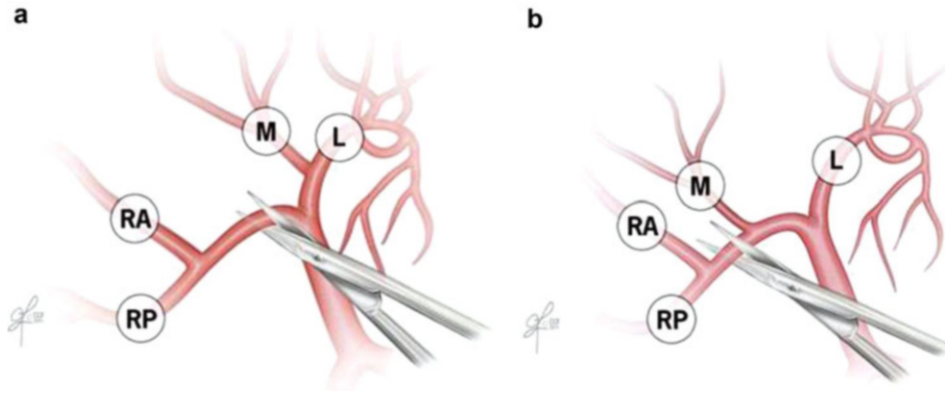

Fig. 5 Back table preparation for hepatic artery in hemiliver grafts. (**a**) When the middle hepatic artery arises from the left hepatic artery, the right hepatic artery is transected distally to the bifurcation. (**b**) When the middle hepatic artery arises from the right hepatic artery, the right hepatic artery is transected distally to the middle hepatic artery. *L* left hepatic artery, *M* middle hepatic artery, *RA* right anterior branch, *RP* right posterior branch

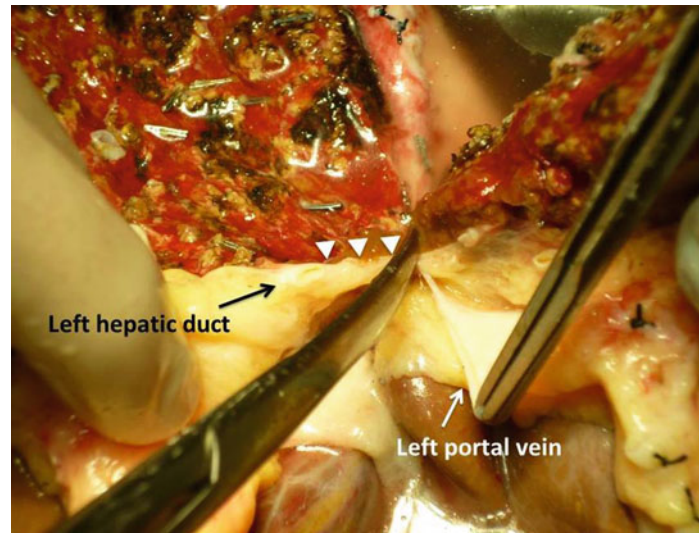

Fig. 6 Transection of the left hepatic duct and the hilar plate in hemiliver splitting. *White arrowheads* indicate the hilar plate

bifurcation. The caudate branch of the left portal vein usually needs to be divided. The defect on the main portal vein is sutured to close transversely. The defect should not be closed longitudinally because the risk of stenosis is high. The arterial component is dissected up to the bifurcation. However, the proper hepatic artery and the right and left hepatic arteries should not be skeletonized unnecessarily. The right hepatic artery is transected distal to the bifurcation (Fig. 5a). When the middle hepatic artery is arising from the right hepatic artery, the right hepatic artery is transected distal to the middle hepatic artery (Fig. 5b).

Finally, the hepatic duct and hilar plate are left at the hilum. Before bile duct division, both hepatic artery and portal vein branches have to be completely divided. The biliary system is probed through the common hepatic duct to confirm the location of the biliary bifurcation. The left hepatic duct with the hilar plate is sharply transected at 0.5 cm from the bifurcation (Fig. 6). The entire stump of the hilar plate should be oversewn because usually there are small caudate ducts. Preservation solution is injected into the left hepatic duct to check for leakage. At this point, the left lobe is ready for implantation.

Reconstruction of Tributaries of the Middle Hepatic Vein

To prevent venous congestion in the anterior segment, a new middle hepatic vein is created on the cut surface of the right lobe graft. A donor iliac vein graft is prepared, and its distal side is anastomosed in an end-to-end or end-to-side fashion to the V5 and V8 of significant size. The proximal end of the vein graft is directly anastomosed to the defect on the vena cava where the common channel of the left and middle hepatic veins was located (Fig. 7). When there are no V5 and V8 of significant size, the defect on the vena cava is closed with a vein graft patch. The defect of the left hepatic duct on the main hepatic duct is sutured to close transversely. The entire stump of the right hilar plate should be oversewn. Preservation solution is injected into the common hepatic duct to check for leakage. Finally, the right lobe graft is ready for implantation.

In Situ Split Technique for Left Lateral Segment and Right Trisegment Grafts

Hilar Dissection and In Situ Splitting

After visual and manual assessment of visceral organs, the left lobe is mobilized in the same manner as hemiliver splitting. If there is a left accessory hepatic artery, it must be preserved. The division of the Arantius ligament allows the surgeon to have better approach to the left hepatic vein. At this stage, the left hepatic vein does not need to be encircled.

The hepatic hilum is examined manually to delineate the arterial anatomy. Intraoperative cholangiogram is not mandatory, but can be done after cholecystectomy. Because hilar dissection can be safely done on the back table, extensive dissection of the hilum can be omitted at this point.

On the surface of the liver, a transection line is marked by electrocautery on the right side of the falciform ligament. The Glissonian triads to the medial segment are tied and divided. Although the medial segment often becomes ischemic after dividing its inflows, the ischemic area does not need to be resected. For parenchymal transection, inflow occlusion (the Pringle maneuver) is not necessary. Vessels are cauterized, tied, or clipped in the same fashion as described in the hemiliver split technique. After liver parenchyma is completely separated into the left lateral segment and right trisegment grafts, the liver is taken out of the donor using a standard cold dissection technique (Fig. 8).

Back Table Preparation

After the standard preparation of the vena cava, the left hepatic vein is transected with a small

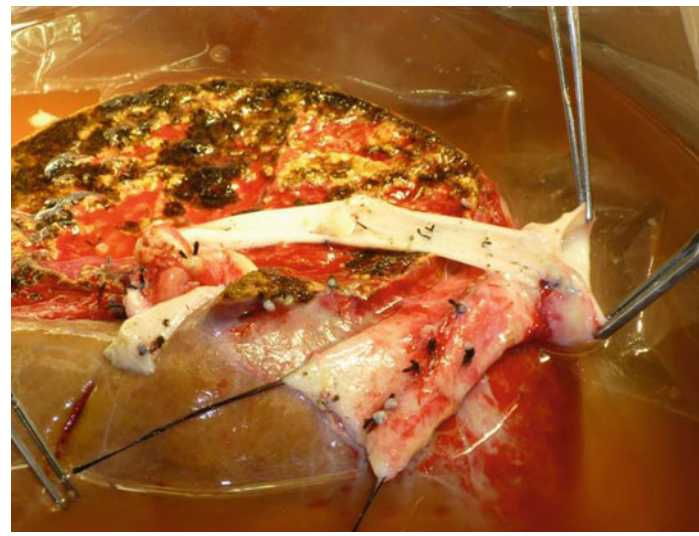

Fig. 7 The right lobe graft with a new middle hepatic vein. The iliac vein graft is used to drain the anterior segment

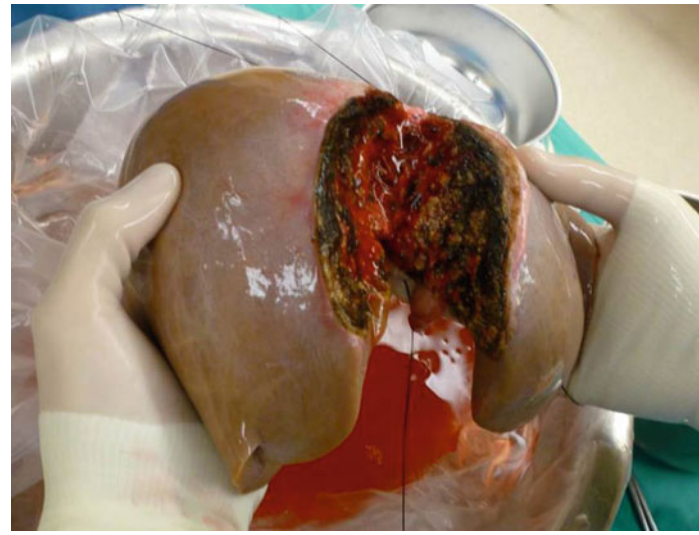

Fig. 8 Appearance of the liver split in situ to the left lateral segment and right trisegment grafts

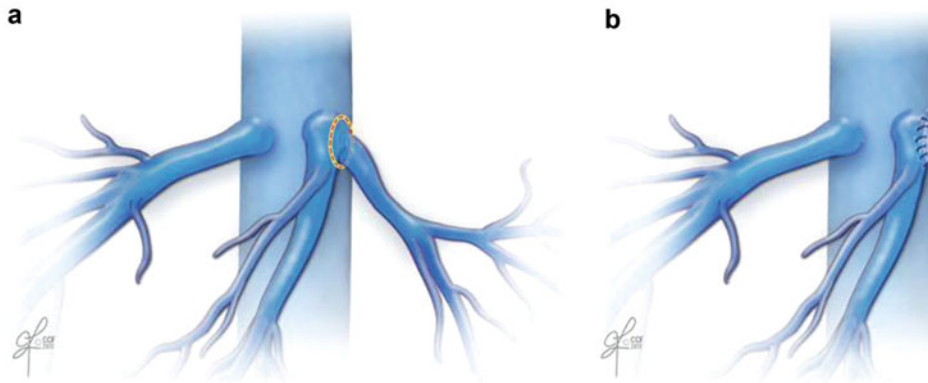

Fig. 9 Transection of the left hepatic vein in the left lateral segment graft. (**a**) The left hepatic vein is transected with a small patch of the vena cava and the middle hepatic vein. (**b**) The defect on the vena cava and the middle hepatic vein is closed with a venous graft patch to prevent stenosis of the middle hepatic vein

venous patch of the vena cava and the middle hepatic vein to secure sufficient length of a venous cuff to the LLS graft (Fig. 9a). The left branch of the portal vein is isolated and divided, and the defect on the main portal vein is sutured to close transversely in the same fashion as described in the hemiliver split technique. The right hepatic artery is transected distal to the bifurcation. The A4 should be kept with the RTS graft to secure arterial supply to the medial segment. However, it can be sacrificed if it arises from the left hepatic artery.

After transecting the artery and portal branches, the biliary system is probed to confirm the biliary anatomy from the stump of the common bile duct. The left hepatic duct and hilar plate are sharply transected on the line of parenchymal transection. The entire stump of the hilar plate should be oversewn to prevent bile leak. Preservation solution is injected into the distal left hepatic duct to check for leakage. At this point, the LLS graft is ready for implantation.

A piece of donor vein graft is used to patch the defect on the vena cava and the middle hepatic vein (Fig. 9b). A primary closure of the defect is not recommended because it can cause serious impairment of venous outflow of the middle

hepatic vein. The defect of the left hepatic duct on the common hepatic duct is oversewn. Preservation solution is injected into the common bile duct to check for leakage. Finally, the RTS graft is ready for implantation.

Ex Vivo Split Technique

In the ex vivo split technique, a whole liver is first retrieved in a standard fashion. As soon as the liver is assessed visually and manually, recipient teams should be notified of the estimated liver weight. If available, intraoperative cholangiogram can be performed to delineate biliary anatomy before cross clamping. On the back table, vessels and bile duct are divided as described in the section of the in situ split technique. Parenchymal transection can be performed by sharp transection by a surgical knife or clamp-crushing technique. Decent-sized vessels and bile ducts on the cut surface should be tied or sutured to minimize bleeding after graft reperfusion. During back table preparation, the liver should be immersed in cold preservation solution to avoid rewarming of the liver.

Recipient Surgical Techniques

LLS Grafts

In pediatric recipients receiving the LLS graft, total hepatectomy is performed by preserving the native vena cava. Because the LLS graft usually retains the celiac trunk but not the main portal vein, the native portal vein should be left as long as possible. To achieve excellent venous outflow in small infants, a vertical cavotomy from the common orifice of the hepatic veins needs to be made to create a triangle-shaped large caval orifice (Emond et al. 1993). Because the graft hilar structures locate laterally in the right side of the abdomen, adequate redundancy is necessary in portal vein anastomosis to prevent stenosis. Biliary reconstruction is usually performed with hepaticojejunostomy with Roux-en-Y limb. When the native bile duct is available, a duct-to-duct anastomosis can be done with comparable outcomes to hepaticojejunostomy.

RTS Grafts

Because the RTS graft usually retains the entire vena cava, caval reconstruction can be done with either the piggyback or the standard technique. For arterial reconstruction, the native hepatic arterial branch should be preserved as long as possible in case the graft right hepatic artery is small. Sometimes, microsurgical technique is necessary to safely perform the anastomosis. The medial segment often looks ischemic due to the lack of adequate inflow (Fig. 10). However, such change is not associated with a higher risk of bile leak or parenchymal necrosis. Therefore, resection of the ischemic parenchyma is not required.

Hemiliver Grafts

As seen in other types of partial grafts, venous outflow is important to successful left lobe SLT. Since the size of the hemiliver donor is usually larger than the recipient, the donor venous orifice (the common channel of the left and middle hepatic veins with a small caval patch) can be directly anastomosed to the recipient caval orifice that is created by all three hepatic veins merged into one large orifice. This technique promises perfect venous outflow of the left hemiliver graft. The native portal vein and common hepatic duct should be left long because the main branch of the portal vein and hepatic duct are not retained with the left lobe graft.

In the right lobe graft, caval anastomosis can be done with either the piggyback or the standard technique. When the vena cava is retained with the right lobe graft, excellent venous outflow almost always can be achieved with a new middle hepatic vein draining into the donor vena cava (Fig. 11). When the vena cava is not retained with the right lobe, a complex venous reconstruction may be needed to avoid graft venous congestion as seen in living donor liver transplantation. Portal and biliary reconstructions can be done in

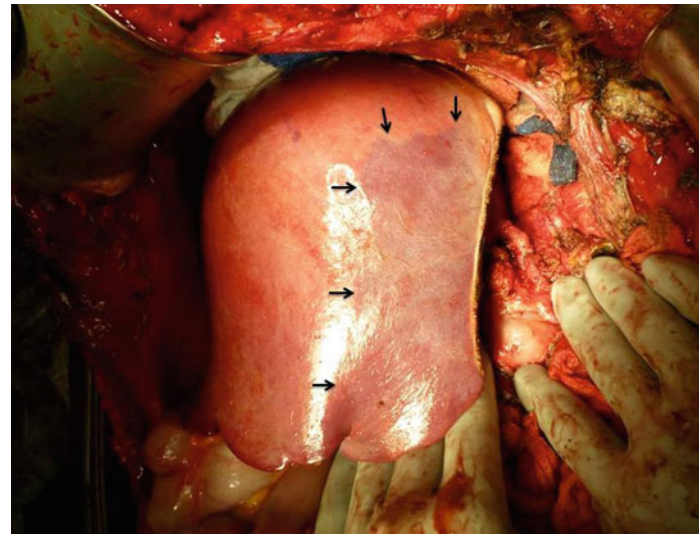

Fig. 10 Ischemic area of the medial segment in the right trisegment graft after implantation (*black arrows*)

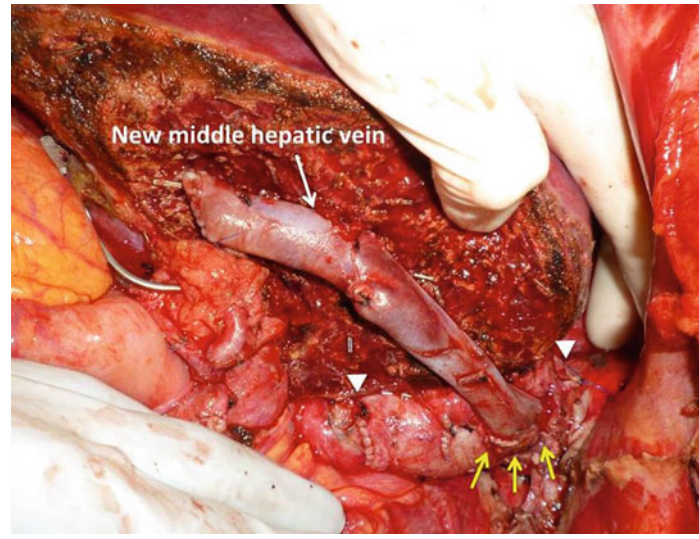

Fig. 11 The right lobe graft after implantation. A new middle hepatic vein created on the cut surface of the graft drains the anterior segment into the donor vena cava (*yellow arrows*). *White arrowheads* indicate caval anastomoses. The graft is transplanted in the standard caval interposition technique

the same fashion as whole liver transplantation. For arterial anastomosis, the native hepatic artery should be left long as described in the technique for the RTS graft.

Because excessive portal flow into the small partial graft can cause arterial insufficiency via hepatic arterial buffer response, the hemiliver graft in adults has a high risk of small-for-size syndrome, particularly when graft size is marginal (GRWR < 1.0 %), and the recipient physiology is characterized by severe portal hypertension. Portal venous pressure and flow volume can be directly measured to assess the severity of portal hyperperfusion. If necessary, surgeons should have a low threshold to modify portal inflow the split graft of marginal size (Boillot et al. 2002). Splenic artery ligation, splenectomy, and hemi-portocaval shunt are well-known techniques for portal inflow modification. Of these, the use of hemi-portocaval shunt is controversial due to the risk of portal steal phenomenon (Lee 2015).

Outcomes

LLS/RTS Grafts

In the last two decades, SLT has been widely observed, particularly for the child/adult combination with LLS and RTS grafts. However, the activity of this technique still accounts for less than 5 % of the total number of liver transplants in the United States and even fewer in Europe. There is no doubt that SLT has helped decrease liver transplant waiting list mortality in the pediatric population. It is equally important that the survival after pediatric SLT is equivalent or even superior to whole liver transplantation. In contrast to the excellent pediatric outcomes with LLS grafts, the outcome for the adult population receiving the RTS graft has been controversial (Mallik et al. 2012). Due to the technical complexity, the rates of biliary and vascular complications can be as high as 40 % and 25 %, respectively. Despite the high risk of surgical complications, the long-term survival of SLT recipients using the RTS graft is satisfactory (Doyle et al. 2013). Under favorable conditions such as short cold ischemia (< 8 h), nonurgent recipient status, and young donor age, outcomes for the RTS graft are promising. Nowadays, experienced centers no longer consider the RTS graft to be marginal (Maggi et al. 2015).

Hemiliver Grafts

Because experience with hemiliver SLT for two adult recipients is limited, its routine use remains controversial, particularly in countries where MELD-based allocation regulates organ distribution. Further, technical and logistical challenges are significant in precluding the efficient diffusion of this technique. A recent Italian multicenter study has shown that hemiliver SLT in adults had significantly inferior 5-year survival compared to whole liver transplantation (63 % vs. 83 %) (Aseni et al. 2014). However, under certain circumstances, the long-term survival of the hemiliver graft is equivalent to whole liver transplantation or living donor liver transplantation (Broering et al. 2005; Zambelli et al. 2012; Lee et al. 2013; Hashimoto et al. 2014). Biliary complications are the most common surgical issue in hemiliver SLT with incidence as high as 30–40 %. Vascular complications are not as frequent as biliary complications, but can be experienced at a rate as high as 20 %. According to the Cleveland Clinic experience, biliary complications were more frequently seen in hemiliver SLT than whole liver transplantation (32 % vs. 11 %), but generally could be managed by endoscopic or radiologic intervention and did not affect long-term survival (Hashimoto et al. 2014).

Ethical Aspect of Split Liver Transplantation

Creating two extended criteria split grafts from one standard criteria whole liver has been a matter of ethical debate (Vulchev et al. 2004; Collett et al. 2008). Since SLT per se is a risk factor for graft failure, especially when hemiliver grafts are used in adults, we often come up with a question about the pros and cons of SLT compared to waiting for a subsequent liver offer of smaller size that could be wholly transplanted. Although SLT has faced logistical challenges and less favorable outcomes, it gives recipients more opportunities to receive a life-saving liver transplant. While concerns exist about the general application of this highly complex surgical technique, which uses a potentially high-risk organ, SLT is expected to achieve comparable or even superior survival to whole liver transplantation. By addressing known challenges and gaining successful experience, sharing deceased donor livers through SLT is possible even with other transplant centers that generally have different strategies. To justify more frequent use of SLT, further accumulation of successful outcomes and general consensus between centers is necessary. Finally, it should be noted that recipients have the unequivocal right to refuse an offer of a split graft. With complete and accurate information, thorough discussion of the risks and benefits of SLT with the liver transplant candidates should take place at the time of evaluation, listing, and organ offer.

Conclusion

SLT is a valid technique to increase the opportunity for both children and adults who are in need of life-saving liver transplantation. After more than two decades of experience, we know that this highly complex surgical technique is feasible and can achieve excellent outcomes under certain circumstances. Despite differences in surgical techniques among centers, various techniques work well, almost equally, including ex vivo vs. in situ, pediatrics vs. adults, and split vs. whole liver. Although technical, logistical, and ethical challenges are still not completely overcome, the transplant community should be encouraged to use split grafts to address the current severe donor shortage.

Cross-References

- ▶ Donor Operation
- ▶ History of Liver and Other Splanchnic Organ Transplantation
- ▶ Live Donor Liver Transplant
- ▶ Orthotopic Liver Transplantation: Complications
- ▶ Orthotopic Liver Transplantation: Surgical Techniques

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Live Donor Liver Transplant

6

Sung-Gyu Lee and Deok-Bog Moon

Contents

Abstract

Adult living donor liver transplantation (LDLT) has become a life-saving procedure due to the limited availability of deceased donor organs in many parts of the world. It continues to be a technically challenging procedure and involves inherently complex ethical issues. Donor safety remains the priority; however, a successful recipient outcome after LDLT is also paramount.

The safety margin is small for both recipient and donor, each case should be tailored to the patients, and every step of the procedure must be planned and performed meticulously.

Over the last two decades, many of the issues related to the technical design of adult LDLT procedures have been solved; there does however remain room for further innovation. A better understanding of the complex surgical anatomy and physiologic differences of adult LDLT helps avoid small-for-size (**SFS**) graft syndrome, graft congestion from outflow obstruction, and graft hypoperfusion from portal flow steal. Size limitations of partial grafts and donor safety issues can be overcome with dual grafts and modified right lobe (**MRL**) grafts that preserve the donor's middle hepatic vein trunk.

LDLT is a more complex operation than DDLT, requiring delicate dissection around the hilum as high as possible in order to obtain maximum length of individual structures, allowing for implantation of the smaller-sized

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living partial liver graft vessels. For technically successful **LDLT**, the following four conditions should be satisfied: adequate graft volume to avoid small-for-size syndrome, good outflow to avoid congestion, adequate portal inflow to enhance graft regeneration, and secure bile duct anastomosis to avoid biliary leak. However, the risk of surgical complications still remains higher when compared to **DDLT**. Crucial to maintaining good outcomes following LDLT is a robust multidisciplinary approach with surgical, radiological, and medical teams and a wide range of ancillary services.

Keywords

Living donor liver transplantation • Right lobe • Left lobe • Dual graft • Intraoperative portogram • Bile duct • Hepatic artery • Hepatic vein • Portal vein

List of Abbreviations

3D CT	Three-dimensional computed tomography
AS	Anterior sector
BD	Bile duct
BS	Biliary stricture
DDLT	Deceased donor liver transplantation
ERL	Extended right lobe graft
GRWR	Graft-to-recipient weight ratio
GSV	Great saphenous vein
HA	Hepatic artery
HPCS	Hemiportocaval shunt
HTK	Histidine-tryptophan-ketoglutarate
HV	Hepatic vein
IOCP	Intraoperative cineportography
IOUS	Intraoperative Doppler ultrasound
IRHV	Inferior right hepatic vein
IVC	Inferior vena cava
LDLT	Living donor liver transplantation
LHA	Left hepatic artery
LL	Left liver
MELD	Model for end-stage liver disease
MHV	Middle hepatic vein
MRI	Magnetic resonance imaging
MRL	Modified right lobe
PTFE	Polytetrafluoroethylene
PV	Portal vein
RHA	Right hepatic artery
RL	Right liver
SFS	Small-for-size
SHV	Short hepatic vein
UW	University of Wisconsin
V5	Middle hepatic vein tributaries of segment 5
V8	Middle hepatic vein tributaries of segment 8

Introduction

Living donor liver transplantation (**LDLT**), particularly in Asia, became the most common type of liver transplantation because of the scarcity of deceased donor liver grafts.

LDLT using left lobe grafts for children (Ozawa et al. 1992) and adults (Hashikura et al. 1994) proliferated in Japan. This procedure has not become widespread due to the inability of these relatively small-sized grafts to meet the metabolic demands of all adult recipients. To overcome the inadequate graft volume and poor results which were encountered by adult recipients with left lobe grafts, transplantation with a right lobe liver graft was introduced for adult recipients in 1996 (Lo et al. 1997).

The surgical technique of deceased donor liver transplantation (**DDLT**) and pediatric and adult LDLT using left liver (**LL**) graft has been standardized; however, LDLT using right liver graft is often technically challenging due to multiple biliary and complex hepatic vein (**HV**) reconstructions. The incidence of biliary complications remains high after right lobe LDLT (Fan et al. 2002), and acceptance criteria of right liver (**RL**) grafts related to the multiplicity of ducts varies among transplant centers (Liu et al. 2004). In addition, outflow occlusion and congestion remain potential hurdles (Lee et al. 2001b). Despite these technical challenges, ongoing innovations have advanced RL LDLT to allow for results comparable to DDLT in many specialized centers. Attention to middle hepatic vein (**MHV**) reconstruction has been a critical factor (Lo et al. 1999b). Severe stenosis and/or thrombosis of the portal vein can be included as an

indication of LDLT by application of PV thrombectomy, plasty, and intraoperative cineportography (**IOCP**) or sometimes various innovative jump graft from the splanchnic bed (Moon et al. 2007).

Not all potential donors can donate their RL. Safe donation is possible only when the estimated remnant liver volume is more than 30 % (Fan et al. 2000) and the volume of the right lobe in the potential donor is more than 70 % to the volume of the whole liver. If a large-sized recipient requires more graft volume than expected liver graft volume from a single donor, dual-graft LDLT may be an alternative in which two grafts from two donors are transplanted into one recipient (Lee et al. 2001a).

Perioperative Considerations

Compared with DDLT, more aggressive peri- and postoperative care of adult LDLT recipients is crucial to achieve comparable outcomes. The degree of portal hypertension is a crucial intraoperative risk factor in adult LDLT.

Favored skin incision for recipients is a bilateral subcostal incision with midline extension or inverted T-shape incision. The surgical technique used for recipients is based on whole liver resection with preservation of the inferior vena cava (**IVC**) (Tzakis et al. 1989). For technically successful LDLT, the following four conditions should be satisfied: (1) adequate graft volume in order to avoid small-for-size syndrome, (2) adequate outflow in order to avoid congestion, (3) adequate portal inflow to enhance graft regeneration, and (4) a secure bile duct anastomosis to avoid biliary leak (Fig. 1) (Moon and Lee 2009).

Operative Procedure

Recipient Hepatectomy

The surgeons need to be aware of both recipient and donor anatomy and must also have a specific plan for how to manage any recipient anatomical problems including the hepatic artery (**HA**), portal vein (**PV**), hepatic vein (**HV**), and bile duct (**BD**). In addition, there must be a plan for how to maintain adequate portal inflow without portal flow steal in the presence of large portosystemic collaterals, massive splenomegaly with enlarged splenic artery, and small graft size with less than 1.0 graft-to-recipient weight ratio (**GRWR**).

At the time of surgery, the recipient's abdomen is prepared and draped; simultaneously preparation and draping of the left groin and thigh may

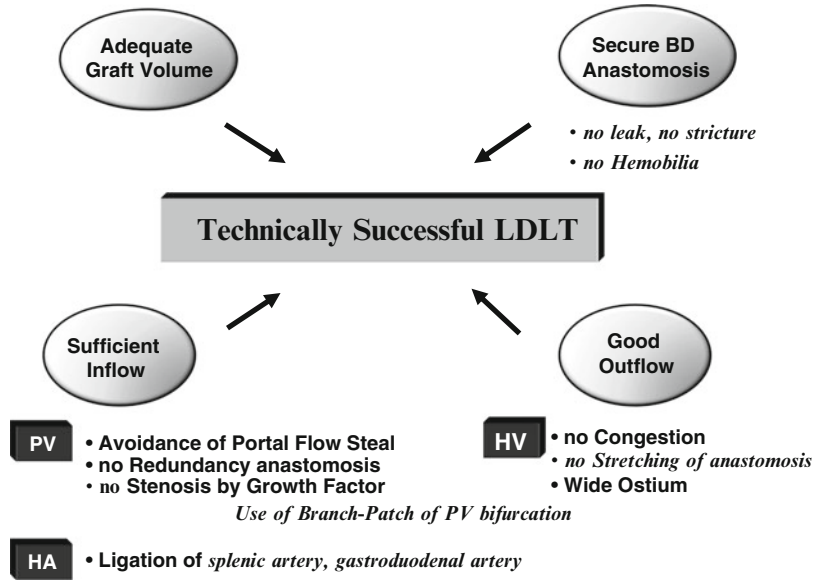

Fig. 1 The four major prerequisites for technically successful LDLT are the following: adequate graft volume to avoid SFS graft syndrome, sufficient PV inflow for liver graft regeneration, good HV outflow to prevent graft congestion, and a secure BD anastomosis to prevent sepsis. *BD* bile duct, *HA* hepatic artery, *HV* hepatic vein, *LDLT* living donor liver transplantation, *PV* portal vein, *SFS* small-for-size

also be necessary to access the great saphenous vein (**GSV**) often used for reconstruction on the back table and also for graft implantation in the recipient.

Before beginning perihepatic dissection, a full laparotomy should be performed, and the decision made as to when the preoperatively planned interventions should be undertaken, i.e., splenic artery ligation, splenectomy, isolation of portosystemic collaterals, etc. Usually splenic artery ligation or isolation of splenorenal shunt causing portal flow steal is undergone at the initial stage because edematous changes of bowel and mesentery after liver graft implantation might hinder those procedures. Other tasks, such as interruption of portosystemic collaterals and splenectomy, are performed after engraftment.

Using electrocautery, both coronary and triangular ligaments are divided; the detachment should be performed along the avascular plane. In some cases, however, it is more effective to peel off the hepatic capsule by thorough cauterization of both diaphragmatic and hepatic surface and ligation of sizable diaphragmatic vessel so as to reduce intraoperative bleeding when perihepatic collateral vessels or dense adhesions are present, such as in salvage or re-transplantation. After adrenal detachment, hemostasis of the perihepatic area becomes easier, and there should be minimal bleeding before dissection of retrohepatic IVC is begun. The following step is often dissection of hepatic hilum prior to retrohepatic IVC dissection. This takes into consideration the possibility of significant bleeding and/or technical difficulty depending on the extent of caudate lobe hypertrophy, Budd-Chiari syndrome, etc. Early dissection and division of hilar structures can facilitate the following procedures with less bleeding, particularly in salvage LDLT patients who have undergone previous major hepatectomy or in secondary biliary cirrhosis patients who underwent repeated surgery for biliary problems. Venovenous bypass through the inferior mesenteric vein or PV or temporary portocaval shunt may be helpful to reduce bleeding and splanchnic congestion during total hepatectomy and the anhepatic phase.

The main technical principle of dissection of the hepatic hilum is to preserve implantation options by maintaining the length and integrity of all hilar structures. In particular, meticulous dissection of the hepatic artery to obtain a sufficient length and adequate diameter is very important in order to match with the small hepatic artery opening of the partial liver graft without tension and to avoid intimal dissection of the recipient hepatic artery, such as is often encountered during hilar dissection of a recipient with portal hypertension. Alternatives are not easily achievable because of the vessels' small diameter of usually less than 3 mm, in contrast to the diameters of the BD and PV.

When cholecystectomy is performed, the cystic duct is divided close to the neck of the gall bladder in order to preserve as much of its length as possible in case the cystic duct might be necessary for duct-to-duct anastomosis of where two bile duct openings are present on the liver graft with a wide gap between them. When LL implantation is being planned, the left hepatic artery (**LHA**) is isolated first at the left hilum and then dissected up to the umbilical portion of the left hilum in order to get enough length and also to get the branch patch of hepatic segment 2 and 3 HAs to accommodate the often larger graft hepatic artery. When RL implantation is planned, this step is a type of insurance procedure, and it is important for a surgeon to proceed following dissection in a comfortable situation. Dissection of the middle and right HA should be performed with preservation of the periductal connective tissue encompassing the axial periductal microcirculation in order to avoid posttransplant biliary complications related to ischemia. The right hepatic artery (**RHA**) should be freed up to the anterior and posterior branches so as to overcome size disparity between the graft and the recipient HAs. Division of HAs without ligation in the recipient side is better than ligation of both sides in order to obtain longer hepatic arteries and to avoid intimal injury.

The division site of bile duct should be decided by size and number of ductal openings of the graft. Pre- and intraoperatively, there should be communication between the recipient and donor surgeons regarding the cholangiogram. If multiple ductal openings are expected and also situated widely

apart in the graft, the Glisson tissue containing the duct in the recipient should be divided at a high level in the hepatic hilum in order to create multiple ductal orifices with wide distances between those of both corners.

The last structure in the hilum to be further identified is the PV. The PV is usually dissected toward the right and left bifurcation of the main PV. For dual-graft LDLT and/or obtaining autogenous vessel graft to use for graft implantation, the PV needs to be dissected toward and beyond the takeoff of the right anterior, posterior, and left portal branches up to the umbilical portion. As for the extent of PV dissection to the opposite side, the PV is mobilized down at least 2 cm in length from the portal bifurcation toward the superior margin of the head of the pancreas.

During the anhepatic phase in LDLT, portal bypass is usually not the preferred procedure because most recipients tolerate portal clamping without hemodynamic instability due to maintaining caval flow, and construction of hepatic and portal vein anastomoses requires less than 60 min. LDLT using a right lobe graft, excluding extended right lobe, left lobe, and dual-lobe LDLTs, does not require systemic bypass because the piggyback technique allows partial clamping of the vena cava with a side-biting clamp and without hemodynamic instability.

The next step is division of the gastrohepatic ligament. At the time of left liver or dual-graft LDLT, if a LHA arises from the left gastric artery, this should be dissected as long as possible for arterial reconstruction of the implanted liver graft. The caudate lobe of the liver is detached from the IVC using a left-side approach in order to enhance the retrohepatic dissection as much as possible.

Before the removal of the recipient's liver, an autologous **GSV** is retrieved from the groin, most commonly on the left side, because the right side is usually used for placement of the femoral artery and vein cannulation by the anesthesiologist.

Considering the harvest time of donor graft and the duration of the bench procedures, the diseased liver is removed as late as possible to reduce anhepatic phase. Hepatic veins (**HVs**) are divided individually using a vascular clamp instead of an endovascular stapler because the recipient's HV openings should be used for anastomosis with the graft HVs after venoplasty.

Anhepatic Phase

Recipient Side

After recipient hepatectomy, bleeding control should first be performed. A frequent bleeding site during this phase includes the retrohepatic dissection area, and particular care should be given to the inferior phrenic artery and adrenal gland because they are difficult to expose after engraftment, and bleeding from these sites often occurs during the postoperative course.

Optimal venous outflow is critical for the success of an LDLT. Making a wide HV orifice in the recipient to accommodate the corresponding donor HV is an essential preparatory step for the engraftment.

For anastomosis of reconstructed MHV tributaries of the modified right lobe (**MRL**) graft, the septum between the recipient's middle and left HV is usually divided, and a single large opening is made using unification venoplasty. Several Allis clamps are placed at the end of the middle and left HV stump, after which the previously applied clamp is removed so as to facilitate deep placement of side-biting clamp to the right hepatic vein (**RHV**) and including the anterolateral wall of the IVC.

Inappropriate ventrodorsal matching of the graft-recipient RHV anastomotic sites was found to be a significant risk factor for the development of RHV stenosis (Hwang et al. 2010). For RHV venoplasty, a large side-biting clamp is placed on the RHV; inclusion of the anterolateral wall of the IVC is necessary. A longitudinal incision only toward caudal side or both longitudinal and transverse incisions of the RHV with the IVC wall toward caudal and ventral sides as well as a wide patch plasty using bisected autologous vessel grafts such as GSV, PV, or cryopreserved iliac vessels are performed. These methods result in acceptably low incidences of early onset RHV stenosis (0–2 %) (Hwang et al. 2010).

For reconstruction of large short hepatic veins (**SHVs**), deep and secure side clamping of the IVC is required in order to prevent unnecessary tension during the anastomosis. It is usually therefore necessary to extensively dissect greater than half of the suprarenal IVC, and some branches of the right adrenal veins to the IVC need to be divided (Hwang et al. 2012a).

Back-Table Procedures

Vascular plasty or reconstruction may be required at the back table as a preparation for engraftment. MHV tributaries of the RL graft should be reconstructed using autogenous vessels harvested from recipient, deceased donor iliac vessels, or synthetic vascular graft. The RHV of the RL graft and the trunk of the middle and left HV of the LL graft may require venoplasty using previously mentioned vessel grafts in order to prevent HV outflow obstruction. When single or multiple SHVs larger than 5 mm in caliber are present, venoplasty is performed according to the previously described guidelines (Hwang et al. 2012a). If two separate pig's nostril-shaped PV orifices (right anterior and posterior branches) in the RL graft are present due to type III or II PV variants, the recipient's Y-graft of PV bifurcation prepared from the recipient's hilar dissection can be used to make a single PV opening with adequate length of the neck for simple and safe anastomosis during engraftment (Lee et al. 2003b). When the recipient's native PV cannot be used for the Y-graft due to severe PV stenosis, or closely attached hepatocellular carcinoma, circumferential fencing of PV by using autogenous bisected GSV or Y-graft from cadaveric fresh iliac vein branches can be used as an alternative (Guler et al. 2013).

Likewise, if two arteries are present in the graft, arterial reconstruction can be performed using a recipient's HA Y-graft including the proper, right, and left hepatic artery on the back table under optimal conditions (Marcos et al. 2001). However, two separate HA anastomosis under a microscope using mostly recipient's lobar or sectoral HAs after reperfusion might be preferred in order to avoid recipient bile duct ischemia and size discrepancy between graft and recipient HAs. Therefore, the recipient HA is dissected as high as possible in order to obtain a long-length and size-matched HA. Rarely, the HA in the graft may be accidentally injured during harvesting procedure, be too short, or be located at the posterior side of the PV with a short stump, all making reconstruction of HA in the recipient's side very difficult or even impossible. Under the microscope on the back table, repair of the injured HA or lengthening the HA using a previously dissected and size-matched recipient's sectoral or segmental HA segment is possible.

If more than two separate orifices of the bile ducts are not too far apart or pig's nostril-shaped orifices are present, unification ductoplasty can be performed to create a large single opening.

These back-table reconstructions may require up to 2 h due to complex anatomy of the HV, PV, and BD. The procedures should therefore be performed while the liver graft is submerged in a 4 °C cold, preservation solution inside an ice-packed container.

Graft Implantation

Hepatic Vein Anastomosis

To obtain optimal venous outflow, not only the anastomosis itself but also the positioning of the graft needs to be considered. A change in graft position due to regeneration can cause outflow problems. Venoplasty of the recipient's HV extended to the IVC wall to make an oval-shaped wide orifice with adequate length of the neck may help to minimize the outflow complications, even though slight torsion of the anastomosis occurs and causes outflow stenosis. The recipient's HV needs to be maximally incised longitudinally and/or transversely and then attached like a fence by using autologous vein patch with a thick wall. For proper alignment at the time of HV anastomosis, two 5–0 nonabsorbable sutures with double needle arms are placed at the cephalic and caudal ends of both the graft and the recipient's HV. Venting of the liver graft on reperfusion is usually not necessary in LDLT when histidine-tryptophan-ketoglutarate (HTK) solution is used as it has low potassium content.

Portal Vein Anastomosis

As mentioned in Fig. 1, adequate portal flow is essential for successful LDLT. The PV anastomosis is performed using the recipient's PV trunk or with PV bifurcation to avoid redundancy of the PV anastomosis. Occasionally, the recipient right or left PV branch is used due to better size match or more favorable alignment than the PV trunk. The PV anastomosis must be constructed without tension, redundancy, or twisting. The preferred suture material is 6–0 Prolene, and the anastomosis is generally performed in a running fashion, incorporating sufficient "growth factor" (Starzl et al. 1984).

In recipients with severe PV thrombosis who cannot undergo a thrombectomy and/or PV plasty to enlarge the diameter of PV, mesenteric or renoportal interposition grafts are necessary using a cadaveric iliac vein or a polytetrafluoroethylene (**PTFE**) vascular graft (Moon et al. 2011). Patients who require caval transposition or arterializations of the PV or both are at significantly higher risk of morbidity and mortality and are perhaps inappropriate candidates for LDLT because adequate portal inflow is mandatory for partial liver graft regeneration.

Prevention of Portal Hyperperfusion or Portal Flow Steal

Virtually all living donor liver grafts in adult recipients are relatively small-for-size (**SFS**) and require optimal portal inflow for immediate graft regeneration, particularly when GRWR is less than 0.7–0.8 %. Portal hyperperfusion can cause excessive shear stress against sinusoidal cell of a SFS graft, which is known to be the primary cause of the SFS syndrome (Troisi et al. 2005). Various remedial procedures such as splenic artery ligation, splenectomy, and small-caliber hemiportocaval shunt (**HPCS**) creation have been utilized to modulate portal inflow (Kiuchi et al. 2003). High portal pressure is related however to not only to portal blood flow, but also to liver graft outflow resistance. The safest and most effective way to manage portal hyperperfusion in a SFS graft is provision of good HV outflow and modulation of high portal venous flow (PVF) and pressure (PVP) by splenic artery ligation or splenectomy (Ito et al. 2003; Ogura et al. 2010). Splenectomy is usually not indicated to decrease portal hyperperfusion because of its inherent complications such as bleeding, pancreatic fistula, abscess formation, PV thrombosis, and serious postsplenectomy infections. HPCS may trigger portal hypoperfusion and result in encephalopathy, graft atrophy, and even allograft necrosis, which may occur during the first 2 weeks postoperatively due to portal flow steal (Moon et al. 2008); thus, permanent HPCS is not an appropriate choice for resolving portal hypertension. In the author's experience, PVF $\geq$250 mL/min/100 g graft weight or early elevation of PVP $\geq$20 mmHg after reperfusion is not associated with poor outcomes in SFS grafts as long as perfect venous outflow is provided and portal flow steal is completely interrupted. Considering portal flow steal phenomenon, it is not an issue limited to small-for-size grafts having less than GRWR $<$0.8 % undergoing HPCS, but a common issue in the field of LDLT using partial liver grafts with more than GRWR $\geq$0.8 % and having sizable spontaneous portosystemic collaterals (Lee et al. 2007; Moon et al. 2008).

Intraoperative Doppler ultrasound (IOUS) has been used to ensure hemodynamics of the implanted liver graft. IOUS however has difficulty in evaluating correct anatomical and hemodynamics parameters of portosystemic collaterals. Even when IOUS showed adequate portal inflow during LDLT, portal flow steal syndrome can manifest a few days after LDLT. To overcome the limitation of IOUS, IOCP has been used to evaluate portal flow to liver graft and to detect stealing hepatofugal flow through persistent portosystemic collaterals (Moon et al. 2007) (Fig. 2). In addition, IOCP is therapeutically utilized to complete interruption of surgically inaccessible portosystemic collaterals by coil embolization and to treat PV stenosis interfering with hepatopetal flow by stent placement (Kim et al. 2007). Measurement of PVP and PVF is stopped after introduction of IOCP and MHV reconstruction. To properly manage the potential small-for-size graft syndrome that may develop,

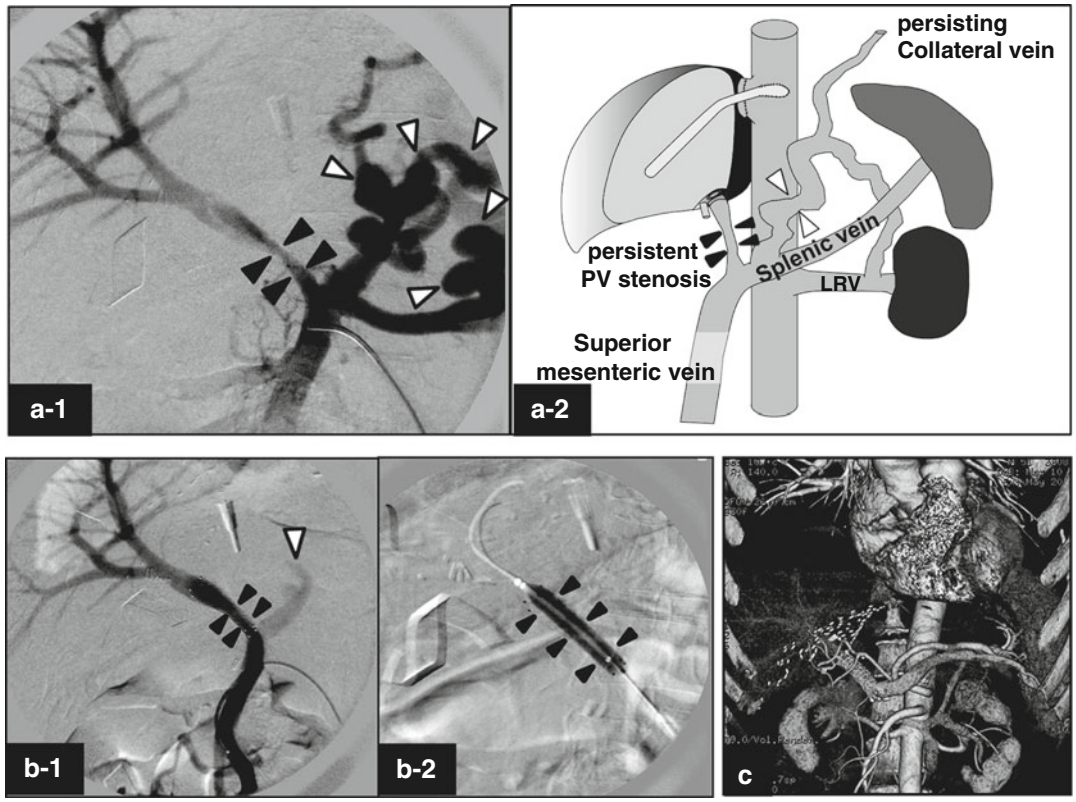

Fig. 2 IOCP may salvage liver graft from portal flow steal. (**a**-1) IOCP and (**a**-2) the schema after engraftment demonstrate persistent PV stenosis in the intrapancreatic portion (*black arrowheads*) and portal flow steal through persisting sizable collateral (*white arrowheads*). (**b**-1) PV stent was placed, and ligation of the collateral vein was performed under guidance of a guidewire through the inferior mesenteric vein during IOCP. Portal flow steal through the collateral vein was not shown (*white arrowhead*), but intrapancreatic PV stenosis was not completely relieved (*black arrowheads*). (**b**-2) Balloon dilatation (*black arrowheads*) of the remnant PV stenosis was performed additionally. (**c**) Follow-up 3D CT after 45 months post-LDLT revealed a patent PV stent without stenosis and disappearance of a large collateral with good liver graft regeneration. *CT* computed tomography, *IOCP* intraoperative cineportography, *LDLT* living donor liver transplant, *PV* portal vein, *LRV* left renal vein

both modulation of graft hyperperfusion by excessive portal hypertension and abolishment of portal flow steal through spontaneous or surgically created portosystemic collaterals are equally important.

Hepatic Arterial Anastomosis

In LDLT, arterial anastomosis is performed after reperfusion in most cases as the donor hepatic artery is thin, small, and short and the anastomosis is tedious and often a time-consuming work requiring great attention. The diameter of the donor hepatic artery particularly in Asians is less than 3 mm in more than three-quarters of the donors (Inomoto et al. 1996; Okochi et al. 2010). These small anastomoses are generally performed in an interrupted fashion with 9–0 or 10–0 Prolene sutures under operating microscope. Introduction of microsurgical technique instead of surgical loop magnification has resulted in a decreased HA complication rate (Inomoto et al. 1996). Selection of the recipient's HA for the anastomosis is decided primarily by size matching with the donor HA. When there is size disparity, the branch patch technique using small branches of donor or recipient HA is useful for wide and tension-free anastomosis (Aramaki et al. 2006). The length, condition of the arterial wall, and feasibility of

stable positioning during anastomosis are also all important factors for choosing the anastomotic artery.

In many cases of LL and a few cases of RL grafts, multiple donor hepatic arteries are present. Whether all accessory vessels require reconstruction remains debatable (Ikegami et al. 1996; Suehiro et al. 2002). All hepatic arteries, including replaced and accessory arteries, are however essentially necessary arterial inflows because hepatic arteries are end vessels that supply a specific area of the liver. In addition, it remains somewhat unclear what impact a smaller ligated artery in the presence of good pulsatile backflow has on the arterial blood supply to segmental bile ducts (Suehiro et al. 2002). Reconstruction of all hepatic arteries is therefore performed to reduce possible HA complications, particularly related biliary complications that remain the Achilles' heel of LDLT.

When extended intimal dissection occurs after hilar dissection of the recipient, a destructed HA is present related to previous transarterial chemoembolization, or HA thrombosis occurs after LDLT; the right gastroepiploic artery can be commonly usable for alternative HA inflow (Ahn et al. 2005). The right gastroepiploic artery is straightforward to dissect, is free from limitation of length, is frequently enlarged as a compensatory mechanism, and is feasible to perform anastomosis with a sizable graft HA. The right gastric artery, gastroduodenal artery, left gastric artery, splenic artery, inferior epigastric artery, internal iliac artery, sigmoid artery, inferior mesenteric artery, radial artery, and saphenous vein are also useful interposition grafts for extra-anatomical HA reconstruction (Uchiyama et al. 2010). When saphenous vein graft for HA reconstruction in LDLT must be used, a saphenous vein harvested from the ankle area is preferred to reduce pseudoaneurysm formation because it has a thick and strong wall and its caliber is usually well matched to that of the graft HA. Occasionally, an interposition graft from the infrarenal aorta using a fresh cadaveric artery or GSV is necessary for the arterial reconstruction when the recipient hepatic artery is thrombosed or obliterated all the way to the origin of the celiac axis.

Biliary Reconstruction

Biliary complications adversely affect the recipient's quality of life and can occasionally even cause graft loss and death (Liu et al. 2004). Careful management in the intraoperative and postoperative period to reduce or treat the expected biliary complications is essential to prevent poor outcomes.

Hepaticojejunostomy with stent or without stent was once the standard biliary reconstruction method. More recently duct-to-duct (D-D) anastomosis became the standard technique for its several advantages over hepaticojejunostomy (Shah et al. 2007). Regardless of technique used, a patient with multiple ductal openings has a higher incidence of biliary stricture (**BS**) than those with single duct. When a LL graft is used, bile duct reconstruction is generally straightforward because 88 % of cases have single ductal orifices. In contrast, nearly 50 % of RL grafts have two or three ductal orifices, and often two orifices are more than 1 cm apart.

When RL grafts are to be used, precise investigation of the donor's biliary anomalies is of paramount importance to minimize the number of ductal reconstructions and to avoid injury to the donor's BD near the hepatic duct confluence. To obtain united bile duct openings, the right hepatic duct should be divided accurately by localizing the division site using a rubber-band tagging method after near-complete parenchymal transection (Lee et al. 2002) (Fig. 3).

Ductoplasty is not suitable for ductal orifices that are further apart than the diameter of the larger ductal orifice. Inappropriate approximation of two ductal orifices under tension may cause ischemia, leakage, and subsequent stricture of anastomosis. Hepaticojejunostomy is a better option in this situation. During ductoplasty, simply joining medial walls of two ducts will narrow the longitudinal diameter of a new opening and may further increase the risk of BS. Here septoplasty to make a much larger orifice is necessary to facilitate reconstruction and reduce BS formation (Fan et al. 2002).

The confirmation of viability of the donor and recipient bile ducts before reconstruction of duct-to-duct anastomosis is important to reduce biliary

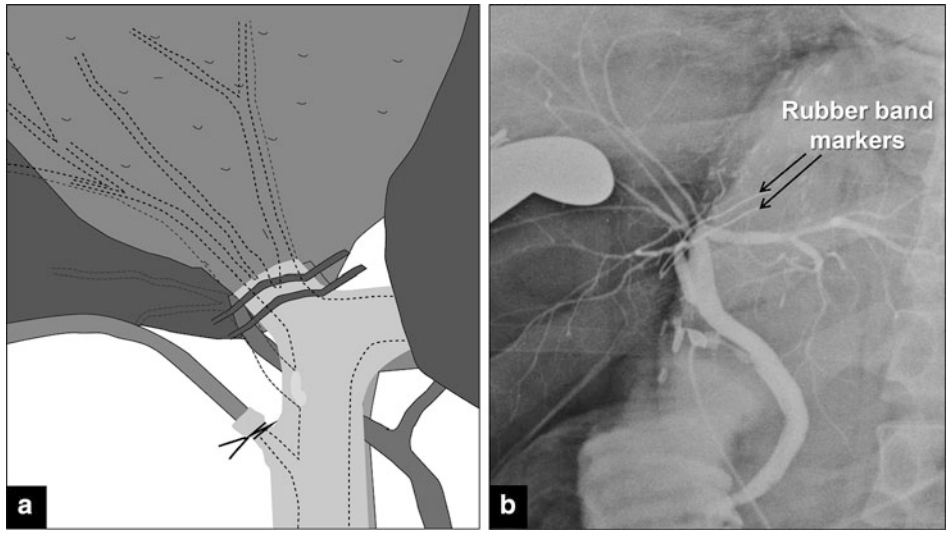

Fig. 3 Rubber-band tagging method for bile duct division. (**a**) Schema of rubber-band tagging method during right hepatic duct division in RL donor hepatectomy. (**b**) Intraoperative cholangiography shows two short segments of radiopaque rubber-band marker sutured transversely 2 mm apart on the presumed division site of bile duct, and three bile duct openings are expected to come out. *RL* right lobe

complications; the viability is decided by the presence of pulsatile arterial bleeding from the cut ends of the BD (Dulundu et al. 2004). The recipient duct opening needs to be one and half times larger than the size of the fully expanded graft duct opening in order to reduce BS.

The role of stenting in biliary anastomosis creation is controversial (Liu et al. 2004). For a large ductal opening, a stent may not be necessary. For small openings, stents may help prevent occlusion of the anastomoses by edema in the early postoperative period or prevent technical error such as catching of the posterior wall during placement of the anterior row of sutures. Routine use of small external drainage tubes exiting via the anterior wall of the common hepatic duct is preferred for several reasons. Firstly, biliary drainage can prevent leakage by minimizing intraductal pressure at the anastomotic site. Secondly, external drainage tubes can help keep lumens open in the early postoperative period. This may be important particularly when dealing with a very small (<2 mm) accessory ducts or a spiral cystic duct. Thirdly, it allows collection of information about bile production and hence about graft function. In addition, cholangiography can be performed to determine occurrence of leakage or stricture (Hwang et al. 2006b; Kasahara et al. 2006). The overall incidence of BS in the Asan Medical Center LDLT using right hemiliver has been less than 10 % in single ductal openings, 14 % in a ductoplasty opening, 24 % in two ductal openings, and 70 % in three ductal openings. All BS have been managed nonsurgically except three adult LDLT patients. Expert and dedicated interventional radiologists and endoscopists are absolute prerequisites to tackle the biliary complications in adult LDLT programs.

Operative Procedures According to the Graft Type

MRL (RL with Reconstructed MHV Tributaries) Graft

Currently, MRL graft is commonly used for adult LDLT. The MHV tributaries (**V5** and **V8**) draining the anterior segment (**AS**, Couinaud segments 5 and 8) had not been reconstructed prior to the introduction of MRL grafts in April 1998 at the Asan Medical Center (Gyu Lee et al. 2002).

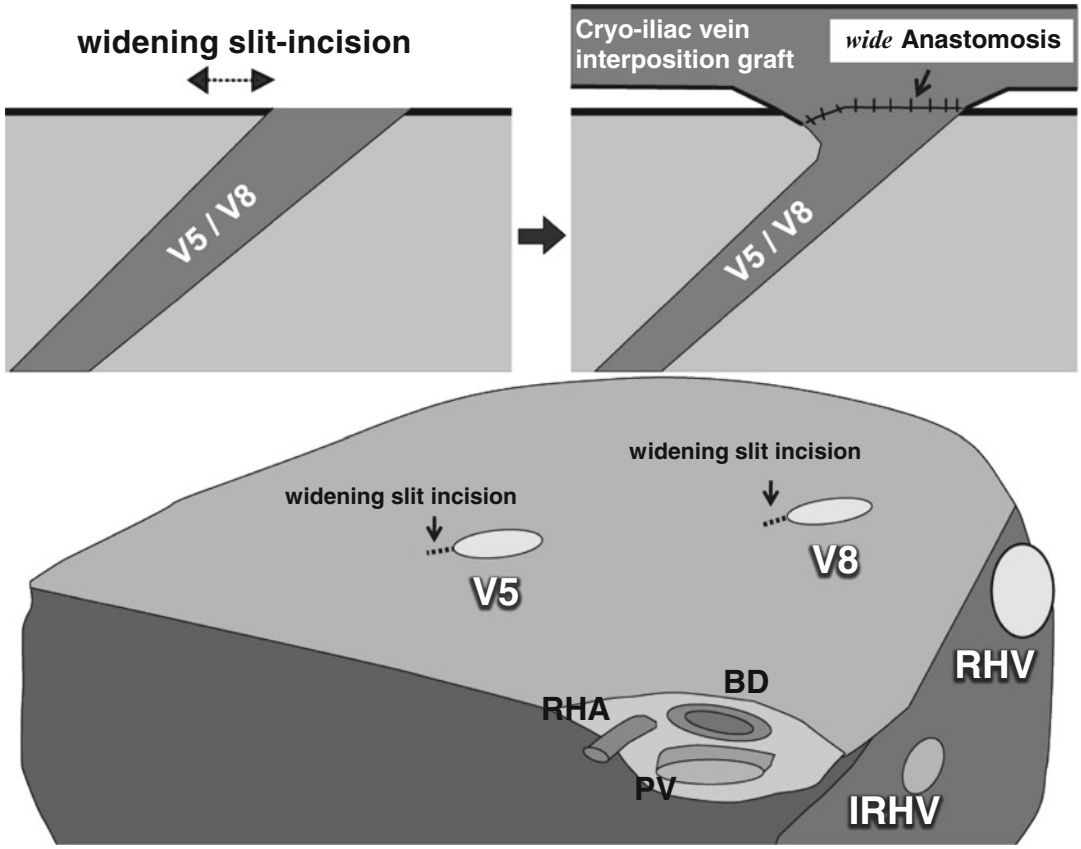

Fig. 4 The schema of alleviating anastomotic stenosis of V5 and V8. Widening of the caudal slit incision of orifices is made at the back table, especially when the caliber of V5/V8 is less than 10 mm. Length of caudal incision is recommended to be not more than 30 % of the diameter of V5/V8. *BD* bile duct, *IRHV* inferior right hepatic vein, *PV* portal vein, *RHA* right hepatic artery, *RHV* right hepatic vein, *V5* middle hepatic vein tributary of segment 5, *V8* middle hepatic vein tributary of segment 8

Initially RL graft without reconstruction of V5 and V8 resulted in severe congestion of the AS, prolonged massive ascites, severe hepatic dysfunction, and even death (Lee et al. 2001b).

Preoperatively sizable V5 and V8 (caliber >5 mm) on 3D CT should be planned for reconstruction of MHV tributaries. Intraoperative estimation of congested volume of the AS in the donor can be made simply and accurately after complete transection of liver parenchyma. Discoloration of the liver surface of the AS will occur after 5 min of hepatic artery clamping.

Congestion of the AS in an RL graft without MHV occurs in 85–88 % of patients to varying degrees. Thus, an MRL graft must be considered particularly when the patient is seriously ill (**MELD** >20), the graft size is relatively small (GRWR <1), the graft is obtained from an older donor (>50 years), the MHV is dominant over the RHV on the donor's three-dimensional computed tomography (**3D CT**) or magnetic resonance imaging (**MRI**), and the AS is larger than the posterior sector by volumetry CT.

Early stenosis or occlusion between V5/V8 and the interposition vascular graft is higher when the orifice of V5/V8 is smaller or the interposition graft caliber is smaller than 10 mm. To alleviate anastomotic stenosis of V5/V8, the slit incision of the orifices is widened in the caudal direction on the back table, and this simple procedure enlarges the orifice's circumference nearly threefold (Fig. 4). As an interposition vascular

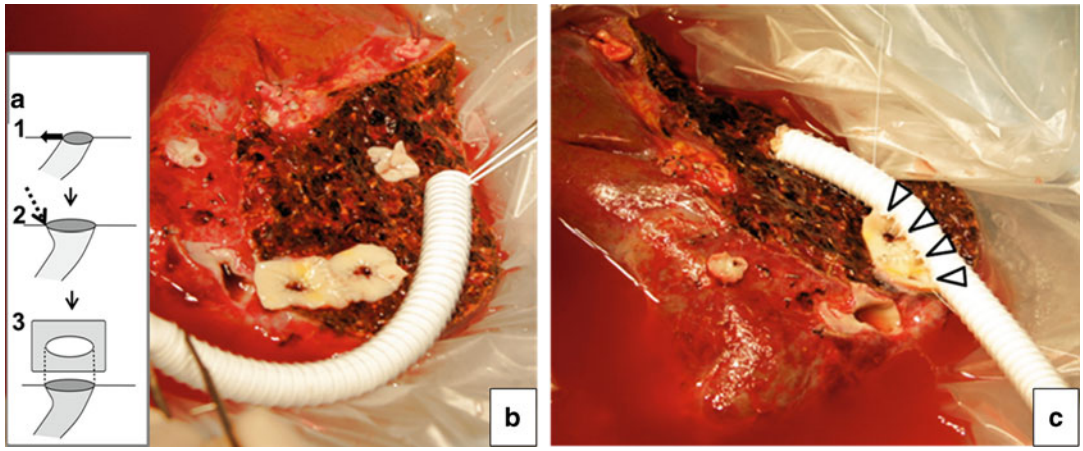

Fig. 5 Placement of a composite vessel patch to offset stenosis-inducing tissue reaction and to avoid tearing of thin-walled V5/V8 during suture when using PTFE graft. (**a**) First, small caudal incision (*thick black arrow*) (**a**1 and 2) is made at V5/V8 to widen orifice (**a**3). (**b**) Composite thick-walled vascular patch (cryopreserved artery or autogenous GSV) is interposed. (**c**) Corresponding site of ringed PTFE graft is elliptically excised and anastomosed for wide patency (*white arrowheads*). *GSV* great saphenous vein, *PTFE* polytetrafluoroethylene, *RHV* right hepatic vein, *V5* middle hepatic vein tributary of segment 5, *V8* middle hepatic vein tributary of segment 8

graft, the autologous GSV, PV, dilated umbilical collateral vein, and HV excavated from the resected liver have all been used (Gyu Lee et al. 2002). Generally, a cryopreserved deceased donor iliac vein is the best conduit because of its adequate diameter (>10 mm), simplicity, and excellent early patency rate (90 %). When cryopreserved homologous vessel grafts are not available, a synthetic vascular graft, expanded PTFE graft, can be used, but these have a low patency rate reported, 1- and 4-month patency rates of 80.8 % and 38.5 % (Yi et al. 2007). To improve this patency rate, only ringed PTFE graft of larger caliber (internal diameter >10–12 mm) combined with placement of composite vessel patches (autologous GSV, cryopreserved artery from tissue bank) between V5/V8 and the PTFE graft has been used (Hwang et al. 2012c). To decrease V5/V8 reconstructions, adjacent tributaries are united into a single common opening with an intervening GSV or a cryopreserved arterial patch between them on the back table.

Placement of composite vessel patches offsets the stenosis-inducing tissue reaction of PTFE grafts to the direct anastomotic site of V5/V8, avoids tearing the thin-walled V5/V8 during suture, yields large orifices, and allows redundancy without subsequent buckling of V8 anastomosis forming a naturally coursing conduit appearance (Fig. 5). Currently, expected short- and midterm patency rates of cryopreserved iliac vein allograft and ringed PTFE grafts are 90 % at 1 month and >60 % at 6 months at the Asan Medical Center. In regard to infection of PTFE grafts, none of the patients with PTFE grafts (n >350) have experienced significant infection. Antiplatelet therapy with aspirin is maintained for 6 months for PTFE graft patency.

These interposition vein grafts are anastomosed mainly to the recipient's middle and left HV trunk or sometimes directly to the IVC by a continuous 6–0 or 5–0 Prolene suture after the liver graft has been reperfused by the portal vein.

RHV Reconstruction

The RHV is the primary outflow pathway for RL grafts, and its successful reconstruction is essential for full graft function. Right lobe grafts however undergo rapid regeneration in all directions within 2–3 weeks within the limited right subphrenic space; this may compress the RHV anastomotic site (Lee 2006). To cope with this

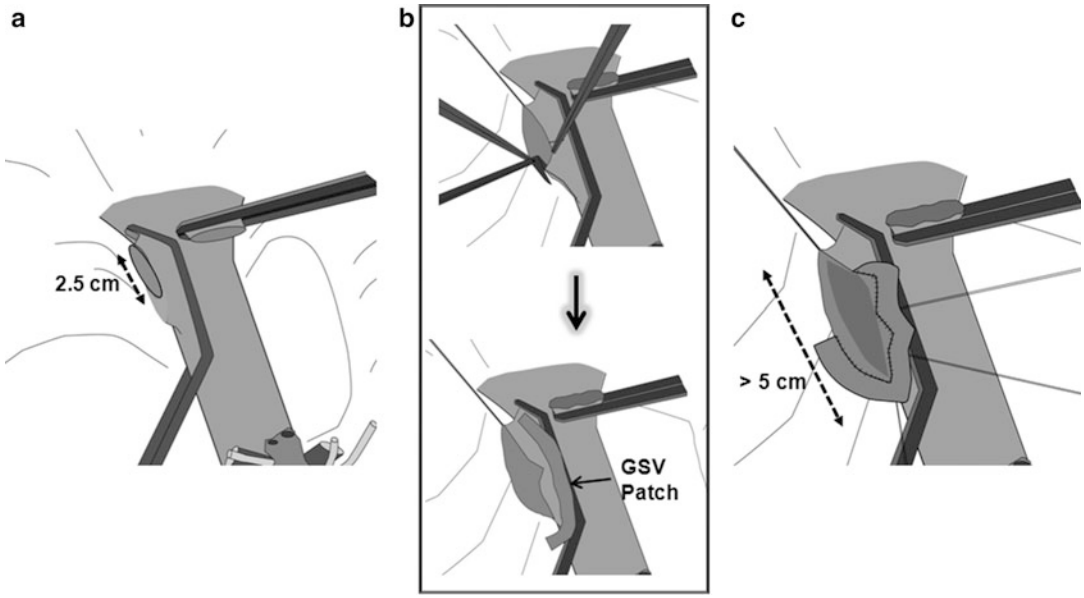

Fig. 6 Recipient RHV widening plasty to counteract conformational change at the anastomotic site by compression of the regenerating liver graft. (**a**) Recipient 2.5 cm RHV orifice is partially clamped. (**b**) Downward and/or transverse incision into IVC compatible to the diameter of the enlarged graft's RHV is made, and a reservoir creation on the ventral wall of anastomosis is formed by a half-circumferential GSV fence. (**c**) RHV orifice larger than 5 cm with provision of a sufficient reservoir by aid of a ventral venous patch likely contributes to preventing RHV anastomotic stenosis. *GSV* great saphenous vein, *IVC* inferior vena cava, *RHV* right hepatic vein

conformational change, a wide ostium is indispensable for prevention of venous outflow obstruction. On the back table, a near half-circumferential GSV patch plasty is performed after downward longitudinal incision of the RHV to avoid anastomotic breaking at the caudal end of the anastomosis. This is the most common form of RHV stenosis, decreasing the longitudinal diameter of the RHV anastomosis at its root (Hwang et al. 2012b; Takahashi et al. 2011).

Another conformational change caused by graft regeneration is tortuous stenosis of the hepatic IVC with oblique elliptical deformity as well as stenosis of RHV. This results from asymmetrical regeneration between anterior and posterior sectors as a result of failed AS drainage, for example, hypertrophy of the posterior sector and atrophy of the AS. To counteract the conformational changes of IVC constriction at the anastomotic site, a half-circumferential fence using autogenous vein graft (GSV, PV) on the ventral side after downward incision and sometimes additional transverse incision creates potbellied reservoir on the ventral wall of the anastomosis and contributes to reduction of RHV anastomotic stenosis (Fig. 6).

SHV Reconstruction

In the case of a single SHV, the back-table procedure is the same as that for the RHV, and anastomosis between the SHV and IVC is also the same except vascular patch plasty to the IVC wall is not performed. In the case of multiple SHVs, however, separate anastomoses are vulnerable to obstruction or regeneration-related torsion, and creation of a common large opening of multiple SHVs is beneficial for simple and safe anastomosis compared to multiple nonaligned SHV anastomoses. The Tokyo University group achieved complication-free reconstruction of multiple SHVs using the double caval method (Kishi et al. 2005). With a shortage of cryopreserved IVC or large-caliber vein graft, quilt venoplasty is performed using autogenous GSV patchwork with or without circumferential patch fence (Lee 2006) (Fig. 7).

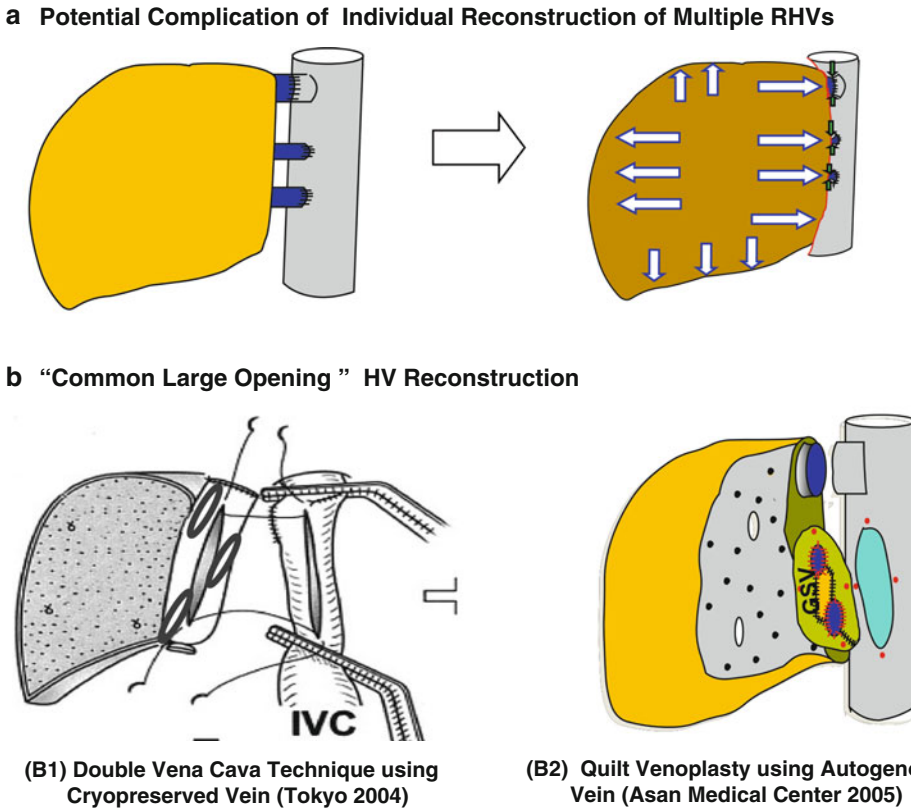

Fig. 7 The mechanism of outflow disturbance and tackling strategies for reconstruction of multiple SHVs. (**a**) Individual anastomoses of multiple short RHVs are vulnerable to obstruction or regeneration-related torsion. Double vena cava technique using cryopreserved deceased donor IVC by Tokyo University (**b**1) and quilt unification venoplasty using autogenous GSV patch with circumferential GSV fence by Asan Medical Center (**b**2) can effectively reduce the outflow complications. *SHV* short hepatic vein, *GSV* great saphenous vein, *IVC* inferior vena cava, *RHV* right hepatic vein

Right Lobe Graft with Middle Hepatic Vein (Extended Right Lobe Graft, ERL Graft)

The Hong Kong group introduced **ERL** graft for adult LDLT because it can secure optimal drainage of the AS, thus avoiding venous congestion, and offers better graft function even for a larger recipient (Lo et al. 1997). Long-term patency of venous conduits draining the anterior sector in an MRL graft is variable depending on technique, number, and size of V5/V8 and types of interposition vascular grafts. Therefore, the ERL graft is generally more beneficial with regard to venous drainage than an MRL graft, even though the extent of donor operation is increased.

ERL grafts currently constitute only 5.7 % of the Asan Medical Center's RL LDLTs. Their mean GRWR (0.92 %) is smaller than those of RL without MHV reconstruction (1.26 %) and MRL grafts (1.15 %) because the use of ERL graft is limited to the patients with small GRWR and high MELD scores in order to reduce the potential donor morbidity and mortality in the absence of MHV in the remnant left liver.

Various methods of HV reconstruction have been introduced to ensure good outflow drainage of ERL grafts. The Hong Kong group introduced short and direct anastomosis after unification venoplasty of the graft's RHV and MHV trunks and corresponding triangular excision of the recipient's IVC (Lo et al. 2003) (Fig. 8a).

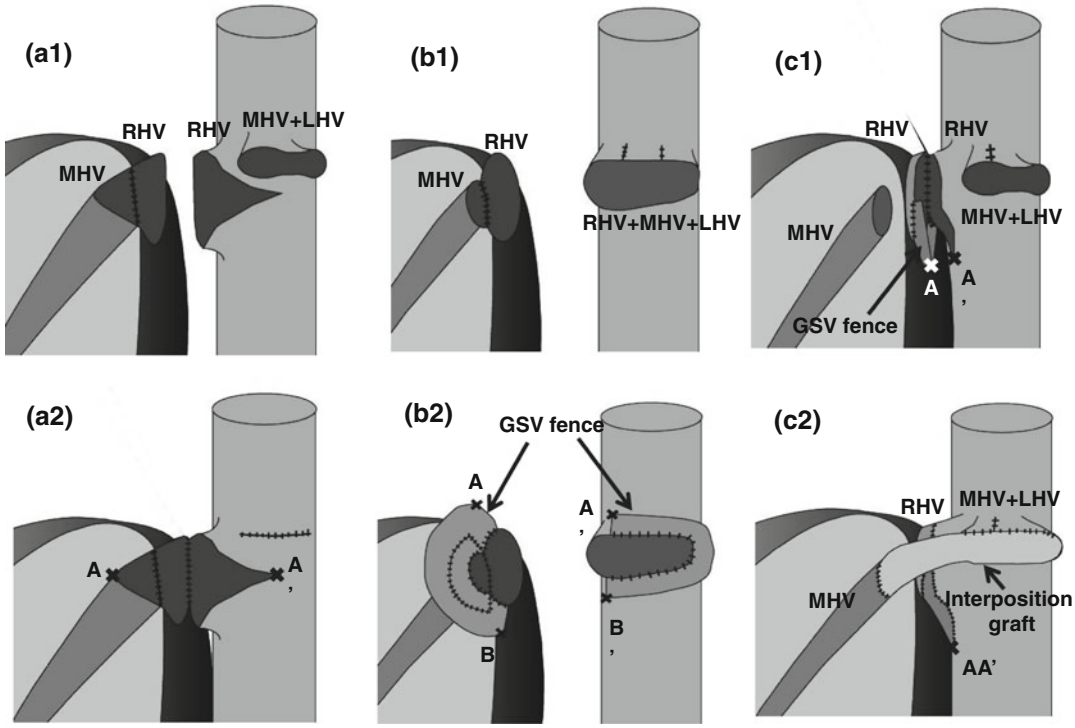

Fig. 8 Various HV reconstruction methods in ERL graft. (**a**) Direct and short anastomosis with triangular caval excision. (**b**) Quilt venoplasty to make the ventrally superabundant dome-shaped anastomosis matches the enlarged IVC orifice. (**b**1) Not only are the RHV and MHV of ERL graft converted to a single opening, but the recipient RHV, MHV, and LHV are also converted to a large common opening by unification venoplasty. (**b**2) Autogenous GSV is fenced to the ventral side of graft MHV orifice and the outer three-quarters of the circumference of recipient common HV opening. The second GSV fence surrounds the ventral side of the graft HV from upper and lower ends of the RHV. A and A' and B and B' indicate the approximation side of the upper and lower corners of the posterior wall of anastomosis. This double quilt venoplasty with autogenous GSV will transform the ventral side of anastomosis to the large dome-shaped reservoir space. (**c**) Separate widened RHV anastomosis and reconstruction of the MHV with an interpositioning large-caliber vessel graft. A and A' indicate the lower corner of RHV anastomosis. *ERL* extended right lobe, *GSV* great saphenous vein, *IVC* inferior vena cava, *LHV* left hepatic vein, *MHV* middle hepatic vein, *RHV* right hepatic vein

A new dome-shaped vein cuff attached to the RHV and MHV orifices by quilt venoplasty with autogenous GSV is anastomosed to a common orifice of the recipient's RHV, MHV, and left hepatic vein (LHV) (Hwang et al. 2006a) (Fig. 8b). Matching this superabundant dome-shaped ventral vein cuff to the enlarged HV orifice might permanently protect the HV anastomosis from stretching or compression, which otherwise could cause outflow obstruction. There however still remain drawbacks to this method due to its complexity and the long wound at the recipient's groin GSV harvest site. Despite its excellent patency, separate anastomosis is preferred currently with the modification that an additional large-caliber vein conduit (cryopreserved common iliac vein, autogenous PV, or tube graft using bisected GSV) is interposed between the graft's MHV and the common opening of recipient's MHV and LHV (Kasahara et al. 2005; Lee et al. 2003a) (Fig. 8c). Placement of large-caliber interposition conduits between both sides of the MHVs prevents stretching of the anastomotic site and allows redundancy that helps lessen compression of the anastomotic side by subsequent liver graft regeneration. This procedure is simple and does not require venovenous bypass.

LL Graft With or Without Caudate Lobe

In adult-to-adult LDLT, the left lobe graft has a limited role because the graft volume is not sufficient to avoid the small-for-size syndrome in many patients. However, as long as the graft size is over 40 % of the recipient's standard liver volume in small-body-sized recipients, a left lobe is still a useful graft for adult-to-adult LDLT (Lo et al. 1999a). Although the caudate lobe is a small part of the whole liver, its volume is not negligible and in the partial liver graft can provide a 6–12 % increase in LL graft weight (Hwang et al. 2004a; Akamatsu et al. 2006).

Considering the relatively small-sized graft volume, large hepatic vein outflow is essential for perfect graft function after transplantation. During total hepatectomy, the retrohepatic IVC from the retroperitoneal attachment has been mobilized. To ensure adequate hepatic vein outflow, venoplasty of the hepatic veins of the liver graft should be performed using an autologous bisected GSV segment. The venoplasty technique is used to make a wide single orifice with a sufficient length of hepatic vein stump. The right side of the MHV only or both the right side of the MHV and the left side of the LHV are incised longitudinally, and the bisected GSV segment is attached to the hepatic vein for venoplasty. On the recipient side, the orifices of the recipient's RHV, MHV, and LHV are completely opened, and venoplasty making an adequate-sized, large orifice is performed to accommodate the enlarged hepatic vein orifice of the graft. Venovenous bypass under clamping of supra- and infra-hepatic IVC is necessary step for the recipient's venoplasty and engraftment.

When the left lobe with caudate lobe graft is used, complete revascularization of the caudate lobe may contribute to full graft regeneration (Sugawara et al. 2002b). The caudate vein resected with a cuff of the IVC, which resembles a Carrel patch, is first reconstructed, after which the enlarged hepatic vein orifice of the graft is anastomosed to the large common opening of recipient's hepatic veins. When the orifice of the caudate vein is located close to the left and middle hepatic veins, the caudate vein with IVC cuff can be made into a single opening with a common orifice of the left and middle HV. A single HV anastomosis is sufficient for the outflow reconstruction (Sugawara et al. 2002a).

Dual-Graft Living Donor Liver Transplantation

One-third of potential live donors are not suitable single liver donors for adult recipients because of advanced age, steatosis, small residual liver volume, and calculations suggesting a small-for-size graft. To ensure donor safety and avoid small-for-size grafts, dual left liver LDLT was introduced at the Asan Medical Center in 2000 (Lee et al. 2001a). When the available single RL graft cannot meet the recipient's metabolic demand, dual LDLT using RL and LL grafts can expand application of adult LDLT by satisfying required GRWR of recipients. The mean GRWR with dual left liver LDLT (median, 0.9 %; range, 0.59–1.2 %) approaches that of an RL LDLT (median, 1.15; range, 0.56–2.63).

During the total hepatectomy, the recipient's IVC should be mobilized from retroperitoneal attachment because venoplasty of the recipient's hepatic veins and graft implantation are performed under clamping of the supra- and infra-hepatic IVC. Venovenous bypass is necessary in most cases to maintain stable hemodynamic stability and to avoid mesenteric congestion during the anhepatic phase.

Before implantation of donor grafts, venoplasty of hepatic veins in the recipient and/or liver grafts should be performed to make wide orifices with thick walls and long cuffs. The recipient's RHV is enlarged and elongated by longitudinal incision at the inferior corner and fencing with bisected GSV. The middle and left HVs are converted to a single opening by division of the septum. These are then enlarged and elongated by a transverse incision at the right corner and fencing with bisected GSV. On the back table, venoplasty of hepatic veins of the liver grafts can be performed considering the size match between the recipient and graft hepatic veins. The methods are identical to the single-graft LDLT mentioned

previously. Venoplasty is important in order for the surgeon to perform engraftment without difficulty during surgery and can also prevent postoperative outflow disturbance. If there is some spared bisected GSV, HV fencing of the left-positioned liver graft allows the surgeon to perform a secure anastomosis without tearing the vein wall even in a difficult operative field.

Engraftment procedures using two left liver grafts have previously been described (Lee et al. 2001a). Engraftment procedures using both RL and LL grafts are the combination of two single-graft LDLTs using RL and LL graft, respectively, with both grafts positioned orthotopically. Firstly, the RL graft is placed into the right upper quadrant space, and reconstruction of the RHV and SHVs, if present, is performed. The interposition graft of the MHV tributaries of MRL is anastomosed to the anterior wall of the IVC below the recipient's middle and LHV common orifice. If this is too low, the right PV may be compressed by the reconstructed MHV interposition conduit. Secondly, the LL graft is placed orthotopically, and its HV and PV are reconstructed sequentially. Thirdly, the anastomosis between recipient's right PV and right liver graft's PV is performed; both liver grafts are now reperfused simultaneously. Lastly, after completion of the HA anastomoses, BD reconstruction to both grafts is performed using Roux-en-Y hepaticojejunostomy or combination of recipient's bile duct and Roux-en-Y hepaticojejunostomy.

Right Posterior Sector (RPS) Graft

A right posterior sector (**RPS**) graft can be a good alternative to a full RL graft when it satisfies the minimum volume requirement for the recipient, which has been set at 40 % of the recipient's standard liver volume (Kokudo et al. 2005). In addition it has a larger volume than the left lobe (Sugawara et al. 2002c). Technically, procurement of RPS graft is the most demanding because it requires the longest parenchymal transection and detailed hilar dissection (Kokudo et al. 2005). The procurement of a RPS graft at the Asan Medical Center is selectively performed so as to reduce surgery-related complications after consideration of anatomical variations including the PV, HA, and BD. When the left lobe volume is disproportionately small (<30 % of whole liver volume) and type II or III PV is present, successful RPS graft procurement is likely (Hwang et al. 2004b).

In the recipient operation, meticulous hilar dissection as high as possible should be performed to obtain a size-matched hepatic artery with a small caliber (1–2 mm in diameter) and/or BD openings for duct-to-duct anastomosis. For successful engraftment, the preparation and implantation procedures are basically the same as those for right lobe implantation. When the PV of the RPS graft has a short stump and/or a weak wall, making a fence to the graft PV using a bisected GSV can be useful to perform safe and wide anastomosis. When the HA of the graft has a too short stump to rotate under clamping of a metallic double micro clamp, HA anastomosis can be successfully performed by posterior wall repair first with interrupted suturing or by interposition of size-matched recipient's first- or second-order HA branch segment with adequate length at the back table under the microscope.

Conclusion

Over the past decade, most of the issues related to the technical design of adult LDLT procedures have been solved. For optimal performance of LDLT in adult recipients, a comprehensive understanding of the dynamic nature of regenerating partial liver grafts is required and must be applied to overcome HV outflow insufficiency and portal inflow steal. Based on the experiences, techniques described above have demonstrably diminished the morbidity and mortality associated with technical errors during adult LDLT procedures.

The possibility of developing surgical complications remains higher in this challenging procedure compared to the DDLT. A multidisciplinary approach with surgical, radiological, and medical teams, and a wide range of ancillary services which can be provided with institutional support, is crucial.

Cross-References

- ▶ Donor Operation
- ▶ Orthotopic Liver Transplantation: Complications
- ▶ Orthotopic Liver Transplantation: Surgical Techniques

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Minimally Invasive Live Donor Liver Hepatectomy

7

Hoonbae Jeon, Tai Ho Shin, Ivo G. Tzvetanov, and Enrico Benedetti

Contents

Abstract

Minimally invasive approach for living donor hepatectomy has been recently applied in liver transplantation. It has invaluable potential to alleviate the vast gap between supply and demand of hepatic allografts, Even though its advantages such as shorter hospital stay and faster return to normal life could attract additional living donors, safety for donors is still being questioned and investigated due to its relatively recent development. Several studies have described different surgical approaches and retrospective comparative analysis to conventional open donor hepatectomy. Preliminary results show relatively lower morbidities and better outcomes, including less blood loss and hospital stay although they vary widely depending on institutional experience. Careful review of existing studies will elucidate the role of minimally invasive donor hepatectomy with the ultimate goal to choose the optimal surgical approach for maximal donor safety.

Keywords

Liver transplantation • Live donor • Minimally invasive surgery • Safety

Introduction

Living donor liver transplant (LDLT) has become an established modality as an alternative of deceased donor liver transplant (DDLT) in recent decades. Together, they are the only existing definitive

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treatments for both acute liver failure and chronic end-stage liver disease to date. LDLT can be the solution to reduce the severe shortage of liver available for transplant (Jeon and Lee 2010; OPTN 2014).

Currently, there are approximately 16,400 patients on the liver transplantation (LT) waiting list in the United States, and the number is growing each year. Among those patients, only 6,400 would receive LT, while around 1,600 would die based on annual average waiting list mortality. In order to alleviate this severe shortage of organs, LDLT was developed as a feasible option and evolved through many phases. In many of Asian countries, nearly 90 % of LT consists of LDLT as they lack deceased donors due to cultural beliefs, different legal definition of death, and administrative reasons (Saidi 2012). However, in the United States, despite more than two decades of history, LDLT has not yet achieved widespread use, as only 252 (3.9 %) are done as LDLT in 2013 (OPTN 2014).

Additional advantages of LDLT over DDLT have been also proposed and investigated. Various comparative study results of LDLT and DDLT remain controversial and highly dependent on institution experience and liver disease type. Nonetheless, LDLT can be accepted as viable option in most cases (Liang et al. 2012; Zimmerman and Trotter 2003).

The biggest benefit of LDLT would be the ability to schedule the transplantation at the best possible time, optimizing both donor and recipient conditions. In consideration of the high mortality on the deceased donor waiting list, proper timing of the transplant is essential in minimizing mortality. Intraoperatively, as procurement and grafting operations occur simultaneously, cold ischemic time of hepatic allograft can be essentially eliminated, resulting in better graft function (Totsukali et al. 2004). It has also been hypothesized that living relatives would provide better immunologically matching liver because of their genetic resemblance and require less aggressive immunosuppressant postoperatively (Zimmerman and Trotter 2003).

Although benefits of LDLT have been well described in the literature, there has been long ethical debate questioning the safety of otherwise-healthy donor who voluntarily risks possible harms during the complex procedure. Several studies analyzed complications that resulted from surgery and concluded donor morbidity rate ranges 16–39 % (Marcos 2000; Middleton et al. 2006; Pomfret et al. 2003) and perioperative mortality rate directly related to the procedure ranges 0.1–0.3 % (Ringe and Strong 2008; Wertheim et al. 2011). In the NIH-funded 9-center Adult-to-Adult Living Donor Liver Transplantation Cohort Study (also known as A2ALL), retrospective review of 393 LDLT revealed high morbidity of 38 %, of which nearly 50 % was Clavien grade 2 or higher (major complications). This study was not able to prove the advantages of the "learning curve" however, as there was no clear association between morbidity and LDLT experience of each institution. One of the possible explanations is the positive influence of non-transplant hepatic surgical experience that was not assessed (Clavien et al. 1994; Ghobrial et al. 2008). On the other hand, Hwang et al.'s (2006) retrospective review of 1,162 living donors of LT from single institution from 1994 to 2005 showed that major complications, Clavien grade 2 or 3, were observed in only 37 donors (3.2 %). They suggest steep learning curve exists as the first 401 donors suffered significantly higher complication rate than later 761, while they performed 3,000 non-transplant hepatectomies concurrently. Current literature clearly demonstrated that, in addition to high level of experience, judicious donor selection, careful surgical technique, and intense postoperative care are necessary to reduce donor morbidity. Most importantly, these valuable data can help physicians to provide better informed decision making to potential donors.

Comparison to Renal Transplant

Similar problems regarding the shortage of allografts exist in renal transplantation (RT). In order to alleviate these issues, minimally invasive donor nephrectomy (MIDN) was developed in 1995 (Ratner et al. 1995) and has been the preferred modality for the past decade. Compared to 1994, a year before minimally invasive RT was pioneered, total number of live donor RT cases in

2013 was increased by 90 %, and 96 % of them were procured through a minimally invasive approach (OPTN 2014).

It is worthwhile to acknowledge some of the fundamental differences between LT and RT. First, the different anatomical position and complex structure of the liver, which is much larger and a single unilateral organ compared to kidneys, make the procedure much more complicated. It makes parenchymal resection necessary to obtain right or left hemi-liver. Complex variation of biliary structure and location of hepatic veins make the hepatic resection more challenging as well to generate an ideal allograft without compromising donor safety. Larger skin incision size for the donor hepatectomy not only causes higher rate of complication, but also leaves the donor with more psychological sense of disfigurement. The patients on the RT waiting list can be maintained for an extended period by hemodialysis which is not an option for LT. Liver allografts from deceased donors are strictly allocated by MELD score system (Wiesner et al. 2003). As scarcity of available livers gets worse, overall status of the patients on the waiting list would continue to get worse. As a result, average MELD score, which indicates severity of illness of potential recipients, inflates and most recipients are becoming much sicker by the time they would receive DDLT. Third, the benefit of living donor to RT recipients has been clearly delineated by many studies (Rocca et al. 2012) whereas that of LT is still controversial as previously described in this chapter. Lastly, one must take account of the fact that a very different learning curve and magnitude of the procedure characterizes donor hepatectomy.

Moreover, it has been nearly 60 years since the first successful living donor RT compared to 25 years in LDLT.

Minimally Invasive Donor Hepatectomy

In order to apply the same benefits of MIDN to LDLT, minimally invasive donor hepatectomy (MIDH) has been developed and tested cautiously. Cherqui et al. (2000) reported the feasibility of laparoscopic hepatectomy in non-transplant setting in 30 cases. Since then, many have reported large studies and breakthroughs in minimally invasive hepatic surgery that lead to donor hepatectomy. In 2008, Louisville Consensus Conference was organized to share the important updates of minimally invasive hepatobiliary surgery in the world, including MIDH. While establishing laparoscopic liver surgery as a safe and effective approach with several benefits, the conference also highlighted some of the limitations and controversies especially in MIDH (Buell et al. 2009).

Evolution of Surgical Techniques in Open Donor Hepatectomy

Conventional open hepatectomy has been achieved by bilateral subcostal incision with midline extension, also known as "Mercedes-Benz" incision (Fig. 1a). Although this incision is the most invasive approach, it provides exceptional exposure to the upper abdominal viscera and the diaphragm. It carries significant disadvantages such as risk of incisional hernia when compared to less invasive, extended right subcostal incision (D'Angelica et al. 2006).

Heisterkamp et al. (2008) compared 60 J-shaped right subcostal to 58 Mercedes-Benz incisions used specifically for LDLT (Fig. 1b). They reported significantly improved early wound-related morbidity and incisional hernia, although the rest of the operative factors did not differ.

In 2011, Lee et al. reported 143 living donor hepatectomies performed via single 12–18-cm upper midline incision alone, demonstrating better cosmetic satisfaction and less wound complications in the following year. Nagai et al. (2012) confirmed that even 10-cm upper midline incision can be used safely without additional use of laparoscopy when patient has smaller body mass (Fig. 1c).

Emergence of Laparoscopic Donor Hepatectomy

In the past two decades, there have been numerous laparoscopic liver resection techniques developed and described in the literature, with many benefits

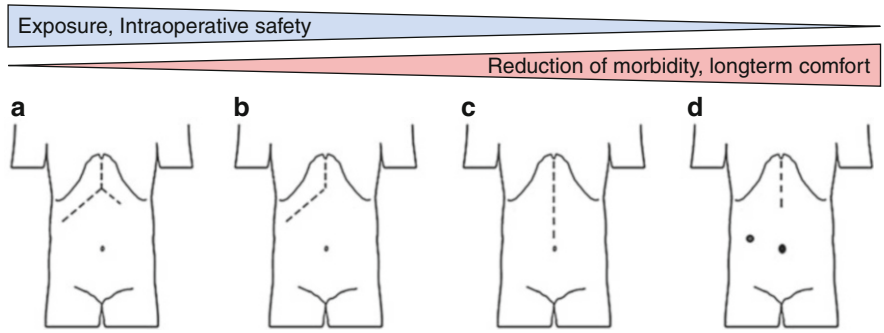

Fig. 1 Progression of techniques for donor hepatectomy. (**a**) Mercedes-Benz incision. (**b**) J-right subcostal incision. (**c**) Upper midline incision. (**d**) Laparoscopic hybrid

Table 1 MIDH case studies and series

	Technique[a]	n	Operative time (min)	Blood loss (ml)	Cold ischemia (min)	Length of stay (d)
Cherqui et al. (2002)	PL (L)	2	420, 360	150, 450	NA	7, 5
Koffron et al. (2006)	H	1	235	NA	35	3
Suh et al. (2008)	HA	2	765, 898	NA	93, 72	10, 14
Suh et al. (2009)	HA	7[b]	489[d]	NA	NA	9.4[d]
Lee et al. (2011)	UMI	141	254 ± 47	352 ± 144	74 ± 31	10.3 ± 3.1
Giulianotti et al. (2012)	RA	1	480	350	35	5
Soyama et al. (2012)	H	15[c]	456[d]	520[d]	NA	NA
Choi et al. (2012)	SPL	40	278 ± 72	450 ± 316	NA	11.8 ± 4.5
Samstein et al. (2013)	PL (L)	2	358, 379	125, 125	NA	17, 8
Troisi et al. (2013)	PL (L)	4	772[d]	1,500[d]	139[d]	5[d]
Soubrane et al. (2013)	PL	1	480	100	NA	7

[a]*PL* pure laparoscopy, *(L)* left, *HA* hand assisted, *UMI* upper midline incision, *H* hybrid, *RA* robot assisted, *SPL* single-port laparoscopy assisted
[b]Excluded overlapping cases from prior report
[c]6 right hepatectomies, 9 left hepatectomies
[d]Calculated mean

compared to traditional open surgery (Nguyen and Geller 2010). Several surgical techniques of MIDH have been created in the literature since the introduction in pediatric (Cherqui et al. 2002) and adult donor hepatectomy (Koffron et al. 2006). Summary of case studies and series is collected in Table 1.

Cherqui et al. was the first group to describe two cases of laparoscopic donor left hemihepatectomy. They performed the left hepatectomy by pure laparoscopy along with a 10-cm Pfannenstiel incision for extraction (Fig. 2i). Two cases took 420 and 360 min with estimated blood loss of 150 and 450 ml, respectively. Those patients were hospitalized for 7 and 5 days with uneventful recovery. They describe these findings very comparable and competitive to conventional open left segmentectomy, which takes 342 min

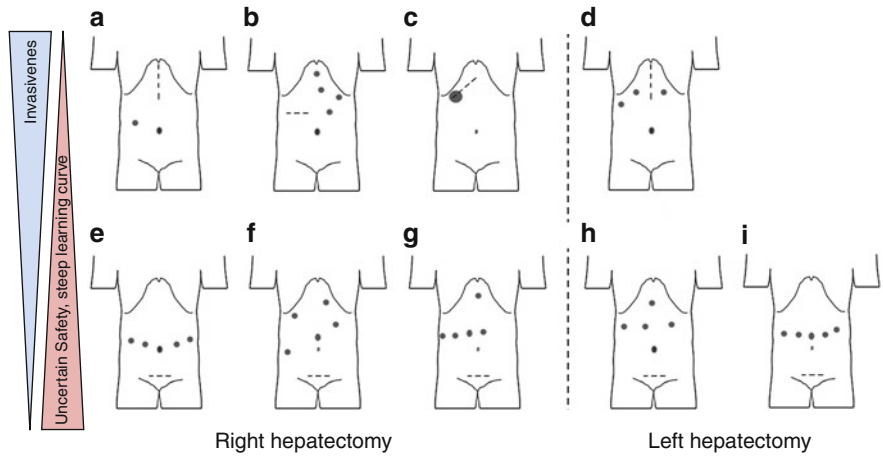

Fig. 2 Incision and trocar sites for minimally invasive approach. (**a**) Hybrid. (**b**) Hand-assisted. (**c**) Single-port laparoscopic. (**d**) Left hybrid. (**e**) Robotic-assisted. (**f**)–(**i**) purely laparoscopic

with blood loss of 192 ml and hospital stay of 15 days on average from the analysis of 282 cases (Fujita et al. 2000).

Koffron et al. (2006) were the first to report a case of laparoscopic-assisted right donor hemihepatectomy in 2006. They used "hybrid technique" that combined two laparoscopic sites with a subxiphoid midline incision for hand assistance and graft extraction during a 235-min operation (Fig. 1d or 2a). They used this incision to directly visualize parenchymal transection to minimize risk of bleeding. Many groups adopted this technique and have made variations. Suh et al. (2008) reported two cases of modified right hemihepatectomy including transection completely by laparoscopy with a 9-cm incision for hand port and extraction at the right upper quadrant (Fig. 2b). They reported operative times of 765 and 898 min, significantly longer than the previous cases, as they spent 218 and 310 min for transection alone. Both patients experienced minor complications of pleural effusion and abdominal fluid collection and required hospitalization for 10 and 14 days. In the following year, the same group also reported seven more cases of laparoscopy-assisted donor right hemihepatectomy while preserving the middle hepatic vein with similar outcomes (Suh et al. 2009). In 2012, Giulianotti et al. (2012) published the first case of robot-assisted donor right hemihepatectomy with operative time of 480 min and blood loss of 350 ml. With known advantage of robotic system in 3-dimensional visualization and versatile manipulation of instruments, this approach enabled the use of sub-umbilical incision for better pain control and prevention of pulmonary complication (Fig. 2e). In the same year, Choi et al. (2012) used the single-port laparoscopy-assisted approach to keep only one 15-cm right subcostal incision at the end of harvest (Fig. 2c). Compared to laparoscopy-assisted or conventional open hepatectomy, they reported significantly less operating time and blood loss. Soubrane et al. (2013) used pure laparoscopy for right hemihepatectomy in a similar fashion described in left hepatectomy by the same group in 2002 and achieved decrease in blood loss to 100 ml during 480 min of operative time (Fig. 2g). Finally, Soyama et al. (2012) reported a case series of 15 hand-assisted laparoscopic donor hepatectomies, including six right and nine left hemihepatectomies. They reported one donor complication of portal venous thrombosis but otherwise comparable results among their cases.

Comparative Studies

Minimally invasive donor hepatectomy has multiple conceivable benefits proven from other minimally invasive surgeries that can be also applied

Table 2 MIDH comparative studies

	n		OR time (min)		Blood loss (ml)		Complication		Length of stay (d)	
	LADH	ODH	LADH	ODH	LADH	ODH	LADH	ODH	LADH	ODH
Kurosaki et al. (2006)	13	13	363 ± 33	320 ± 68	302 ± 191	283 ± 371	NA	NA	11 ± 2.7	12.8 ± 4.9
Baker et al. (2009)	33	33	265 ± 48	316 ± 61	417 ± 217	550 ± 305	21 %	21 %	4.3	3.9
Marubashi et al. (2009)	31	79	435 ± 103	383 ± 73	353 ± 396	456 ± 347	10 %	21 %	10.3 ± 3.3	18.3 ± 16.7
Kim et al. (2011)[a]	11	11	330 ± 68	306 ± 29	396 ± 72	464 ± 78	0 %	9 %	6.9 ± 0.3	9.8 ± 0.9
Nagai et al. (2012)	28	30	371 ± 52	363 ± 53	371 ± 52	316 ± 121	25 %	23 %	5.9 ± 1.2	7.8 ± 2.3
Ha et al. (2013)	20	20	335 ± 94	305 ± 88	290 ± 67	250 ± 111	5 %	10 %	10.7 ± 2.6	10.9 ± 2.5
Makki et al. (2014)	26	24	702 ± 124	675 ± 117	336 ± 89	395 ± 126	15 %	21 %	NA	NA
Zhang et al. (2014)	25	25	386 ± 47	378 ± 59	378 ± 112	423 ± 139	16 %	28 %	7 ± 1.4	8.7 ± 2.4

[a]Left lateral sectionectomy

to the organ donors. The minimally invasive procedure reduces the hospital stay length and recuperation time while improving long-term quality of life. Smaller incision size would also decrease need for pain medication and risk for incisional hernia. To date, a few studies have compared laparoscopic versus conventional incision donor hepatectomy for LDLT (see Table 2). Baker et al. (2009) published a comparative analysis between 33 of each laparoscopy-assisted and open donor right hepatectomy that showed reduced operative times and less estimated blood loss, while having similar complication rates, length of stay, and hospital costs. Nagai et al. (2012) compared 28 minimally invasive cases, which include hand-assisted laparoscopy and mini-laparotomy, to 30 conventional donor hepatectomy cases. More recent study by Makki et al. (2014) also compared 24 laparoscopy-assisted donor hepatectomies to 26 conventional donor hepatectomies with 6-month follow-up and concluded that patients from former procedures experienced significantly less pain, reduced complication, and better quality of life without compromising safety. Another prospective case-matched study by Zhang et al. (2014) showed improved outcomes in similar fashion when two study groups of 25 cases were matched with age, gender, and body mass index. While all the above studies mainly examine donor right hemihepatectomy for adult, Marubashi et al. (2009) compared laparoscopy-assisted donor left hemihepatectomy to conventional open procedure, resulting in similar pattern of outcome. There is an interesting trend that even though the reported morbidity is generally lower in Eastern countries, the overall length of hospital stay is longer. One possible explanation is different healthcare reimbursement system that drives faster discharge in the United States.

Is It Ready for Widespread Use?

Like any other surgery, the imperative of minimally invasive donor liver surgery is safety. In the United States, the number of LDLT cases peaked in 2001 then trended down as a few mortalities were reported. In 2005, Vancouver Forum was convened to address the care of different organ donors. With no doubt, considerably high morbidity and mortality of LDLT became key factors that resulted in strict guidelines to assess between recipient benefits and donor risks. As of 2005, there were 17 catastrophic complications from 6,000 to 7,000 LDLT cases worldwide, with

right liver donor surgery having five times higher mortality as the left side (0.5 % vs. 0.1 %) (Barr et al. 2006). Since then, there were two more deaths reported in the United States alone in 2010 that included one known death associated with laparoscopic attempt as reported in the news media (Cohen 2012).

Even though the minimally invasive approach for hepatectomy has been rapidly evolved and studied, risks for different complications still remain to be determined. As in open donor hepatectomy, safety of both the donor and the recipient must be guaranteed above all through various guidelines and self-report. The most important element of laparoscopic liver surgery is known as the bleeding control, since surgeon's view is limited and immediate intervention can be challenging. Wakabayashi (2009) argue that standardization of procedures is the determining factor for the safety of laparoscopic liver surgery. As there is no centralized standard for donor evaluation or adverse event report, many publications discuss the need for strong self-regulation and clear informed consent especially when experience and skill levels are highly variable among institutions (Cronin et al. 2001; Simpson and Pomfret 2012).

In order to proceed with wide use of LDLT, the following question needs to be addressed: to what extent of risk can be accepted to justify the benefit of minimally invasive operation? In an example of cholecystectomy, since its introduction in 1989, laparoscopic cholecystectomy has rapidly become the gold standard treatment for many of gall bladder diseases in the United States. More than 90 % of 750,000 annual cases are now performed in laparoscopic approach currently (Csikesz et al. 2010). However, after a decade of experience, MacFadyen et al. (1998) noted that the bile duct injury, one of the most feared complications from cholecystectomy, was as high as 0.5 % compared to 0.1–0.25 % in open cholecystectomy. This risk still remains the same today to 0.4 %, and laparoscopy is one of the known risk factors for bile duct injury (Fullum et al. 2013; Gluszek et al. 2014), and yet this risk is generally overlooked for remarkable advantages that the minimally invasive approach brings to both patients and providers.

From Mercedes-Benz incision to robot-assisted hepatectomy, countless efforts have been made to make the procedure safer and prevent iatrogenic injury. For instance, indocyanine green fluorescent cholangiography (IGFC) is one of the newest innovations which can enable the surgeon to directly visualize the biliary structure in real time and to avoid damage (Ishizawa et al. 2010). A recent study looked over 184 robotic cholecystectomies that utilized IGFC and confirmed its safety and efficacy (Daskalaki et al. 2014). It is expected that invaluable techniques such as IGFC can be applied to MIDH including robotic assist to establish safer environment for donors in the near future.

Conclusion

Since its introduction nearly two decades ago, LDLT has evolved many phases to become an accepted solution to the ever-growing deficit of available livers for transplantation. Minimally invasive approach is one of the recent innovations in LDLT with several inherent advantages including quicker recovery, less pain, shorter hospital stay, and less scarring while maintaining safety. Widespread use of MIDH has a great potential to increase donor pool and therefore resolve current burden of LT in the United States, as previously shown in the RT. In order to understand current status, case studies, series, and comparative studies including retrospective case-matching analysis were carefully reviewed. Different methods included pure laparoscopy, hand-assisted laparoscopy, hybrid technique, and robot-assisted hepatectomy that showed various ranges of operative time, estimated blood loss, and length of hospitalization. As the procedure becomes less invasive and new techniques are tested, the safety of these new methods must be ensured and investigated to find the optimal modality for the patient.

In comparative analysis, the trend of more recent MIDH shows longer operative time, less blood loss and complication rate, and shorter hospital stay although the number of subjects is too limited to have statistical value. Further comparison to conventional open procedure

will provide more data to confirm these preliminary results and evaluate safety and effectiveness.

Cross-References

- Live Donor Liver Transplant
- Liver Transplantation in the Third Millennium in North America: The Strategy for Success
- Orthotopic Liver Transplantation: Surgical Techniques

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Orthotopic Liver Transplantation: Complications

8

Carlo Gerardo B. Ramirez

Contents

Abstract

Orthotopic liver transplantation (OLT) can be complicated by medical or surgical complications. Medical complications include delayed graft function or primary nonfunction (PNF), rejection, neurologic complications (encephalopathy, tremors, central pontine myelinolysis, and seizures), pulmonary complications (pleural effusions, hospital-acquired pneumonia, pulmonary edema, adult respiratory distress syndrome), and cardiovascular complications (hypertension, hyperlipidemia, diabetes, and obesity). Surgical complications may include hemorrhage, vascular complications (hepatic artery thrombosis or stenosis, pseudoaneurysm, portal vein stenosis or thrombosis, hepatic vein or vena cava stenosis), and biliary complications (anastomotic stricture and biliary leak). Hepatic artery thrombosis is the leading cause of graft loss and mortality after OLT. Re-transplantation is the treatment of choice for most cases of hepatic artery, and portal vein thrombosis, and percutaneous balloon angioplasty for hepatic artery, portal vein, and hepatic vein stenosis. Biliary complications such as biliary leak or stricture can be managed successfully by endoscopic or percutaneous biliary drainage, while surgical biliary reconstruction is the treatment of choice for biliary drainage nonresponders. Medical and surgical complications remain significant causes of morbidity

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and mortality post-OLT requiring early recognition, diagnosis, and immediate treatment.

Keywords
Liver transplantation • Immunosuppression • Primary nonfunction • Rejection • Neurologic complications • Pulmonary complications • Cardiovascular complications • Stenosis • Thrombosis • Biliary leak • Biliary stricture • Pseudoaneurysm • Hemorrhage

Introduction

Liver transplantation (OLT) is the treatment of choice for patients with chronic liver disease, acute liver failure, and selected patients with hepatocellular carcinoma. In the last decades, several major advancements in surgical techniques of organ procurement and recipient OLT, introduction of better preservation fluid and more potent immunosuppressive drugs, and improvement in peri- and postoperative care of OLT recipients have led to improved patient and graft survival post-OLT. However, medical and surgical complications, although uncommon, remain a significant cause of morbidity and mortality post-OLT. Most of these complications, which usually present during the first month post-OLT, require early recognition and diagnosis and immediate treatment. The incidence rates, clinical presentation, diagnosis, and treatment of various medical and surgical post-OLT complications are discussed below.

Medical Complications

Immediately after OLT, majority of recipients are transferred directly to the surgical intensive care unit where their vital signs, neurologic, hemodynamic, and respiratory status are monitored closely. Initially, frequent laboratory examinations are done to assess and correct any metabolic or electrolyte imbalances and evaluate liver graft synthetic function. Typically, patients with a functioning liver graft awaken from anesthesia immediately post-OLT. They are usually weaned from mechanical ventilation within a few hours after OLT after they are determined to be hemodynamically stable and can safely be extubated.

Primary Graft Nonfunction (PNF)

The usual manifestations of preservation injury include an initial rise in serum transaminases (AST and ALT) in the first 2 days post-OLT, followed by elevation of cholestatic enzymes (alkaline phosphatases and gamma-GTP), and sometimes total bilirubin levels from 3 to 5 post-OLT days, which peak at 7–10 post-OLT days before they start to trend down. During this time, there is slow but progressive improvement in prothrombin time and INR.

Primary nonfunction is a severe form of preservation injury which is usually associated with hepatic necrosis. The incidence of PNF is less than 5 %. PNF may be due to several factors such as advanced donor age, severe donor macrosteatosis, and prolonged cold and warm ischemia time (Marino et al. 1995). There are conflicting reports on the clinical impact of prolonged and uncorrected hypernatremia in liver donors on post-OLT graft function (Totsuka et al. 1999; Mangus et al. 2010).

Clinical manifestations of PNF include hepatic coma, hemodynamic instability, poor quantity and quality of bile, renal dysfunction, severe coagulopathy refractory to plasma transfusion, persistent hypothermia, elevated bilirubin and transaminases, lactic acidosis, and hypoglycemia. Duplex ultrasound shows patent portal vein and hepatic artery with low resistance index (RI) of 0.2. These findings eliminate technical causes of liver graft dysfunction. Transjugular liver biopsy shows massive zonal necrosis, mixed inflammatory infiltrates, and ballooning hepatocytes. Urgent re-transplantation is the treatment of choice.

Rejection

There are three types of rejection: hyperacute, acute, and chronic (ductopenic) rejection.

Acute rejection, which is the most common type of rejection post-OLT, usually develops within the first 1–2 weeks after OLT. This immune process results from liver graft tissues being attacked by activated recipient T-lymphocytes after exposure of the recipient immune system to donor tissue antigens. Acute rejection is observed less frequently in recipients with tacrolimus-based immunosuppressive therapy, in the elderly group, and in patients transplanted for alcoholic liver disease (Wiesner et al. 1993). The usual clinical presentation of acute cellular rejection includes malaise, fever, right upper quadrant pain, jaundice, and low quantity and poor quality of bile. This is usually associated with elevation of cholestatic enzymes, i.e., serum bilirubin, alkaline phosphatase, and gamma glutamyl transferase. Since biochemical abnormalities may also be present in biliary, vascular, or infectious complications, liver biopsy, which may be performed percutaneously or through transjugular approach, is the gold standard for diagnosis of acute rejection. Typical biopsy findings include lymphocytic infiltration of the bile duct, endothelialitis, and portal tract expansion. In most centers, the first line of treatment for acute rejection is intravenous bolus of high-dose methylprednisolone followed by tapering doses over 3–5 days and maintenance prednisone dose daily. Antithymocyte globulin (1.5 mg/kg/dose for four doses) may be used for steroid-resistant acute rejection. During treatment, maintenance immunosuppression is increased to prevent recurrence of rejection. Liver biopsy may be repeated if there is no response to treatment or if there is recurrence of rejection. This is necessary to determine the presence of rejection or to document other pathologic diagnoses such as recurrent HCV, infection, etc.

Hyperacute rejection occurs within a few minutes or hours after transplantation and is dependent on the presence of preformed antibodies in the recipient which are specific to donor antigens. This occurs very rarely in liver transplantation and more commonly in kidney and heart transplantation. It is usually associated with tissue cross match and ABO blood type incompatibility. The typical clinical appearance is similar to severe liver graft ischemic injury. It is associated with poor graft survival, and urgent re-transplantation is the treatment of choice.

Chronic rejection, in contrast to acute rejection, usually occurs later after OLT. Precipitating factors observed include recurrent episodes of acute rejection, chronic allograft ischemia secondary to hepatic artery stenosis, CMV infection, and chronic antibody-mediated rejection. It has a pathologic feature characterized by bile duct loss (ductopenia) and arteriolar obstruction by macrophages. It is usually refractory to steroid therapy. Most patients will develop graft loss and may require re-transplantation. However, there were success stories of patients who responded to conversion to high-dose tacrolimus particularly when they were caught prior to developing significant hyperbilirubinemia and ductopenia (Van Hoek et al. 1992).

Neurologic Complications

Neurologic complications are common after OLT and are associated with significant morbidity and mortality (Guarino et al. 1996). They usually occur in the first month post-OLT but may be observed later after 1-year post-OLT (Bronsted et al. 2000). They may manifest as encephalopathy, seizures, and focal motor deficits in descending order of frequency (Bronsted et al. 2000). Encephalopathy may be due to multifactorial causes like poor liver graft function, anoxia, sepsis, drugs (calcineurin inhibitors and steroids), and central pontine myelinolysis (CPM). CPM is a demyelinating disorder affecting the central pons and extrapontine (basal ganglia, thalamus, and lateral geniculate body) areas of the brain and is more commonly observed in malnourished and chronic alcoholic patients (Adams et al. 1959). Although CPM has a low incidence of 0.94–3 % in liver transplant patients, CPM is one of the most serious neurologic complications after OLT (Lee et al. 2009; Campagna et al. 2010). Liver transplant patients only constitute the third largest group of patients affected with CPM, after chronic alcoholic patients and patients with severe electrolyte imbalance (Lampl and Yazdi 2002). Rapid changes of

serum sodium concentration, osmotic imbalances, as well as isolated hypernatremia are main risk factors for CPM (Crivellin et al. 2014). Seizures are the second most common neurologic complication after OLT. They may be due to calcineurin inhibitor (CNI) or steroid neurotoxicity, serum electrolyte imbalances (calcium, magnesium), hypoglycemia, CNS infections, mass lesions, cerebrovascular infarction, and hemorrhage. CNI neurotoxicity may be managed by switching from a more to a less neurotoxic drug, i.e., tacrolimus to cyclosporine. Other metabolic causes usually resolve with supportive measures such as correction of fluid and electrolyte imbalances and adequate oxygenation, while CNS infections and cardiovascular events are managed appropriately.

Pulmonary Complications

Pulmonary complications are common after OLT and they may cause significant morbidity and mortality post-OLT. Perioperative risk factors for post-OLT pulmonary complications include preoperative pulmonary disorders and other comorbidities associated with chronic liver disease; significant fluid shift intraoperatively due to extensive surgical dissection, prolonged surgical time, blood loss, massive fluid, and blood transfusion; and hemodynamic changes associated with post-reperfusion syndrome. Pulmonary complications post-OLT may be classified as infectious and noninfectious (Feltracco et al. 2013).

Pleural effusions mainly involving the right side are common and do not usually pose a serious complication early post-OLT. They are thought to be due to disruption of diaphragmatic lymphatics coupled with seepage of ascites into the pleural cavity through diaphragmatic defects created by extensive dissection during hepatectomy (Judson and Sahn 1996). Small pleural effusions are usually asymptomatic and resolve spontaneously without any surgical intervention within a few weeks post-OLT. Persistent pleural effusions, though rare, may cause atelectasis leading to pulmonary dysfunction and putting patients at risk of developing pneumonia.

Hospital-acquired pneumonia (HAP) post-OLT, which is reported to occur in 5–38 % of cases, is characterized by the presence of pulmonary infiltrates, fever, leukocytosis, and new-onset respiratory symptoms, such as cough, productive sputum, and dyspnea (Feltracco et al. 2013). Most HAP is reported to be associated with prolonged orotracheal intubation and mechanical ventilation, prolonged ICU stay, and higher mortality rates. Immediate isolation of nosocomial microorganisms causing HAP and treatment with appropriate antibiotics, while decreasing or temporarily withholding immunosuppressive drugs, is crucial to achieving a favorable outcome.

Pulmonary edema is uncommon in early post-OLT unless the recipient has acute-onset left ventricular dysfunction or fluid overload due to renal insufficiency. This is diagnosed based on clinical symptoms, chest X-ray findings, PaO2/ FIO2 (PF) ratio (<300), and hemodynamic measurements (Feltracco et al. 2013).

Adult respiratory distress syndrome (ARDS), which has a reported incidence of 4.5–16 % post-OLT and mortality rate of almost 80 %, may develop within the first few days to several weeks post-OLT (Thompson et al. 1988; Takaoka et al. 1989). Risk factors for ARDS include massive intraoperative blood loss, significant crystalloid fluid infusion and blood transfusion, prolonged operative time, hemodynamic instability, pulmonary aspiration, and sepsis (Obrien and Ettinger 1996). Major clinical findings in ARDS include impaired pulmonary oxygen diffusion and severe pulmonary edema associated with normal pulmonary capillary filling and oncotic pressures (Feltracco et al. 2013). Treatment for ARDS is mainly supportive, with fluid restriction, lung-protective mechanical ventilation, mild hypercapnea, and optimal PEEP, with the addition of inhaled nitric oxide and prostaglandins in severe forms of ARDS (Dellinger et al. 1998; Meade et al. 2008).

Cardiovascular Complications

Significant improvements in graft and patient survival following OLT in recent years has led to

longer life expectancy for OLT recipients, with increasing prevalence of medical complications, such as hypertension, hyperlipidemia, diabetes, and obesity. These complications can lead to an increased risk of cardiovascular disease (CVD), a major cause of late mortality in OLT patients, and accounting for 21 % of deaths with a functioning graft in recipients who survived more than 3 years post-OLT (Pruthi et al. 2001). It has also been estimated that the risk of coronary artery disease (CAD) is higher in OLT recipients compared to the general population, with a 10-year CAD risk of 11.5 % in OLT recipients vs. 7 % in matched non-transplant population (Mazuelos et al. 2003). Another study has shown that the incidence of cardiovascular events in OLT recipients increases from 9.4 % to 25 % at 5- and 10-year post-OLT (Ciccarelli et al. 2005). Risk factors that may promote or exacerbate CVD post-OLT include chronic immunosuppression, pre-transplant cardiovascular and metabolic diseases, and recipient lifestyle.

Hypertension is the most common CVD risk factor in OLT recipients with a prevalence of 36–77 % (Mells and Neuberger 2007). Several factors contribute to post-transplant hypertension, namely, pre-transplant hypertension, preexisting or worsening renal disease, obesity, and the use of steroids and calcineurin inhibitors (CNI). Management plan should include non-pharmacologic and pharmacologic regimens. Non-pharmacologic approaches such as weight reduction, regular moderate exercise, moderate alcohol intake, and dietary sodium restriction may be helpful for those with a systolic blood pressure within 10 mmHg of target blood pressure (BP). However, in cases where lifestyle modification is not effective, pharmacologic treatment with vasodilating agents, such as calcium channel blockers may be used (Desai et al. 2010). Specific indications such as proteinuria, graft vasculopathy, or preexisting CVD may warrant the use of angiotensin-converting-enzyme inhibitors or beta blockers as initial agents. Loop diuretics should be added in the presence of fluid and water retention. Furthermore, the use of CNI-free and steroid avoidance immunosuppressive regimens may also help achieve improvement in systemic BP control and reduction in the number of required antihypertensive drugs. The prevalence rates of hypertension have been shown to be lower with tacrolimus compared to cyclosporine, and the addition of mycophenolate mofetil has also been demonstrated to improve hypertension by permitting lower doses of CNI.

Hyperlipidemia is present in 27–66 % of OLT patients (Fellstrom 2001). Risk factors for hyperlipidemia in a transplant recipient include genetic predisposition, age, pre-transplant hyperlipidemia, obesity, allograft dysfunction (e.g., recurrent primary biliary cirrhosis), hyperinsulinemia, diabetes, and immunosuppressive drugs, particularly steroids, sirolimus, and CNIs. Treatment of dyslipidemia includes lifestyle modification and pharmacologic therapy, such as statin medications (Desai et al. 2010). Reducing CNI doses may be beneficial in hyperlipidemic states in addition to steroid avoidance. Sirolimus is also well known to cause hypercholesterolemia and should be avoided if possible in patients who are at risk for CVD.

Diabetes mellitus (DM) is a major cause of premature atherosclerosis and increases cardiovascular morbidity and mortality. Approximately 25 % of transplant recipients will develop new-onset insulin resistance and chronic hyperglycemia requiring insulin or hypoglycemic agents. This is partly due to the influence of steroids and CNI. The prevalence of post-transplant DM (PTDM) after OLT ranges from 13 % to 21 % (Mells and Neuberger 2007). Numerous studies have shown that kidney and liver transplant recipients who develop PTDM are at two- to threefold increased risk of developing fatal or nonfatal CVD events (Kasiske et al. 2003). Since many of the risk factors for PTDM are modifiable, the incidence of CVD due to PTDM can be mitigated by early diagnosis and treatment with periodic screening of fasting blood sugar levels, lifestyle changes to minimize post-transplant weight gain, steroid avoidance regimen in high-risk patients, CNI minimization and CNI-free regimens, aggressive blood sugar control, and periodic surveillance for CVD in patients with PTDM using appropriate cardiac imaging studies.

Obesity (body mass index >30 kg/m^2) is a significant risk factor for CVD in the general population, and obese patients often have other concurrent cardiac risk factors (DM, hypertension, hyperlipidemia). It is clear that obesity has a direct relationship to insulin resistance and PTDM as well as CVD and death. Post-transplant obesity is a significant problem, occurring in up to 50 % of patients, with multiple contributing factors such as decreased physical activity, DM, dietary habits, genetic factors, and side effects of immunosuppressive drugs. Dietary counseling, weight loss, increased physical activity, steroid-free immunosuppression, and bariatric surgical procedures are some of the common lifestyle change strategies and medical interventions that can promote weight loss.

Surgical Complications

Hemorrhage

Intra-abdominal bleeding occurs in about 5 % of cases and is the most common cause of hypotension in the immediate period after OLT. Contributing factors may include delayed graft function due to the use of expanded criteria liver, i.e., fatty liver (with >30 % macrosteatosis), liver from older donors, prolonged cold ischemia time, etc. Clinically, patients usually have increased abdominal girth, bloody drainage, and decreased urine output. This may be associated with decreasing serial hemoglobin, prolonged INR, and thrombocytopenia. Majority of cases resolve spontaneously and are usually managed conservatively with blood and fluid replacement. Coagulopathy and thrombocytopenia may be corrected with plasma or platelet transfusion. However, the need for more than two units of blood transfusion in the last 12 h or patients who become hemodynamically unstable may be indications for emergent reoperation. No specific site of bleeding is identified intraoperatively in most cases. However, in cases where overt bleeding is identified, they are usually found at the anastomotic site.

Hepatic Artery Thrombosis

Hepatic artery thrombosis (HAT) is the leading cause of graft loss and mortality (20–60 %) after OLT (Quiroga et al. 1991). It can be classified as early (onset within 1-month post-OLT) or late (onset after 1-month post-OLT) HAT. Early HAT occurs more commonly in children (42 %) than in adults (12 %), while late HAT has a lower incidence of 1–25 % (Gunsar et al. 2003; Bekker et al. 2009). Early HAT is manifested by a sudden elevation in liver enzymes, increased INR, and abrupt change in mental status, fever, and hemodynamic instability. In OLT, the hepatic artery is the sole arterial supply to the liver graft and the only blood supply to the biliary tree. Therefore, early HAT can lead to acute liver failure, bile duct necrosis with bile leak, or intrahepatic abscess formation. Late HAT is usually asymptomatic but may manifests with multiple intrahepatic biliary strictures. Doppler ultrasonography is the most accurate and reliable diagnostic screening test for detecting HAT (Flint et al. 1991). The absence of main and intrahepatic arterial flow on Doppler ultrasound should warrant a hepatic arteriography. An abrupt cutoff in the main hepatic artery with absence of intrahepatic arterial flow on hepatic arteriography confirms the diagnosis of HAT. Treatment for HAT is arterial revascularization by thrombectomy or surgical revision. Catheter-based treatments may be tried, but are rarely successful. Urgent re-transplantation is the treatment of choice for most early HAT. For late HAT, the treatment of choice is also re-transplantation, because the biliary tract is usually damaged by the time HAT is diagnosed (see Fig. 1).

Hepatic Artery Stenosis

Hepatic artery stenosis (HAS) is not a very common vascular complication post-OLT with a reported incidence of 4–10 % (Duff et al. 2009). It may be due to narrowing at the anastomosis, trauma to the intimal layer due to catheter manipulation, and twisting or kinking of the hepatic artery. Although it is generally thought that HAS

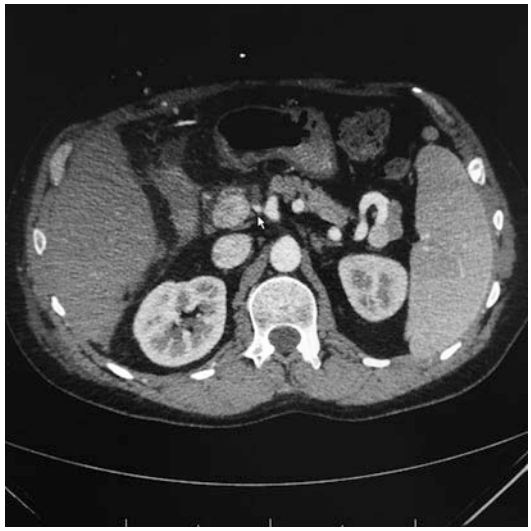

Fig. 1 Hepatic artery thrombosis

may lead to biliary ischemia or liver graft dysfunction and can progress to HAT, its clinical significance remains unclear as many patients remain asymptomatic without liver dysfunction. High flow velocity (>200 cm/s) at the site of stenosis with turbulence distal to the stenosis and low resistive index (RI) of <0.5 in the main, right, or left hepatic artery are typical Doppler ultrasound findings of HAS. Mild stenosis may not demonstrate any changes on Doppler ultrasound (Dodd et al. 1994). Percutaneous angioplasty is an alternative treatment to surgery for HAS. However, the former is not as effective as surgical resection of the stenotic segment with arterial reconstruction (Rostambeigi et al. 2012). Without intervention, more than half of cases may develop HAT.

Hepatic Artery Pseudoaneurysm

Hepatic artery pseudoaneurysm (HAPA) is a rare, life-threatening complication after OLT with a reported incidence of 1–2 %, and usual occurrence of 2–3 weeks post-OLT (Marshall et al. 2001). They usually involve the extrahepatic portion of the hepatic artery and commonly originate from a local infection around the arterial anastomosis. Rarely, they may be located intrahepatically, and these are frequently due to percutaneous interventional procedures such as liver biopsy, percutaneous transhepatic cholangiography, or transhepatic drainage catheter placements (Zajko et al. 1990). The initial clinical presentation of HAPA may be nonspecific, i.e., unexplained fever, liver graft dysfunction, or decreasing hemoglobin level. Therefore, it is very important to have a high index of suspicion to make an early diagnosis and initiation of treatment for HAPA before they rupture and develop bleeding complications. Liver grafts can also be lost because of ischemia secondary to HAPA thrombosis. Rupture of an intrahepatic aneurysm can cause arterio-portal venous leading to portal hypertension or arteriobiliary fistula leading to hemobilia or gastrointestinal hemorrhage (Pawlak et al. 2003). Likewise, rupture of an extrahepatic aneurysm can lead to profound shock and massive intraperitoneal hemorrhage.

Color and spectral Doppler ultrasound is a useful diagnostic study to differentiate HAPA from a cystic mass close to the hepatic artery by demonstrating arterial flow within the cystic lesion (Crossin et al. 2003). CT scan may also demonstrate fluid collections and may identify HAPA and other pathologies. Arteriography remains the definitive study to identify and localize HAPA and aid in planning further treatment (Marshall et al. 2001). If discovered before bleeding complications occur, HAPAs are often treated with surgical resection of the aneurysm with revascularization using interposition vascular or arterial grafts. However, in the presence of acute hemorrhage, particularly HAPAs involving the extrahepatic arterial anastomosis, aneurysm inflow occlusion using coil embolization is necessary to control bleeding and stabilize patients in preparation for re-transplantation. The occurrence of HAPA after OLT is associated with a high mortality rate of 69 % (Marshall et al. 2001). The presence of prior poor graft function or complicated post-OLT course of the recipient further worsens outcome after revascularization and re-OLT for bleeding HAPA (see Fig. 2).

Portal Vein Thrombosis and Stenosis

Portal vein thrombosis and stenosis are a rare vascular complication after OLT with a reported

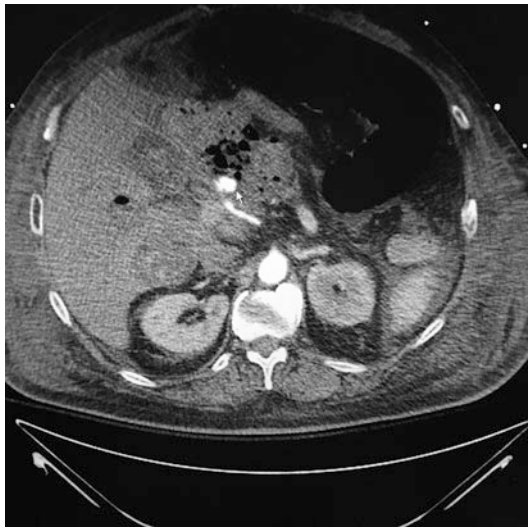

Fig. 2 Hepatic artery pseudoaneurysm

incidence of 1–2 % (Langas et al. 1991). Portal vein stenosis or thrombosis may be due to surgical technical errors, i.e., anastomotic stricture, portal vein twisting, compression or kinking due to redundant vein reconstruction or use of vein graft extension, low portal vein inflow, and recipient hypercoagulable state. They usually manifest with severe liver graft dysfunction associated with hypoglycemia, coagulopathy, lactic acidosis, massive ascites, bleeding esophageal varices, renal failure, and hemodynamic instability. Portal vein thrombosis shows absence of flow within the portal vein on color or spectral Doppler ultrasound, which is confirmed by angiography (Friedwald et al. 2003). Although thrombectomy and portal vein reconstruction in conjunction with thrombolytic and anticoagulant agents may be tried, urgent re-transplantation is the only treatment of choice in most cases. However, re-transplantation may be challenging, particularly in patients with extensive portal vein thrombosis involving the superior mesenteric vein.

Ultrasound findings of portal vein stenosis include focal narrowing of the portal vein to 2.5 mm with increased flow velocity at the site of stenosis and decreased flow velocity in the portal vein. Flow velocities of >150 cm/s or anastomotic to pre-anastomotic flow velocity ratio of >4:1 is specific for anastomotic portal vein stricture (Pawlak et al. 2003). The treatment of choice for portal vein stenosis is percutaneous balloon angioplasty which can be done via transhepatic or transjugular approach (Glanemann et al. 2001; Ko et al. 2007).

Hepatic Vein and Caval Stenosis

Venous outflow complications due to vena cava or hepatic vein outflow stenosis are relatively uncommon with reported incidence of between 1 % and 6 % depending on anastomotic technique and transplant type (Darcy 2007). Hepatic vein stenosis is slightly more common than vena caval stenosis with higher incidence (6 %) reported in living compared to deceased donor OLT pediatric recipients (Egawa et al. 1993). It usually presents early post-OLT and may be due to technical complications, i.e., tight anastomosis, big donor-recipient vein size discrepancy, vein twisting, extrinsic compression of hepatic vein or vena cava, or intimal vein flap formation. The usual presentation of venous outflow obstruction may be similar to patients with portal hypertension, i.e., massive ascites, lower extremity edema, abdominal pain due to ascites or hepatomegaly, and sometimes variceal bleeding. Patients commonly develop renal insufficiency and liver graft dysfunction. Doppler ultrasound examination is the most commonly used initial diagnostic test to detect venous outflow obstruction, while venography with pressure gradient measurement is used to confirm the diagnosis (Egawa et al. 1993; Darcy 2007). Typical findings on Doppler ultrasound may include decreased hepatic and portal vein mean velocities and dampened hepatic vein wave forms. A pressure gradient of greater than 10 mmHg is a commonly used threshold to confirm the diagnosis (Raby et al. 1991; Borsa et al. 1999; Weeks et al., 2000). The treatment of choice for hepatic vein and caval stenosis is percutaneous transjugular balloon angioplasty with stent placement. However, repeated sessions of angioplasty may be necessary to achieve long-term patency due to the increased incidence of recurrent stenosis after a single angioplasty. The use of stents after angioplasty is reported to have

an increased long-term patency rate (Borsa et al. 1999). Surgical revision of the anastomosis may be warranted in cases that cannot be dilated with percutaneous balloon angioplasty. Surgical technique involves dissecting around the cava, which may include opening the diaphragm around the cava for better exposure and access. Other surgical options include the use of caval patch venoplasty and bypass.

Biliary Complications

Biliary complications such as biliary leak or stricture occur in 1.6–19 % of cases after OLT (Hintze et al. 1997; Rabkin et al. 1998). Biliary leakage usually occurs within the first month post-OLT, and surgical technical errors, i.e., undue tension at the anastomosis and bile duct necrosis due to HAT, are the most common causes. They can originate from the biliary anastomotic site, T-tube exit site, cystic duct remnant, bile duct damage after liver biopsy, bile duct necrosis due to HAT, or cut surface of the liver in split liver or living donor liver transplantation. Biliary anastomotic leak and T-tube exit site leak account for more than 80 % of all bile leakages (Greif et al. 1994; Boraschi et al. 2001). Patients with biliary leak can be asymptomatic, but when symptomatic, they usually present with fever and abdominal pain and elevated liver enzymes. Doppler ultrasound of the liver should be performed initially to rule out HAT as a possible cause of bile leak. The diagnosis of bile leak may be suggested by HIDA scan but the definitive diagnosis can be confirmed by T-tube cholangiogram. In the absence of a T-tube, ultrasonography and HIDA scan can be used to detect bile leaks. However, ERCP can be used to diagnose and treat bile duct leaks in recipients with duct-to-duct anastomosis, while MRCP is the most appropriate diagnostic tool for recipients with Roux-en-y choledochojejunostomy (Thuluvath et al. 2003). Percutaneous transhepatic cholangiography (PTCD) may also be used in these cases, although oftentimes unsuccessful due to difficulty in accessing non-dilated intrahepatic ducts. Small, asymptomatic anastomotic bile leaks may be

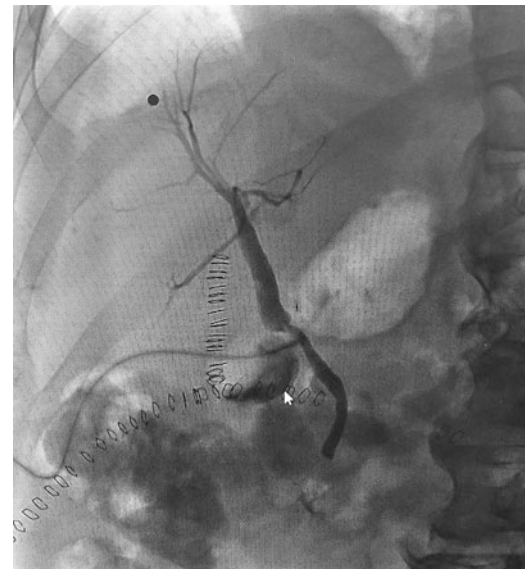

Fig. 3 Biliary leak

treated by opening the T-tube to decompress the biliary tree with follow-up cholangiogram after 2 weeks to check for resolution of bile leak. On the other hand, most persistent and symptomatic bile leaks post-T-tube removal can be managed successfully by ERCP and bile duct stent placement, with or without sphincterotomy. Biliary reconstruction by converting to Roux-en-Y choledochojejunostomy is the treatment of choice for bile leaks that do not respond to endoscopic or percutaneous approach. In patients with primary Roux-en-Y choledochojejunostomy with large bile leak or nonresponse to PTCD, revision of the Roux-en-Y anastomosis is the treatment of choice (see Fig. 3).

Biliary anastomotic strictures have a reported incidence of 5–10 %, majority of which occur within the first-year post-OLT (Verdonk et al. 2006). They may be associated with surgical technical complications, bile duct ischemia, previous bile duct leakage, and hepatic arterial flow problems, i.e., HAS or HAT. They manifest with progressive elevation of total bilirubin and canalicular enzyme levels. Although MRCP can be used to diagnose biliary strictures, T-tube cholangiogram, ERCP, or PTCD is still considered the gold standard in diagnosis of biliary anastomotic strictures. A simple bile duct stricture may be

Fig. 4 Biliary anastomotic stricture

treated by dilatation and stent placement. However, biliary reconstruction with conversion to a Roux-en-y choledochojejunostomy may be the only treatment for long bile duct strictures, ampullary dysfunction, or failure of endoscopic and percutaneous techniques. Since bile duct complications may be secondary to hepatic artery thrombosis or stenosis, ultrasound Doppler studies should be part of the work-up to evaluate hepatic artery patency (see Fig. 4).

Conclusion

Most post-OLT complications occur in the first month after OLT and can cause significant morbidity and mortality. Early recognition, diagnosis, and treatment of post-OLT complications are critical to successful short- and long-term graft and patient survival outcomes after OLT.

Cross-References

- ▶ HCC: The San Francisco Criteria
- ▶ Hepatopulmonary Syndrome and Portopulmonary Hypertension
- ▶ Infections and Sepsis After Liver Transplantation
- ▶ Liver Transplantation for HCC: The Milan Criteria

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Part III

Anesthesia Management

Anesthesia Management of Liver Transplantation

9

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Contents

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Abstract

Anesthesia for liver transplantation pertains to a continuum of critical care of patients with end-stage liver disease. Hence, anesthesiologists, armed with a comprehensive understanding of pathophysiology and physiologic effects of liver transplantation on recipients, are expected to maintain homeostasis of all organ function. Specifically, patients with fulminant hepatic failure develop significant changes in cerebral function, and cerebral perfusion is maintained by monitoring cerebral blood flow and cerebral metabolic rate of oxygen, and intracranial pressure. Hyperdynamic circulation is challenged by the postreperfusion syndrome, which may lead to cardiovascular collapse. The goal of circulatory support is to maintain tissue perfusion via optimal preload, contractility, and heart rate using the guidance of right-heart catheterization and transesophageal echocardiography. Portopulmonary hypertension and hepatopulmonary syndrome have high morbidity and mortality, and they should be properly evaluated preoperatively. Major bleeding is a common occurrence, and euvolemia is maintained using a rapid infusion device. Pre-existing coagulopathy is compounded by dilution, fibrinolysis, heparin effect, and excessive activation. It is treated using selective component or pharmacologic therapy based on the viscoelastic properties of whole blood. Hypocalcemia and hyperkalemia from massive transfusion, lack of hepatic function, and the postreperfusion syndrome should be aggressively treated. Close communication between all parties involved in liver transplantation is also equally valuable in achieving a successful outcome.

Keywords

Anesthesia • Cirrhosis • Coagulation • Liver transplantation • Fibrinolysis • Hepatopulmonary syndrome • Hypocalcemia • Hyperkalemia • Physiology • Portopulmonary hypertension • Postreperfusion syndrome • Rapid infusion device • Transesophageal echocardiography • Thromboelastography

Introduction

Dr. Thomas Starzl of Denver, Colorado, USA, who believed that "liver transplantation is an effective treatment providing exactly what is needed for patients with end-stage liver disease (ESLD)," performed the first successful orthotopic liver transplantation (OLT) in a 3-year-old boy with biliary atresia in 1963 (Starzl et al. 1963). During the first two decades of the procedure's history, liver transplantation led by Starzl and Sir Roy Calne of Cambridge encountered almost insurmountable challenges, including complexity of surgical technique, primitive anesthesia and intensive care, less-than-adequate immunosuppression and organ preservation, and devastating infection. The number of procedures performed was relatively few, and the success rate was low. However, their keen observations on these early clinical experiences laid the foundation of modern liver transplantation (Starzl and Putnam 1969; Calne 1983).

Breakthroughs were made in each decade following the first transplantation. In the 1980s, venovenous bypass was introduced to maintain better hemodynamic stability (Shaw et al. 1984), cyclosporine was found to be a superior immunosuppressant to azathioprine, and anesthesiologists answered important clinical questions, including those relating to the monitoring and treatment of coagulopathy, hemodynamic changes, and the role of the electrolyte imbalance. In the 1990s, FK506 (tacrolimus) became the immunosuppressant of choice (Starzl et al. 1989), University of Wisconsin solution was introduced to extend the safe cold ischemia time to 24 h (Kalayoglu et al. 1988), and the piggyback technique simplified surgery in select patients (Tzakis et al. 1989). In the past 15 years, liver transplantation has been performed in most major medical centers with a 1-year survival rate of greater than 85 %, and living donor liver transplantation has become a valuable alternative.

Liver transplantation requires a true multidisciplinary approach, and anesthesiologists and intensivists have played a major role in the successful outcome of liver transplantation. In support of the important role of anesthesiologists in

liver transplantation, the American Society of Anesthesiologists (ASA) developed the *Guidelines for Director of Liver Transplant Anesthesia* in 2001. The guidelines specified that the Director should have fellowship training in critical care medicine, cardiac anesthesiology, or transplantation anesthesiology that includes the perioperative care of at least ten liver transplant recipients or experience in the perioperative care of at least 20 liver transplant recipients in the operating room. In addition, the Director is expected to obtain a minimum of 8 h of Accreditation Council for Continuing Medical Education (ACCME) Category I continuing medical education (CME) credit in transplantation-related educational activities within the most recent 3-year period.

In this chapter, physiology and pathophysiology of liver disease and anesthesia care of liver transplantation are described based on clinical experience at the University of Pittsburgh (Pittsburgh, PA, USA) and Thomas Jefferson University (Philadelphia, PA, USA).

Anatomy of the Liver

The liver, which weighs 1200–1500 g in adults, is traditionally divided into the right and left lobe in reference to the location of the falciform ligament. Couinaud, however, divided the liver into the right and left hemiliver using the Cantlie's line, which extends from the inferior vena cava (IVC) to the gall bladder, and each hemiliver is further divided into four segments (Couinaud 1954). The left hemiliver is composed of the traditional left lobe along with the caudate and quadrate lobe. Liver resections based on these segmental definitions are right hepatectomy (segments 5–8), right lobectomy (segments 4–8), left hepatectomy (segments 1–4), and left lobectomy (segments 1–3) (Fig. 1) (Bismuth 1982).

The liver has a unique dual blood supply: arterial supply from the hepatic artery, a branch of the celiac axis, and venous supply from the portal vein formed by the union of the splenic and superior mesenteric vein. Despite liver mass constituting only 2.5 % of the total body weight, the total hepatic blood flow is approximately 100 mL/100 g/min, or 25 % of cardiac output. The hepatic artery supplies approximately 25–30 % of hepatic blood flow and 45–50 % of the oxygen requirement, while the portal vein supplies 70–75 % of hepatic blood flow and 50–55 % of oxygen. The venous drainage is through the right, middle, and left hepatic veins, which merge into the IVC. The valveless portal vein is a low pressure/low resistance circuit, while the hepatic artery is a high pressure/high resistance system. Hepatic

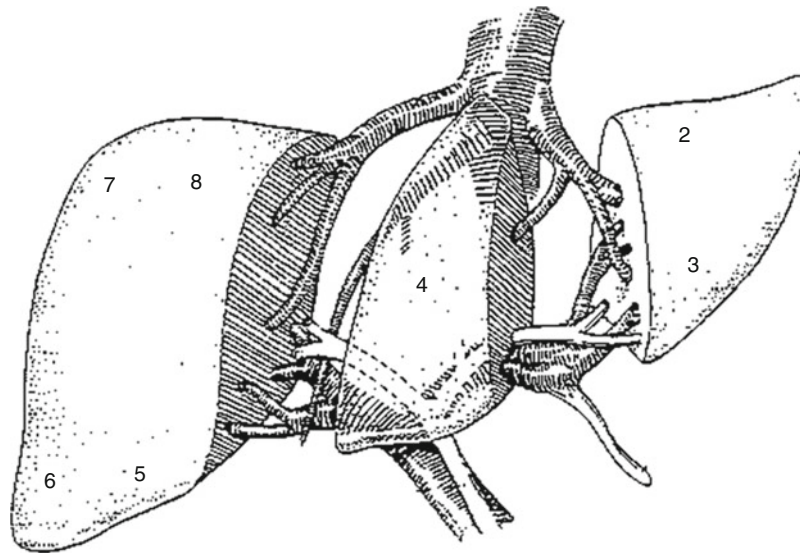

Fig. 1 Segments of the liver (Reprinted from Clin Liver Dis, 4, Ghobrial RM, Amersi F, Busuttil RW, Surgical advances in liver transplantation. Living related and split donors, 553–565, Copyright (2000), with permission from Elsevier)

blood flow is primarily regulated by local metabolic demand with an inverse relationship between portal venous and hepatic arterial flow: an increase in the hepatic adenosine level triggered by a reduced portal venous flow increases hepatic arterial blood flow (Gelman and Ernst 1977; Lautt et al. 1985). The hepatic artery buffer response appears to be functional even after liver transplantation (Payen et al. 1990), and this response may be responsible for the development of the small-for-size syndrome after living donor or split liver transplantation (Kiuchi et al. 1999). Small-for-size syndrome develops in a patient who received a donor graft that was less than 1 % of the recipient's body weight and is caused by decreased hepatic arterial flow in response to increased portal venous flow and pressure. Subsequently, a prolonged postoperative reduction in hepatic arterial flow can lead to centrilobular tissue necrosis, biliary ischemia, and hepatic arterial thrombosis (Smyrniotis et al. 2002). There is no buffer response in the portal system because the portal vein cannot regulate its blood flow. Therefore, alterations in the hepatic arterial blood flow do not induce compensatory changes in the portal blood flow (Lautt 1983).

The mean pressure in the hepatic artery is similar to that in the aorta, while portal vein pressure ranges between 6 and 10 mmHg. The portal pressure depends primarily on the degree of constriction or dilatation of the splanchnic arterioles and on intrahepatic resistance. Both afferent systems merge at the sinusoidal bed, where the pressure is estimated to be 2–4 mmHg higher than that in the IVC. The liver serves as a blood reservoir, and it replenishes blood volume of up to 25 % rapidly in the case of an acute bleeding episode (Lautt 2007). Hepatic blood volume may expand considerably in cardiac failure by venous congestion.

The liver is innervated by the left and right vagi, the right phrenic nerve, and fibers from the T7–T10 sympathetic ganglia. The hepatic artery is innervated mainly by sympathetic fibers, and hepatocytes, by the unmyelinated sympathetic fibers. The bile ducts are innervated by both sympathetic and parasympathetic fibers. The role of hepatic innervation is unclear, as denervation of the transplanted liver does not affect its function (Kjaer et al. 1994).

Bile flow begins from the bile canaliculi to the common bile duct. Hepatic lymph forms in the space between the sinusoid and the hepatocyte (space of Disse) and flows to lymph nodes in the hilum and IVC. The transdiaphragmatic lymphatic flow is the cause of pleural effusions in the presence of large ascites.

The liver is made of parenchymal cells (hepatocytes) and non-parenchymal cells (sinusoidal endothelial, Kupffer, stellate, dendritic, and lymphocyte). Hepatocytes make up 60–80 % of liver cells and carry out hepatic metabolic, synthetic, and detoxification functions. Polyhedral hepatocytes are arranged in one-cell thick plates with endothelium-lined sinusoids on both sides. Each hepatocyte cell membrane has three distinct membrane domains. The sinusoidal membrane is adjacent to the sinusoidal endothelium and has numerous microvilli abutting into the space of Disse. Fenestrae within the sinusoidal endothelium without the basement membrane permit intimate contact between sinusoidal blood and the hepatocytes to allow the passage of big molecules, including lipoproteins. Liver sinusoidal endothelial cells make up 15–20 % of liver cells and release nitric oxide to regulate vascular resistance. They are, along with dendritic cells and lymphocytes, part of the innate immune system. The space of Disse contains phagocytic Kupffer cells that participate in the hepatic inflammatory process. The Ito cells, also known as stellate cells, are the major site of vitamin A storage, and their activation results in hepatic fibrosis and cirrhosis. Reticulin fibers in the space of Disse support the sinusoidal framework, and weakening of these supporting fibers results in rupture of sinusoidal walls and formation of blood-filled cysts known as peliosis hepatis, a forerunner of cirrhosis. The apical membrane circumscribes the canaliculus, the earliest component of the biliary system. The lateral hepatic membrane is found between adjacent hepatocytes.

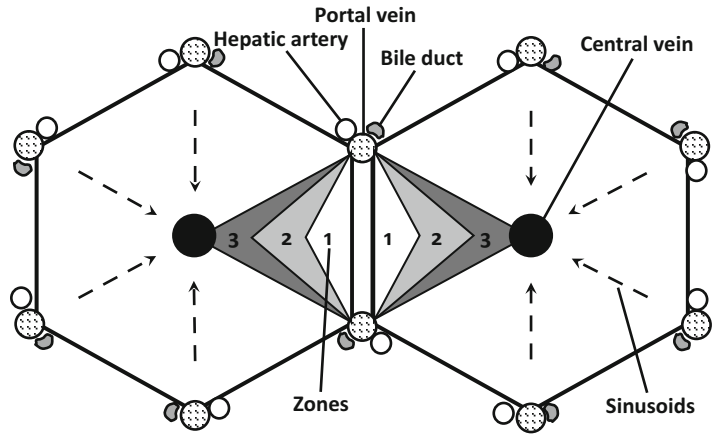

Fig. 2 Schematic diagram of the acinus

The functional unit of the liver is the acinus. Terminal portal veins communicate with terminal hepatic venules, with sinusoids bridging the gap between the two vessels (Fig. 2). Each sinus contains three zones with equal blood pressure and oxygen content. The periportal zone (Zone 1) receives blood highest in oxygen content and the pericentral or perivenular zone (Zone 3) receives blood lowest in oxygen content. As a result, the hepatocytes in the perivenular zone (Zone 3) are more vulnerable to ischemic damage and nutrient depletion. Oxidative and reductive functions are predominantly performed by hepatocytes at the periportal zone and glucuronidation is performed by those at the perivenular zone, although hepatocytes of the two different zones are functionally integrated (Lamers et al. 1989). The unique structure of the liver acinus is well-suited for bidirectional transfer of nutrients. The low pressure in the portal venous system allows blood to flow slowly through the sinusoids. Hepatic arterial blood flows mainly to the terminal bile canaliculi, although it augments sinusoidal flow to give a gentle pulsatility. In patients with liver cirrhosis, the sinusoids acquire features of systemic capillaries: the space of Disse widens with collagen deposits at the basement membrane, endothelial fenestrations become smaller and fewer, and hepatic microvilli efface. All of these changes reduce transport across the sinusoidal walls and result in hepatic dysfunction. Furthermore, widespread fibrosis and scarring reduce the number and size of the small portal and hepatic veins and increase intrahepatic vascular resistance to the development of portal hypertension (Popper 1977). The sluggish blood flow in the altered vascular architecture promotes thrombosis, causing further cell necrosis and fibrosis (Wanless et al. 1995).

The liver undergoes rapid regeneration through proliferation of hepatocytes to maintain the critical mass necessary for normal liver function. For example, the newly transplanted hemiliver from a living related donor regenerates to about 85 % of its original whole liver size in 7–14 days. The major hepatic growth factors are epidermal growth factor and hepatocyte growth factor (Michalopoulos 1990). Administration of the epidermal or hepatocyte growth factor to normal rats, however, does not cause hepatocyte replication. This negative response suggests that liver regeneration involves a two-step process: the initial signal generated by an acute increase in metabolic demand associated with the loss of hepatocytes triggers a set of early response genes that prime hepatocytes to respond to various growth factors. In apoptosis or programmed cell death, aging hepatocytes are removed and new cells are produced in a continuous manner (Ellis et al. 1991).

Hepatic Function

The liver has three major functions: metabolism, bile production and secretion, and filtration of harmful substances.

Carbohydrate Metabolism

The principal role of the liver is to provide the body with normal glucose levels, which are regulated by insulin, glucagon, growth hormone, and catecholamines (Pilkis and Granner 1992). The liver converts glucose into glycogen (glycogenesis) and utilizes glucose for the synthesis of fatty acids.

Cirrhotic patients are frequently hyperglycemic although their insulin level is elevated (Petrides and DeFronzo 1989). This insulin resistance is caused by multiple mechanisms. Cirrhotic patients have an increased basal metabolic rate and use preferentially fatty acids as an energy source. Reduced glucose uptake and limited glucose storage in the liver and muscle lead to hyperglycemia. Other contributing factors are increased serum fatty acids, which inhibit glucose uptake by muscle; altered second messenger activity after insulin binding to its receptors; an increased concentration of serum cytokines associated with elevated levels of endotoxins; and increased levels of glucagon and catecholamines.

Protein and Amino Acid Metabolism

The liver is the major organ for protein synthesis, and albumin is the most important protein product. Albumin is the major contributor to plasma oncotic pressure and binds and transports bilirubin, hormones, fatty acids, and other substances. Hypoalbuminemia is commonly caused by decreased hepatic synthetic function, although it can be secondary to an enlarged volume of distribution, reduced level of amino acid precursors, and losses into the urine, peritoneum and pleural cavity, and leads to peripheral edema, ascites, and pleural effusions. The low serum oncotic pressure stimulates the hepatic albumin synthesis in healthy subjects, but this is impaired in patients with cirrhosis (Pierrangelo et al. 1992). The liver synthesizes all coagulation factors (except von Willebrand factor) and protein C and S. Factors II, VII, IX, and X undergo a posttranslational vitamin K-dependent modification involving γ-carboxylation of specific glutamic acid residues in the liver.

The liver is the primary site of interconversion of amino acids. Anabolic processes synthesize proteins from amino acids, while catabolic processes convert amino acids either to keto acids by transamination or ammonia by oxidative deamination. Ammonia, in turn, is converted to urea by the Krebs-Henseleit cycle. In patients with liver disease, derangement of both anabolic and catabolic processes results in decreased production of blood urea nitrogen (BUN) and accumulation of ammonia, a contributing factor in the development of hepatic encephalopathy. The liver produces acute-phase reactants, such as α-fetoprotein, ceruloplasmin, fibrinogen, transferrin, complement, and ferritin. They are expressed during acute and chronic systemic inflammation, and their activation is mediated by interleukin-6, tumor necrosis factor, interferon- γ, and glucocorticoids.

Lipid Metabolism

The liver takes up fatty acids and cholesterol from diet and peripheral tissues to produce and release lipoprotein complexes into circulation. Fatty acids released from adipocytes are bound to serum albumin and transported to the liver for the synthesis of phospholipids and triglycerides. The liver produces fatty acids from small molecular weight precursors, and cholesterol synthesis is regulated by the rate-limiting enzyme 3-hydroxyl-3 methylglutaryl coenzyme A reductase (HMG-CoA reductase). Lipids are exported out of the liver by very low-density lipoprotein (VLDL) particles, which are the major carriers of plasma triglycerides during non-absorptive states. Lipids are temporarily stored in the liver as fat droplets, or as cholesteryl esters in the case of cholesterol, and are directly excreted

into bile or metabolized into bile acids. The liver is the major site for sterol excretion and production of bile acids.

Various abnormalities in lipid metabolism are common in liver disease. Hypertriglyceridemia (250–500 mg/dL) is the most common presentation and may be caused by decreased synthesis of lipoproteins, decreased hepatic clearance of lipoprotein complexes, or re-entry of biliary content into the serum. Alcoholic liver injury results in increased fatty acid synthesis and steatosis (Lieber 1993). Paradoxically, an increased high-density lipoprotein (HDL) 3 level has been noted with moderate alcohol consumption, which may explain the reduced risk of atherosclerosis in these patients (Chait and Brunzell 1990). Patients with cholestatic liver diseases have elevated total serum cholesterol and triglycerides because the bile is rich in cholesterol, phospholipids, and lecithin.

Detoxification and Hormone Alteration

The liver eliminates drugs through two types of reactions. The phase 1 reactions include oxidation, reduction, hydroxylation, sulfoxidation, deamination, dealkylation, and methylation of reactive substances. These reactions involve systems such as cytochrome P450 and typically occur in the periportal area of the liver. The phase 2 reactions, which transform lipophilic agents into more water-soluble compounds, take place in the pericentral area. In patients with liver disease, hepatic drug clearance is usually reduced due to the enlarged volume of distribution and decreased hepatic metabolism. As a result, a large initial dose of medications followed by small, titrated maintenance doses are required to achieve the desired pharmacologic effects.

Several hormones are deactivated or altered in the liver. The deactivated hormones are insulin, glucagon, steroid hormones, aldosterone, thyroxine, and triiodothyronine. The liver converts testosterone into androsterone and estrogen into estrone and estriol. Abnormal levels of estrogen and testosterone in patients with liver disease lead to testicular atrophy, loss of pubic and axillary hair, spider angioma, and gynecomastia.

Excretory Function

The liver removes various substances from the body, and bile formation is one of the most important excretory functions. When membranes of old erythrocytes rupture, the released hemoglobin is taken up by the reticuloendothelial cells and is split into heme and globin. Heme converts to biliverdin, which, in turn, is reduced to free bilirubin and released into the plasma. The free bilirubin–albumin complex is taken up by the hepatocytes. Bilirubin conjugates primarily with glucuronic acid and is actively transported into the bile. A small portion of conjugated bilirubin returns to the plasma directly from the sinusoids or indirectly by absorption from the bile ducts and lymphatics. Bilirubin is converted into urobilinogen by the intestinal bacterial flora. Some urobilinogen is reabsorbed through the intestinal mucosa and is re-excreted into the intestine. Bile acids, which enhance absorption of vitamin K, are also excreted into the bile by the liver.

Filtration Function

The liver, located between the splanchnic and systemic venous system, acts as a vascular filter. Kupffer cells phagocytose immune complexes, endotoxins, and bacteria in the portal venous blood and process antigens for presentation to immunocompetent cells. The liver also removes activated coagulation elements from circulation to prevent excessive coagulation or fibrinolysis.

Pathophysiology of Liver Cirrhosis

Liver cirrhosis is defined as progressive fibrosis and the formation of regenerative nodules, and is the final common pathway in which hepatocytes are replaced by connective tissue after various, repetitive insults. The amount of remaining functional hepatic mass and the degree of architectural distortion determine the functional state of the

Table 1 Child-Pugh score

	Points		
Presentation	1	2	3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4–6	>6
INR	<1.7	1.7–2.3	>2.3
Bilirubin (mg/dL)			
Hepatocellular disease	<2	2–3	>3
Cholestatic disease	<4	4–10	>10
Ascites	Absent	Mild–moderate	Tense
Encephalopathy	None	Grade 1–2	Grade 3–4

Class A = 5–6 points, B = 7–9 points, and C = 10–15 points
INR international normalized ratio

liver. Portal hypertension is inevitable in advanced cirrhosis and leads to ascites, variceal bleeding, and encephalopathy. The severity of cirrhosis is frequently classified using the Child-Pugh score (Table 1), and a score of >6 suggests a short life expectancy.

Central Nervous System

Hepatic encephalopathy is a reversible neuropsychiatric condition in both acute and chronic liver failure. In chronic liver disease, hepatic encephalopathy develops in 28 % of patients within 10 years of compensated cirrhosis and is associated with spontaneously developed or surgically created portosystemic shunting (Butterworth 2001). The degree of encephalopathy is stratified by a coma scale: Grade 1, subtle confusion; Grade 2, somnolence; Grade 3, unconsciousness with response to pain stimulation; and Grade 4, deep coma. Clinically, asterixis, flapping tremor, and *fetor hepaticus* (musty, sweet breath odor) are confirmatory of hepatic encephalopathy.

The main cause of hepatic encephalopathy is the altered expression of several genes for various neurotransmitter proteins in the brain (Butterworth 2001). Decreased expression of the glutamate transporter (GLT-1) increases extracellular brain glutamate. An increased expression occurs in some receptors: monoamine oxidase increases degradation of monoamine transmitters, the peripheral-type benzodiazepine receptor increases inhibitory neurosteroids, and neuronal nitric oxide synthase increases nitric oxide production. Although its plasma level is not closely related to the severity of encephalopathy, ammonia is still considered to be a major contributing factor. Ammonia and manganese are known to alter the expression of the peripheral-type benzodiazepine receptor and neuronal nitric oxide synthase in exposed cells (Warskulat et al. 2001).

Magnetic resonance spectroscopy reveals brain edema and increased brain glutamine/glutamate in the frontal and parietal lobes; histologic findings are swelling and glycogen deposition in astrocytes. These changes in the brain coincide with impairment in the visuopractic capacity, visual scanning, and perceptual–motor speed on neuropsychiatric testing (Tarter et al. 1984). Subclinical hepatic encephalopathy can be detected by having patients perform a simple timed connect-the-numbers test.

Treatment of hepatic encephalopathy is based on the ammonia-lowering strategy, such as protein restriction, oral non-absorbable antibiotics, and lactulose. Rifaximin reduces the plasma ammonia level by destroying intestinal bacteria that produce urease. Metronidazole (800 mg/day) is another antibiotic, although its adverse effects limit its use to 1 week at a time. Lactulose is a substrate for gut bacteria and reduces the formation of ammonia by lowering intestinal pH. Rifaximin

and lactulose are commonly used together, and the antibiotic is discontinued once eradication of disaccharide-metabolizing intestinal bacteria is indicated by an increase in stool pH. Oral or parenteral ornithine aspartate, a substrate for the conversion of ammonia to urea and glutamine, has effects similar to those of lactulose, but with fewer adverse effects. In patients with severe encephalopathy, the molecular-absorbent recycling system (MARS) may be utilized to remove small and middle molecular weight water-soluble substances (Sorkine et al. 2001). The system appears to increase blood pressure and systemic vascular resistance, possibly by removing nitric oxide.

In fulminant hepatic failure, progressive hepatic coma is accompanied by a gradual increase in cerebral blood flow and intracranial pressure (ICP) (see ▶ Chap. 12, "Fulminant Hepatic Failure: Diagnosis and Management"). Subsequently, vasogenic cerebral edema and severe intracranial hypertension develop and approximately 30–50 % of patients die of brain herniation. Monitoring of ICP using a Ladd epidural sensor is useful in detecting intracranial hypertension, monitoring the therapeutic effects, and identifying patients who would survive after transplantation without neurologic damage (Lidorsky et al. 1992). Non-invasive neurologic assessment includes transcranial Doppler (TCD) to measure cerebral bloodflow velocity, determination of the cerebral metabolic rate for oxygen by calculating the oxygen content difference between arterial and jugular bulb venous blood, evoked potentials, and serial computed tomography (CT) scans (Aggarwal et al. 1994). Treatment includes osmotic and loop diuretics, barbiturate-induced coma, and hypothermia. The definitive treatment is usually transplantation.

Cardiovascular System

The presence of hyperdynamic circulation with a markedly increased cardiac output and decreased systemic vascular resistance was first described by Kowalski and Abelmann in the early 1950s (Kowalski and Abelmann 1953). Several hypotheses have been proposed to explain this phenomenon, including an overactive sympathetic nervous system, inadequate clearance of vasoactive substances by the diseased liver, the presence of arteriovenous shunts, nitric oxide-induced vasodilation, and relative hypoxia in peripheral tissues (Benoit et al. 1984; Yokoyama et al. 1989; Kalb et al. 1993; D'Souza et al. 1993).

Although cardiac output is frequently two to three times normal, impaired systolic and diastolic function together with attenuated cardiac responsiveness to stimuli suggests that cardiomyopathy is present in cirrhotics (cirrhotic cardiomyopathy) (Lee 1989). Caramelo et al. noted a 50 % decrease in cardiac output with volume expansion in a CCl_4-induced cirrhotic rat model (Caramelo et al. 1986). In another rat model, the chronotropic response to isoproterenol was attenuated compared with that in control animals (Lee et al. 1990). Cardiac response to physical exercise is blunted in patients with cirrhosis, indicated by alterations in the pre-ejection period, isometric contraction time, and ratio of the pre-ejection period to left ventricular ejection time. In addition, abnormalities in myocardial diastolic indices suggest non-compliant ventricles. Histologically, myocardial fibrosis, mild subendocardial edema, and vacuolation of myocyte nucleus and cytoplasms are observed. The development of cirrhotic cardiomyopathy is multifactorial. It appears that the β-receptor system, the main stimulant of the ventricle, is dysfunctional. In humans, lymphocyte β-receptor density, which reflects cardiac β-receptor status, is reduced in patients with severe ascites (Gerbes et al. 1986), and β-receptor density of the cardiomyocyte sarcolemmal plasma membrane is reduced in cirrhotic rats (Liu and Lee 1999). Further, the β-receptor signal transduction pathway is impaired at several levels (Ma et al. 1996). Although cardiac contractile impairment may result from overactivity of the muscarinic M_2 receptor, the receptor density and binding affinity are unchanged, suggesting normal parasympathetic function (Jaue et al. 1997). High serum catecholamine levels, a result of desensitization and down-regulation of β-receptors, may lead to myocardial dysfunction

in the presence of α-mediated coronary vasoconstriction. Additionally, overproduction of nitric oxide inhibits β-receptor-stimulated cyclic adenosine monophosphate (cAMP) release, causing myocardial dysfunction and vasodilation (Hare and Colucci 1995).

Coronary artery disease (CAD) was previously believed to be relatively uncommon in patients with cirrhosis as a result of generalized vasodilation and elevated levels of HDL and estrogen. In addition, autopsy findings showed relatively fewer atherosclerotic changes and myocardial infarction. However, studies have shown that CAD is not uncommon, and moderate-to-severe CAD was found in approximately 27 % of patients who underwent coronary artery catheterization as a part of liver transplantation workup (Carey et al. 1995). In another study of 161 liver transplantation candidates who were at risk for CAD and referred for coronary angiography, 25 % of patients had at least one moderate or severe (>50 %) coronary stenosis (Tiukinhoy-Laing et al. 2006).

Endocarditis is three times more common in patients with liver disease (Snyder et al. 1977). This is attributed to translocation of intestinal bacteria through the intestinal wall and portosystemic collaterals, and reduced immune response. The incidence of pericardial effusion in cirrhotic patients is approximately 32–63 % and correlates with the degree of liver failure (Shah and Variyam 1988). The effusion is usually small and may require drainage if it affects cardiac function. Patients with liver disease exhibit three common cardiac electrophysiological disturbances: electromechanical dissociation, prolongation of ventricular repolarization (the Q–T interval), and chronotropic incompetence (Milani et al. 2007).

Pulmonary hypertension associated with portal hypertension was first described in 1951 (Mantz and Craige 1951). Pulmonary hypertension defined as a mean pulmonary artery pressure of >25 mmHg and pulmonary vascular resistance of >240 dyn/s/cm^{-5} (3 Wood units) is more common in patients with liver disease, with a prevalence of 0.25–0.73 % (Lebrec and Capron 1979; McDonnell et al. 1983). Pulmonary artery pressure is a function of pulmonary venous pressure, pulmonary vascular resistance, and cardiac output [(Pulmonary artery pressure = Pulmonary venous pressure + (Pulmonary vascular resistance × Cardiac output)]. Therefore, pulmonary hypertension is not uncommon in patients with liver disease because of their poor left ventricular compliance, increased pulmonary vascular resistance, and increased pulmonary blood flow from portosystemic shunting. The pathophysiology and management of pulmonary hypertension are well-described in ▶ Chap. 10, "Hepatopulmonary Syndrome and Portopulmonary Hypertension".

Portal hypertension is caused by an increased intrahepatic vascular resistance and increased splanchnic blood flow. Endothelin-1, a powerful vasoconstrictor produced by the sinusoidal endothelial cells, is known to increase intrahepatic vascular resistance and activates stellate cells, and its level increases as cirrhosis progresses (Kojima et al. 2002; Gandhi et al. 1996). Normally, vasodilatory compounds, such as nitric oxide, counterbalance the increased intrahepatic vascular resistance induced by endothelin. In liver cirrhosis, however, nitric oxide production is inhibited by caveolin-1, a hepatic membrane protein that binds with endothelial nitric oxide synthase.

Pulmonary System

Hypoxemia of varying severity is present in 45–69 % of patients with significant liver disease (Krowka and Cortese 1985). The common causes are pleural effusions, impaired diffusion capacity, arteriovenous shunting, atelectasis caused by ascites or diaphragmatic dysfunction, aspiration secondary to encephalopathy, and deconditioning (Hourani et al. 1991). Ventilation–perfusion mismatch, pulmonary vasodilation, and infection also contribute to hypoxemia. Mild forms of hypoxemia are most common, although moderate-to-severe hypoxemia may be found in patients with advanced liver disease complicated by adult respiratory distress syndrome (ARDS), infection, and multiple organ failure.

Hepatopulmonary syndrome, first described by Fluckiger in 1884 (Fluckiger 1884), may cause severe hypoxemia in a subset of patients with liver disease. The syndrome consists of a triad of liver dysfunction, severe hypoxemia ($PaO_2 < 70$ mmHg in room air), and pulmonary vasodilation, and is characterized by dyspnea, cyanosis, clubbing of the digits, exercise desaturation, and orthodeoxia (hypoxemia in upright position). Other concomitant clinical signs are a markedly increased alveolar–arterial oxygen gradient, portal hypertension, and vascular abnormality such as spider angioma and pulmonary vasodilation. The pulmonary vascular dilation (from 8–15 μ to 15–100 μ) at the precapillary level is believed to be the main pathology of the hepatopulmonary syndrome, which is caused by decreasing erythrocyte transit time and impairing diffusion of oxygen to the erythrocytes at the center of the bloodstream (Genovesi et al. 1976). In contrast with other pulmonary diseases, oxygenation improves dramatically with a high inspired oxygen concentration (FiO_2), because a high alveolar concentration of oxygen overcomes the diffusion barrier and oxygenates the erythrocytes in the center of the bloodstream. The pathophysiology and management of hepatopulmonary syndrome are described in ► Chap. 10, "Hepatopulmonary Syndrome and Portopulmonary Hypertension".

Non-cardiogenic pulmonary edema occurs in 37–79 % of patients with advanced liver disease, particularly in those with fulminant hepatic failure, and appears to be associated with sepsis and a neurogenic mechanism. The presence of this complication is ominous: Matuschak and Shaw reported that all 29 patients who developed non-cardiogenic pulmonary edema died before liver transplantation (Matuschak and Shaw 1987). In contrast, a rapid reversal of ARDS after liver transplantation has been reported (Doyle et al. 1993). Pulmonary edema caused by fluid overload responds to diuretics and has a relatively benign course.

Pleural effusions are found on chest X-rays in about 10 % of patients. These are caused by the unidirectional passage of ascites via diaphragmatic defects into the pleural space. Diagnostic thoracentesis is necessary to confirm the transudative nature and to exclude infection, malignancy, or embolic disease. Optimal control of ascites may prevent symptomatic pleural effusions, and transjugular intrahepatic portosystemic shunt (TIPS) is effective in treating refractory hydrothorax in 84 % of patients (Siegerstetter et al. 2001).

Renal System

Approximately 10 % of hospitalized cirrhotic patients with ascites develop the hepatorenal syndrome, which is a form of acute pre-renal kidney injury caused by circulatory dysfunction secondary to an imbalance between circulating vasodilatory and vasoconstrictive substances. The primary contributing factor for the hepatorenal syndrome is nitric oxide-induced vasodilation of the splanchnic vascular bed causing systemic arterial underfilling and relative hypovolemia (Arroyo et al. 1996). This relative hypovolemia activates baroreceptor-mediated sympathetic and the renin–angiotensin system to constrict all vascular beds including the renal vasculature (Guevara et al. 1998). The initial prostaglandin-mediated compensatory renal vasodilation is followed by renal arterial vasoconstriction and renal hypoperfusion. A striking feature of the hepatorenal syndrome is the lack of any histologic change and its reversibility: the affected kidneys resume their function after successful liver transplantation. The renal failure may be rapid (Type 1) or insidious (Type 2) and results in sodium and water retention and dilutional hyponatremia. Since the hepatorenal syndrome is a functional renal failure, the urine is similar to that found in pre-renal azotemia: oliguria, low urinary sodium, and an increased urine osmolality and urine to plasma osmolality ratio.

The major criteria for the diagnosis of the hepatorenal syndrome are as follows: (1) advanced hepatic disease and portal hypertension; (2) low glomerular filtration rate (serum creatinine >1.5 mg/dL or creatinine clearance <40 mL/min); (3) absence of nephrotoxic drug use, shock, systemic infection, or recent fluid losses; (4) lack of sustained improvement after diuretic

withdrawal and volume resuscitation with 1.5 L of normal saline; (5) proteinuria (<500 mg/dL); and (6) no ultrasound evidence of urinary obstruction or parenchymal disease. Minor criteria include oliguria (<500 mL/day), urinary sodium <10 mEq/L, urinary osmolality greater than plasma osmolality, urinary red blood cells (RBCs) <50/hpf, and serum sodium <130 mEq/L. It is noteworthy that conventional renal function tests, such as BUN and creatinine levels, overestimate renal function in patients with liver failure because malnutrition and muscle wasting contribute to a low creatinine level and liver dysfunction impairs urea synthesis.

The hepatorenal syndrome is treated with the administration of vasopressin-1 agonists (i.e., terlipressin), TIPS, and, most reliably, liver transplantation. One uncontrolled trial using terlipressin with albumin for a median duration of 26 days (range 8–68 days) showed improvement in serum sodium as well as a decrease in the creatinine level below 2 mg/dL (Mulkay et al. 2001). Hemodialysis is a temporary measure and its efficacy is not reliable. The only primary preventive measure showing some promise is the administration of albumin along with antibiotics as soon as the presence of spontaneous bacterial peritonitis is diagnosed; this possibly works by preventing hypovolemia and subsequent activation of vasoconstrictor systems.

Coagulation System

All phases of hemostasis are impaired in patients with liver disease, including clot formation, fibrinolysis, and their inhibitory processes. Thrombocytopenia is found in 30–64 % of cirrhotic patients, and platelet count is commonly below 75,000/mm^3. Thrombocytopenia is primarily caused by splenomegaly associated with portal hypertension, which pools up to 90 % of platelets in the spleen. However, the degree of thrombocytopenia does not closely correlate with the size of the spleen. Impaired hepatic synthesis of thrombopoietin also leads to thrombocytopenia. Thrombopoietin is involved in the maturation and formation of platelets, and its return to a normal level coincides with a gradual increase in platelet count by the fifth day after liver transplantation (Kawasaki et al. 1999). Other contributing factors are increased destruction of platelets by immune mechanisms, excessive activation of coagulation, and direct bone marrow suppression by toxins such as ethanol and folate deficiency. Additionally, platelet dysfunction is common, as demonstrated by impaired platelet aggregation to adenosine diphosphate (ADP), collagen, and thrombin (Rubin et al. 1979).

The liver produces all coagulation factors except for von Willebrand factor. Therefore, plasma levels of clotting factors are directly related to the severity of liver disease, and prothrombin time (PT) is considered to be one of the most sensitive hepatic synthetic function tests. The plasma fibrinogen level, being an acute-phase reactant, typically is normal or increased in chronic liver disease. A reduction in the fibrinogen level may indicate either a greatly reduced hepatic reserve or significant extravascular loss to ascites. Markedly prolonged thrombin time indicates the presence of dysfibrinogenemia in some patients. Dysfibrinogenemia is characterized by an excessive number of sialic acid residues in the fibrinogen molecule and abnormal polymerization of fibrin monomers. Its clinical significance is unclear.

Patients with liver disease have a tendency to develop fibrinolysis due to decreased hepatic clearance of plasminogen activators, especially tissue plasminogen activator (tPA), and reduced production of α_2-antiplasmin and thrombin activatable fibrinolysis inhibitors (Van Thiel et al. 2001). Elevated levels of D-dimers, fibrin degradation products, and plasminogen are present in ascitic fluid, indicating that absorption of ascitic fluid may contribute to the hyperfibrinolysis.

On the other hand, excessive activation of coagulation is common in liver disease because of inadequate hepatic clearance of activated coagulation factors, reduced level of coagulation

inhibitors, and enlarged vascular beds. The hypercoagulable state may lead to localized or disseminated intravascular coagulation (DIC), particularly in the presence of sepsis, trauma, or major surgery. The diagnosis of excessive activation of coagulation is based on the presence of a known triggering factor and the progressively worsening of coagulation with thrombocytopenia.

Anesthesia Consultation

An anesthesia consultation is performed once a patient with ESLD is referred to the liver transplantation center. The type of liver disease is identified because patients with hepatocellular disease may have more pronounced hepatic dysfunction than those with cholestatic disease or hepatocellular cancer, and certain types of liver disease may affect other vital organ function (i.e., hemochromatosis, familiar amyloidosis, etc.). The anesthesia consultation is focused on evaluation of the functional reserve of extrahepatic organs, and various tests or specific consultations may be requested (Table 2).

Cardiovascular Assessment

Cardiovascular assessment is performed to determine two things: (1) whether a patient can be expected to survive the operation and immediate postoperative period; and (2) whether transplantation in patients with severe cardiopulmonary disease would be futile and an inappropriate use of a scarce donor organ (Lentine et al. 2012). A suggested strategy for cardiac assessment is shown in Fig. 3 (Raval et al. 2011). Overall cardiac performance is evaluated by transthoracic echocardiography to assess myocardial contractility, abnormality in cardiac anatomy, intracardiac or intrapulmonary shunting, and pulmonary artery pressure. Most patients over age 50 years undergo non-invasive stress testing because they may have multiple CAD risk factors (i.e., diabetes, hypertension, hyperlipidemia, and pre-existing cardiovascular disease), and limited physical activity masks underlying ischemic heart disease. An exercise stress test may not be feasible in many patients with advanced liver disease, and dobutamine stress echocardiography (DSE) is commonly used, although adenosine or dipyridamole may be used when dobutamine-induced tachycardia is not desirable. DSE, with its high sensitivity and specificity, appears to be the most reliable screening test (Plotkin et al. 1998), and dobutamine-induced tachycardia may mimic intraoperative stress on the cardiovascular system. On the contrary, DSE has been reported to have poor sensitivity (as low as 13 %) and negative predictive value (as low as 75 %) (Harinstein et al. 2008), and its results may not correlate with adverse cardiac events within 30 days after transplantation (Safadi et al. 2009).

Cardiac CT scan is a non-invasive technique measuring calcium deposits within the coronary vasculature. The total amount of calcium, adjusted to the age and gender of the patient, is reported as a calcium score. High scores suggest a greater potential for coronary artery stenosis (Shaw et al. 2003; O'Rourke et al. 2000), and a calcium score of >400 has a predictive value of cardiac complications within 1 month after transplantation (Kemmer et al. 2014). This test, however, may have limited predictive value as a single screening study for CAD. Cardiac CT angiography is an alternative to invasive coronary angiography. It does appear to have negative predicting value of 100 % for clinical coronary events in patients undergoing liver transplantation (Cassagneau et al. 2012) but may not be suitable for the diagnosis of obstructive lesions at this time.

Because of the difficulty in diagnosing CAD using non-invasive testing methods, coronary angiography is recommended for patients with a positive DSE or multiple high-risk factors to identify the degree and type of obstruction. In addition, coronary angiography should be able to detect non-obstructive lesions (coronary artery stenosis <50 %), which are unlikely to be detected by stress tests but can be

Table 2 Liver transplantation evaluation at the Thomas Jefferson University Hospital

Jefferson Transplant Institute

David Sass, MD • Steven K Herrine MD • Jesse Civan, MD • Dina Halegoua, MD • Jonathan Fenkel, MD • Manish Thapar, MD • Scott Fink, MD • Victor Araya, MD

Liver Transplant Evaluation
Lab/Diagnostic Testing Request

Phone: 215-955-8900 Fax: 215-503-2626
email: liver.evals@lists.jefferson.edu

Patient Name _____ Patient DOB _____

Hepatologist _____ Date _____ Referring Gastroenterologist _____

Laboratory
Chemistry/Hematology
☐CBC with diff and platelets
☐PT/PTT/INR
☐Comprehensive metabolic profile
☐Fe, TIBC, Ferritin
☐Alpha-Fetoprotien (tumor marker)
☐Serum Protein Electrophoresis
☐TSH and Free T4
☐UA (urinalysis)
☐Alpha 1 anti-trypsin level with phenotype
☐Ceruloplasmin
☐*PSA (men over 40)
☐* Blood Type (ABO)
Virology/Micro
☐*HIV
☐*HCV Antibody
☐*HBsAg, HBsAb, HBcAb
☐*HAV IgG+ IgM
☐*CMV, EBV, VZV Ab
☐*RPR
☐*Quantiferon Gold
Immunology
☐ANA
☐ASMA
☐AMA

Diagnostic Testing
☐*PPD with Anergy Panel
☐*Chest X ray, PA and Lateral
☐*Upper GI endoscopy
☐Colonoscopy (age/risk factor appropriate)
☐*Mammography (women over 40)
☐Pap Smear
Hepatobiliary Imaging
☐MRI with gadolinium
☐CT of abdomen & pelvis with contrast
☐US with Doppler
Cardiac Testing
☐Echocardiogram with Doppler and Bubble Study
☐12 Lead EKG
Pulmonary Studies
☐ABG on 100% O2
Vaccinations
☐Hepatitis B
☐Hepatitis A
☐Pneumovax
Consultations
☐Anesthesiology (transplant)
☐Social Work
☐Transplant Surgery
☐Dental

Tests below to be done only if clinically indicated

Laboratory
☐Drug & Alcohol Screen
☐HCV Quantitative RNA by PCR
☐HCV Genotype
☐HBV DNA, HbeAg, HbeAb
☐HDV Ab
☐HFE (genetic testing for Hemochromatosis)
☐HLA A, B, C, DR & PRA (for liver/kidney patients only)
☐Other: _____
Consultations
☐Pulmonary
☐Cardiology
☐Psychiatry
☐Substance Abuse Evaluation
☐Rehab Medicine
☐Nephrology
☐Endocrinology
☐Infectious Disease
☐Nutrition
***Indicates test/consults acceptable within 12 months of evaluation**

Diagnostic Testing
☐Dobutamine Stress Echo (preferred; beta blockers must be held for 48 hrs before)
☐Adenosine Stress test (Wt. <175lbs)
☐SESTA MIBI (Wt > 175 lbs; large ascites)
☐Full Pulmonary Function Tests, (age > 50 and /or smoking hx)
☐Carotid study/Cerebrovascular Duplex (Age >50 with h/o vascular disease)
☐Chest CT scan (for HCC patients)
☐DEXA scan if clinically indicated
☐ERCP
Liver Biopsy
☐Percutaneous , by Hepatologist
☐Ultrasound Guided, by Radiology
☐Transjugular, by CVIR
Vaccinations
☐Meningococcal
☐Hemophilus influenza B
☐Seasonal influenza
MELD: _____
MELD-Na _____
Expedite: ☐**YES** ☐**NO**
Indication for Expedited: _____

responsible for acute coronary syndromes (unstable angina, myocardial infarction, or sudden cardiac death) (Rubin et al. 1994; Gulati et al. 2009). Cardiac catheterization, however, can be difficult in patients with severe liver disease due to bleeding complications and the increased risk of contrast-induced nephropathy (Sharma et al. 2009).

If significant coronary artery stenosis (>70 % stenosis) is detected, revascularization may be

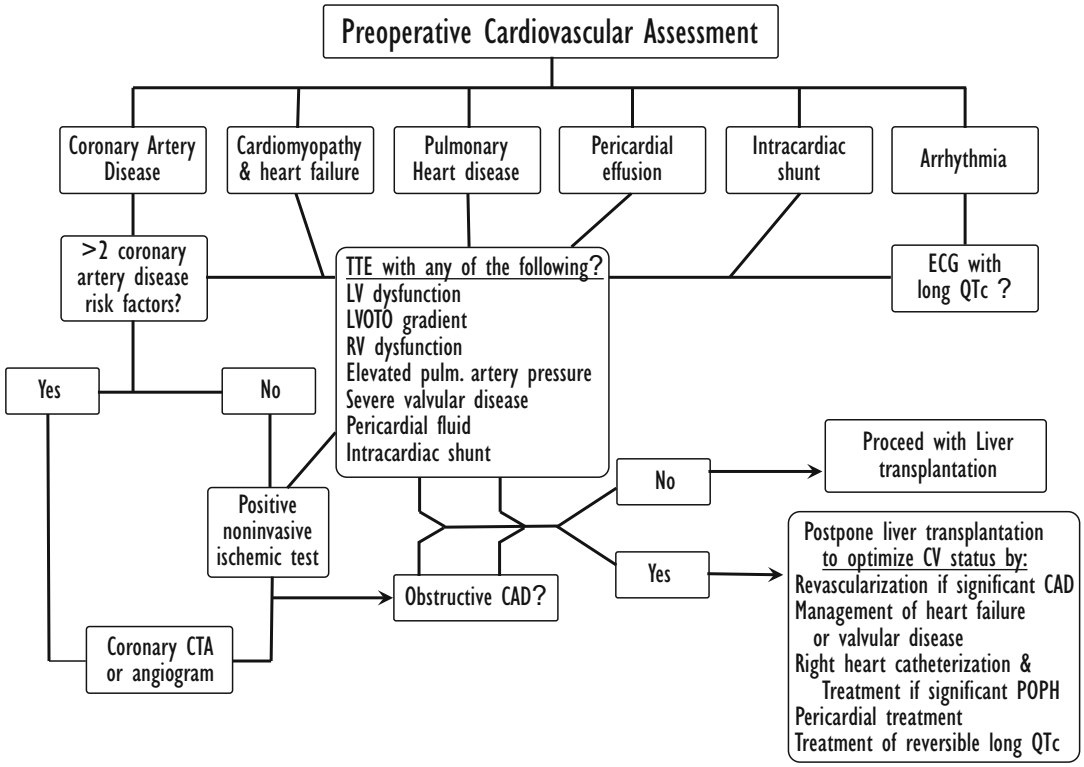

Fig. 3 Suggested strategy for preoperative cardiac assessment of liver transplantation candidates (Reprinted from JACC, 58, Raval Z, Harinstein ME, Skaro AI et al., Cardiovascular risk assessment of the liver transplant candidate, 223–231, Copyright (2011), with permission from Elsevier)

attempted before liver transplantation. Bare metal stents are favored over drug-eluting stents to avoid the need for long-term antiplatelet therapy (6 weeks vs. 1 year). When angioplasty is not amenable, coronary artery bypass grafting (CABG) is performed. It is clear that 1-year survival after CABG is greater in patients with Child-Pugh Class A (80 %) than with Child-Pugh Class B (45 %) and C (16 %) (Filsoufi et al. 2007). Therefore, patients with Child-Pugh Class A can undergo CABG relatively safely while waiting for liver transplantation. On the other hand, patients with Child-Pugh Class B and C may require simultaneous CABG and liver transplantation.

Patients with mild-to-moderate valvular disease undergo liver transplantation without excessive complications. Similar to that of CABG, mortality after corrective valvular surgery depends on the severity of liver disease. Therefore, Child-Pugh Class C patients with severe aortic or mitral valve stenosis may undergo percutaneous balloon valvuloplasty or simultaneous valve replacement with cardiopulmonary bypass and liver transplantation.

Myocardial disease is commonly detected by transesophageal echocardiography (TEE). Patients with chronic cardiomyopathy may have attenuated systolic contraction and diastolic relaxation, altered repolarization, and reduced cardiac response to β stimulation (Liu et al. 2002). Patients with moderate-to-severe cardiomyopathy may be excluded from candidacy. Moderate-to-severe hypertrophic obstructive cardiomyopathy (HOCM) can cause left ventricular outflow obstruction by systolic anterior motion (SAM) of the anterior leaflet of mitral valve, especially in the presence of tachycardia, hypovolemia, and β stimulation. In these patients, preload and

afterload should be optimized under the guidance of TEE, and tachycardia and β stimulation should be avoided. Surgical correction of the condition should be considered before or at the time of liver transplantation.

Pulmonary Evaluation

For pulmonary evaluation, results of chest X-ray, arterial blood oxygen tension in 100 % oxygen, and spirometry are reviewed to identify the degree of pulmonary shunting, obstructive, or restrictive disease. When the hepatopulmonary syndrome is suspected, contrast TEE or TC-99 m macro aggregated albumin scintigraphy may be performed for its definitive diagnosis (Krowka et al. 2000).

Renal Function

For evaluation of renal function, results of BUN, creatinine, glomerular filtration rate, levels of serum and urine electrolytes, urine output, and renal ultrasound are reviewed. The diagnosis criteria of the hepatorenal syndrome have been described earlier. In patients with chronic renal failure, simultaneous liver and kidney transplantation is performed, the criteria for which are end-stage renal disease with dialysis, no dialysis but a glomerular filtration rate <30 mL/min and proteinuria >3 g/day with a 24-h urine protein/creatinine ratio >3, and acute kidney injury requiring dialysis at least twice per week for more than 6 weeks (Charlton et al. 2009).

Fulminant Hepatic Failure

In patients with fulminant hepatic failure, reversibility of the neurologic function should be investigated using clinical signs, EEG, brain CT scan, the cerebral metabolic rate of oxygen, and TCD. In addition, ICP monitoring is recommended when a high ICP (>25 mmHg) is suspected, although its benefit should be weighed against potential complications (Vaquero et al. 2005). Poor prognostic indicators of fulminant hepatic failure are progressive hepatic failure for 7–14 days, grade 3–4 encephalopathy, intracranial hypertension, cerebral swelling, severe coagulopathy, rapid shrinkage of the liver, metabolic acidosis, hemodynamic instability, and sepsis.

Coagulation System

For the coagulation system, PT, activated partial thromboplastin time (aPTT), and platelet count are reviewed. In general, no specific coagulation therapy is requested because of the potential long waiting period and fluid overloading. Abdominal magnetic resonance imaging (MRI) is reviewed to assess the degree of portosystemic shunting and anatomy of hepatic vasculature. Additional consultation may be requested from various specialists to identify the type and severity of the specific organ dysfunction.

Contraindications

After the evaluation, all information of the potential recipient is compiled to stratify whether the patient's condition can be optimized or meet the criteria of contraindications. Contraindications are diseases or conditions patients could have that may not improve survival after liver transplantation. They include malignancy with poor prognosis, active bacterial and viral infection, severe cardiopulmonary dysfunction, and technical difficulties. Active alcoholism is a contraindication, although demonstrable abstinence for 6 months is considered acceptable. The presence of multiple organ dysfunction is a relative contraindication for liver transplantation as the 2-year survival is approximately 25 %. Indications and contraindications of liver transplantation, however, have evolved over the past 50 years, and further modifications are expected to occur.

Candidate Selection

Anesthesiologists participate in the Transplantation Candidate Selection Committee for discussion of the hepatic disease, its complications, and the extrahepatic organ function of each patient. Once the patient is placed on the active candidate list, the United Network for Organ Sharing (UNOS) is notified and the patient is given a MELD (Model for End-Stage Liver Disease) or PELD (Pediatric End-Stage Liver Disease) score for fair distribution of donor livers.

Surgical Aspects of Liver Transplantation

Although surgical techniques are fully described elsewhere, a brief description of their physiologic effects is warranted here.

In OLT, after removal of the diseased liver, the donor liver is placed anatomically in the right upper quadrant. For the convenience of description, the procedure is divided into three stages: stage 1 (dissection stage), stage 2 (anhepatic stage), and stage 3 (neohepatic stage). The dissection stage begins with an inverted Y-shaped bilateral subcostal skin incision and ends with the skeletonization of the diseased liver. The anhepatic stage begins with the occlusion of the hepatic artery, portal vein, and IVC for hepatectomy. However, the patient is virtually anhepatic once the hepatic artery or portal vein is occluded. Three surgical techniques are used for hepatectomy and vascular reconstruction during the anhepatic stage: OLT with simple venous cross-clamping, OLT with venovenous bypass, and the piggyback technique.

Orthotopic Liver Transplantation (OLT) with Simple Venous Cross-Clamping

In OLT with simple venous cross-clamping, the diseased liver is removed together with the retrohepatic portion of the IVC after cross-clamping of the suprahepatic and infrahepatic IVC, hepatic artery, and portal vein (Fig. 4). After surgical hemostasis of the hepatic bed, the donor liver is placed in the right upper

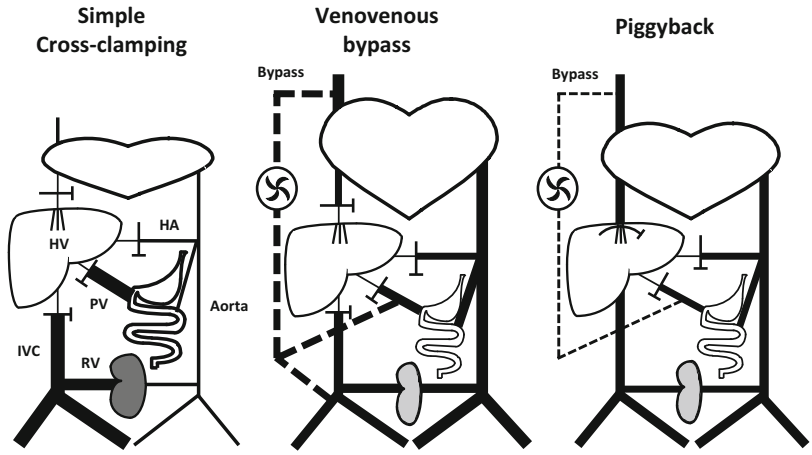

Fig. 4 Schematic diagram of three surgical techniques during the anhepatic stage. *Line thickness* indicates relative blood flow to each vasculature. The simple cross-clamping technique reduces venous return and cardiac output and leads to congestion of the viscera, kidneys, and lower extremities. The venovenous bypass technique maintains venous return without visceral congestion. Hemodynamic changes in the piggyback technique are between the two other techniques. *HA* hepatic artery, *HV* hepatic vein, *IVC* inferior vena cava, *PV* portal vein, *RV* renal vein)

quadrant, and sequential anastomoses of the suprahepatic IVCs, infrahepatic IVCs, portal veins, and hepatic arteries are performed. During the infrahepatic IVC anastomosis, the liver allograft is flushed with 1000 mL of cold lactated Ringer's solution or 5 % albumin solution through a cannula in the portal vein. This flush technique allows preservation solution, metabolites, and air in the donor liver to escape through the incompletely anastomosed infrahepatic IVC. A second flush may be used by allowing 300–500 mL of blood to escape through the incompletely anastomosed portal vein by unclamping the infrahepatic IVC (back-bleeding technique). When the portal vein of the recipient is less than optimal, the superior mesenteric vein, collateral vein, or venous graft may be used for portal blood supply. The hepatic artery is reconstructed by end-to-end hepatic arterial anastomosis. However, an arterial graft is placed between the graft hepatic artery and the infrarenal aorta of the recipient with a side clamp on the aorta when the size or anatomy of the recipient hepatic artery is less than optimal.

The liver is reperfused by the sequential unclamping of the infrahepatic IVC, portal vein, suprahepatic IVC, and hepatic artery. After hemostasis, choledochocholedochostomy is performed frequently with a T-tube. Choledochojejunostomy using a Roux-en-Y loop is performed when the bile ducts are diseased or mismatched in size. The abdomen is closed once the absence of foreign bodies in the peritoneal cavity is confirmed. In patients with a large graft or swollen intestine, the abdomen may require secondary closure.

OLT with Venovenous Bypass

OLT with venovenous bypass was developed in 1983 to minimize reduction of venous return associated with the cross-clamping of the IVC and portal vein by diverting blood from the IVC and portal vein to the axillary vein using a centripetal magnetic pump (Shaw et al. 1984). Once the hepatic hilum is dissected, cannulas are inserted into the left superficial femoral vein (7 mm) and portal vein (9 mm) for outflow from the patient and into the left axillary vein (7 mm) for venous inflow. The cannula site and size may vary depending on the preference of the surgical team or anatomic variations. The cannulas and heparin-bonded tubings are flushed with heparin solution (2000 U/L) to avoid thrombosis during preparation. Systemic heparinization is not used because of the presence of pre-existing coagulopathy and the use of heparin-bonded tubings. The bypass run begins by unclamping all cannulas while the pump speed is gradually increased to achieve the maximal flow rate. Hepatectomy and anastomoses of the suprahepatic and infrahepatic IVC are performed once full bypass is achieved. The removal of the portal cannula for portal venous anastomosis leads to a partial bypass, which reduces venous return. Bypass is terminated after the engrafted liver is reperfused, and cannulas are removed.

The advantages of venovenous bypass are (1) well-preserved cardiac output by uninterrupted venous return from the viscera and lower extremities; (2) effective decompression of the portal venous system, which decreases bleeding and intestinal congestion; (3) avoidance of renal congestion, oliguria, and hematuria; and (4) simplified anhepatic stage allowing meticulous hepatectomy and vascular anastomoses. Long-term complications are neurovascular injury, thrombosis, infection, lymphocele, and seroma at the cannulation sites.

As an alternative to the traditional venovenous bypass technique, percutaneous cannulation was introduced. In this technique, inflow to the patient is achieved by percutaneous cannulation of the right internal jugular vein (16–20 French) performed by the anesthesia team using a Seldinger technique, and outflow from the patient by percutaneous cannulation of the left femoral vein (16–20 French) and a portal cannula by the surgical team. This technique is generally safe, but the inadvertent extravascular placement of an inflow cannula may cause a massive hemothorax (Sakai et al. 2007).

Piggyback Technique

The piggyback technique was originally designed for patients with significant cardiovascular disease, portacaval shunt, superior vena caval syndrome, or small donor livers (Tzakis et al. 1989). In this technique, the diseased liver is removed without the retrohepatic portion of the IVC by peeling the diseased liver off the IVC after transaction of the hepatic veins, hepatic artery, and portal vein. Therefore, systemic venous return can be relatively well preserved via the intact IVC during the anhepatic stage. Vascular anastomoses are made between the reconstructed ostia of the recipient by combining hepatic veins and the suprahepatic IVC of the graft for the drainage of the hepatic venous blood. The portal vein of the recipient and the graft are anastomosed for portal blood supply, and the infrahepatic IVC of the graft is ligated.

The neohepatic stage begins with reperfusion of the grafted liver by sequential unclamping of the infrahepatic IVC, portal vein, suprahepatic IVC, and hepatic artery, although the sequence of unclamping may vary depending on the surgical technique. Reperfusion is followed by hepatic arterial anastomosis (if it has not been performed already), biliary reconstruction, and closure of the abdomen.

Preparation and Anesthetics

Immediate preoperative consultation is made when a donor organ is identified. The patient is re-evaluated to identify any interval changes during the waiting period. Anesthetic and postoperative management and their risks are explained to the patient one more time. In general, pre-medication is withheld in most cases because of potential encephalopathy and hypovolemia, and narcotics (e.g., fentanyl 1–5 μg/kg) are commonly administered intravenously in the operating room.

Necessary medications and anesthesia equipment are listed in Table 3. A device that delivers fluids and blood rapidly on demand is considered standard equipment (i.e., FMS2000® fluid warming system, Belmont Instrument Corp., Billerica, MA, USA) (Elia and Kang 2002). An autotransfusion system is helpful in minimizing the need for bank blood (Dzik and Jenkins 1985; Kang et al. 1991). A system that monitors coagulation, either a conventional coagulation profile, Thromboelastography R with circle (TEG; Haemonetics, Braintree, MA, USA), or

Table 3 Anesthesia equipment and medications for liver transplantation

Equipment
Anesthesia machine with volume ventilator
Mass spectrometer or capnograph
Multiple-channel vital-sign monitor
Pulse oximeter
Cardia output computer (oximetry or right ventricular ejection fraction)
Transesophageal echocardiograph
Drug infusion pumps
Thromboelastograph or thromboelastometer
Rapid-infusion device
Autotransfusion system
Warming blanket
Defibrillator
Medications
Induction agents
Propofol
Etomidate
Intravenous agents
Midazolam
Fentanyl
Inhalation agents
Isoflurane
Muscle relaxants
Succinylcholine
Rocuronium
Vecuronium
Other drugs
Atropine (0.4 mg)
Calcium chloride (100 mg/mL, 200 mL)
$NaHCO_3$ (40 mmol/50 mL, 400 mmol)
Tromethamine (THAM) (500 mL, 1500 mL)
Ephedrine (5 mg/mL, 20 mL)
Epinephrine (4 μg/mL, 20 mL)
Epinephrine (40 μg/mL, 20 mL)
ε-Aminocaproic acid (EACA) (250 mg/mL, 10 mL)
Protamine (10 mg/mL, 10 mL)
Insulin: available in the refrigerator
Potent vasoactive drips: as needed

Rotational Thromboelastometry R with circle (ROTEM; TEM International, Basel, Switzerland), is essential in monitoring and management of coagulation (Kang 1986, 1997). TEG and ROTEM provide similar physical properties of blood coagulation, although TEG monitors shear elasticity and ROTEM monitors viscoelasticity. In general, 20 units each of cross-matched packed RBCs (PRBCs) and fresh frozen plasma (FFP) are available at all times, and 10 units of each are prepared in the operating room. Platelets (10–20 units) should be available on demand.

Two large-bore intravenous (IV) catheters (up to 8.5 or 9 French) are secured, typically in the right antecubital and right or left internal jugular vein. When the antecubital vein is unavailable, two catheters may be placed in the same internal jugular vein. Catheter patency is confirmed by noting the line infusion pressure of $<$300 mmHg during fluid infusion at 500 mL/min. Sterile technique should be followed during catheterization, and antiseptic ointment or antiseptic patch is applied at the skin puncture site. A nasogastric tube is placed with copious lubrication and topical vasoconstrictor to avoid nasal or esophageal variceal bleeding.

Proper monitoring is prerequisite to a successful outcome because patients undergoing liver transplantation develop clinically significant hemodynamic, hematologic, metabolic, and other homeostatic abnormalities. Non-invasive monitoring is similar to that for patients undergoing any major surgery. For invasive monitoring, two intra-arterial catheters (20 gauge in the left radial artery and 16–18 gauge in the right femoral artery) are used at the Thomas Jefferson University Hospital. Femoral arterial pressure monitoring is preferred because it reflects central arterial blood pressure more accurately in the presence of low systemic vascular resistance, particularly after reperfusion (Lee et al. 2015). Radial arterial pressure monitoring is useful for blood sampling and backup pressure monitoring when the aorta is partially or completely clamped during aorta-to-hepatic artery anastomosis. A pulmonary artery catheter (PA catheter) is inserted via the right internal jugular vein to monitor cardiac output, intracardiac pressures, and core temperature. Carotid artery puncture should be assiduously avoided because of the presence of coagulopathy. An oximetric-type PA catheter provides additional information on mixed venous hemoglobin oxygen saturation (SvO_2). The right ventricular ejection fraction-type PA catheter monitors the right ventricular ejection fraction and right ventricular end-diastolic volume. It has been shown that central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) are not as sensitive as right ventricular end-diastolic volume in estimating preload, particularly during the anhepatic stage (DeWolf et al. 1993b). Recently, non-invasive, continuous cardiac output monitoring was introduced; however, the technique is not reliable in monitoring cardiac output in hyperdynamic patients. In some centers, a CVP catheter is used instead of a PA catheter. This, of course, is justified if hemodynamic derangement is kept minimal during the entire surgical procedure. However, most centers use a PA catheter for three reasons: (1) hemodynamic instability can be unpredictable during liver transplantation; (2) determination of cardiac output and preload is more clinically significant than CVP monitoring; and (3) it is an important educational tool for trainees. TEE is used in all patients at the Thomas Jefferson University Hospital to monitor myocardial contractility, ventricular end-diastolic volume, wall motion abnormality, air or thromboembolism, intrapulmonary shunting, and patency of the reconstructed major veins. A TEE probe may cause esophageal variceal bleeding (Burger-Klepp et al. 2012) and it should therefore be placed gently.

Various laboratory tests are performed, including arterial blood gas tension and acid–base state, and serum level of electrolytes, ionized calcium, glucose, lactate, and ionized magnesium if available. Typical test times are before and after induction of anesthesia, every hour during the dissection stage, 5 min after the onset of the anhepatic stage, every 30 min during the anhepatic stage, 15 min before reperfusion, 5 and 30 min after reperfusion, and every hour thereafter. Coagulation is monitored by conventional coagulation profile (PT, aPTT, fibrinogen level, and platelet count) and TEG or ROTEM at the following times: before

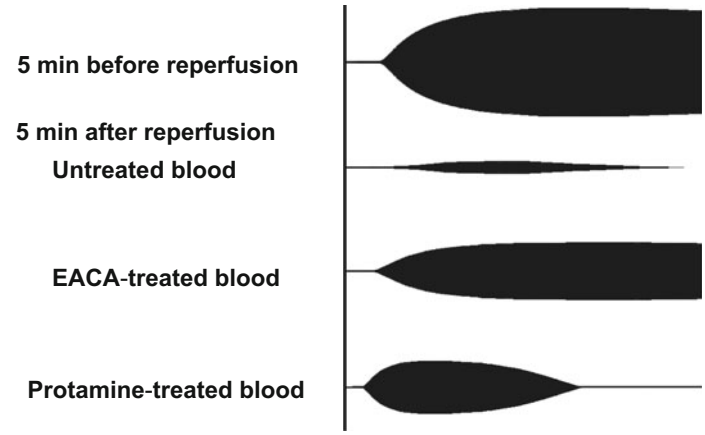

Fig. 5 Effects of pharmacologic agents on pathologic coagulation immediately after reperfusion (From Kang YG (1986) Monitoring and treatment of coagulation. In: Winter PM, Kang YG (ed) Hepatic Transplantation, anesthetic and perioperative management. Prager, New York, with the permission of the publisher)

induction of anesthesia, every hour during the dissection stage, 15 and 60 min after onset of the anhepatic stage, 15 min before reperfusion, 5 and 30 min after reperfusion, and every hour thereafter.

Monitoring of TEG or ROTEM and the platelet count is preferable as a conventional coagulation profile has several drawbacks when used during liver transplantation (Kang 1995). PT is a very sensitive hepatic function test and is prolonged in most patients undergoing liver transplantation. Administration of FFP to correct the PT may not be possible or desirable in the course of surgery. aPTT follows a similar time course to PT, and its correction may not be practical. It is a sensitive test for the heparin effect, and its prolongation indicates the presence of heparin released from the bypass circuit or grafted liver. The fibrinogen level is frequently maintained within the acceptable range, although severe hypofibrinogenemia may indicate either active fibrinolysis or excessive activation of coagulation. The level of fibrin(ogen) degradation products is usually elevated in most patients due to excessive activation of coagulation and reabsorption of defibrinated blood from the abdominal cavity and does not have any immediate clinical significance. Further, coagulation profile results may not be available in a timely manner.

TEG/ROTEM has several advantages over a conventional coagulation profile and has been accepted as a standard coagulation monitoring tool by the ASA (American Society of Anesthesiologists 2015). It rapidly and reliably measures blood coagulability (quality) instead of the quantity of each coagulation component. An accurate differential diagnosis can be made for replacement therapy and pharmacologic therapy by comparing TEG/ROTEM of untreated blood with that of blood treated with various blood components (FFP, platelets, cryoprecipitate) or pharmacologic agents (protamine sulfate, heparinase, ε-aminocaproic acid [EACA], aprotinin) (Fig. 5) (Kang et al. 1987).

Lastly, circumferential identification tags around the wrists or ankles are removed to avoid the compartment syndrome. Both arms are placed on padded arm boards in an abducted position, and excessive abduction should be avoided to prevent a plexus stretch injury. The extremities are protected with foam padding to avoid pressure injuries.

A rapid-sequence induction is preferred because of uncertain gastric emptying. Anesthesia is commonly induced with propofol (2–3 mg/kg) or etomidate (0.3 mg/kg), and fentanyl (2–5 μg/kg) is frequently added. Succinylcholine (1–2 mg/kg) or rocuronium bromide (1.2 mg/kg) is used to facilitate intratracheal intubation. Anesthesia is maintained using volatile inhalation agents and narcotics. Isoflurane is the preferred inhalation agent because its effect includes less myocardial depression and biotransformation. Nitrous oxide is avoided because it distends the bowel and increases the size of any entrained air. Midazolam (1–4 mg) may be added for amnesia. For muscle relaxation,

rocuronium bromide, vecuronium bromide, or cisatracurium besilate are commonly used.

Antibiotics and immunosuppressants administered during surgery may vary from center to center. At the Thomas Jefferson University Hospital, Unasyn® (ampicillin/sulbactam 3 g) is given before incision and every 4 h thereafter. For patients allergic to cephalosporin or penicillin, vancomycin is administered within 2 h before skin incision (1 g for patients <80 kg and 1.5 g for those >80 kg). For immunosuppression, methylprednisolone (500 mg IV) and basiliximab (20 mg IV) are given during the anhepatic stage and tacrolimus is given in the postoperative period.

Physiologic Homeostasis During Liver Transplantation

Liver transplantation imposes a great deal of physiologic stress on patients, and maintenance of physiologic homeostasis is essential to a successful outcome.

Cardiovascular Homeostasis

The goal of hemodynamic management is to optimize tissue perfusion by maintaining the hyperdynamic state characteristic of ESLD. In general, there are two schools of thought about maintaining hemodynamic stability. The first endorses maintaining the hyperdynamic state to optimize cardiac output and tissue perfusion. Patients with ESLD have generalized vasodilation and are known to have oxygen debt at the tissue level. Therefore, maintaining the hyperdynamic state, instead of 'normal blood pressure,' ensures ample oxygen delivery to tissues and avoids tissue acidosis. This, in turn, optimizes tissue metabolism and hepatic blood flow. The second school of thought endorses maintaining arterial blood pressure within the normal range. This may include the use of various vasopressors (phenylephrine, norepinephrine, vasopressin, etc.) with or without hypovolemia. In extreme cases, blood is removed from the patient to induce hypovolemia, and blood pressure is supported by vasopressors (Massicotte et al. 2010); it has been claimed that blood loss is minimal without increasing perioperative complications, although fluid restriction may lead to tissue ischemia, renal failure, and air embolism (Melendez et al. 1998; Schroeder et al. 2004). Further, α-vasopressors (norepinephrine and phenylephrine) decrease hepatic blood flow by reducing portal venous flow dramatically in the presence of a limited hepatic arterial buffer response (Mehrabi et al. 2005).

Dissection Stage

Hemodynamic instability represented by reduced cardiac output and hypotension is typically caused by hypovolemia associated with drainage of ascites, rapid third-space fluid loss, surgical bleeding, and inadvertent compression of major vessels (IVC, portal vein, hepatic veins, and aorta). Intravascular volume is usually replenished by administration of a mixture of PRBCs and FFP (typically, PRBC:FFP:PlasmaLyte-A® = 200:300:250 mL) using a rapid-infusion device. This mixture yields hematocrit of 26–28 vol.% and coagulation factor levels of 30–50 % of normal. A low hematocrit is chosen to optimize microcirculation and minimize the RBC wastage. Calcium-containing fluid (i.e., lactated Ringer's solution) should not be used to prevent clot formation in the reservoir of the rapid-infusion device. Continuous administration of FFP is necessary to compensate for the loss of coagulation elements (procoagulants, prolysins, and their inhibitors) by surgical bleeding and excessive activation of coagulation. In patients with minimal blood loss, colloids (albumin or FFP) and crystalloids may be required to compensate for the third-space fluid loss and continuous production of ascites. Close communication with the surgical team is essential to identify the cause of hemodynamic instability, as is communication with the blood bank to facilitate adequate supply of blood products. Intraoperative autotransfusion has been shown to be effective and safe during liver transplantation, and its use may be considered when the PRBC requirement is >5 units. Its use is not recommended for patients with peritoneal infection or malignancy (Liang et al. 2008).

When lower cardiac output and/or hypotension persists even with adequate preload, dopamine or epinephrine may be infused for patients with hypotension, while dobutamine can be used when patients are normotensive. High venous pressures (CVP and PCWP) may be seen in patients with volume overload, large ascites, and pleural or pericardial effusion. Drainage of ascites and effusion may decrease intrathoracic pressure and central venous pressures and improve cardiac performance. Thoracentesis and pericardiocentesis can be performed after the abdomen is opened to minimize the risk of injury to the thoracoabdominal organs.

Unexpected pulmonary hypertension may be observed in some patients. Because of the high perioperative mortality in patients with pulmonary hypertension, it deserves a thorough intraoperative investigation. The PA catheter should be able to differentiate between pulmonary hypertension with high pulmonary vascular resistance and pulmonary hypertension with fluid overloading. Pulmonary hypertension caused by fluid overloading may dissipate gradually by intraoperative fluid loss, and phlebotomy may be required in severe hypervolemia. In portopulmonary hypertension with increased pulmonary vascular resistance, the presence of right ventricular function is investigated. A low cardiac output with a high CVP suggests the presence of right ventricular dysfunction. TEE findings of right ventricle dysfunction are low fractional area change (FAC), tricuspid annular plane excursion (TAPSE) of <16 mm, flattening of the ventricular septum, apicalization of the right ventricle, and right ventricular dilation. Additionally, the pulmonary vascular response to various vasodilators (i.e., diltiazem, nitroglycerin, epoprostenol, and nitric oxide) may be evaluated. Liver transplantation may continue when pulmonary hypertension is mild to moderate with normal right ventricular function. In such cases, right ventricular function is supported by maintaining optimal preload and improving myocardial contractility by inotropes.

Complications of massive blood transfusion (ionic hypocalcemia, ionic hypomagnesemia, hyperkalemia, and acidosis) may develop at this stage and should be treated aggressively. Normothermia can be well-maintained even during massive transfusion when a rapid-infusion device is used.

Anhepatic Stage

Hemodynamic changes that occur during the anhepatic stage are caused primarily by interruption of venous return from the IVC and portal vein. In the simple cross-clamping technique, clamping of the IVC and portal vein reduces venous return by up to 40 %, leading to low cardiac output, hypotension, and compensatory tachycardia (Pappas et al. 1971). Calculated systemic vascular resistance is frequently elevated, although this is a reflection of the exclusion of the vascular tree of the lower extremities and splanchnic bed. It is noteworthy that cross-clamping of the IVC and the portal vein decreases the central blood volume and pressure (CVP and PCWP) but progressively increases total intravascular blood volume as blood is sequestered in the vascular bed of the gastrointestinal and pelvic organs, kidneys, and lower extremities. A prolonged low output state, portal hypertension, and renal venous congestion may lead to acidosis, intestinal swelling, and hematuria. We, at Thomas Jefferson University Hospital, prefer to treat the low output state by administration of fluid and/or inotropes (dopamine or dobutamine 2–5 μg/kg/min).

Venovenous bypass is more physiologic technique than a simple cross-clamping technique as it returns venous blood from the portal and IVC system (Shaw et al. 1984). Hence, hemodynamic changes that occur during the anhepatic stage with venovenous bypass are minimal when the bypass flow rate is greater than 25 % of the baseline cardiac output and, therefore, the bypass flow should be monitored and adjusted as needed. Improper positioning of the cannula tip in the femoral or portal vein, or a kinked bypass circuit, may not drain blood adequately and the surgical team should correct their positions. A low pump speed reduces venous return, while a high pump speed collapses the outflow venous wall and decreases the bypass flow. The perfusionist, therefore, should adjust the pump speed to maximize the bypass flow. In addition, hypovolemia decreases the

bypass flow, and it should be corrected by the anesthesia team. The anesthesia and surgical teams should be prepared for potential acute complications of venovenous bypass. Bleeding or air entry may result from venous laceration during cannulation or improperly secured cannulas. Entry of a small volume of air (up to 50 mL) into the bypass pump may not cause immediate systemic air embolism because it is trapped in the cone-shaped pump head by centripetal force. Thromboembolism may be caused by the migration of pre-existing thrombi or those developed during a low bypass flow rate (<1000 mL/min), particularly in hypercoagulable conditions (i.e., Budd-Chiari syndrome, neoplasms, and congenital protein C deficiency). Most importantly, the bypass may have to be terminated unexpectedly when serious complications occur. Therefore, the anesthesia team should be prepared for unexpected cross-clamping of the IVC and portal vein at all times. After completion of the IVC anastomosis, the portal cannula is removed to facilitate the portal venous anastomosis, resulting in partial bypass. Low bypass flow and low cardiac output during this period can be improved by the administration of fluids or dopamine, but full correction of central hypovolemia, as reflected on CVP, PCWP, or TEE, is avoided to prevent fluid overload on reperfusion.

In the original description of the piggyback technique, adequate venous return is maintained through the intact IVC and portal vein using portoaxillary venovenous bypass (Tzakis et al. 1989). Currently, many transplantation centers do not incorporate the portoaxillary venovenous bypass in the piggyback technique, which makes patients vulnerable to significant hypovolemia. Hepatectomy in the presence of portal hypertension can be difficult, and hypovolemia is not uncommon as a consequence of inadvertent compression of the IVC and portal vein, partial side-clamping of the IVC, and cross-clamping of the portal vein during portal anastomosis. Hence, temporary portacaval shunt or portal-axillary venovenous bypass may be instituted in surgically challenging patients to maintain preload.

As described earlier, 1000 mL of cold lactated Ringer's solution or albumin (5 %) is flushed through the portal vein and drained via the incompletely anastomosed IVC to remove preservative solution, metabolites, and air from the allograft. Additionally, approximately 300–500 mL of blood may be allowed to escape through the incompletely anastomosed portal vein to enhance the washout by partial unclamping of the infrahepatic IVC (back-bleeding technique) immediately before reperfusion of the grafted liver. In this case, blood should be administered simultaneously to avoid hypovolemia.

Other factors that affect circulation during the anhepatic stage are similar to those of the dissection stage, although lactic acidosis, citrate intoxication, hypomagnesemia, hyperkalemia, and coagulopathy are more pronounced. Hyperkalemia is treated by dextrose (5–10 g) and insulin (5–10 units) to move potassium intracellularly (DeWolf et al. 1993a). In severe hyperkalemia, PRBC or phlebotomized blood can be washed using an autotransfusion system to remove potassium before transfusion (Ellis et al. 1987). At the end of the anhepatic stage, all biochemical variables are normalized to prepare for reperfusion.

Neohepatic Stage

Significant hemodynamic changes occur on reperfusion of the grafted liver (Fig. 6). Unclamping of the infrahepatic IVC and portal vein results in transient hypovolemia and hypotension due to acute sequestration of the blood in the engrafted liver. Unclamping of the suprahepatic IVC increases preload by mobilizing blood from the low extremities and splanchnic circulation. This is followed by severe hemodynamic changes, the so-called postreperfusion syndrome (Aggarwal et al. 1993). The postreperfusion syndrome, which occurs in approximately 30 % of patients, is defined by abrupt hypotension (below 70 % of the baseline value) that develops within 5 min of reperfusion and lasts for more than 1 min. Other associated hemodynamic changes are bradycardia, high CVP and PCWP, low systemic vascular resistance, and conduction defects. Acute reduction in myocardial contractility is observed in TEE. The postreperfusion syndrome appears to

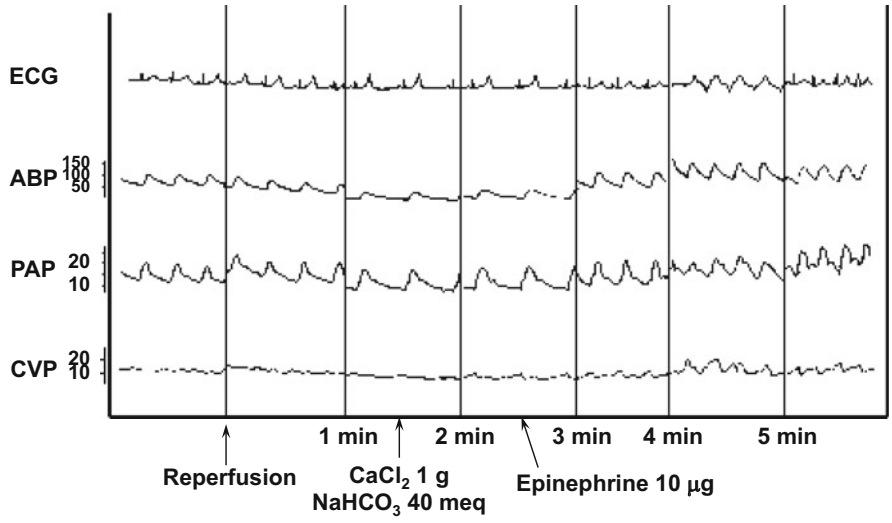

Fig. 6 Postreperfusion syndrome and its treatment (This article was published in Kang YG, Gelman S, Liver transplantation. In: Gelman S (ed) Anesthesia and organ transplantation. WB Saunders, Philadelphia, Copyright Elsevier (1987))

be caused by a combination of several factors. For example, an acute increase in preload may result in right ventricular strain and an acute decrease in blood temperature (2–3 °C) by the systemic entry of the cold preservation solution may decrease cardiac conduction and contractility. Other physical factors are air embolism and thromboembolism, which may cause right ventricular strain or right ventricular outflow tract obstruction (Ellis et al. 1989; Suriani et al. 1996). Chemical factors involved are acute hyperkalemia and acidosis. Systemic entry of hyperkalemic preservation solution increases serum potassium level to a very high level (up to 12 mmol/L), causing severe bradycardia and conduction defects (Martin 1986). Return of the acidic blood from the viscera and lower extremities increases the base deficit by 5–10 mmol/L. In addition, unknown endogenous vasodilators or myocardial depressants (i.e., vasoactive intestinal polypeptide, nitric oxide, and eicosanoid) released from the allograft or congested viscera may decrease systemic vascular resistance and impair myocardial function.

Several measures may be taken to prevent the postreperfusion syndrome, although they are not always successful. At the end of the anhepatic stage, blood volume is adjusted to avoid fluid overloading on reperfusion, and ionic hypocalcemia, hyperkalemia, and metabolic acidosis are corrected. Prophylactic administration of $CaC1_2$ (15 mg/kg), $NaHCO_3$ (0.5–1 mmol/kg), regular insulin (10 units), 50 % dextrose (1 mL/kg), and epinephrine (5–10 µg) are recommended by some centers (Ellis et al. 1989). Once the postreperfusion syndrome develops, severe hypotension and bradycardia are treated with small doses of epinephrine (5 µg increments) to support contractility, heart rate, and vasomotor tone, followed by a dopamine or epinephrine infusion, if necessary. Symptomatic hyperkalemia (tall, peaked-T wave, and widening QRS complex with bradycardia) is treated by administration of $CaC1_2$ (15 mg/kg) and $NaHCO_3$ (0.5–1 mmol/kg). Arrhythmias are treated in the standard fashion. When pulmonary edema develops, positive end-expiratory pressure (PEEP) is applied and inotropes may be given. Patients who develop intracardiac or pulmonary embolism are supported by inotropes. When severe fluid overloading is a concern, phlebotomy may be considered.

The postreperfusion syndrome dissipates gradually over the next 5–15 min, although low

systemic vascular resistance and hypotension with a high cardiac output may persist for several hours. When hypotension is suspected to cause tissue and myocardial ischemia, it may be treated with ephedrine, dopamine, or epinephrine. Overzealous administration of fluids may result in hepatic congestion, while norepinephrine may interfere with hepatic blood flow by decreasing portal venous flow. Octreotide and vasopressin may increase arterial blood pressure by decreasing portal pressure and flow, although its effects on hepatic circulation and metabolism are unclear (Fayed et al. 2013; Wagener et al. 2008). Hemodynamic changes that occur during hepatic arterial and biliary reconstruction are relatively minor, except for intermittent fluctuation of the preload associated with continuous third-space fluid loss and compression of the liver and great vessels.

Pulmonary Homeostasis

Gas exchange is maintained satisfactorily in most patients. Minute volume is gradually decreased during the anhepatic stage to match the reduced oxygen consumption and carbon dioxide production, and is increased during the neohepatic stage. Alveolar recruitment maneuvers are performed intermittently to avoid atelectasis caused by pleural effusions, cephalad traction of the rib cage, and compression of diaphragm. Intermittent endotracheal suctioning, using a suction catheter or bronchoscope, may be required to remove secretions. Drainage of pleural effusions and ascites decreases intrathoracic pressure and improves oxygenation within 2 h. Patients with preoperative ARDS may require a high FiO_2 and a high level of PEEP to ensure adequate gas exchange, and a volume ventilator may be necessary to overcome the high airway pressure. Frank pulmonary edema can develop, particularly after reperfusion, from the increased pulmonary capillary permeability or fluid overload. In such cases, patients are ventilated with a high level of FiO_2 and PEEP, while the underlying cause is treated. Closure of the abdominal cavity may interfere with ventilation by increasing intrathoracic and airway pressures. Primary closure with mesh or secondary closure may be necessary.

Cerebral Homeostasis

In patients with fulminant hepatic failure, preoperative cerebral monitoring is continued as cerebral hyperemia and intracranial hypertension persist during surgery, although they are somewhat attenuated by general anesthetics. However, a sudden increase in preload may dramatically exacerbate intracranial hypertension on reperfusion of the grafted liver. Hence, optimal preload should be maintained during the entire procedure. After reperfusion, cerebral hyperemia may gradually decrease as the liver begins to function.

Coagulation

Intraoperative changes in coagulation are summarized in Table 4. Surgical bleeding is common due to numerous collateral vessels associated with portal hypertension, difficulty in dissection of the diseased liver, pre-existing coagulopathy, and pathologic changes in coagulation. The average blood loss in adults is 5–15 units each of PRBC and FFP, although blood loss may reach more than 100 units each.

During the dissection stage, dilutional coagulopathy develops as bleeding reduces the levels of coagulation factors and platelets (Fig. 7). Fibrinolysis may develop, particularly in patients with hepatocellular disease, as a result of a low level of inhibitors of fibrinolysis and impaired hepatic clearance of tPA (Lewis et al. 1989a). Excessive activation of coagulation, evidenced by a gradual increase in thrombin–antithrombin complex, develops at the end of the dissection stage (Kratzer et al. 1991). Management of coagulation begins with normalization of physiologic variables, such as ionic hypocalcemia, hypothermia, and acidosis impair coagulation (Rohrer and Natale 1992). This is followed by continuous infusion of coagulation factor-rich blood (RBC:FFP: PlasmaLyte-A® or normal saline = 1 unit:1 unit:250 mL) to maintain coagulation factor

Table 4 Intraoperative changes in coagulation

	Dissection stage	Anhepatic stage	Neohepatic stage	
			Early	Late
Pre-existing coagulopathy	++	++	++	+
Dilution	+++	+++	++	+
Hypocalcemia	+	+++	++	+
Hypothermia	+	++	+++	+
Fibrinolysis	+	++	++++	–
Excessive coagulation	+	++	++++	–
Heparin effect	–	+[a]	++	–

[a]In patients with venovenous bypass with heparin in the priming solution. + mild increase; ++ moderate increase; +++ severe increase; and - no change

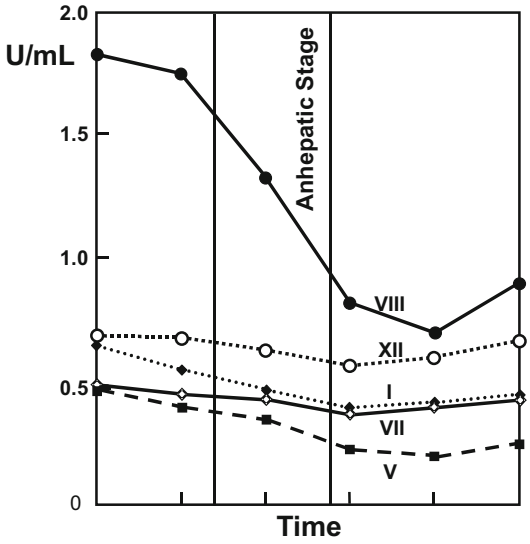

Fig. 7 Intraoperative change in coagulation of 100 patients (Modified from Lewis et al. (1989a), with the permission of the publisher)

levels above the critical level (30–50 % of normal). Specific blood components may be administered based on TEG/ROTEM. In general, platelets (5–10 units) are administered for a small maximum amplitude (MA) (<40 mm). Platelet administration, in addition to increasing MA, improves reaction time (r) and clot formation rate (α), because the coagulation cascade leading to fibrin formation occurs on the surface of platelets. Its administration, however, is withheld during the anhepatic stage to avoid potential thrombosis and during massive blood transfusion (>150 mL/min) to minimize wastage. Two units of FFP may be administered when the reaction time is prolonged (r> 12 min) even after platelet administration Cryoprecipitate (6 units) containing factors I and VIII are rarely required unless severe fibrinolysis is left untreated because plasmin selectively destroys factors I, V, and VIII. However, cryoprecipitate may be used for patients with severe hypofibrinogenemia (<100 mg/dL).

Pathologic coagulation superimposes on dilutional coagulopathy during the anhepatic stage. The heparin effect is seen as a prolonged aPTT and reaction time on TEG/ROTEM at the onset of the venovenous bypass as a small dose of heparin (2000–5000 units) in the bypass circuit enters systemic circulation. This heparin effect dissipates over the next 30–60 min. The effects of the absence of the hepatic synthetic and clearance function begin to develop during this stage. The absence of hepatic clearance of tPA promotes fibrinolysis in approximately 30 % of patients (Kang et al. 1987). Similarly, the absence of hepatic clearance of activated coagulation factors results in excessive activation of coagulation evidenced by a progressive increase in thrombin–antithrombin complex and fibrin (ogen) degradation products. Severe fibrinolysis (fibrinolysis time <60 min) may be treated by the administration of a single, small dose of EACA (250–500 mg) (Kang et al. 1987). Administration of a large or repeated dose of EACA is not recommended in order to avoid potential thromboembolism (Gologorsky et al. 2001).

The postreperfusion syndrome occurs in coagulation at the onset of the neohepatic stage. A typical coagulation profile shows prolonged PT, aPTT, reptilase time, and thrombin time. A generalized decrease in coagulation factors (I, V, VII, and VIII) and platelets is accompanied by a sharp increase in the tPA level, a shortened euglobulin lysis time, and a moderate increase in fibrin(ogen) degradation products and thrombin–antithrombin complex. Fibrinolysis is observed in up to 80 % of patients and is severe in about 40 % (Kang et al. 1987). Fibrinolysis is caused by a 20-fold increase in tPA being released from the allograft and congested viscera, which overwhelms the activity of the plasminogen activator inhibitor (Virji et al. 1989; Porte et al. 1989). There are ample data to support the finding that fibrinolysis is primary in origin: a relatively steady antithrombin level, only moderate levels of fibrin(ogen) degradation products and D-dimers, selective decreases in factors I, V, and VIII, and no known microthrombi formation (Lewis et al. 1989a, b). Fibrinolysis resolves over the 120 min following reperfusion. The heparin effect occurs in approximately 30 % of patients, as heparin is released from the allograft and dissipates over the next 60–90 min.

To identify the presence of fibrinolysis and the heparin effect, TEG/ROTEMs of untreated blood (native), blood treated with antifibrinolytic agent (EACA or aprotinin), and blood treated with an agent neutralizing heparin (protamine sulfate or heparinase) are compared 5 min after reperfusion. When fibrinolysis is present, early treatment using a single, small dose of EACA (250–500 mg) is recommended in order to reduce delayed oozing and to minimize the loss of factors I, V, and VIII (Kang et al. 1997). Prophylactic administration of EACA or tranexamic acid (AMCA) is a common practice in many centers, but has not shown scientific efficacy. Fibrinolysis prophylaxis is not recommended by the authors, because the presence of fibrinolysis can easily be detected by TEG/ROTEM and can be treated effectively with a small dose of EACA in most patients. When the heparin effect is present, a small dose of protamine sulfate (25–50 mg) may be given in severe cases. In addition, blood coagulability can be impaired by reperfusion hypothermia, acidosis, and ionic hypocalcemia.

In contrast, excessive activation of coagulation leading to fatal intracardiac or pulmonary embolism may occur in some patients (Gologorsky et al. 2001; Warnaar et al. 2008). This complication appears to be associated with a massive transfusion, release of a large quantity of tissue thromboplastin from the less than optimal allograft, impaired tissue perfusion, and possibly antifibrinolytic therapy. Intracardiac thrombosis can be treated by infusion of tPA (40–100 mg over 2 h) while observing resolution of thrombi using TEE (Boone et al. 2011; Jackson et al. 2006).

Coagulopathy improves gradually after reperfusion. Generalized oozing, however, may occur even in the presence of acceptable coagulation profiles and TEG/ROTEM, possibly due to delayed bleeding caused by the loss of a poorly formed clot or by the residual effects of reperfusion fibrinolysis.

Several other pharmacologic agents are reported to improve coagulation. Aprotinin (2,000,000 KIU followed by 500,000 KIU/h), a non-specific inhibitor of plasminogen and serine protease, may reduce blood loss by inhibiting fibrinolysis and excessive activation of coagulation (Neuhaus et al. 1989; Cottam et al. 1991). However, clinical use of aprotinin declined even before the drug was withdrawn by the manufacturer: clinical reports did not show a significant reduction in blood loss (Ickx et al. 1993; Groh et al. 1993), and fibrinolysis can be treated with EACA or AMCA more efficiently with negligible side effects (Kang et al. 1987; Boylan et al. 1996). Recombinant factor VIIa (rFVIIa) has been suggested to improve coagulation and reduces bleeding by actively enhancing coagulation and stimulating fibrin formation in the presence of tissue factor. Its beneficial effects have been shown in patients with fulminant hepatic failure, "critical bleeding," and a ruptured liver (Meadows et al. 2011; Merchant et al. 2004; Yamaguchi et al. 2015). However, results of

clinical trials are controversial (Planinsic et al. 2005; Gasperi and Baudo 2006; Niemann et al. 2006) and a European consensus concluded that a paucity of data from clinical trials with rFVIIa limits both the strength and the scope of clinical recommendations (Vincent et al. 2006). Recently, the use of prothrombin complex concentrate has been assessed in a limited number of centers. Prothrombin complex concentrate is prepared from FFP and contains clotting factors II, VII, IX, and X, protein C, and protein S, and its use may improve coagulation without increasing preload (Arshad et al. 2013). However, it has limited components of coagulation and its clinical advantage requires further investigation. Desmopressin acetate (DDAVP), a synthetic analog of 8-arginine vasopressin, increases the endothelial release of factor VIII, von Willebrand factor, and plasminogen. Its beneficial effects have been demonstrated in vitro and in patients with liver disease, and it may be used to improve coagulation (0.3 μg/kg) (Kang et al. 1993). Conjugated estrogen has been reported to improve coagulation and reduce blood loss (Frenette et al. 1998), although its use has not been accepted widely.

Electrolyte and Acid–Base Homeostasis

Calcium Metabolism

Patients with hepatic dysfunction invariably develop ionic hypocalcemia during massive blood transfusion, which is caused by chelation of serum calcium with citrate in the banked blood. Ionic hypocalcemia begins to appear during the dissection stage (Marquez et al. 1986) and becomes severe during the anhepatic stage. The serum-ionized calcium level is inversely related to the serum citrate level, as the absence of hepatic metabolism of citrate increases the serum citrate level close to that in the banked blood (Fig. 8). Significant hypocalcemia (Ca^{2+} <0.55 mmol/L) is associated with a prolonged Q–T interval and decreases in the cardiac index, stroke–work index, and blood

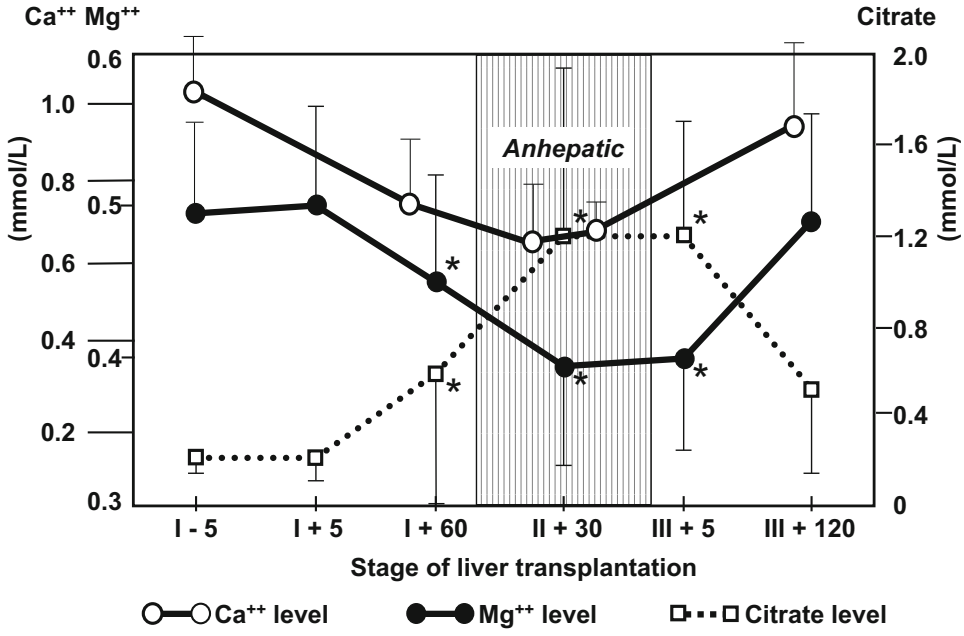

Fig. 8 Intraoperative changes in serum calcium, magnesium, and citrate level (Results of two studies (Marquez et al. 1986 and Scott et al. 1996) are superimposed, with the permission of the publisher)

pressure. Therefore, the ionized calcium concentration is monitored hourly or more frequently, and $CaC1_2$ (15 mg/kg) or calcium gluconate (30 mg/kg) is administered to maintain a normal level (Martin et al. 1990). Ionic hypocalcemia improves gradually as the engrafted liver begins to metabolize citrate, unless the speed of the transfusion exceeds the metabolic function of the liver.

Potassium Metabolism

Hypokalemia is not uncommon in patients with liver disease due to poor dietary intake of potassium and its loss from chronic diuretic therapy and diarrhea. Severe hypokalemia (<2.5 mmol/L) is treated with potassium chloride to increase its level to 3.0–4.0 mmol/L. Moderate hypokalemia (<3.5 mmol/L) is not treated because it is well-tolerated by patients and self-corrected by blood transfusion. Hyperkalemia is a serious concern because it interferes with myocardial conduction and contractility, particularly in the presence of acidosis and hypocalcemia. Progressive hyperkalemia (up to 6–7 mmol/L) may occur in patients with renal dysfunction or those requiring massive blood transfusion. Mild hyperkalemia (up to 5.5 mmol/L) is treated with insulin (10 units) and glucose (12.5 g). It has been shown that glucose and insulin therapy is effective in lowering the serum potassium level even in the absence of hepatic function (Dewolf et al. 1993a). For moderate-to-severe hyperkalemia (>5.5 mmol/L), in addition to insulin therapy, PRBC or phlebotomized blood can be washed to remove potassium using an autotransfusion system before transfusion (Ellis et al. 1987).

Reperfusion hyperkalemia is caused by potassium influx from the preservation solution and hepatocytes, and its systemic effects and treatment have been described previously. Acute hyperkalemia returns to a normal range within 5–10 min as a result of redistribution. The potassium level gradually returns to the baseline value as the RBCs and the engrafted liver take up excess potassium. Hypokalemia (<3.5 mmol/L), which occurs toward the end of procedure, is treated using a KCl infusion (20 mmol increments).

Sodium Metabolism

Hyponatremia (<130 mmol/L) is a common occurrence in patients with liver disease, particularly those with fluid retention, ascites, diuretic therapy, and restricted sodium diet. The serum sodium level gradually increases towards normal during surgery via administration of blood products and a balanced salt solution. A rapid rise in the serum sodium level (>10 mmol/L) is a clinical concern because it may contribute to the development of central pontine myelinolysis, a serious neurological injury caused by the destruction of the myelin sheath in the pons (Videira et al. 1991). Therefore, the preoperative serum sodium level should be raised to >130 mmol/L, if possible, and a rapid increase in sodium should be prevented by administration of low sodium-containing crystalloids during surgery. In addition, tromethamine (THAM) is the preferred drug for treatment of metabolic acidosis as it does not contain sodium. Hypernatremia may be seen in some patients who receive a large dose of $NaHCO_3$ preoperatively. This hypernatremia is gradually normalized by administration of blood products and a balanced electrolyte solution.

Ionic Hypomagnesemia

A clinical investigation showed that the serum ionized magnesium level, similar to the ionized calcium level, has an inverse relationship with the serum citrate level as magnesium ion chelates with citrate in banked blood (Scott et al. 1996). Although the clinical significance of ionic hypomagnesemia during liver transplantation is unclear, $MgSO_4$ (1–4 g) can be administered to minimize potential cardiac irritability and myocardial depression.

Metabolic Acidosis

Metabolic acidosis begins to appear during the dissection and anhepatic stages because of impaired hepatic metabolism of the acid load from the banked blood and the peripheral tissues. The base deficit and lactate level increase further (approximately 5 mmol/L) on reperfusion due to the acid load from the graft and congested viscera and lower extremities. It gradually improves as hepatic

function is restored and tissue perfusion improves during the neohepatic stage. Persistent lactic acidosis (>15 mmol/L) appears to be associated with graft dysfunction (Begliomini et al. 1989).

Metabolic acidosis is aggressively corrected by administration of $NaHCO_3$ to maintain base deficit levels <5 mmol/L because acidosis is frequently progressive and leads to myocardial depression, inadequate cellular respiration, and decreased sensitivity to catecholamines. As described earlier, THAM is preferred in hypo- or hypernatremic conditions to minimize fluctuation of the serum sodium level: 150 mL of 0.3 M THAM is equivalent to 50 mmol of $NaHCO_3$. Alternatively, dichloroacetate (40 mg/kg every 4 h) appears to reduce lactate production by stimulating pyruvate oxidation (Shangraw and Robinson 1997).

Metabolic Alkalosis

Metabolic alkalosis may develop during the neohepatic stage, and this was believed to be associated with $NaHCO_3$-administered and citrate metabolism-generating bicarbonate. However, it has been shown that the degree of metabolic alkalosis is unrelated to the citrate and $NaHCO_3$ load (Fortunato et al. 1987) and may be associated with residual hyperaldosteronism.

Metabolic Homeostasis

Body temperature may gradually decrease to 34 °C during the dissection stage as a result of the exposure of the abdominal contents to the cold environment, vasodilatation, and lack of shivering. Hypothermia continues during the anhepatic stage as energy production decreases further. An abrupt decrease in core temperature (2–3 °C) occurs on reperfusion as cold preservation solution enters systemic circulation. The temperature increases during the neohepatic stage, and the surgery ends with a body temperature of approximately 35–36 °C. Hypothermia is difficult to avoid, although raising the room temperature, application of forced warm air devices, use of a warming blanket, and a heat exchanger in the venovenous bypass system may be beneficial.

The blood glucose level is relatively well-maintained (100–200 mg/dL) with blood transfusion, as the banked blood contains glucose (approximately 200 mg/dL). A gradual decrease in glycogenolysis reduces the blood glucose level during the dissection and anhepatic stages. In patients with fulminant hepatic failure or severe hepatocellular disease, the blood glucose level may decrease precipitously, making glucose supplementation necessary. Hyperglycemia (up to 300 mg/dL) occurs on reperfusion as glucose is released from the engrafted liver (DeWolf et al. 1987). Insulin does not appear to be effective in treating reperfusion hyperglycemia because glucose reuptake requires restoration of hepatic function. The insulin level is relatively steady during surgery, and the glucagon level increases after reperfusion. The blood glucose level usually returns to normal within 12–24 h. Persistent hyperglycemia caused by impaired hepatic glucose reuptake and hormonal imbalance is an early sign of poor graft function (Mallett et al. 1989).

Renal Homeostasis

Urine output is well-preserved in most patients once the intravascular volume is optimized. Oliguria or anuria, however, may persist in patients with the hepatorenal syndrome or underlying renal disease. The presence of oliguria and hematuria during the anhepatic stage of the simple cross-clamping technique has been described earlier. Urine output increases during the neohepatic stage as a result of the restoration of renal function and circulation. Various agents have been tried to protect or improve renal function: the role of dopamine is controversial, dopexamine appears to be beneficial, and triple-drug therapy (dopamine [2–3 μg/kg/min], mannitol [250 mg/kg], and furosemide) improves urine output but not renal function (Gray et al. 1991; Planinsic et al. 1997). When fluid overload or severe electrolyte imbalance is a concern, intraoperative venovenous ultrafiltration or hemodialysis may be utilized.

Conclusion of Surgery

The restoration of hepatic function is evident about 2 h after reperfusion: levels of citrate and lactate decrease, the glucose level returns toward normal, coagulopathy improves, and bile production begins. Persistent citrate intoxication, acidosis, hyperglycemia, coagulopathy, and pale-colored bile are poor prognostic signs.

Recently, tracheal extubation in the operating room has been successful in several centers when the patient meets the liver transplantation-specific extubation criteria, including the severity of pre-existing liver disease, blood loss, and hemodynamic stability (Mandell et al. 2002; Biancofiore et al. 2005; Glanemann et al. 2007). However, most patients are still transported to the intensive care unit (ICU) while receiving invasive monitoring and ventilatory support. Upon arrival to the ICU, the ventilator setting is reported to the respiratory therapist, the lungs are auscultated, and vital signs are displayed on the ICU monitor. Detailed intraoperative information is reported to the ICU physician and nursing staff.

Postoperative Complications

Hepatic Complications

Primary Non-Function

Primary non-function is defined as graft failure occurring within 90 days after liver transplantation in the absence of either rejection or technical factors such as hepatic arterial thrombosis (Bzeizi et al. 1997). This complication occurs in up to 10 % of patients and is frequently caused by hepatic dysfunction of the donor liver or prolonged cold ischemia (>18 h). The patient develops progressive multi-organ failure including encephalopathy, coagulopathy, minimal bile production, and oliguria. Supportive therapy may be helpful until the liver resumes its function, although urgent retransplantation is the only solution in many patients.

Acute Rejection

Worsening liver function without technical complications in the second week after liver transplantation suggests acute cellular rejection. Biopsy findings are inflammation of the intrahepatic endothelium and bile duct and a mononuclear cell infiltration with eosinophilia (Wiesner 1996).

Vascular Complications

Hepatic arterial stenosis occurs in approximately 5 % of patients, and is four times more common in children. Common clinical signs are biliary tract breakdown, recurrent bacteremia, hepatic abscess, and occasionally massive hepatic necrosis (Tzakis et al. 1985). Hepatic arterial stenosis is suspected when an ultrasound examination reveals increased focal arterial flow velocities and is confirmed by angiography. In the immediate postoperative period, direct repair or reconstruction using an infrarenal arterial conduit is usually successful. Stenosis occurring several weeks after transplantation is treated with percutaneous hepatic arterial angioplasty, which has a success rate of more than 90 % in achieving long-term patency.

Vena caval stenosis and thrombosis occur in 1–2 % of patients. In traditional liver transplantation, outflow obstruction is managed by balloon angioplasty with or without a metallic stent placement (Simo et al. 1993). In the piggyback technique, it is treated with end-to-side anastomoses between the donor infrahepatic IVC and the recipient retrohepatic IVC (Stieber et al. 1997).

Portal venous stenosis and thrombosis are relatively uncommon in the adult population and present with graft dysfunction, massive ascites formation, and hemodynamic instability. This complication is corrected by an urgent reconstruction of the portal vein or construction of a superior mesenteric venous graft to the liver, together with a ligation of large collaterals that may reduce the portal flow.

Biliary Complications

Biliary complications are more common in children and have an overall incidence of 8–15 %. Early recognition is difficult, leading to high

morbidity and mortality. Bile leaks usually occur at the anastomotic site, although they may be found at the T-tube site or aberrant ducts. Most biliary complications occur within the first 3 months and are diagnosed by liver function tests (serum bilirubin, γ-glutamyltransferase, and alkaline phosphatase) and imaging techniques. These complications are treated by percutaneous or endoscopic drainage of bile collections. In cases of Roux-en-Y choledochojejunostomy, surgical reconstruction is required.

Intra-Abdominal Bleeding

Intra-abdominal bleeding occurs in about 7–15 % of patients and requires exploration in about half of these cases (Ozaki et al. 1994). Gastrointestinal bleeding may develop from ulcers, viral enteritis, varices, and an afferent Roux-en-Y loop. Variceal bleeding is usually associated with portal vein thrombosis and requires an urgent ultrasound or angiographic evaluation. Bleeding from the Roux-en-Y limb occurs 1 week after surgery and is usually self-limited. Additionally, bleeding can be caused by persistent thrombocytopenia associated with splenic sequestration, drug toxicity, heparin-induced thrombocytopenia, and immunologic reactions.

Intestinal Perforation

Intestinal perforation is caused by serosal injury to the intestines and usually occurs in patients who have had a technically difficult hepatectomy, prolonged portal venous clamping, or a massive blood transfusion. Intestinal perforation or leakage is treated by urgent surgery and antifungal therapy.

Extrahepatic Complications

Cardiac Complications

Any type of cardiac complication can develop in the postoperative period. Hypotension can occur due to hypovolemia, either from under-resuscitation or ongoing bleeding, decrease in contractility secondary to the pre-existing myocardial disease, or new onset of dilated or ischemic cardiomyopathy. Other potential causes are acidosis, hypocalcemia, or vasodilation from sepsis or graft failure. Management of cardiac complications is based on the underlying cause.

Hypertension occurs in patients with pre-existing hypertension, inadequate pain control, hypoglycemia, and cerebral edema. Restoration of normal liver function may increase systemic vascular resistance, and calcineurin inhibition can increase systemic blood pressure. Calcium channel blockers (i.e., diltiazem and verapamil) are avoided because they can increase the levels of the calcineurin inhibitors.

Myocardial infarction is relatively rare due to thorough preoperative evaluation being undertaken to detect CAD. However, when it does develop, a cardiologist should be consulted for possible emergent cardiac catheterization during surgery and revascularization. Pulmonary edema is commonly seen postoperatively and may be caused by significant transfusion requirements, increased capillary permeability, prolonged intubation, and reversible dilated cardiomyopathy.

Reversible dilated cardiomyopathy with pulmonary edema may develop in the first 5 days after transplantation. Sampathkumar et al. reported that 1 % of patients who did not have ventricular dysfunction developed dilated cardiomyopathy postoperatively, most of whom recovered completely without any long-term complications (Sampathkumar et al. 1998). The cause of this condition is unknown, although it may be a form of stress-induced cardiomyopathy.

Atrial fibrillation, ventricular tachycardia, and other arrhythmias may develop as a result of electrolyte abnormalities (i.e., hypomagnesemia, hyperkalemia, and hypocalcemia), cardiac ischemia, or irritation from CVP or PA catheters. In a study by Xia et al., atrial fibrillation was observed in 7.4 % of patients and was associated with increased mortality, graft failure, and acute kidney injury (Xia et al. 2015). All arrhythmias are treated following the standard guidelines.

Thromboembolism is a common cause of sudden postoperative death. Deep vein thrombosis should be prevented by early extubation and mobilization, use of compressive stockings, and administration of heparin (subcutaneous or low molecular weight).

Pulmonary Complications

Most patients require mechanical ventilation for only a few hours or days after transplantation. However, prolonged ventilatory support is required in some patients with atelectasis, pleural effusions, and central nervous system (CNS) depression. Intraoperative cross-clamping of the IVC occasionally results in right phrenic nerve crush injury and diaphragmatic paralysis in the immediate postoperative period (McAlister et al. 1993). ARDS may develop in patients with intra-abdominal infection, pancreatitis, hepatic necrosis, acute cellular rejection, and occasionally with Muromonab-CD3 (OKT3) treatment. Bronchoalveolar lavage and bacterial culture are frequently performed to rule out pulmonary infection from any other pulmonary pathology. Pre-existing pulmonary hypertension may persist postoperatively and is controlled by epoprostenol or nitroglycerin.

Neurological Complications

Neurological complications occur in 12–20 % of patients, mostly in the first week of transplantation (Singh et al. 1994). These are more common in adults and present as mental status changes ranging from dysphasia to frank coma. Dysfunction of the CNS is commonly caused by medications, such as cyclosporine, tacrolimus, histamine H_2-blockers, acyclovir, and antibiotics such as imipenem. Non-convulsive seizures may occur, and an EEG is performed for patients with unexplained mentation changes. Intracranial hemorrhage and watershed infarcts are ruled out using CT scans. Hyponatremia and hypomagnesemia can also delay awakening. Central pontine myelinolysis may develop several days after transplantation, and recovery is often slow and incomplete (Winnock et al. 1993). Hepatic encephalopathy may be present for several days after transplantation in patients with persistent portosystemic shunting. Meningitis should be ruled out when the mental status change is accompanied by fever. Disseminated aspergillosis is a devastating complication in a patient with multiple brain infarcts and fever. Peripheral neuropathy presenting as weakness is usually myopathic in nature and is more common in patients with preoperative severe liver disease, poor graft function, high steroid doses, and uremia, and are confirmed by electromyography and muscle biopsy.

In patients with fulminant hepatic failure, cerebral hyperemia and hypertension usually decrease gradually, and the patient regains consciousness as the liver begins to function.

Renal Dysfunction

Renal dysfunction is usually transient and is commonly associated with intraoperative hypovolemia and hypotension, allograft dysfunction, and nephrotoxicity of cyclosporine and tacrolimus. Oliguria is an early sign of renal dysfunction and is managed by restoring intravascular volume and renal perfusion. The hepatorenal syndrome may persist after transplantation, and its recovery depends on its preoperative severity and allograft function. In some patients, addition of vasoconstrictive immunosuppressants (cyclosporine and tacrolimus) may lead to acute tubular necrosis. In general, renal function returns to the normal range in most patients, and approximately 10 % of patients require temporary dialysis (McCaulley et al. 1990). Long-term prognosis is fair, although hypertension, diabetes, and chronic nephropathy induced by steroids and the calcineurin inhibitors may result in chronic renal failure.

Infectious Complications

More than half of the postoperative infections following liver transplantation are bacterial in origin. These infections typically occur in the first 2 weeks, when blood levels of immunosuppressants are high. The most common sites of infection are the liver, biliary tract, peritoneal cavity, and pulmonary system. Common organisms in the abdomen are aerobic Gram-positive organisms (*Streptococci* and *Staphylococci*) and Gram-negative bacilli (*Escherichia coli*, *Enterobacter* species, and *Pseudomonas*), while *Pseudomonas* infection is most common in the lungs. Approximately 20 % of infections are caused by fungus, with *Candida* species accounting for more than 80 % of all fungal infections. The risk factors are a high steroid dosage, usage of broad-spectrum antibiotics, and prolonged surgical time. *Candida* infection is

treated with amphotericin or fluconazole. *Aspergillus* infection accounts for 15 % of all fungal infections and is associated with a very high mortality; high-dose liposomal amphotericin B followed by prolonged itraconazole is the treatment of choice. Viral infections are seen 2–3 months after transplantation, with cytomegalovirus and herpes simplex accounting for the bulk of these infections. Epstein-Barr virus is not usually seen until approximately 6 months after transplantation, but is an important cause of lymphoproliferative disease. *Pneumocystis* pneumonia, an opportunistic infection, responds to trimethoprim–sulfamethoxazole.

Late Metabolic Complications

Late metabolic complications following liver transplantation include diabetes, hyperlipidemia, weight gain, and hypertension. Diabetes is induced by steroids, cyclosporine, and tacrolimus and may respond to oral hypoglycemic agents or insulin. Hyperlipidemia is associated with diabetes, obesity, steroids, and immunosuppressive drugs and is treated by diet and exercise. Hypertension is seen in as many as 85 % of patients after transplantation; the use of steroids or tacrolimus is the most likely cause. Hypomagnesemia has been implicated as the cause of the hypertension in some cases.

Anesthesia for Specific Conditions

Retransplantation of the Liver

Approximately 15 % of all patients require retransplantation of the liver. Early retransplantation is performed within several days after the primary transplantation to rescue patients from primary non-function (graft factor), acute rejection, and technical failure (vascular thrombosis), or secondary non-function (host factor) associated with poor hepatic perfusion. Hepatic necrosis is the common pathway of graft non-function and results in progressive, severe encephalopathy, ARDS, lactic acidosis, coagulopathy, hypoglycemia, and significant circulatory instability. Although infrequent, hepatectomy with a portacaval shunt may be performed to protect the patient from the ill effects of the necrotizing liver on extrahepatic organ functions. In such a case, retransplantation should be performed as soon as the donor organ is available. The surgical procedure itself is relatively simple because surgical dissection has already been made and adhesions have not yet formed. Anesthetic management of these patients is similar to that of patients undergoing primary transplantation.

Late retransplantation is performed in patients with chronic rejection, vascular complications, and recurrence of the original disease. The physical condition of the patient may have improved, but complications of immunosuppression (i.e., hypertension, renal insufficiency) may be present. Adhesions and the steroid-induced fragile tissues frequently complicate late retransplantation. Anesthetic management is similar to that of primary liver transplantation, but a large amount of blood loss is anticipated.

Pediatric Liver Transplantation

In pediatric liver transplantation, rapid-sequence IV induction is preferred, although mask induction is chosen in patients in whom there is difficulty obtaining IV access (Borland et al. 1985). Large-bore IV catheters are placed in the upper extremities after induction of anesthesia. A central venous catheter with CVP monitoring is the usual procedure, and pulmonary arterial catheterization is rarely indicated. Blood pressure is monitored using a femoral intra-arterial catheter. It appears that children tolerate cross-clamping of the IVC and portal vein reasonably well without significant hemodynamic changes, possibly by compliant vasomotor tone. Therefore, venovenous bypass is rarely used in children under 20 kg. Coagulation changes that occur during liver transplantation are not as severe as those of adults, and this may be associated with more prevalent cholestatic diseases in children (Kang et al. 1989). Blood loss in children with biliary atresia can be large due to the technical difficulty associated with previous biliary surgery (i.e., Ksai procedure). Maintenance of body temperature is difficult, as the large surface area promotes heat loss.

Live-Donor Hepatectomy

Live-donor hepatectomy is usually a challenging procedure. The young and healthy donors (ASA Physical Status [PS] 1 or 2) undergo a complete evaluation by hepatologists, surgeons, anesthesiologists, and psychologists. The anesthetic goals are minimizing surgical blood loss and allogeneic blood transfusion, maintaining liver blood flow, facilitating early extubation, preventing deep venous thrombosis and infection, and providing adequate postoperative pain control. Preoperatively, donors may be given erythropoietin to boost RBC production and they can donate 2 units of autologous whole blood 2–3 weeks before surgery. On the day of surgery, donors may be given heparin (5000 units, subcutaneous injection) to prevent deep venous thrombosis, and 6 units of typed and cross-matched PRBCs are prepared. In the holding area, a peripheral IV catheter is secured, anxiolytics are administered, and donors may elect to receive thoracic epidural anesthesia for postoperative analgesia. The need for epidural local anesthetics with or without narcotics is determined by the attending anesthesiologist and pain service.

In the operating room, Unasyn® (3 g IV) or vancomycin (if allergic to penicillin) is administered to prevent infection, and the patient is positioned with minimal stress to the brachial plexus to avoid neurologic injury (Dulitz et al. 2005). Induction and maintenance of anesthesia follows the standard guidelines of any major surgical procedure. Ultra-short-acting narcotics such as remifentanil may be beneficial for early extubation after surgery as it is rapidly metabolized by plasma esterase and does not have a prolonged effect in the presence of hepatic and renal dysfunction.

Intraoperative monitoring is similar to that of patients undergoing major surgery, and a radial arterial catheter and CVP are placed for hemodynamic monitoring. Additional IV access is secured to prepare for the potential need for rapid infusion of fluids using a rapid-infusion system. Immediately after induction of anesthesia, isovolemic hemodilution may be performed: 2 units of the patient's whole blood is collected in CPDA (citrate phosphate dextrose adenine) blood collection bags, agitated to prevent clot formation, stored at room temperature, and returned to the patient within 8 h.

Intraoperatively, physiologic condition should be maintained at all times to ensure adequate perfusion of all tissues including the liver by monitoring the cardiopulmonary system and stat laboratory. Metabolic acidosis should be avoided, and use of a balanced salt solution (lactated Ringer's solution or PlasmaLyte-A®) is the preferred choice in order to avoid the acid load from normal saline (Waters et al. 2001). Blood loss is not excessive and pre- and intraoperatively donated autologous blood and intraoperative autotransfusion are sufficient in most patients. The relationship between the CVP level and surgical blood loss is controversial: Chhibber et al. reported that intraoperative blood loss did not correlate with CVP (<5 mmHg) in their study (Chhibber et al. 2007), while Jones et al. demonstrated a significant reduction in blood loss with low CVP (Jones et al. 1998). The authors recommend euvolemia to maintain hepatic blood flow during dissection of the liver. However, fluid overloading should be avoided after hepatectomy because relatively high portal venous flow to the reduced liver mass may lead to liver congestion and small-for-size syndrome (Dahm et al. 2005). At the conclusion of surgery, the patient can be extubated safely in the operating room and transported to the ICU.

Surgery After Liver Transplantation

All types of surgical procedures may be necessary in the early postoperative period. Within the first 2 months after transplantation, surgical procedures are performed to treat complications of transplantation, such as exploratory laparotomy for abdominal bleeding or reconstruction of the biliary system. Some degree of hepatic dysfunction may still be present, and ventilatory and circulatory support and invasive monitoring may be required. Regional anesthesia is not recommended because of potential bleeding and infectious complications. Anesthesia care of these patients is similar to that of other urgent abdominal procedures.

Patients may return to the operating room at any time for biliary reconstruction, replacement of a hip joint, or almost any other procedure. Liver function and drug metabolism are usually within the normal range, and anesthetic management differs little from that of other patients. Side effects of immunosuppressants (hypertension and renal insufficiency) and drug interactions should be considered.

Cadaveric Donor Procurement

The main goal of organ procurement is the maintenance of optimal conditions for all organ systems to promote as normal as possible an environment for the organs prior to harvesting. Specifically, integrity of organs should be maintained by optimizing organ perfusion and preventing further damage associated with pre-existing illness or trauma. Therefore, donor care during procurement is a continuum of the intensive care provided before brain death. The donor is reviewed and examined by the anesthesia team to evaluate their medical history and vital organ function.

The equipment and medications necessary for multiple organ procurement are shown in Table 5. A multiple-channel vital-sign monitor is an essential piece of equipment because of the unavoidable hemodynamic changes associated with the absence of brain stem function, surgical manipulation, and fluid shift. A volume ventilator may be required for donors requiring high levels of PEEP or airway pressure. A large volume of crystalloids and colloid solutions is prepared, and 5 units of PRBCs are frequently required. The transit from the ICU to the operating room is a crucial period; the anesthesia care team directs the transportation while the donor is continuously monitored, ventilated, and treated.

Intraoperatively, blood pressure is monitored by an indwelling radial or brachial arterial catheter as abrupt changes in blood pressure are anticipated. CVP monitoring is essential, and a PA catheter may be used in unstable donors. General anesthesia is provided as donors respond to surgical stimulation by dramatic hemodynamic changes such as tachycardia, hypertension, perspiration, and involuntary movement (Wetzel et al. 1985). This so-called mass reflex is caused by the neurogenic vasoconstriction and stimulation of adrenal medulla by reflex spinal arc. Isoflurane is the most commonly used agent, because its myocardial depression is relatively benign, and short-acting narcotics (i.e., fentanyl, up to 5 μg/kg/min) may be used in unstable donors. Rocuronium bromide or vecuronium bromide is administered for muscle relaxation.

The specific goals of ventilatory care are to maintain normal PaO_2 (70–100 mmHg), arterial hemoglobin oxygen saturation (>95 %), and $PaCO_2$ (35–45 mmHg) as well as to avoid pulmonary complications. This goal is frequently achieved by ventilating with a tidal volume of 10–15 mL/kg, FiO_2 of 30–40 %, respiratory rate of <20/min, and a low level of PEEP

Table 5 Anesthesia checklist for donor procurement

1. Family consent and permission from the coroner
2. Donor support guidelines
Systolic blood pressure >100 mmHg
Central venous pressure < 12 cmH_2O
Urine output >100 mL/h blood glucose
3. Equipment
Transport monitor
Anesthetic gas machine
Warming blanket and blood warmer
Defibrillator
Multiple-channel vital-sign monitor
Ventilator
Infusion devices
4. Laboratory tests
Hemoglobin and hematocrit
Serum electrolytes, calcium, lactate
Arterial blood gas tension and acid–base state
5. Medications
Packed red blood cells (5 units)
Dopamine (400 mg)
Methylprednisolone (30 mg/kg)
Mannitol (25 %, 100 g)
Lactated Ringer's solution (12–15 L)
Heparin (20,000 units)
Chlorpromazine (250 mg)
Furosemide (100 mg)

(<5 cmH_2O). However, in donors with pulmonary complications, adjustments are made in tidal volume (up to 20 mL/kg), respiratory rate (up to 20/min), and PEEP (up to 10 cmH_2O).

Aggressive circulatory care is essential because hemodynamic instability may impair organ perfusion. Specifically, hypotension (systolic blood pressure <80 mmHg or mean arterial pressure <40 mmHg) is associated with a high incidence of acute tubular necrosis, non-function of the graft kidneys, and poor hepatic function. It is generally agreed that systolic blood pressure should be within the normal range (100–120 mmHg) and CVP should be <10 cmH_2O with minimal vasopressor support. Maintaining circulatory homeostasis, however, can be challenging. Preload is frequently decreased because of blood loss, vasomotor paralysis, diuretic therapy, and diabetes inspidus, although fluid resuscitation may result in overload. The heart rate may vary depending on the degree of brain injury, ranging from tachycardia to bradycardia. Arrhythmia is not uncommon, and myocardial contractility is frequently impaired by myocytolysis, myocardial necrosis, coronary spasm, and reduction of myocardial energy storage (Novitzky et al. 1988). Afterload may be high, from excessive sympathetic tone, or low, from vasomotor paralysis. Volume deficit is usually corrected with lactated Ringer's or colloid solution, and transfusion of PRBCs (1–3 units) may be necessary to maintain hematocrit between 25 and 35 % (Hardesty and Griffith 1986). Once the fluid deficit is corrected, a glucose-containing hypotonic solution (5 % dextrose in 0.45 % NaCl 1 mL/kg/h) is administered to replace urine output and insensible loss, guided by CVP and urine output. Excessive urine output (>200–250 mL/h) is replaced using a hypotonic electrolyte solution with supplementation of KCl (20 mEq/L). Tachycardia with hypertension should be avoided as it may cause pulmonary edema, decrease organ perfusion, and increase myocardial oxygen consumption. A β-antagonist (i.e., labetalol hydrochloride or esmolol hydrochloride) or a calcium channel blocker (verapamil hydrochloride) is used to treat tachycardia and arrhythmia (Novitzky et al. 1984). For bradycardia, isoproterenol or epinephrine is used for positive chronotropic effects because donors are unresponsive to centrally acting chronotropic drugs (i.e., atropine). Supraventricular or ventricular arrythmia is treated using antiarrhythmic drugs. Low afterload is compensated for by increasing preload because α-vasopressors increase the myocardial work load and decrease splanchnic and coronary blood flow. In severely hypertensive donors, an α-blocker (hydralazine or sodium nitroprusside) may be given to reduce the afterload. When cardiac output and organ perfusion are impaired, inotropes (dopamine hydrochloride, dobutamine hydrochloride, and isoproterenol hydrochloride) are recommended to improve cardiac contractility. In brain-dead animal models, serum levels of triiodothyronine, insulin, and cortisol have been found to be low, and the administration of triiodothyronine may improve hemodynamic stability by maintaining myocardial high-energy stores and glycogen (James et al. 2010). Circulatory arrest, which occurs in 10 % of potential donors (Emery et al. 1986), is managed in the standard fashion, except atropine is not effective.

Adequate diuresis (>0.5 mL/kg/h, preferably 1–1.5 mL/kg/h) is recommended as urine output (>100 mL/h) is the most significant factor that determines the outcome of the kidney and liver graft. Oliguria is generally caused by hypovolemia and hypotension and frequently responds to fluid administration. Diabetes insipidus leads to polyuria, hypovolemia, and electrolyte imbalance. In addition to the fluid replacement, DDAVP (0.5–1 units/h) may be administered (Richardson and Robinson 1985), although an excessive dose of DDAVP may increase the risk of acute tubular necrosis and reduce hepatic blood flow (Burggraaf et al. 1994).

Donors are poikilothermic, and hypothermia plays a major role in hemodynamic instability. Body temperature should be kept above 35 °C by raising the operating room temperature, infusing all fluids through a blood warmer, and using heating lamps, a warming blanket, and a heated humidifier in the ventilation circuit. Metabolic acidosis, caused by inadequate tissue

perfusion, is corrected by administration of $NaHCO_3$ or THAM. Commonly seen electrolyte imbalances are hypernatremia, hypokalemia, hypocalcemia, hypophosphatemia, and hypomagnesemia, and they are treated in a standard fashion. Glucose metabolism is relatively well-maintained, and any abnormality in glucose metabolism is corrected by administration of insulin or glucose on the basis of the serum glucose level.

Dilutional coagulopathy is common, and consumption coagulopathy may develop secondary to the release of tissue thromboplastin from injured tissues and the ischemic organs (Kaufman et al. 1984). Fibrinolysis is not uncommon in donors, possibly as a result of the release of tPA from the necrotic brain. Replacement of coagulation factors and platelets or any pharmacologic therapy is rarely indicated as donors are fully heparinized when the aorta is cannulated. Once cardiac arrest is induced by cardioplegia, no further supportive care is necessary.

Conclusion

Liver transplantation is one of the most stressful procedures for patients with multiple organ dysfunction and it is a challenge for anesthesiologists. It is remarkable that anesthesiologists have played a major role in the progress of liver transplantation and its successful outcome. It cannot be overemphasized, however, that a thorough understanding of pathophysiology and close communication and cooperation among hepatologists, surgeons, anesthesiologists, intensivists, and other healthcare workers are vital to successful outcomes and further progress in this field.

Cross-References

▶ Hepatopulmonary Syndrome and Portopulmonary Hypertension

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Hepatopulmonary Syndrome and Portopulmonary Hypertension

10

Rodrigo Cartin-Ceba, Vivek N. Iyer, and Michael J. Krowka

Contents

Abstract

Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH) are pulmonary vascular complications of portal hypertension with or without cirrhosis. The prevalence among liver transplant candidates is roughly 5–32 % for HPS and approximately 6 % for POPH. Although these two conditions may initially present with dyspnea and are pathologically linked by the presence of portal hypertension, their pathophysiologic mechanisms are significantly different. HPS is characterized by low pulmonary vascular resistance secondary to intrapulmonary vascular dilatations and hypoxemia; on the other hand, POPH features elevated pulmonary vascular resistance and constriction of the pulmonary vasculature. Medical treatment for HPS has been disappointing overall. POPH patients can be treated with pulmonary artery-specific vasodilatory therapy. Whereas liver transplantation (LT) results in the resolution of HPS and is an indication per se for LT, its effect on POPH is highly unpredictable. LT poses a high risk of death in those with significant POPH, where pulmonary artery-specific vasodilatory therapy may improve functional status and allow successful LT in a small number of select patients. Modern strategies in managing HPS and POPH rely on a thorough screening and grading of the disease's severity, in order to tailor the appropriate therapy and

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select only the patients who will benefit from LT.

Keywords
Cirrhosis • Liver transplant • Hepatopulmonary syndrome • Portal hypertension • Pulmonary arterial hypertension • Portopulmonary hypertension

Introduction

Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH) are pulmonary vascular complications of portal hypertension with or without cirrhosis. Although these two conditions may initially present with dyspnea and are pathologically linked by the presence of portal hypertension, their pathophysiologic mechanisms are significantly different and hence their management and therapeutic approach. HPS is characterized by low pulmonary vascular resistance secondary to intrapulmonary vascular dilatations and hypoxemia; on the other hand, POPH features elevated pulmonary vascular resistance and constriction of the pulmonary vasculature. Both conditions have different implications regarding liver transplantation (LT). A comprehensive evaluation of these two conditions must be performed in order to ensure adequate management and optimization for LT.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome (HPS) is a clinical syndrome defined by the triad of (1) chronic liver disease, (2) hypoxemia (typically defined as a Pa02 $\leq$ 80 mmHg), and (3) presence of intrapulmonary vascular dilatations (IPVDs) on contrast "bubble" echocardiography. It is seen in roughly 5–32 % of patients with advanced liver disease presenting for transplant evaluation, and its varying prevalence reflects varying hypoxemia criteria used in different HPS studies in the literature (Rodriguez-Roisin and Krowka 2008). The occurrence of cyanosis and clubbing in cirrhosis was first described in 1884 by Flūckiger (Krowka and Cortese 1994). In 1935, Snell described three cirrhotic patients with hypoxemia, and in 1956 Rydell and Hoffbauer from the University of Minnesota described a 17-year-old patient with juvenile cirrhosis and significant pulmonary vascular shunting and hypoxemia. Autopsy findings in that patient revealed dilated pulmonary vessels and direct arteriovenous communications in the lung (Krowka and Cortese 1994). The term "hepatopulmonary syndrome" was first suggested in 1977 by Kennedy and Knudson who described the association of severe hypoxemia with intrapulmonary vascular dilatations in patients with liver disease (Kennedy and Knudson 1977). HPS is an independent risk factor for mortality and morbidity in patients with advanced liver disease resulting in a doubling of the risk of death in patients with advanced liver failure (Fallon et al. 2008). The presence of HPS is independent of the etiology and severity of the underlying liver disease and may be seen in patients with mild liver disease. HPS has also been diagnosed in patients with pre-sinusoidal portal hypertension with otherwise normal liver function.

Pathophysiology and Pathogenesis

The pulmonary vasculature in patients with cirrhosis has been demonstrated to have decreased pulmonary vascular tone with a poor or absent hypoxemic vasoconstrictor response (Andrivet et al. 1993; Nakos et al. 1993; Agusti et al. 1996). The capillary network is the "choke" point in the pulmonary circulation with a normal diameter of between 8 μm and 15 μm. The capillary network in patients with HPS is characterized by the presence of abnormally dilated precapillary and capillary vessels ($\geq$15 μm) that result in diffusion abnormalities and shunting of blood across the pulmonary vasculature (Krowka and Cortese 1994; Schraufnagel and Kay 1996). These dilated vessels are called intrapulmonary vascular dilatations (IPVDs) and can be detected noninvasively by the passage of

microbubbles (contrast echocardiogram) or 99 m technetium-macroaggregated albumin (brain shunt study). IPVDs are typically too small to be seen on regular pulmonary angiography (Keal and Harington 1970; Wolfe et al. 1977). The pulmonary angiogram can appear to be "busy" or "spongy" in appearance due to these diffuse capillary dilatations. Pulmonary and pleural-based arteriovenous malformations may also be seen occasionally (Krowka and Cortese 1994). In addition to these vascular changes, another component of HPS pathophysiology relates to the accumulation of predominantly CD 68 (+) macrophages in the pulmonary capillaries (Thenappan et al. 2011; Schraufnagel and Kay 1996). These macrophages appear to secrete vasodilatory, proangiogenic, and vascular proliferative growth factors such as inducible nitric oxide synthase, platelet-derived growth factor, and vascular endothelial growth factor (Thenappan et al. 2011). The pathophysiology of both the cellular and vascular changes in HPS has been studied extensively in animal models. One of the core elements of HPS pathophysiology appears to be an activation of the inducible nitric oxide synthase (iNOS) pathway in the pulmonary circulation. Systemic endotoxemia from portal hypertension and poor liver function activates pulmonary macrophages to secrete cytokines such as TNF-α which in turn activate iNOS. This leads to increased local NO production and eventually to vascular dilatations (IPVDs). CD 68 (+) macrophages appear to be key in the activation of iNOS as well as activation of other proangiogenic factors. Genetic studies have identified single-nucleotide polymorphisms in pathways relating to estrogen metabolism and angiogenesis (Fallon et al. 2008; Roberts et al. 2010).

Hypoxemia in HPS is thus thought to relate to a number of factors including (1) shortening of the pulmonary transit time across IPVDs resulting in reduced exposure of the capillary blood to the alveolus, (2) impaired diffusion across IPVDs due to increased alveolar–capillary distance and decreased diffusion efficiency, and (3) true intrapulmonary shunting across IPVDs and across pulmonary and pleural-based arteriovenous malformations.

Clinical Manifestations

HPS is defined by the triad of liver disease (portal hypertension with or without cirrhosis), hypoxemia, and the presence of IPVDs **(see list below)**. Patients typically present with dyspnea and hypoxemia in the setting of a chronic liver disease. The presence of chronic liver disease stigmata along with clubbing and cyanosis is classic for the diagnosis of HPS. The degree of hypoxemia can vary from mild to severe and in some cases be quite refractory to standard oxygen supplementation (Table 1). Hypoxemia can be evaluated noninvasively with a finger pulse oximeter with the patient in different positions (sitting, supine, and standing). This may uncover evidence for platypnea–orthodeoxia (worsening dyspnea and hypoxemia on assuming an upright or sitting/standing position). Most patients with HPS experience a gradual worsening in the degree of hypoxemia over time, but this is quite variable and does not always correlate with the status of the underlying liver disease. An important point to note is that all potential causes of hypoxemia need to be considered before a diagnosis of HPS is made. For example, in patients with coexisting lung disease (COPD, lung fibrosis, etc.), it is very important to determine the extent of hypoxemia related to HPS versus the underlying lung disease. A 99 m technetium-macroaggregated albumin perfusion lung scan can provide a quantitative estimation of the degree of intrapulmonary shunting and is very helpful in this situation. A high brain shunt index fraction (normal $\leq$6 %) would argue for HPS being the dominant cause of the patient's hypoxemia since other intrinsic lung disorders causing hypoxemia have normal brain uptake.

Table 1 Severity of hypoxemia in hepatopulmonary syndrome (HPS) (Adapted from Rodriguez-Roisin and Krowka 2008)

Degree of hypoxemia	Alveolar–arterial gradient (mmHg)	Pa02 (mmHg)
Mild	$\geq$15	$\geq$80
Moderate	$\geq$15	$\geq$60 and <80
Severe	$\geq$15	$\geq$50 and <60
Very severe	$\geq$15	50

The following are hepatopulmonary syndrome (HPS) diagnostic criteria:

Chronic liver disease (portal hypertension with/without cirrhosis)
AND
Evidence for hypoxemia (Pa02 < 80 mmHg)[a]
AND
Evidence for intrapulmonary vascular dilatations (via contrast "bubble" echocardiogram)

[a]Hypoxemia definitions can vary across centers; however, patients with Pa02 > 70 are unlikely to have clinically significant HPS.

Screening for HPS

Given the frequency of HPS in patients with cirrhosis, a screening as well as diagnostic algorithm should be followed for the detection of HPS. Patients with cirrhosis can be screened for HPS via pulse oximetry. Patients with screening Sp02 values ≥96 % have Pa02 values consistently greater than 60 mmHg (Arguedas et al. 2007). Alternatively, all patients with cirrhosis presenting for transplant evaluation can undergo a room air arterial blood gas (ABG) in the sitting position. Patients with a sitting room air Pa02 < 80 mmHg can be then evaluated further with a bubble echo study to confirm HPS (Krowka et al. 2006b). One must remember that hypoxemia is a continuum and the prevalence of HPS in patients with cirrhosis will vary significantly based on the criteria used to define hypoxemia (A-a gradient vs. different Pa02 cutoff values) (Schenk et al. 2002). In patients with low Sp02 or Pa02 values, a bubble echo study will confirm the presence of intrapulmonary shunting as well as exclude structural heart disease, intracardiac shunts, and coexistent pulmonary hypertension. The last point is very important because portopulmonary hypertension (POPH) can also present with significant hypoxemia but requires a markedly different diagnostic and therapeutic strategy as discussed elsewhere in this chapter (see main differences between POPH and HPS in Table 2). Room air and 100 % oxygen blood

Table 2 Differences between portopulmonary hypertension (POPH) and hepatopulmonary syndrome (HPS)

	POPH	HPS
Primary pathophysiology	Pulmonary arterial hypertension (PAH)	Intrapulmonary shunting
Pathology	PAH due to plexiform lesions, thrombosis, obliterative pulmonary arteriopathy	Intrapulmonary vascular dilatations (IPVDs) causing intrapulmonary shunting and consequent hypoxemia
Severity of hypoxemia	+ (typically mild)	+++ (mild to very severe depending on degree of shunting)
Right ventricular function	Significantly elevated right ventricular systolic pressure (RVSP) with right ventricular (RV) dilatation/systolic dysfunction and low cardiac output	Normal or mildly elevated RVSP (due to high flow state) with normal RV size and function
Clinical findings	Loud 2nd heart sound, systolic murmur, RV heave, lower extremity edema along with features of portal hypertension (varices, splenomegaly, ascites, etc.)	Clubbing, cyanosis, systolic flow murmur, platypnea, orthodeoxia along with signs of end-stage liver disease
Treatment	Pulmonary arterial-specific therapy (e.g., ambrisentan, sildenafil, epoprostenol, etc.)	Supportive care and management of underlying liver disease until liver transplantation (which is curative for HPS)
Is liver transplantation recommended/feasible?	Only in patients where the pulmonary hypertension is adequately controlled prior to transplantation	Recommended/feasible in all patients (even in severe hypoxemia)
MELD exception points available	Yes	Yes

gases can be obtained in the supine and sitting position to quantify the degree of hypoxemia and estimate the shunt fraction (Rodriguez-Roisin and Krowka 2008). A chest X-ray will identify the presence of obvious pulmonary parenchymal disease. A chest CT is very helpful in clarifying and quantifying abnormalities seen on the chest X-ray and is crucial in patients with coexistent pulmonary parenchymal disease (such as emphysema or interstitial lung disease). Pulmonary function tests typically show a reduced diffusing capacity that is reduced in proportion to the severity of the hypoxemia. Nonspecific spirometry abnormalities including restriction may also be noted. Pulmonary angiography is not extensively used nowadays due to easy availability of chest CT scans, but can reveal pleural-based and pulmonary arteriovenous malformations along with a generalized increase in pulmonary capillary size and density giving a "spongy" appearance on angiography (Afessa et al. 1993). A summary of initial testing is presented in Table 3.

Table 3 Initial workup of portal hypertension/cirrhosis patient with hypoxemia

Test	Rationale
Transthoracic echocardiography with "bubble" study	Confirms HPS (presence of intrapulmonary shunt) and excludes other entities (POPH, intracardiac shunting, valvular disease, left ventricular systolic/diastolic dysfunction)
Pulmonary function testing with diffusing capacity	Identifies obstructive (e.g., COPD) and restrictive (e.g., interstitial lung disease) pulmonary disease and establishes degree of impairment
Room air sitting and standing Pa02	Establishes degree of hypoxemia
100 % oxygen shunt study (sitting and standing)	Establishes degree of hypoxemia and shunting
Chest X-ray and/or chest CT scan	Identifies other pulmonary pathologies (e.g., COPD, interstitial lung disease, chest wall and pleural disease)
Overnight oximetry	Establishes need for nocturnal O2 supplementation. Also useful in identifying sleep apnea if clinically suspected
Oxygen titration study	Establishes supplemental O2 needs at rest and during exercise

Detecting Intrapulmonary Vascular Dilatations

The most sensitive method of detecting IPVDs in HPS is the contrast-enhanced transthoracic echocardiogram (bubble study). The most commonly used method involves injection of agitated saline via either a central or peripheral intravenous catheter. The saline bubbles are typically 10–90 μm in diameter and considerably larger than the diameter of normal pulmonary capillaries (8–15 μm) which do not allow passage into the left heart (Krowka et al. 2006b). However, IPVDs (typically $\geq$ 15 μm) allow free passage of these bubbles into the left heart resulting in the detection of an intrapulmonary shunt (Rodriguez-Roisin and Krowka 2008). In patients with an intracardiac shunt, bubbles typically appear in the left cardiac chambers within 1–2 cycles of their appearance in the right atrium. In a "positive" bubble study for intrapulmonary shunting, bubbles will appear in the left atrium 3–6 cardiac cycles after their first appearance in the right ventricle. The degree of shunting can be visually (semiquantitatively) estimated as being trivial, mild, moderate, or severe based on the quantity of bubbles passing through to the left heart. Although very sensitive for detecting IPVDs, the bubble study is not specific for the diagnosis of HPS, and many patients with liver cirrhosis may have some degree of intrapulmonary shunting and not otherwise qualify for a diagnosis of HPS due to lack of hypoxemia (Abrams et al. 1998). A more specific test appears to be the 99 m technetium-macroaggregated albumin perfusion lung scan (Abrams et al. 1998). A significantly abnormal shunt fraction (normal $\leq$6 %) is almost always associated with a clinical diagnosis of moderate to severe HPS (Abrams et al. 1998). As mentioned earlier, the 99 m technetium-macroaggregated scan can also be useful in quantifying the degree

of hypoxemia due to intrapulmonary shunting versus coexistent intrinsic lung disease.

Management and Treatment

Medical therapies in HPS: Several medical treatments have been tried for HPS over the years in an attempt to manipulate the inducible nitric oxide synthase (iNOS) or endotoxin pathways (Miyamoto et al. 2010; Afessa et al. 1993; Schenk et al. 2000) (Schiller et al. 2011; Tanikella et al. 2008). Norfloxacin was shown not to be effective in one randomized blinded crossover trial in nine patients (Gupta et al. 2010). Anecdotal case reports have documented a beneficial response from inhaled nitric oxide (Durand et al. 1998) as well as inhaled iloprost (Krug et al. 2007). These agents probably work by redistributing ventilation perfusion imbalances in the lung by causing a generalized pulmonary vasodilatation. One of the more promising recent reports has been a randomized controlled trial of oral garlic in HPS (Nath et al. 2004). Patients in this study were followed over a period of 9–18 months and showed a significant reduction in the degree of hypoxemia. Partial or complete resolution of HPS was also seen in a substantial proportion of patients. Overall, medical therapies other than liver transplant have not achieved consistent results in large cohorts of patients, and these therapies should only be resorted to when other options do not exist in critically ill patients with refractory hypoxemia.

Liver transplantation: The first attempt at human liver transplantation was made in 1963, and the first successful transplantation occurred in 1967 (Starzl et al. 1982). Since then, the role of liver transplantation in HPS has undergone a significant evolution. In the 1980s, HPS was first considered to be an absolute (Van Thiel et al. 1984) and then a relative contraindication to LT (Maddrey and Van Thiel 1988). A series of case reports in the 1990s documented essentially complete reversal of intrapulmonary shunting and clubbing in a number of patients with severe HPS (Stoller 1990; Laberge et al. 1992; Schwarzenberg et al. 1993; Hobeika et al. 1994). Oxygenation normalized from severely low values and pulmonary diffusing capacity showed continued improvement even 2 years after transplantation in one report (Laberge et al. 1992). These initial reports led to a wave of subsequent studies that looked at post-LT outcomes and resolution of HPS in these patients (Gupta et al. 2010; Lange and Stoller 1995; Arguedas et al. 2003; Taille et al. 2003; Krowka et al. 2006b; Schiffer et al. 2006; Iyer et al. 2013). These studies are summarized in Table 4. Earlier series reported higher mortality rates for HPS patients post-LT (Schiffer et al. 2006). However, recent reports (Gupta et al. 2010; Iyer et al. 2013) challenge the notion that HPS is associated with higher post-LT mortality. Recent reports from our group (Iyer et al. 2013) and Gupta et al. (Gupta et al. 2010) have challenged the traditional notion that severely hypoxemic HPS patients have inferior post-LT outcomes (Fig. 1). A large number of patients in both these series (11/21) Gupta and (23/49) Iyer had Pa02 $\leq$ 50 mmHg. No increase in perioperative mortality was noted in either series in these patients. Further studies exploring this difficult subgroup of patients will likely be very influential in modifying current apprehensions regarding transplantation for these patients.

Before 2002, organ allocation for LT was based on both disease severity and waitlist time. In 2002, implementation of standard MELD criteria standardized organ allocation across the country and prioritized severity of liver dysfunction over waitlist times. The understanding that patients with some diseases such as HPS, hepatocellular carcinoma, etc., were at a disadvantage with the new point allocation system leads to the development of MELD exception criteria. MELD exception points for HPS were formalized in 2006 and allowed for the granting of additional MELD points to HPS patients with a room air sitting Pa02 $<$ 60 mmHg. Prior to 2006, extra MELD points were based on the requests of individual centers and were not standardized. Our center has published on LT outcomes in the MELD exception era and has shown excellent outcomes in these patients (Iyer et al. 2013). However, there continues to be some debate about the utility and

Table 4 Post-LT outcomes in HPS (Adapted from Iyer et al. 2013)

Study	N	Early mortality[a]	Late mortality[b]	Pre-LT $Pa0_2$[c]
Scott et al. (1993)	6	0 %	0 %	59
Hobeika et al. (1994)	9	44 %	0 %	59
Fewtrell et al. (1994)	8	13 %	0 %	83[d]
Barbe et al. (1995)	11	36 %	0 %; 48 months f/u	57
Egawa et al. (1999)	21	10 %	28 %; 12 months f/u	57
Collisson et al. (2002)	6	0 %	50 %; 28 months f/u	52
Taille et al. (2003)	23	9 %	22 %; 72 months f/u	52
Arguedas et al. (2003)	25	29 %	0 %; 12 months f/u	54
Schenk et al. (2003)	7	0 %	43 %; 24 months f/u	75
Kim et al. (2004)	13	8 %	0 %; 90 days f/u	NR
Krowka et al. (2004)	32	17 %	no f/u beyond Tx hosp	51
Schiffer et al. (2006)	9	32 %	0 %; 6 months f/u	60
Deberaldini et al. (2008)	25	32 %	8 %; 48 months f/u	75
Gupta et al. (2010)	21	0 %	5 %; 70 months f/u	51
Iyer et al. (2013)	49	10 %	20 %; 120 months f/u	58

[a]30-day or during transplant hospitalization mortality
[b]Variable follow-up time periods from the time of transplant up to the month listed
[c]Mean or median PaO_2 mmHg at time of diagnosis
[d]Oxygen saturation

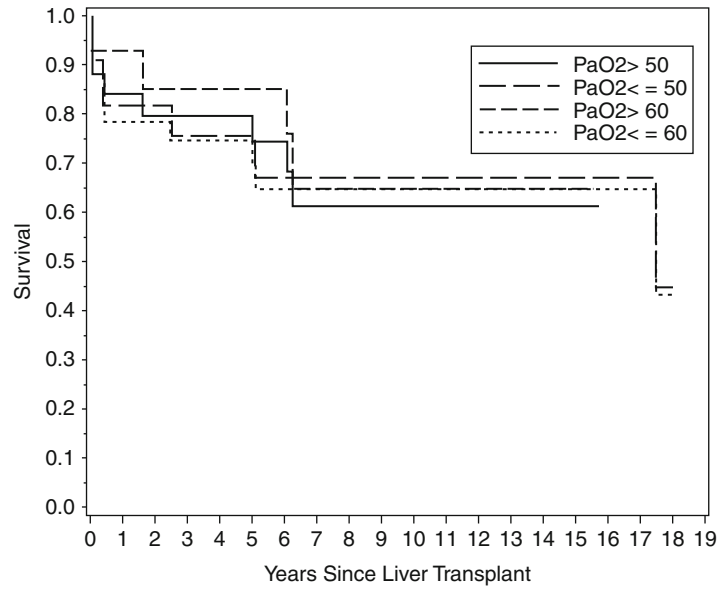

Fig. 1 Post-liver transplant survival based on baseline PaO2 values (Adapted from Iyer et al. 2013)

implementation of MELD exception points for HPS (Goldberg et al. 2014).

Post-liver transplantation management: HPS patients require additional care in the posttransplant setting mainly as a result of persistent hypoxemia. Over the past two decades, tremendous strides have been made in the understanding of critical illness and lung protective ventilation. These changes have significantly improved the care of HPS patients in the postoperative period. Even severely hypoxemic patients can be safely managed using a variety of ventilatory support tools (Fig. 2). Our group reported on posttransplant care details on 32 HPS patients

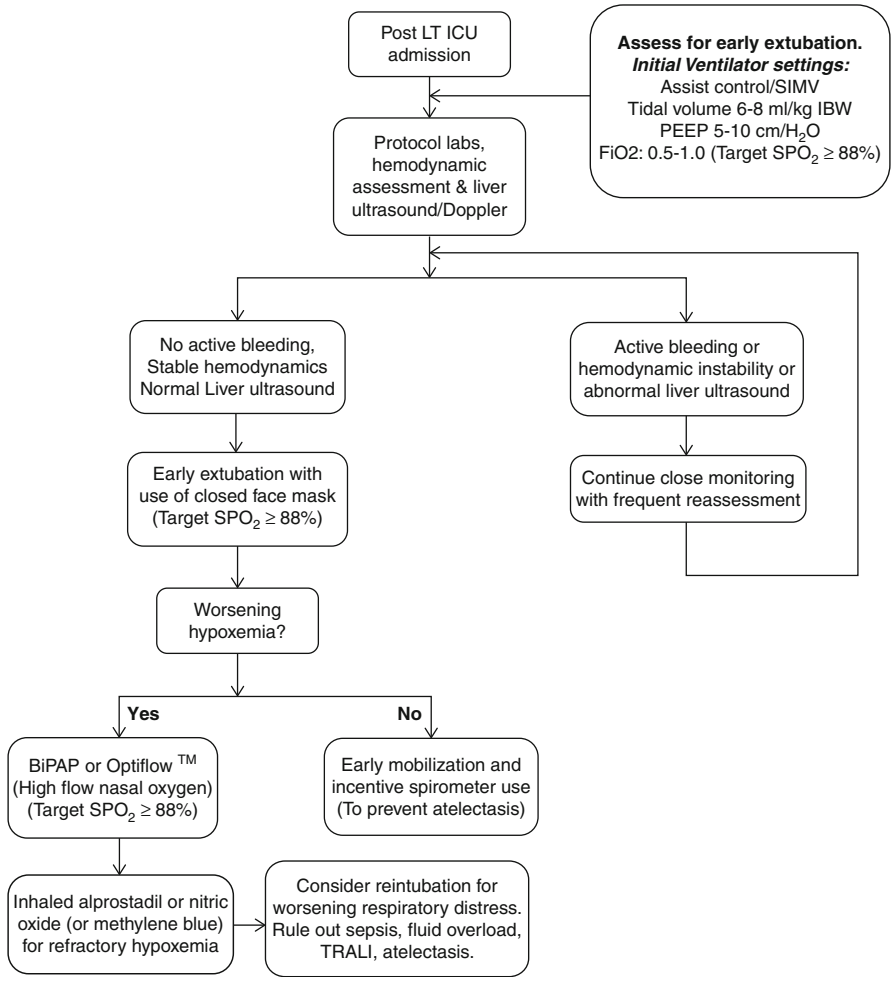

Fig. 2 Post-LT ICU management (Adapted from Iyer et al. 2013)

undergoing LT (Iyer et al. 2013). No patient required a tracheostomy for prolonged mechanical ventilation. The median ICU length of stay (LOS) was 2 days with a median hospital LOS of 14 days. Median duration of intubation and mechanical ventilation post-LT was 10 h (range 1–230 h). It is important to note that 13 of these 32 patients had very severe HPS with baseline Pa02 values <50 mmHg. Most importantly, post-LT survival was essentially identical between HPS and non-HPS patients in our cohort (Iyer et al. 2013). Based on contemporary experiences from our group and others, it appears that LT can be safely accomplished with excellent outcomes even in patients with profound baseline hypoxemia (Gupta et al. 2010; Iyer et al. 2013).

Resolution of HPS is almost universal post-LT. This has been confirmed across multiple studies from different centers (Gupta et al. 2010; Iyer et al. 2013). The time to resolution is varied, and it is generally thought that the cases with the most severe hypoxemia pre-transplant generally take the longest to resolve posttransplantation. Improvements in oxygenation generally precede improvements in pulmonary diffusing capacity (Laberge et al. 1992).

Development of POPH Post-LT in Patients with HPS

The coexistence of POPH and HPS as well as the occurrence of POPH post-LT in HPS patients has

been reported in the literature (Atz and Wessel 1999; Galie et al. 2004; Aucejo et al. 2006; Pham et al. 2010). It is important to note that HPS patients have been shown to have features of right atrial and ventricular enlargement along with RV hypertrophy (Fallon et al. 2008). Activated CD 68 (+) macrophages in the pulmonary circulation may be the common pathophysiological link for the development of both HPS and POPH given the angioproliferative, vasodilatory, and prothrombotic cytokines produced by them (Thenappan et al. 2011). One explanation for the emergence of POPH post-LT may be the fact that nitric oxide-mediated vasodilatation is reversed post-LT due to the presence of a functioning liver. This then leads to the emergence of unopposed vasoconstriction and development of PAH in a pulmonary circulation that had been previously vasodilated by nitric oxide. Clinicians should remain vigilant about this possibility and should appropriately investigate persistent or new dyspnea or hypoxemia with an echocardiogram or cardiac catheterization.

Portopulmonary Hypertension (POPH)

Portopulmonary hypertension (POPH) is a serious pulmonary vascular complication of portal hypertension that is associated with significant mortality and is related to neither the etiology of liver disease nor the severity of portal hypertension. The first clinical and pathological report of what we now know as POPH was provided by Mantz and Craige in 1951 (Mantz and Craige 1951). These authors described necropsy results of a 53-year-old female with spontaneous portacaval shunt (due to a probable congenital portal vein narrowing) that originated at the confluence of the portal, splenic, and mesenteric vein, coursed through to mediastinum, and was lined by varying amounts of thrombus thought to have embolized via the innominate vein into the right heart and pulmonary arteries. In addition to embolized small pulmonary arteries, an extreme endothelial proliferation and recanalization process was documented (Mantz and Craige 1951). Since the 1980s, enhanced recognition and renewed importance of POPH have evolved with the evolution of liver transplantation (LT) and potential outcomes associated with POPH. Specific screening recommendations and diagnostic criteria are now clearly defined for this syndrome. Despite the lack of randomized controlled trials for its medical treatment, extrapolation of the therapeutic advances in treating pulmonary arterial hypertension with specific effects in POPH has stimulated ongoing interest and importance in this syndrome.

Definition of POPH

Portopulmonary hypertension (POPH) is defined as pulmonary arterial hypertension (PAH) that occurs as a consequence of portal hypertension with or without cirrhosis (Simonneau et al. 2013). During the 5th World Symposium on Pulmonary Hypertension, POPH was included in group 1 because of its pathological and hemodynamic similarities with other causes of precapillary pulmonary hypertension (Table 5) (Simonneau et al. 2013). In the presence of documented portal hypertension, POPH is defined according to the following hemodynamic data obtained during a right heart catheterization (RHC):

A. Mean pulmonary artery pressure (MPAP) $\geq$25 mmHg
B. Pulmonary vascular resistance (PVR) $\geq$ 240 dyn/s/cm^{-5} or $\geq$3 Wood units
C. Pulmonary arterial wedge pressure (PAWP) $\leq$15 mmHg

It has been described that approximately 20 % of patients with cirrhosis have a moderate increase in pulmonary arterial pressures as assessed by echocardiography; however, only a fraction of these patients truly have POPH (Castro et al. 1996). This observation is likely related to other pulmonary hemodynamic patterns encountered in advanced liver disease such as excess volume due to fluid retention (with increased left-sided filling pressures) or a hyperdynamic state with increased cardiac output (Rodriguez-Roisin et al. 2004; Krowka et al. 2006b). Distinguishing these patterns by RHC is

Table 5 Updated classification of pulmonary hypertension by the 5th World Symposium on Pulmonary Hypertension (Simonneau et al. 2013)

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″. Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

BMPR bone morphogenetic protein receptor type II, *CAV1* caveolin-1, *ENG* endoglin, *HIV* human immunodeficiency virus, *PAH* pulmonary arterial hypertension

important in order to provide correct management (Krowka and Edwards 2000) (Table 6). Impaired sodium and water handling is a common problem in chronic liver disease patients, and excess volume due to fluid retention is very often seen in these patients and is reflected by increased PAWP during RHC. An increase in *both* PVR and PAWP can confuse the interpretation of pulmonary hemodynamics (Krowka et al. 2006b), a phenomenon that is seen in up to 25 % patients with POPH (Krowka 2012). In these cases, true precapillary pulmonary hypertension (POPH) is manifest by an increased transpulmonary gradient (MPAP-PAWP $>$ 12 mmHg). These patients should not be excluded from the diagnosis of POPH due to an elevated PAWP alone.

POPH should be distinguished from hepatopulmonary syndrome (HPS) (Rodriguez-Roisin et al. 2004; Rodriguez-Roisin and Krowka 2008). In HPS, arterial hypoxemia (which may be severe) is caused by intrapulmonary vascular dilatations, as opposed to vascular obstructions of POPH. HPS presents with normal PVR and a high flow state characterized by increased cardiac output (CO). This distinction is important if liver transplantation (LT) is being considered due to differences in risk, treatment options, and outcomes (Rodriguez-Roisin and Krowka 2008).

Epidemiology of POPH

This pulmonary vascular condition affects predominantly adults and is notably rare in the pediatric age group (Krowka 2012). Autoimmune liver disorders and female gender are more frequently associated with POPH (Kawut et al. 2008). Poor correlation exists between the severity of POPH and the degree of liver dysfunction as characterized by the Child–Turcotte–Pugh (CTP) or Model for End-Stage Liver Disease (MELD) scores (Hadengue et al. 1991; Krowka 2012). When compared to idiopathic pulmonary arterial hypertension (IPAH) hemodynamics, POPH is characterized by higher CO and less severity as measured by MPAP and PVR (Kuo et al. 1997b; Krowka et al. 2012; Chiva et al. 2014).

Table 6 Pulmonary hemodynamic patterns documented by right heart catheterization in advanced liver disease

	Mean pulmonary artery pressure (normal 9–18 mmHg)	Pulmonary vascular resistance (normal <2 Wood units)	Cardiac output (normal 4.0–8.0 L/min)	Pulmonary artery wedge pressure (normal 6–12 mmHg)
Vasoconstriction with vasoproliferation (POPH)	Elevated	Elevated	Low or normal	Normal
Fluid overload or pulmonary venous hypertension (excess volume)	Elevated	Normal or elevated	Elevated[a]	Elevated
Hyperdynamic circulatory state (high flow)	Elevated	Normal	Elevated	Normal

POPH portopulmonary hypertension
[a]In the absence of underlying heart disease

The term POPH was apparently first coined by Yoshida et al. in 1993, as they described the first case of POPH to undergo successful LT (Yoshida et al. 1993). Subsequently, several small series and case reports with autopsy results have described pulmonary arterial obstruction and pulmonary plexogenic arteriopathy (Naeye 1960; Lebrec et al. 1979; Matsubara et al. 1984; Edwards et al. 1987; Sankey et al. 1993). An unselected series of 17,901 autopsies revealed that PAH was five times more likely in cirrhotic patients than those without liver disease (McDonnell et al. 1983). Within the 1981–1987 NIH national registry of "primary" pulmonary hypertension from 32 centers reported by Rich (Rich et al. 1987), additional analyses by Groves concluded that 8.3 % likely had POPH (17/204; 187 had primary pulmonary hypertension) (Groves et al. 1990). Hadengue reported the largest prospective study of patients with portal hypertension ($n = 507$) in which portopulmonary hemodynamic measurements concluded that 2 % had POPH (Hadengue et al. 1991).

Prospective studies have demonstrated that POPH is a relatively common condition among LT candidates and in pulmonary hypertension registries. In the French pulmonary hypertension registry experience over a 12-month period (2002–2003), Humbert reported a 10.4 % frequency of POPH (70/674) from 17 university hospitals (Humbert et al. 2006). In the United States, the REVEAL (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) registry documented a 5.3 % POPH frequency (174/3,525), in which there were 68 % prevalent and 32 % incident cases satisfying the criteria of a MPAP $\geq$ 25 mmHg, PVR $\geq$ 240 dyn.s.cm^{-5}, and PAWP $\leq$ 15 mmHg (Krowka et al. 2012). Following slightly different PVR diagnostic criteria as part of outpatient RHC diagnostic assessments, the largest POPH-liver transplant center experiences reported to date are as follows: 8.5 % (Baylor Dallas, 102/1,205; PVR > 120 dyn.s.cm^{-5}), 6.1 % (Clichy, France 10/165; PVR > 120 dyn.s.cm^{-5}), and 5.3 % (Mayo Clinic 66/1,235; PVR > 240 dyn.s.cm^{-5}) (Ramsay et al. 1997; Colle et al. 2003; Krowka et al. 2006b).

Pathophysiology and Pathogenesis

The pulmonary histopathology of POPH individuals is indistinguishable from other PAH phenotypes (Edwards et al. 1987; Krowka and Edwards 2000). Based upon autopsy and lung explant studies, POPH is characterized by a spectrum of obstructive and remodeling changes in the pulmonary arterial bed. Initially, medial hypertrophy with smooth muscle proliferation and a transition

to myofibroblasts has been documented. As this proliferative pathologic process advances, plexogenic arteriopathy eventually develops (Edwards et al. 1987; Krowka and Edwards 2000).

Multiple circulating growth factors, neurohormone levels, and cytokine levels are present in portal hypertension with many potential candidate mediators in the development of POPH. The pulmonary vascular pathology occurs within the context of a hyperdynamic state caused by extrahepatic (splanchnic) vasodilation (Krowka 2012). It is unknown if this persistent high flow state initiates (by shear stress) or exacerbates (in combination with circulating mediators) the pulmonary vascular proliferative process. In addition, it is possible that a genetic predisposition may also play a role, since not all patients with portal hypertension due to cirrhosis develop POPH (Roberts et al. 2009b). A single-nucleotide polymorphism analysis of the serotonin transporter showed no association with POPH (Roberts et al. 2009a). A case–control study of 31 POPH cases and 104 controls evaluating single-nucleotide polymorphisms showed associations with estrogen receptor 1, aromatase, phosphodiesterase 5 (PDE5), angiopoietin 1, and calcium-binding protein A4 (Roberts et al. 2009b). The mechanistic link between estrogen signaling, serum estradiol levels, circulating endothelial progenitor cells, and the development of POPH is a current research hypothesis of interest (Arnal et al. 2010; Yeager et al. 2011). Pulmonary endothelial cells lack prostacyclin synthase in patients with POPH (hence a lack of prostacyclin vasodilation) (Tuder et al. 1999). The pulmonary vascular bed is exposed to increased levels of circulating endothelin-1 in the setting of cirrhosis (a potent vasoconstrictor and facilitator of smooth muscle proliferation) (Kamath et al. 2000; Benjaminov et al. 2003) and may be deficient in local nitric oxide effect (for vasodilation) (Pellicelli et al. 2010). The role of other circulating and receptor factors that may affect the pulmonary endothelium due to the existence of portal hypertension is speculative. These factors include vasoconstrictive/proliferative mediators such as serotonin, thromboxane, vasoactive intestinal peptide, and VEGF (vascular endothelial growth factor), as well as the possible imbalance of endothelin receptors (ET_A-mediating vasoconstriction, ET_B-mediating vasodilation) in the pulmonary arterial bed (Pellicelli et al. 2010).

As the pulmonary vasoproliferative process progresses, the increasing resistance to flow restricts the degree of CO flowing through the pulmonary vascular bed. Strain on the right ventricle will be seen with dilation of the right ventricle and reduction in systolic function. Progressive reduction in CO will evolve with right heart failure leading to hepatic venous engorgement and worsening portal hypertension. Death from either right heart failure or portal hypertension complications will inevitably occur without therapeutic intervention (Krowka 2012).

Clinical Manifestations

The most common and predominant symptom of POPH is dyspnea at rest or with exertion. POPH may be unnoticed as patients with advanced liver disease have multiple reasons for dyspnea including ascites, anemia, fluid retention, and muscle wasting. Chest pain and syncope are symptoms suggestive of severe POPH (Krowka 2012). Physical findings in POPH may be absent or subtle and nonspecific; however, the presence of a hyperdynamic precordium, an accentuated 2nd heart sound (best heard at the apex), and a systolic murmur due to tricuspid valve regurgitation may be noted. With severe POPH, findings of right heart failure such as marked distension of the jugular veins, peripheral edema, ascites, and a right ventricular third heart sound (S3) could be seen. The lung examination is usually normal and it is uncommon to have clubbing or cyanosis (as seen in HPS). Mild hypoxemia is common and often associated with abnormal overnight pulse oximetry. The chest roentgenogram usually demonstrates cardiomegaly and enlargement of the central pulmonary arteries as the duration and severity of POPH progress (Krowka 2012). The electrocardiogram may show rightward electrical axis and right bundle branch block pattern, and when POPH is severe, the presence of

inverted T waves in the precordial V1–V4 leads can be seen which suggests a severe effect on the right ventricle. Pulmonary function tests are usually not helpful in the diagnosis or management of POPH because reduced single-breath diffusing capacity (a common abnormality seen in PAH) is frequently seen in most patients with advanced liver disease. Some of the most important clinical distinctions between POPH and HPS have been described in Table 2.

Screening for POPH

Transthoracic echocardiography (TTE) has been the most practical method to screen for POPH (Donovan et al. 1996; Kim et al. 2000; Cotton et al. 2002). By assessing the tricuspid regurgitant peak velocity (TR), estimating the right atrial pressure by inferior vena cava changes with inspiration, and using the modified Bernoulli equation, an estimate of right ventricle systolic pressure (RVSP) can be determined in ~80 % of patients with portal hypertension (Kim et al. 2000). This quantitative approach allows one to decide which patients should precede to RHC for the definitive characterization of pulmonary hemodynamics. RVSP > 50 mmHg has been the cutoff criteria used to proceed to RHC in the current Mayo Clinic algorithm (Krowka et al. 2006b); rarely immeasurable TR with abnormal qualitative right ventricular size or function results in RHC. TTE was noted to have a 97 % sensitivity and 77 % specificity to detect moderate to severe PAH prior to LT (Kim et al. 2000). Based on different RVSP cutoffs, others have recommended that LT candidates with an RVSP > 38 mmHg should be referred for RHC (Raevens et al. 2013a). More recently, the measurement of the main pulmonary artery diameter by computed tomography combined with echocardiography improved the accuracy in the diagnosis of POPH (Devaraj et al. 2014).

Management and Treatment

The most important decisions in the management of POPH is deciding who needs PAH-specific therapy, and determining the risks for potential LT is critical in the management of patients with POPH (Fig. 3). POPH patients with MPAP >35 mmHg are particularly vulnerable to poor outcomes with attempted LT, especially if there

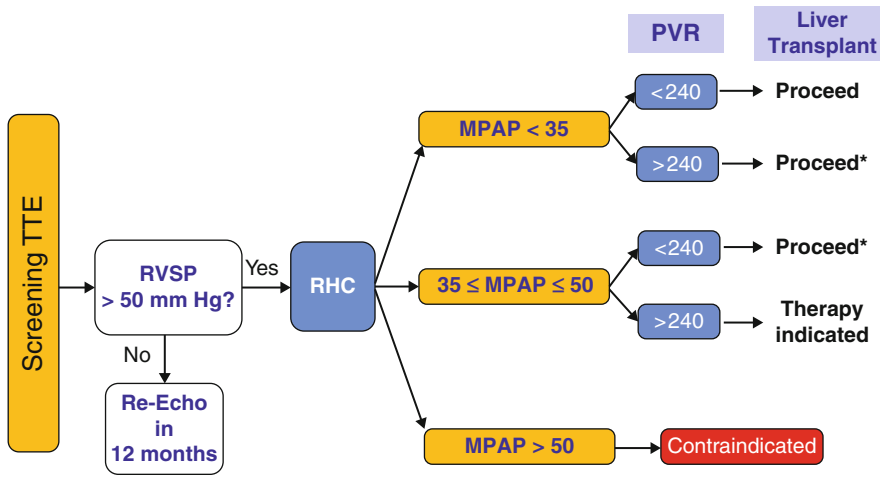

Fig. 3 Current portopulmonary hypertension screening evaluation and treatment algorithm used at the Mayo Clinic. *TTE* transthoracic echocardiography, *RVSP* right ventricular systolic pressure estimated by transthoracic echocardiography, *RHC* right heart catheterization, *MPAP* mean pulmonary artery pressure (normal <25 mmHg), *PVR* pulmonary vascular resistance [normal <240 dyn.s. cm^{-5} (or three Wood units)], contraindicated high risk of intraoperative event at graft reperfusion (*provided right ventricular size and function are adequate)

is no attempt to treat the POPH with current PAH-specific medications. The immediate goal in the treatment of POPH is to improve pulmonary hemodynamics by reducing the obstruction to pulmonary arterial flow (↓MPAP, ↓PVR, and ↑CO), ultimately improving and/or normalizing RV function. This can be accomplished by medications that result in vasodilation and antiplatelet aggregation and have antiproliferative effects (Krowka 2012). Drug therapy may augment the lack of pulmonary endothelial prostacyclin synthase deficiency (prostacyclin infusion), block circulating endothelin-1 effects (endothelin receptor antagonists), and enhance local nitric oxide vasodilatation effects (phosphodiesterase inhibitors and soluble guanylate cyclase stimulator) (Krowka 2012; Ghofrani et al. 2013).

Aside from one study evaluating the effect of riociguat (a soluble guanylate cyclase stimulator) in PAH (Ghofrani et al. 2013), randomized controlled trials evaluating PAH-specific therapies have generally excluded POPH patients. A summary of the evidence regarding therapy in POPH is presented in Table 7. These data originate from uncontrolled studies, whereby PAH-specific therapies used for other types of PAH proved to be beneficial for patients with POPH (Kuo et al. 1997a; Krowka et al. 1999; Reichenberger et al. 2006; Sussman et al. 2006; Ashfaq et al. 2007; Fix et al. 2007; Hoeper et al. 2007; Gough and White 2009; Hemnes and Robbins 2009; Hoeper 2009; Sakai et al. 2009; Melgosa et al. 2010; Cartin-Ceba et al. 2011; Eriksson et al. 2011; Halank et al. 2011; Kahler et al. 2011; Hollatz et al. 2012; Raevens et al. 2013b). Improvements in both MPAP and PVR are the ideal goals in treating POPH. However, MPAP may not decrease as much as desired (may even increase) because as the CO improves due to improvement in pulmonary vascular resistance (measured by decreased PVR), the higher flow will increase the pulmonary arterial pressures.

Prostacyclin analogues: In a summary of 48 patients treated with intravenous epoprostenol from 5 studies, MPAP decreased by 25 % (48 → 36 mmHg), PVR decreased by 52 % (550 → 262 dyn.s.cm^{-5}), and CO increased by 38 % (6.3 → 8.7 L/min, all $p < 0.01$) (Matsubara et al. 1984; Fix et al. 2007; Gough and White 2009; Eriksson et al. 2011; Halank et al. 2011). Other prostanoids (intravenous treprostinil and inhaled iloprost) have resulted in significant pulmonary hemodynamic improvement in POPH (Sakai et al. 2009; Melgosa et al. 2010; Hollatz et al. 2012). An ongoing observational, open-label, multicenter trial is evaluating the efficacy and safety of treprostinil in patients with POPH (ClinicalTrials.gov/NCT01028651).

Endothelin Receptor Antagonists: Both bosentan and ambrisentan have been found to be well tolerated in POPH patients. Hoeper et al. documented 1- and 3-year survival of 94 % and 89 %, respectively, in 18 patients with POPH and Child class A severity of liver disease using the nonselective endothelin antagonist bosentan (Hoeper et al. 2007). No liver toxicity was noted. Cartin-Ceba et al. reported 13 POPH patients using the ET_A receptor antagonist ambrisentan (10 mg daily) and documented at 1-year improvement in each of eight POPH patients (MPAP 58 → 41 mmHg and PVR 445 → 174 dyn.s.cm^{-5}; $p = 0.004$). Of note, five of the eight patients normalized their PVR (Cartin-Ceba et al. 2011). In further support of ambrisentan in POPH, Halank et al. described significant improvement in both exercise capacity and symptoms in 14 POPH patients (Halank et al. 2011). Importantly, neither of the uncontrolled ambrisentan studies was associated with significant hepatic toxicity. More recently, Savale et al. described 34 patients with POPH (Child class A or B severity of liver disease) treated with bosentan documenting significant hemodynamic improvement (more so in the Child class B subgroup), and event-free survival estimates were 82 %, 63 %, and 47 % at 1, 2, and 3 years, respectively (Savale et al. 2012). An ongoing observational, open-label, multicenter trial is evaluating the efficacy and safety of ambrisentan in patients with POPH (ClinicalTrials.gov/NCT01224210).

Phosphodiesterase-5 inhibitors: The use of phosphodiesterase inhibition (sildenafil) to enhance nitric oxide vasodilating effect, either alone or in combination with other PAH-specific

Table 7 Pulmonary arterial-specific therapy use in portopulmonary hypertension

PAH-specific therapy group	Drug	Study's first author	Number of subjects included	Study main outcomes
Endothelin receptor antagonist	Bosentan	Hoeper et al. (2007)	18	1- and 3-year survivals 94 % and 89 %, respectively
	Bosentan	Savale et al. (2012)	34	Event-free survival estimates were 82 %, 63 %, and 47 % at 1,2, and 3 years, respectively
	Ambrisentan	Cartin-Ceba et al. (2011)	13	At 1 year, MPAP and PVR improved in 8/8; PVR normalized in 5
	Ambrisentan	Halank et al. (2011)	14	Improvement in 6 min walk distance, no adverse effects
Phosphodiesterase inhibitors	Sildenafil	Reichenberger et al. (2006)	12	Improvement at 3 months; not sustained at 1 year
	Sildenafil	Gough and White (2009)	11	PVR decreased in all at first RHC follow-up
	Sildenafil	Hemnes and Robbins (2009)	10	At 1-year MPAP and PVR, decreased in 3/5 patients
Prostanoids	Epoprostenol	Kuo et al. (1997a)	4	MPAP and PVR improved
	Epoprostenol	Krowka et al. (1999)	15	15 MPAP and PVR improved
	Epoprostenol	Ashfaq et al. (2007)	16	Successful LT in 11 patients; 5-year survival 67 %
	Epoprostenol	Fix et al. (2007)	19	PVR improved in 14/14; MPAP improved in 11/14
	Epoprostenol	Sussman et al. (2006)	8	MPAP and PVR improved in 7/8
	Treprostinil	Sakai et al. (2009)	3	Successful LT in two patients (moderate portopulmonary hypertension)
	Inhaled iloprost	Hoeper et al. (2007)	13	1- and 3-year survivals 77 % and 46 %, respectively
	Inhaled iloprost	Melgosa et al. (2010)	21	Acute, but not long-term, hemodynamic improvement
	Epoprostenol	Awdish and Cajigas (2013)	21	Clearance for transplant in 52 % of patients within 1 year
Combination therapy	Sildenafil alone or combined with prostacyclins in 9 patients	Hollatz et al. (2012)	11	MPAP and PVR improved in all patients, all underwent LT, and 7/11 are off PAH-specific therapy
	Sildenafil and bosentan combined in 6 patients, 1 patient only on prostacyclins	Raevens et al. (2013b)	7	MPAP and PVR improved in the 5/6 patients treated with combination of sildenafil and bosentan, 2 underwent LT

MPAP mean pulmonary artery pressure, *PVR* pulmonary vascular resistance, *LT* liver transplantation, *IV* intravenous

therapies, has successfully improved POPH pulmonary hemodynamics and facilitated successful LT. Most of the published experiences have been in patients with less severe forms of POPH (Reichenberger et al. 2006; Gough and White 2009; Hemnes and Robbins 2009).

Other conventional therapies: Right ventricular function may be impaired by the use of beta

blockers which are usually used to prevent gastrointestinal bleeding by reducing the degree of portal hypertension. In moderate to severe POPH ($n = 10$; mean MPAP = 52 mmHg), withdrawal of beta blockade increased CO by 28 %, decreased PVR by 19 % with no change in MPAP, and increased 6 min walk by 79 m (Provencher et al. 2006). Transjugular intrahepatic portosystemic shunt (TIPS), as a treatment for gastrointestinal bleeding or refractory ascites, can temporarily increase MPAP, CO, and PVR. In a study of 16 cirrhotic patients without pulmonary hypertension, the increase in MPAP was greater than that noted in CO, suggesting an increase in the PVR after TIPS (Van der Linden et al. 1996). It is also important to correct nocturnal hypoxemia if present as this could potentially worsen the degree of pulmonary hypertension.

Liver transplantation: Although it is very well known that POPH can occur in non-cirrhotic portal hypertension, the vast majority of cases in the United States are secondary to cirrhosis and hence the importance of LT consideration. LT is a potentially curative intervention for POPH, at least from a hemodynamic perspective in a highly selected group of patients. However, the outcome of POPH following LT remains unpredictable despite screening, careful patient selection, higher allocation priority, and advances in single and combination PAH-specific therapies (Castro et al. 1996; Taura et al. 1996; Starkel et al. 2002; Krowka et al. 2004; Kawut et al. 2005; Saner et al. 2006; Austin et al. 2008; Bandara et al. 2010; Fukazawa and Pretto 2010; Scouras et al. 2011). Effective PAH-specific therapy has resulted in successful LT and subsequent liberation from pre-LT PAH-specific therapy in some individuals. Since 2006, LT waitlist candidates with POPH have been eligible to receive waitlist priority upgrades (MELD exceptions) based on formalized criteria set forth by the Organ Procurement and Transplantation Network (OPTN) (Freeman et al. 2006; Krowka et al. 2006a); these criteria are summarized in Table 8. However, the data used to develop this policy derived from small single-center studies, and while in place to guide regional review boards, do not mandate that exception points be restricted only to patients meeting these criteria. Recently, Goldberg et al. evaluated data on 155 POPH patients with MELD score exception approved from the OPTN database during the years 2006–2012 and demonstrated that since the implementation of a formalized MELD exception policy for POPH, the majority of patients awarded such points have not met OPTN criteria for such exception points due to missing or incomplete data, with nearly one-third not having hemodynamic data consistent with POPH (Goldberg et al. 2014). In addition, the authors of that study found that this subset of patients with POPH MELD exceptions presented a significant risk of waitlist mortality, particularly in those with hemodynamic criteria consistent with POPH, with several early post-LT deaths in both groups attributable to right heart failure/persistent pulmonary hypertension (Goldberg et al. 2014). In summary, POPH is not considered an indication for LT; it can be a contraindication if the MPAP remains significantly elevated (>50 mmHg) despite optimal therapy.

Table 8 Model end-stage liver disease exception criteria for portopulmonary hypertension

1. Moderate to severe POPH diagnosis confirmed by right heart catheterization
(a) MPAP $\geq$ 35 mmHg
(b) PVR $\geq$ 240 dyn/s/cm^{-5}
(c) PAWP $\leq$ 15 mmHg
2. PAH-specific therapy initiated; improvement documented
(a) MPAP < 35 mmHg
(b) PVR < 400 dyn/s/cm^{-5}[a]
(c) Satisfactory right ventricular function by transthoracic echocardiography
3. MELD exception updated every 3 months
(a) Give additional MELD exception if RHC data satisfies criteria # 2

POPH portopulmonary hypertension, *PAH* pulmonary arterial hypertension, *MPAP* mean pulmonary artery pressure, *PVR* pulmonary vascular resistance, *PAWP* pulmonary arterial wedge pressure, *RHC* right heart catheterization, *MELD* model end-stage liver disease

[a]If PVR is normal, higher MPAP may be allowed and reconsidered due to physiology that is now high flow rather than obstruction to flow due to the therapy

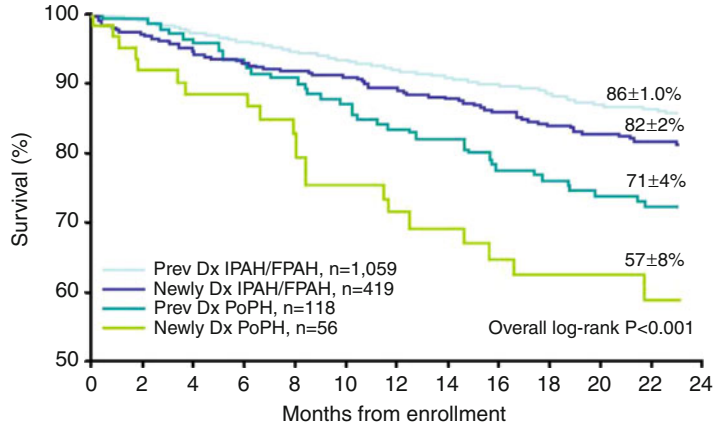

Fig. 4 Registry to evaluate early and long-term pulmonary arterial hypertension (REVEAL, Reprinted with permission from CHEST, Krowka et al. 2012), 2-year survival patterns for POPH and idiopathic pulmonary arterial hypertension categorized by previous versus newly diagnosed at the time of entry into the registry. POPH, portopulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension; FPAH, familial pulmonary arterial hypertension

Prognosis

The overall prognosis of POPH has been confounded by small series from eras in which none of the current PAH-specific medications were available compared with the present, when there is increasing experience in PAH-specific therapies and LT. Robalino and Moodie reported a 5-year survival of 4 % ($n = 78$) in an era prior to the availability of continuous IV prostacyclin infusion (Robalino and Moodie 1991). Swanson reported a 14 % 5-year survival in POPH patients ($n = 19$) denied LT and not treated with any of the current PV therapies (Swanson et al. 2008). From the French National Center for PAH ($n = 154$ over a 20-year span until 2004), Le Pavec described 1-, 3-, and 5-year survivals of 88 %, 75 %, and 68 %, respectively, for patients with POPH (mainly Child class A and alcohol as the etiology of cirrhosis) (Le Pavec et al. 2008). Causes of death in all series mentioned herein were equally distributed between right heart failure due to POPH and direct complications of liver disease (bleeding, sepsis, hepatocellular carcinoma). More recently, the REVEAL registry reported two important POPH observations (Krowka et al. 2012). First, the use of any PAH-specific therapy for POPH was delayed compared to patients diagnosed with IPAH. Specifically, at the time of entry into the registry, only 25 % were on PAH-specific therapy; by the end of a 12-month follow-up, 74 % of those alive were on treatment. Second, although baseline hemodynamics in POPH (MPAP and PVR) were significantly better than those with IPAH, the 1- and 3-year survivals were worse (Fig. 4); the 5-year survival for all POPH patients was 40 % versus 64 % for IPAH. Liver disease etiologies and causes of death were not determined, and survival was not analyzed by the type of PAH-specific therapy. A recent report by Khaderi et al. described excellent long-term outcomes of 7 POPH patients that underwent LT, with all patients able to come off intravenous epoprostenol after LT, and a survival of 85 % after 7.8 years of follow-up (Khaderi et al. 2014).

Conclusion

Hepatopulmonary syndrome is associated with significantly increased morbidity and mortality in ESLD patients. Implementation of a routine HPS screening program in patients undergoing LT evaluation improves detection rates. Liver transplantation currently is the only well-accepted treatment option for HPS and results in uniform resolution of hypoxemia even in severe cases. MELD exception points for HPS facilitate earlier transplantation.

Patients with HPS have excellent post-LT outcomes, and the presence of severe hypoxemia in particular is an indication and not a contraindication for pursuing expedited transplantation.

POPH is an uncommon, serious, yet treatable pulmonary vascular complication of portal hypertension that can lead to right heart failure and death, if untreated. Due to the spectrum of pulmonary hemodynamic variations associated with hepatic dysfunction, screening by TTE and confirmation by RHC are necessary for accurate diagnosis and therapy. Despite the lack of controlled studies, PAH-specific therapies in POPH can significantly improve to "cure" POPH, at least hemodynamically, with a combination of PAH-specific therapy and LT appears to be an attainable goal in a cohort of POPH patients yet to be optimally characterized.

Cross-References

- ▶ Anesthesia Management of Liver Transplantation
- ▶ Interventional Radiology for the Pre-transplant Patient
- ▶ Liver Transplantation in the Third Millennium in North America: The Strategy for Success
- ▶ Orthotopic Liver Transplantation: Complications
- ▶ Orthotopic Liver Transplantation: Indications and Contraindications

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Part IV

Transplant Hepatology

NASH: The Ethical Dilemma

11

Laura Connor and Scott Andrew Fink

Contents

Abstract

Nonalcoholic fatty liver disease, the hepatic manifestation of the metabolic syndrome, is a disease whereby increasing steatosis can potentially lead to steatohepatititis or nonalcoholic steatohepatitis. Continuing inflammation may lead to cirrhosis in as many as 25 % of patients. Nonalcoholic fatty liver disease is considered to be the most common form of chronic liver disease, and current population trends dictate that more patients will need liver transplants for this disease. While overall survival outcomes are equivalent to other forms of liver disease, this may at least partly be a result of current screening of patients which eliminates those patients who have the most risk factors for cardiovascular disease, the most common cause of poor outcomes following liver transplant in patients with nonalcoholic fatty liver disease. Immunosuppression may accelerate recurrence of the metabolic syndrome and nonalcoholic steatohepatitis post transplant.

Keywords

Nonalcoholic fatty liver disease • Nonalcoholic steatohepatitis • Cirrhosis • Liver transplant • Metabolic syndrome • Insulin resistance • Obesity

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Introduction

As the population of the United States becomes older, heavier, and more likely to have elements of the metabolic syndrome, more patients develop nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Though a minority of these patients will progress to cirrhosis, the large numbers of patients with nonalcoholic steatohepatitis and the possible decline in the future of patients who will be transplanted for other causes means that the liver transplant physician will evaluate increasing numbers of patients for orthotopic liver transplantations whose end-stage liver disease derives from nonalcoholic fatty liver disease.

This chapter will discuss the epidemiology and physiology of nonalcoholic fatty liver disease as well as its treatment. Transplant considerations will be reviewed including a discussion of the forecast of numbers of patients predicted to need transplant due to nonalcoholic fatty liver disease. Outcomes following transplant will be explored. Finally, the unique ethical considerations regarding transplanting patients with nonalcoholic fatty liver disease will be addressed.

Epidemiology

The reported prevalence of nonalalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) varies widely in the literature and has been assessed using a variety of diagnostic modalities such as transaminases, imaging studies, and liver biopsy. Liver biopsy is considered the gold standard for diagnosing NASH, and the prevalence of NASH reported in biopsy-based studies has been estimated to range from 3 % to 5 % (Vernon et al. 2011; Williams et al. 2011; Lazo et al. 2013).

In the United States, the prevalence of NAFLD has been estimated to range from 2.8 % to 46 %. The incidence of NAFLD and NASH is not well reported, and data has varied. A study from England showed the annual incidence of NAFLD to be 29 cases per 100,000 person-years (Whalley et al. 2007). Two studies from Japan have found much higher incidences of 31 cases per 1,000 person-years and 86 cases per 1,000 person-years (Suzuki et al. 2005; Hamaguchi et al. 2005).

As with most chronic liver diseases, NAFLD seems most apparent in older patients. A retrospective cohort study has shown NALFD to mainly affect the middle-aged (50–60 year old) and the elderly (>60 year old). This is likely due to the fact that older patients have more risk factors for NAFLD such as obesity, diabetes, and hyperlipidemia. Older patients also had greater fibrosis on biopsy as well as a higher prevalence of cirrhosis (Frith et al. 2009). It is important to note the possibility that disease progression to fibrosis and cirrhosis may be related to disease duration rather than age independently.

It is unclear whether NAFLD affects predominantly males or females. Some older, small, non-population-based studies indicate that NAFLD is more common in women (Ludwig et al. 1980; Lee 1989). More recent population-based studies, however, have found the prevalence of NAFLD to be higher in men than women (Arun et al. 2006; Browning et al. 2004; Williams et al. 2011; Lazo et al. 2013).

Population-based studies have shown the prevalence of NAFLD to be highest in Hispanics compared to whites and blacks. Non-Hispanic whites have a higher prevalence than non-Hispanic blacks (Williams et al. 2011; Browning et al. 2004; Lazo et al. 2013). The reason for this higher prevalence in Hispanics may be due to a higher prevalence of obesity and insulin resistance in this group (Lazo et al. 2013). Additionally, a genome-wide association study (GWAS) has identified a variant in the patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene that is strongly associated with increased hepatic fat levels (Koutsari and Lazaridis 2010). This allele was most common in Hispanics (Weiskirchen and Wasmuth 2009).

Projected Growth

The prevalence of NAFLD has been steadily rising. Results from a large population-based study assessing the changes in prevalence of chronic

liver disease (CLD) over the course of two decades in the United States has shown the prevalence of CLD to be increasing over time. The rising prevalence of NAFLD was the reason for this increase as the prevalence of hepatitis C, hepatitis B, and alcoholic liver disease has remained stable. The prevalence of NAFLD increased from 5.51 % (1988–1994) to 9.84 % (1999–2004) to 11.01 % (2005–2008). Additionally, from 1988 to 1995, NAFLD accounted for 46.8 % of CLD cases, which rose to 75.1 % of CLD cases from 2005 to 2008. During this time period, rises in obesity, insulin resistance, type II diabetes, and hypertension were also observed (Younossi et al. 2011). With the prevalence of obesity continuing to rise, it is projected that we will continue to see a rise in the prevalence of NAFLD and its complications (Charlton et al. 2011).

Cost to Society

The diagnosis and management of NAFLD poses a great cost to society. Baumeister et al. (2008) showed that patients with sonographic fatty liver disease and high serum ALT levels increased overall healthcare cost by 26 % at 5-year follow-up. The estimated lifetime medical cost for a patient with NASH is approximately $31,000 (Younossi and Singer 2006). With the prevalence of NAFLD on the rise, there will be an increasing cost to society in the upcoming years.

Nature of Disease and Associated Disease

It has become apparent that fatty liver, previously thought to be a benign entity, can progress to nonalcoholic steatohepatitis. Up to 25 % of patients with NASH can progress to cirrhosis. The presence of the metabolic syndrome appears to be a risk factor for development of NASH. NAFLD is essentially considered the hepatic sequel of the metabolic syndrome (Donnelly et al. 2005). NAFLD and its association with the metabolic syndrome will be discussed in more detail in a later section.

Pathophysiology

The exact mechanism behind the development of NAFLD and NASH is not entirely known and is likely multifactorial. NAFLD, like many other diseases, probably occurs from interplay between genetic and environmental factors. The main mechanisms identified in NAFLD are insulin resistance and increased free fatty acids in the liver. In 1998, Day et al. proposed the "two hit" hypothesis that describes two "hits" which lead to steatohepatitis. The first hit is the buildup of hepatic steatosis and the second hit is liver injury and inflammation (Day and James 1998). Insulin resistance leads to increased secretion of free fatty acids from adipocytes, which leads to increased free fatty acid influx into the liver (Peverill et al. 2014). It has been shown that in patients with NAFLD, insulin does not suppress adipose tissue lipolysis to the same extent that it does in healthy individuals (Sanyal et al. 2001).

It appears that hepatocyte injury occurs in the setting of excess free fatty acids rather that due to simple triglyceride accumulation (Peverill et al. 2014). Several mechanisms have been proposed as potential etiologies of fat accumulation in the liver. There can be increased importation of free fatty acids into the liver, decreased secretion of triglyceride-rich lipoproteins out of the liver, and impaired free fatty acid beta-oxidation (Musso et al. 2003).

Insulin resistance appears to not only be a marker of NALFD but also for progression to NASH. Insulin resistance is found in the majority of patients with NASH, irrespective of obesity (Chitturi et al. 2002). Insulin resistance has also been found in NAFLD patients who are lean and have normal glucose tolerance testing (Marchesini et al. 1999). Additionally, insulin resistance has been shown to correlate independently with hepatic fibrosis (Ryan et al. 2005).

Presentation

Forms of Disease (NAFLD, NASH, Cirrhosis)

According to the American Association for the Study of Liver Disease (AASLD), nonalcoholic fatty liver disease (NALFD) is defined as hepatic

steatosis diagnosed by either imaging or histology with no other causes of hepatic fat accumulation identified such as alcohol consumption. Histologically, NAFLD can be further categorized as nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). NAFL is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury or fibrosis. NAFL has a low risk of progression to cirrhosis and liver failure. NASH is defined as the presence of hepatic steatosis plus inflammation with hepatocyte injury with or without fibrosis. NASH can progress to cirrhosis, liver failure, and hepatocellular carcinoma (Chalasani et al. 2012). As NAFLD is an umbrella term that encompasses NASH, the two terms are often used interchangeably though not all patients with NAFLD have NASH. All patients with a diagnosis of NASH, however, have NAFLD.

NASH cirrhosis is defined as the presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis (Chalasani et al. 2012). Additionally, there is indirect evidence that patients with cryptogenic cirrhosis (CC) may have developed cirrhosis as a progression of NASH. A higher prevalence of obesity and diabetes mellitus was found in patients with CC compared to those with cirrhosis secondary to hepatitis C or primary biliary cirrhosis. This prevalence was found to be similar to those with NASH. Patients with NASH, on average, were about 10 years younger than patients with CC suggesting that NASH may progress to cirrhosis over the course of a decade (Caldwell et al. 1999).

Clinical Findings

Most patients with NAFLD are asymptomatic and the disease is discovered due to abnormal transaminases incidentally found on blood work. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are typically two to five times the upper limit of normal. To help distinguish NAFLD from alcoholic liver disease (ALD), the ratio of AST to ALT can be used. This ratio will typically be less than 1.0 in NAFLD and greater than 2.0 in ALD (Sorbi et al. 1999). Heavy alcohol use should also be excluded by history. According to the National Institutes of Health (NIH), male patients must consume no more than two standard drinks per day (140 g ethanol/week) and female patients must consume no more than one standard drink per day (70 g ethanol/week) to be classified as having nonalcoholic fatty liver disease (Hu et al. 2012). Before a diagnosis of NAFLD can be made, other causes of elevated transaminases must be excluded such has viral hepatitis, autoimmune hepatitis, and hemochromatosis.

Imaging studies also play a role in the diagnosis of NAFLD as they can confirm the presence of steatosis in a patient suspected of having NAFLD. Ultrasound is typically used due to its low cost and noninvasive nature. On ultrasound, fatty infiltration of the liver is identified by findings of a diffuse increase in echogenicity of the liver. Alternatively computed tomography (CT) and magnetic resonance imaging (MRI) can also detect hepatic steatosis and are more sensitive in quantifying steatosis. No imaging modality can distinguish between simple steatosis and NASH. Liver biopsy is the only modality that can distinguish simple steatosis from NASH, however its role in the diagnosis and management of NAFLD is unsettled. Liver biopsy is an invasive procedure and does have the limitation of sampling errors, which can over- or underestimate the severity of disease. Additionally, distinguishing NAFL and NASH will likely not change management. Noninvasive biomarkers for NASH and evaluation of fibrosis are underway (Schwenzer et al. 2009).

Treatment

Weight Loss

Despite the rising prevalence of NAFLD, treatment modalities remain limited. Patients without steatohepatitis have a favorable prognosis. Therefore, it is recommended that treatment aimed at improving liver disease be limited to those with NASH (Chalasani et al. 2012). The approach with the most evidence behind its benefit is weight loss. Gradual weight loss is optimal as rapid weight

loss can exacerbate NASH (Andersen et al. 1991). Weight loss first can be attempted by lifestyle modifications, which include decreasing caloric intake and increasing physical activity. This has been shown to improve liver enzymes and histology as well as improve glycemic control (Hickman et al. 2004; Peterson et al. 2005). A randomized controlled trial studying the effects of weight loss in obese patients with NASH showed that participants who achieved a weight loss goal of greater than or equal to 7 % compared to those who lost less than 7 % after 48 weeks of intervention had significant improvement in steatosis, lobular inflammation, ballooning injury, and NASH histology severity score (Promrat et al. 2010). A second randomized controlled trial studying type 2 diabetics revealed that intensive lifestyle intervention leading to an 8 % reduction in weight successfully reduced hepatic steatosis measured by magnetic resonance spectroscopy compared to controls (Lazo et al. 2010).

Often, attempts at lifestyle modifications are unsuccessful as patients have difficulty adhering to the necessary diet and exercise regiments. Orlistat is a weight loss medication that has been shown to improve ALT levels and steatosis on ultrasound in patients with NAFLD (Zelber-Sagi et al. 2006). It has also been shown to reverse fatty liver disease and improve fibrosis while decreasing body weight (Hussein et al. 2007). Conversely, a study by Harrison et al. (2009) did not show orlistat to enhance weight loss or improve liver enzymes or liver histology. However, patients who did achieve >9 % reduction in body weight did have improved hepatic histological changes (Harrison et al. 2009). Orlistat can be considered in patients with NAFLD who have had unsuccessful attempts at lifestyle modifications to achieve weight loss.

Bariatric surgery may be of benefit to help achieve weight loss in morbidly obese patients with NAFLD who qualify for this surgery. There are no randomized controlled trials investigating bariatric surgery to treat NASH, however there are several retrospective and prospective studies looking at liver histology after bariatric surgery. Overall, improvement in histopathologic features of NAFLD has been seen in more than three fourths of patients postbariatric surgery (Mummadi et al. 2008). Though bariatric surgery may lead to improvement of NAFLD, there is not enough data to support its use specifically for the treatment of NASH.

Pharmacological Therapy

Pharmacological therapies that have been studied in NALFD include vitamin E, insulin-sensitizing agents, and lipid-lowering medications. Oxidative stress plays a key role in the pathogenesis of NASH, prompting the antioxidant vitamin E to be investigated as a potential treatment modality in NASH. The PIVENS trial, a randomized, multicenter, double-masked, placebo-controlled trial, evaluated the effect of vitamin E and pioglitazone versus placebo on hepatic histology in nondiabetic patients with NASH. The primary outcome was improvement in histological features of nonalcoholic steatohepatitis, assessed using a composite of standardized scores for steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis. Vitamin E (α-tocopherol) 800 IU/day administered for 96 weeks was associated with a significantly higher rate of improvement in nonalcoholic steatohepatitis compared to placebo (Sanyal et al. 2010). The TONIC trial, another large multicenter randomized controlled trial, also showed improvements in NAFLD activity score and resolution of NASH compared to placebo, though their primary outcome of sustained reduction of ALT was not attained (Lavine et al. 2011). Although there are some positive results regarding the benefit of vitamin E in NASH, there is also some concern that vitamin E may increase all-cause mortality, particularly at higher doses (Miller et al. 2005; Bjelakovic et al. 2007). Based on the current available data, vitamin E should be considered in nondiabetic patients with biopsy-proven NASH, however it should not be used in diabetic patients with NASH, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis (Chalasani et al. 2012).

Insulin-sensitizing agents have been investigated for the treatment of NASH since insulin

resistance is known to be a major contributor to the pathogenesis of NASH. Studies investigating the effect of metformin on aminotransferases and liver histology in NASH have shown a reduction in insulin resistance, however no significant improvement in liver histology (Uygun et al. 2004; Nair et al. 2004). Therefore, metformin is not recommended as a specific treatment for NASH (Chalasani et al. 2012). The thiazolidinediones (pioglitazone and rosiglitazone) have also been studied and have shown more promising results compared to metformin. Results from the PIVENS trial regarding pioglitazone showed pioglitazone to reduce hepatic steatosis and lobular inflammation; however, it did not show improvement in fibrosis score when compared to placebo. Though pioglitazone did not achieve the primary endpoint of this study, it did show significant improvement in the histological features of NASH compared to placebo (Sanyal et al. 2010). Pioglitazone can be used to treat biopsy-proven NASH; however, it is important to note that the long-term safety and efficacy of pioglitazone in patients with NASH is not established (Chalasani et al. 2012).

Patients with NAFLD are at increased risk of cardiovascular events, making statins often indicated for cardiovascular risk reduction. Therefore, it is important to note that the use of statins in patients with NAFLD is safe and does not place patients at increased risk of hepatotoxicty (Chalasani et al. 2004; Cohen et al. 2006; Lewis et al. 2007). Randomized controlled trials evaluating histological response in NASH to lipid-lowering agents are lacking. Statins should not be used for the primary purpose of treating NASH; however, they can be used to treat dyslipidemia in these patients.

Associated Conditions

Metabolic Syndrome (Diabetes, Obesity, Hypercholesterolemia)

NAFLD is associated with insulin resistance, diabetes, obesity, and hyperlipidemia. These are all the main features of the metabolic syndrome. The metabolic syndrome is defined as having at least three of the following: (1) central obesity (waist circumference >102 cm in men and >88 cm in women), (2) fasting glucose >110 mg/dl, (3) hypertension (>130/80 mmHg), (4) hypertriglyceridemia (>150 mg/dl), and (5) low high-density lipoprotein (HDL) level (<40 mg/dl in men and <50 mg/dl in women). The presence of the metabolic syndrome shown to carry a high risk of NASH among NALFD patients was associated with a high risk of fibrosis (Marchesini et al. 2003).

Studies involving bariatric surgery patients show the prevalence of NAFLD to be as high as 90 % and NASH to be as high as 70 % in this obese population. Insulin resistance was found to be an independent predictor of NASH. Additionally, NASH was found to be present in 75 % of patients who carried the diagnosis of type II diabetes (Boza et al. 2005). Obese patients with NASH have been found to have more severe insulin resistance, more severe hypertriglyceridemia, and a higher prevalence of the metabolic syndrome than those with simple steatosis. This implies that insulin resistance may play an important role in the progression of simple steatosis to steatohepaitis and fibrosis (Gholam et al. 2007).

The prevalence of hyperlipidemia in NAFLD varies from 20 % to 92 %. It appears hypertriglyceridemia carries a greater risk than hypercholesterolemia. Low HLD levels have also been frequently observed in patients with NAFLD (Parekh and Anamia 2007). Hypertension, also a part of the metabolic syndrome, has also been linked to NAFLD. A study of nondiabetic, nonobese patients with arterial hypertension showed the prevalence of NAFLD to be higher in hypertensive patients compared to controls (30.9 % versus. 12.7 %). This increased prevalence appears to be related to increased insulin resistance (Donati et al. 2004).

NAFLD and Transplant

As nonalcoholic fatty liver disease continues to escalate its importance as a major cause of

morbidity and mortality, so, too, has its impact been on liver transplantation. Numbers of transplants performed for cryptogenic cirrhosis presumed secondary to nonalcoholic fatty liver disease and nonalcoholic steatohepatitis have risen (Quillin et al. 2014), and some have predicted a dramatic rise in the percentage of patients in the future who will be transplanted for nonalcoholic fatty liver disease-associated conditions.

Since nonalcoholic steatohepatitis is seen as a marker for associated conditions with the metabolic syndrome such as cardiovascular disease, there is particular concern about the fitness of patients with nonalcoholic fatty liver disease to undergo transplant. Perhaps more importantly, significant concerns exist about these patients' long-term morbidity and survival after transplant. Considering that most immunosuppression regimens are associated with some elements of the metabolic syndrome, a perfect storm is feared whereby patients already at risk for cardiovascular and metabolic morbidity will have these risks compounded significantly in the posttransplant setting leading to worsening outcomes.

Along with these concerns about patients transplanted for nonalcoholic fatty liver disease-associated liver failure come additional concerns regarding donor livers. If the population as a whole is becoming heavier with higher rates of obesity and metabolic syndrome, would it not be a fair assumption that the donor liver pool, too, will reflect these changes? What impact will these global epidemiological trends have on liver transplantation?

Recurrence after liver transplantation is also a concern. Unless lifestyle changes and rigorous medical monitoring are implemented, one can assume that the metabolic changes that led to nonalcoholic fatty liver disease will be present in the posttransplant setting this time being magnified by immunosuppression and other factors. Indeed, many patients transplanted for other etiologies may develop hepatic steatosis in allografts as a direct result of these posttransplant factors.

In the remainder of this chapter, the impact of pretransplant and posttransplant factors on outcomes for orthotopic liver transplant for nonalcoholic fatty liver disease will be discussed. Overall survival and outcomes will be assessed as well as both pre- and posttransplant strategies to mitigate the risk of recurrence. Finally, ethical issues regarding the selection of patients with nonalcoholic fatty liver disease for transplant will be explored.

Transplant Statistics

Nonalcoholic steatohepatitis represents the third most common indication for liver transplant in the United States and is surpassed by only hepatitis C virus and alcoholic liver disease (Charlton 2004; Charlton et al. 2011; Khullar et al. 2014). It has increased in frequency from accounting for 1.2 % of liver transplants in 2001 to 9.7 % in 2009 making it the third most common indication for liver transplantation (Fig. 1). NASH was found to be the third most common indication for liver transplant in the United States and is on course to become the most common indication for liver transplantation in the next 10–20 years (Charlton et al. 2011). It has been predicted that end-stage liver disease secondary to nonalcoholic fatty liver disease will be the common indication for liver transplantation within the next two decades (Charlton 2004; Khullar et al. 2014).

O'leary (2014), however, looked at Scientific Registry of Transplant Recipient data from 2012 and suggested that when extrapolated out to 2020, nonalcoholic steatohepatitis will not surpass hepatitis C virus as the most common indicator. Indeed, O'leary notes that using this methodology, hepatocellular carcinoma will become the most common indication for transplant in 2020 barring changes in allocation policy. While the indication of nonalcoholic steatohepatitis has increased many times from 2002 to 2012, cryptogenic cirrhosis has fallen quite significantly by a similar percentage over the same period suggesting, perhaps, that some patients whose indication for liver transplant was previously listed as cryptogenic cirrhosis are now being categorized at time of listing for transplant as having nonalcoholic steatohepatitis. It is possible that better appreciation of the scope of the disease

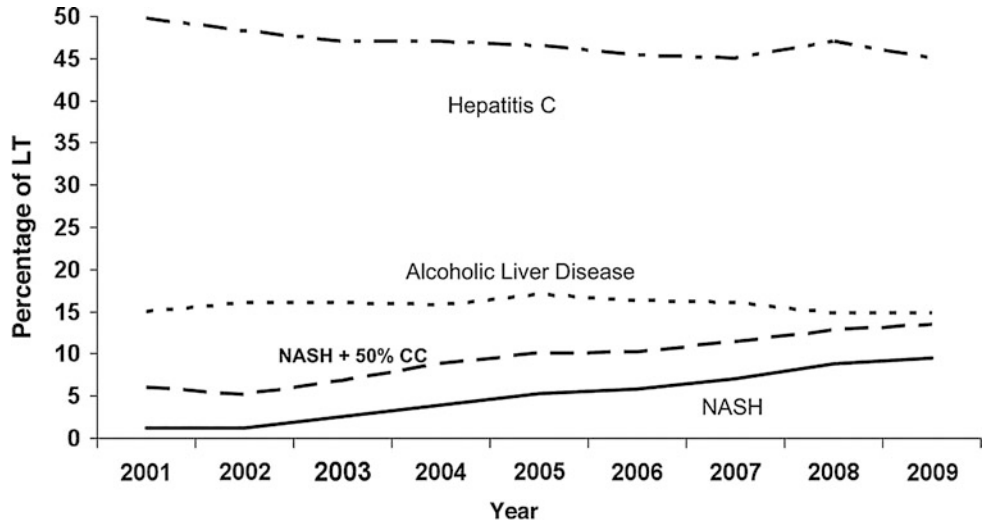

Fig. 1 Increasing frequency of NASH as an indication for orthotopic liver transplantation. NASH is on course to become the most common indication for liver transplantation in the coming decades and in recent years has been the third most common indication for liver transplantation in the United States (Adapted from Charlton et al. 2011)

has altered listing practices rather than the disease truly accounting for higher percentages of patients being listed. However, Yalamanchili et al. (2010) showed that nonalcoholic fatty liver disease is twice as common in patients transplanted from nonalcoholic steatohepatitis than in those transplanted for cryptogenic cirrhosis suggesting that only a minority of patients with cryptogenic cirrhosis have cirrhosis tied to nonalcoholic steatohepatitis.

The cohort that is being listed for transplant for nonalcoholic steatohepatitis is dramatically different than the overall cohort of patients who are listed. Charlton's analysis of the Scientific Registry of Transplant Recipients (2004) showed that patients who were transplanted for nonalcoholic steatohepatitis-associated cirrhosis were older, had larger body mass indices, and greater prevalences of diabetes and hypertension than other patients listed for liver transplantation.

These risk factors suggest that patients transplanted for nonalcoholic steatohepatitis may present with greater risk factors for poor graft and patient survival after transplant. However, large-scale examinations of patients transplanted for NASH and cryptogenic cirrhosis were similar to overall survival rates. In an examination of data from the Scientific Registry of Transplant Recipients of patients transplanted from 2001 to 2009, survival rates at 1 and 3 years following transplant for NASH were 84 % and 78 %, respectively, compared with 86 % and 79 % for CC and 87 % and 78 % (Charlton et al. 2011) (Fig. 2).

Compounding the problem is the fact that the rise in obesity and the metabolic syndrome that has led to increasing numbers of patients with end-stage liver disease due to nonalcoholic steatohepatitis is also reflected in the general population. The increasing prevalence of obesity has led to further increases in hepatic steatosis in potential liver donors thus potentially reducing the numbers of organs available for transplant (Khullar et al. 2014). This concern will likely grow in the coming years if projections of increasing rates of obesity and the metabolic syndrome come to fruition raising concerns for a dual problem- increasing numbers of patients requiring transplant for end-stage liver disease due partly to the metabolic syndrome and obesity facing a diminishing pool of organs caused by a decrease due to the same proportional rise in obesity.

As significant differences in morbidity and mortality following orthotopic liver transplantation for nonalcoholic fatty liver disease are not

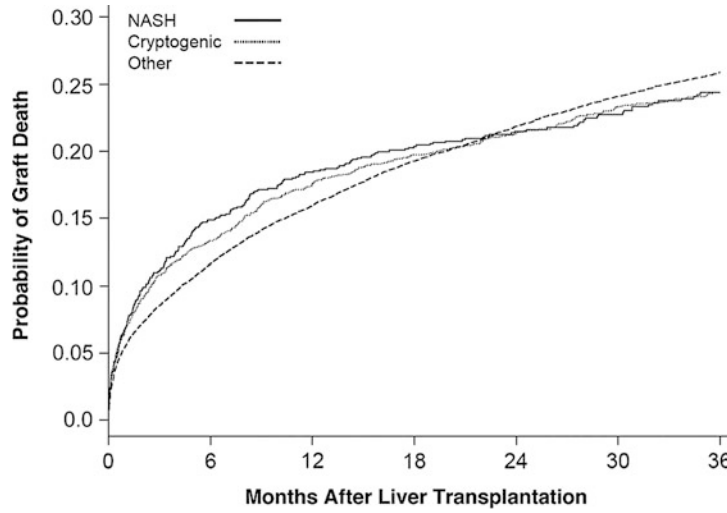

Fig. 2 SRTR outcomes data for liver transplant recipients transplanted for NASH (Data from the Scientific Registry of Transplant Recipients has shown that survival rates at 1 and 3 years following liver transplant are similar among patients transplanted with NASH and those overall) (Adapted from Charlton et al. 2011)

seen, some have advocated for more rigorous screening of liver transplant candidates with nonalcoholic fatty liver disease-induced end-stage liver disease. Indeed, O'leary in 2014 proposed that the focus should be in identifying patients at risk for posttransplant complications and treating them. Data have shown that morbidity and mortality in these patients are mostly tied to cardiovascular morbidity and mortality following liver transplant and not to direct transplant-related complications such as delayed graft function, rejection, biliary complications, and other factors. If controlling for the risk factors in this at-risk population results in equal outcomes, then intense scrutiny should be taken to identify those patients who are most at risk for cardiovascular disease and engage in preventative measures.

Another argument made to explain the lack of a significant rise in patients being transplanted for nonalcoholic fatty liver disease as an indication is that as time on the waiting list has gone up significantly over the past decade, so have the chances that those patients with multiple comorbid conditions due to nonalcoholic fatty liver disease-related conditions such as diabetes mellitus and cardiovascular disease will be removed from the waiting list due to these comorbid conditions while waiting for transplant (O'Leary 2014). As a result, while more patients with nonalcoholic fatty liver disease-related end-stage liver disease are being listed, fewer patients make it to transplant. Longer waiting list times have in essence "selected" the fittest patients for transplants thus resulting in equivalent outcomes.

Adding to this is data showing that patients with nonalcoholic liver disease are less likely to be transplanted than their counterparts with other forms of liver disease. One such study showed that patients with nonalcoholic steatohepatitis-induced cirrhosis were more commonly denied listing due to comorbid conditions than patients with hepatitis C virus-induced cirrhosis (72 % vs. 27 %) (O'Leary et al. 2011).

If one examines patients with elements of the metabolic syndrome with regard to posttransplant outcomes, there are indications that some patients have poorer outcomes than patients overall. In one study of 37 patients with body mass indices greater than 35 who were referred for liver transplant, for example, patients with a body mass index greater than 35 were more likely to experience weight gain, steatosis on biopsy, graft loss, and death. Consequently, there have been series examining pretransplant sleeve gastrectomy prior to liver transplantation (Heimbach et al. 2013).

Obesity continues to be an active area of interest with regard to posttransplant outcomes out of concerns that obese patients will suffer from increased morbidity and mortality following transplant as a result of the metabolic consequences of obesity. Indeed, in their landmark guideline on selection for liver transplantation,

the AASLD in 2005 unequivocally said that it considered morbid obesity a contraindication to liver transplant. It also recommended weight loss in all patients awaiting liver transplantation with a body mass index greater than 35 (Murray and Carithers 2005).

Nair et al. showed that morbidly obese patients with a body mass index greater than 40 kg/m^2 had significantly higher rates of primary graft nonfunction and significantly increased 1 and 2 year mortality rates. Five year mortality and morbidity rates were also significantly higher in severely obese (body mass index between 35.1 and 40 kg/m^2) and morbidly obese patients due to increased cardiovascular mortality. Their data also showed that 7 % of all patients undergoing orthotopic liver transplantation are morbidly obese (Nair et al. 2002).

Another perspective on outcomes following liver transplant for nonalcoholic fatty liver disease is that nonalcoholic fatty liver disease is a systemic disease and that orthotopic liver transplant only treats the hepatic complications (O'Leary 2014). Nonalcoholic fatty liver disease is felt to be a marker for worsening complications of the metabolic syndrome meaning that the systemic complications of the core disease, the metabolic syndrome, may be coexistent. One study of patients receiving renal transplants revealed that patients with nonalcoholic fatty liver disease had more carotid atherosclerosis and higher proportions of plaque than other patients (Mikolasevic et al. 2014).

A major tenet of liver transplant evaluation in all patients is that risk factors for poor outcomes following transplant should be identified and, when possible, be treated. As a consequence, patients with the metabolic syndrome should be medically optimized prior to liver transplantation in addition to encouragement that they undergo supervised weight loss (Khullar et al. 2014). Blood pressure should be brought under control and better glycemic control achieved in patients with diabetes mellitus.

Nonalcoholic fatty liver disease does recur after transplant in addition to appearing as a de novo complication in patients transplanted for other indications (Contos 2001; Patil and Yerian 2012). Unlike in pretransplant populations where elevated aminotransferases in the presence of hepatic steatosis on imaging absence of evidence of other etiologies is enough to make a diagnosis, in posttransplant patients biopsy is necessary. This is because the posttransplant patient has many other reasons to have abnormal aminotransferases.

Transplant Outcomes

They may have acute cellular rejection, recurrent viral hepatitis, biliary complications, and other common posttransplant complications that need to be eliminated prior to diagnosing a posttransplant patient with elevated aminotransferases with nonalcoholic steatohepatitis. A thorough search for other causes should be executed prior to making a diagnosis.

Studies on recurrence demonstrate great variability in recurrence rates. This is thought due to differences in populations, biopsy timeline protocols, and differences in histological criteria making it difficult to establish recurrence rates. Histology is important both in differentiating nonalcoholic steatohepatitis from other posttransplant complications and in assessing severity. While posttransplant steatosis is relatively common, steatohepatitis is less common and steatohepatitis-induced cirrhosis even less. Histology is thus the most reliable assessment for recurrent disease in the transplant recipient (Patil and Yerian 2012).

The risk factors that lead to the pretransplant diagnosis of nonalcoholic fatty liver disease oftentimes remain present in the posttransplant syndrome. The metabolic syndrome of obesity, hyperlipidemia, and impaired glucose tolerance are also accelerated in the posttransplant setting. One major reason for this is the immunosuppression regimen itself. The most commonly used calcineurin inhibitors, tacrolimus and cyclosporine, both promote elements of the metabolic syndrome. While generally not used chronically, the prednisone dose used in liver transplantation promotes weight gain and hyperglycemia. Tacrolimus is associated with the development

of diabetes mellitus and cyclosporine with hypertension and hyperlipidemia (Haddad et al. 2006; Tueck 2003).

For many reasons extending beyond prevention of the development of the metabolic syndrome and nonalcoholic steatohepatitis, steroid avoidance regimens in transplant patients have been extensively studied. Steroid-avoidant protocols post transplant have shown no differences in death, graft loss, and infection in patients who have been on steroid-free protocols and have the potential to reduce the diabetes mellitus and obesity associated with steroids thus reducing risk factors for nonalcoholic fatty liver disease (Khullar et al. 2014; Segev et al. 2013).

Rates of de novo steatosis have been shown to be 18–40 % and rates of de novo nonalcoholic steatohepatitis 9–13 % (Lim et al. 2007; Seo et al. 2007). If the patient has a body mass index increase post transplant of 10 % more than their pretransplant body mass index, then they have a higher risk of developing nonalcoholic fatty liver disease.

These data make it clear that while nonalcoholic fatty liver disease itself may not be a risk factor for poor outcomes following orthotopic liver transplant, the conditions that are associated with the disease may put patients at risk for poor outcomes following liver transplantation. Most prominently, obesity, cardiovascular disease, and diabetes mellitus may present challenges for outcomes following liver transplant. It may not be that nonalcoholic fatty liver disease alone leads to increases in morbidity and mortality, but this disease may increase the likelihood that patients will have concurrent conditions which may bring out cardiovascular disease which in turn may lead to poor outcomes.

It has been mentioned earlier in this chapter that some have suggested that the reason for relatively good outcomes following liver transplantation among patients transplanted for an indication of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis is the fact that those patients who make it to transplant are those patients who have been screened for cardiovascular risk and obesity beforehand and transplanted precisely because they have been rigorously identified as being low risk for these conditions. This reasoning would suggest that current methodologies' being used nationally to screen patients for transplant has been adequate at controlling for any increased risk for poor cardiovascular outcomes that these patients may bring.

These survival data do not, however, take into account worsening rates of obesity in this country and the possibility that in the future, patients with nonalcoholic fatty liver disease may be worse off metabolically than patients today due to longer-term obesity and diabetes mellitus. Furthermore, these data do not look at very long-term outcomes. Though survival rates may be similar at 5 and 10 years, we do not yet know what they will look like at 20 and 25 years.

We are currently using indirect markers of the metabolic syndrome such as obesity and insulin resistance as surrogates for the true nature of the disease. Perhaps soon we will be able to use molecular markers in clinical practice to better predict outcomes of the metabolic syndrome. In turn, precision will improve in the ability to predict long-term morbidity and mortality among patients with nonalcoholic fatty liver disease.

Transplant Evaluation

For now, the transplant physician must continue to rely on current assessments of risk for poor outcomes. Focus must be placed both on assessing global cardiovascular risk in patients with nonalcoholic steatohepatitis as cardiovascular disease is the predominant cause of poor outcomes following liver transplantation. As well, it should be appreciated that any metabolic issues prior to transplant such as obesity, hyperlipidemia, and diabetes mellitus will likely only be compounded following liver transplant mostly due to the effects of immunosuppression.

With regards to obesity, the American Association for the Study of Liver Disease recommend that patients with morbid obesity and a body mass index greater than 40 should not be offered transplant. Patients who have a body mass index between 35 and 40 should be asked to lose significant amounts of weight prior to listing. Any

overweight patient with a body mass index less than 35 should also be encouraged to lose weight (Murray and Carithers 2005).

The patient with nonalcoholic fatty liver disease being evaluated for transplant who has diabetes mellitus or hyperlipidemia should show that they have brought their lipid levels and hemoglobin A1C under good control. All patients with nonalcoholic fatty liver disease regardless of age or risk factors should also have rigorous cardiovascular stress testing with liberal use of cardiac catheterization to assess directly for coronary atherosclerosis.

With a population that is rapidly growing more overweight, such tactics in selection criteria may appear to be overly utilitarian in their approach to obese patients. However, the ethics of liver transplantation are by nature extraordinarily utilitarian given the mismatch in numbers between organ donors and recipients. When seen in this regard, rigorous selection criteria simply maximize benefit while minimizing risk.

One analogy that is frequently cited in ethical discussions about selection of patients for transplant for nonalcoholic steatohepatitis is that of the patient with alcoholism. While alcoholism is now seen to be a multifactorial illness based on a complex interplay of genetics, physiology, and behavior, patients are still not offered liver transplant unless they have had significant periods of abstinence from alcohol and have passed muster with a rigorous psychosocial evaluation that examines risk factors for recidivism.

In much the same way, it can be argued that patients with obesity and the metabolic syndrome should be asked to make behavioral changes as alcoholic patients are asked to abstain from alcohol. While the arguments for obesity being a purely behavioral problem are weak, the behavior is under some control of the patient, and this component needs to be used in order to ensure the best outcomes following transplant. Significant weight loss will reduce risk factors prior to liver transplant as well as reducing the chances of recidivism post transplant thus minimizing the inevitable worsening of metabolic risk factors that occurs following liver transplant.

Conclusion

Nonalcoholic fatty liver disease which includes the subset of patients with nonalcoholic steatohepatitis is a common condition associated with the metabolic syndrome of obesity, insulin resistance, and hyperlipidemia that can lead to cirrhosis and end-stage liver disease. The prevalence and morbidity from this condition is only expected to grow as the metabolic risk factors for nonalcoholic fatty liver disease such as obesity and diabetes mellitus continue to grow in the US population. With this come predictions that the future will see growing numbers of patients undergoing liver transplant with an indication of nonalcoholic steatohepatitis.

As nonalcoholic steatohepatitis is also seen as a risk factor for other diseases, in particular cardiovascular disease, concern has arisen regarding risk factors for poor outcomes following liver transplantation. While overall morbidity and mortality do not seem to be significantly different among patients transplanted for nonalcoholic steatohepatitis when compared with other indications, this may be a result of rigorous screening of candidates for risk factors for cardiovascular disease and nonlisting of morbidly obese candidates in most cases. Such rigorous selection criteria should continue unless transplant programs are better able to directly identify those candidates at risk for morbidity and mortality from the metabolic syndrome.

Cross-References

- ▶ Orthotopic Liver Transplantation: Complications
- ▶ Orthotopic Liver Transplantation: Indications and Contraindications
- ▶ Pathology of Liver Transplantation

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Fulminant Hepatic Failure: Diagnosis and Management

12

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Contents

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Abstract

Fulminant hepatic failure (FHF) is a condition resulting in rapid deterioration of liver function often followed by a cascade of fatal consequences. This rare syndrome is incited by a catastrophic insult to the liver. The causes of FHF can be classified into six general categories: viral infections, drugs and toxins, and cardiovascular, metabolic, miscellaneous, and indeterminate causes. FHF can result in sudden onset of hepatic encephalopathy, coagulopathy, jaundice, and multisystem organ failure. An improvement in the morbidity and mortality associated with FHF has been seen over the last several years with an advanced understanding of the mechanisms of injury, early initiation of intensive medical therapy, and the use of orthotopic liver transplant. This chapter will review the topic of FHF with a focus on the etiologies and clinical management.

Keywords

Acute liver failure • Acute liver injury • Hepatic failure • Acetaminophen-induced liver injury • Liver support systems • Multisystem organ failure

Introduction

Fulminant hepatic failure (FHF), also known as acute liver failure, is a rare condition resulting in rapid deterioration of liver function often followed by a cascade of devastating consequences. The syndrome is incited by a catastrophic insult to the liver in an otherwise healthy individual. This liver injury can result in sudden onset of hepatic encephalopathy, often in association with coagulopathy, jaundice, and multisystem organ failure. FHF is a true medical emergency and carries a very high mortality rate. An improvement in the morbidity and mortality outcomes associated with FHF has not been seen until recently with advanced understanding, intensive medical therapy, and monitoring and the use of orthotopic liver transplant (Ostapowicz et al. 2002). The goal of this chapter is to review the topic of FHF with a focus on the etiologies and clinical management. Particular attention will be paid to the critical care management, the role of liver transplantation, and experimental therapies.

Definitions

The term "fulminant hepatic failure" was first introduced more than 30 years ago by Trey et al. to describe the onset of altered mental status within 8 weeks of initial symptoms in an individual with no previous history of liver disease (Sass and Shakil 2003; Polson and Lee 2005). Based on this, the most widely accepted definition includes evidence of coagulation abnormality, usually an INR $\geq$1.5, any degree of mental alteration in a patient without preexisting cirrhosis, and illness duration of $<$26 weeks (O'Grady et al. 1989; Sass and Shakil 2003). Patients with Wilson disease, vertically acquired hepatitis B infection (HBV), or autoimmune hepatitis may be included despite the possibility of cirrhosis if their disease has been recognized for $<$26 weeks.

Various modifications to the original use of the term have occurred. It has been suggested that the term "fulminant hepatic failure" be reserved for cases in which encephalopathy develops within 2 weeks of the onset of jaundice and that "subfulminant hepatic failure" be applied to cases in which encephalopathy develops beyond 2 weeks. Other terms signifying length of illness such as hyperacute ($<$1 week), acute (8–28 days), and subacute (29 days to 12 weeks) have been proposed (Hoofnagle et al. 1995; Sass and Shakil 2005). This classification reflects differences in survival rate for these groups with the best prognosis begin in the hyperacute group, possibly because most of these are due to acetaminophen toxicity (Ostapowicz et al. 2002).

Epidemiology

The actual incidence of FHF has never been fully established. The International Classification of Diseases, Ninth Revision (ICD-9), has no specific

billing code for FHF which has limited the use of databases to derive an estimate (Hoofnagle et al. 1995; Lee et al. 2008). However, it is thought that FHF affects about 2,000 patients annually, as determined by evaluation of reports from liver transplant centers, population surveillance programs, and various counties (Lee et al. 2008). Additionally, based on a FHF workshop in 1995, it is thought that FHF represents 6 % of liver-related deaths and accounts for ~7 % of liver transplants (Lee et al. 2008).

Etiology

The etiology of FHF can result from a wide variety of causes and is often one of the best predictors of prognosis (Ostapowicz et al. 2002). Additionally, the etiology of FHF varies depending on patient demographics, geographic location, and timing of the event. The causes of FHF can be classified into six general categories: viral infections, drugs and toxins, and cardiovascular, metabolic, miscellaneous, and indeterminate causes (Polson and Lee 2005). In a historical series from the 1980s, viral hepatitis (predominately hepatitis B) was the most common etiology in the United States (USA); however, more recent data from the US Acute Liver Failure Study Group has identified acetaminophen (46 %), indeterminate (15 %), and idiosyncratic drug reactions (12 %) as the most frequent causes (Lee et al. 2008; Navarro 2009; Lee 2012).

Causes of FHF

A. Viral
HAV, HBV ± HDV, HEV, HSV, CMV, EBV, HVZ, adenovirus, hemorrhagic fever viruses
B. Drugs and toxins
Examples: Acetaminophen, CCl_4, yellow phosphorus, *Amanita phalloides*, sulfonamides, tetracycline, herbal remedies, halothane, INH, rifampicin, valproic acid, NSAIDs, disulfiram
C. Vascular
Right heart failure, Budd-Chiari syndrome, veno-occlusive disease, shock liver (ischemic hepatitis), heat stroke
D. Metabolic
Acute fatty liver of pregnancy, Wilson disease, Reye's syndrome, galactosemia, hereditary fructose intolerance, tyrosinemia
E. Miscellaneous
Malignant infiltration (liver metastases, lymphoma), autoimmune hepatitis, sepsis
F. Indeterminate
Includes primary graft nonfunction in liver-transplanted patients

Abbreviations: HAV hepatitis A virus, *HBV* hepatitis B virus, *HDV* hepatitis D virus, *HEV* hepatitis E virus, *HSV* herpes simplex virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *HVZ* herpes varicella zoster virus, *CCl_4* carbon tetrachloride, *INH* isoniazid, *NSAIDs* nonsteroidal anti-inflammatory drugs

Viral Hepatitis

Several viruses have been associated with FHF, particularly hepatitis A, B, C, D, and E. In addition, acute liver failure can be seen with herpes simplex virus, varicella zoster virus, Epstein-Barr virus, adenovirus, and cytomegalovirus (Lee et al. 2008; Lee 2008). Hepatitis serological testing should be done for identification of acute viral infection even when another possible etiology is identified. Acute viral hepatitis causes hepatic failure in ~1 % of cases of hepatitis A and B. FHF due to acute hepatitis C infection remains controversial and at most is very uncommon and occurs in <1 % of patients (Farci et al. 1996; Schiodt et al. 2003).

Overall during the past decade, viral hepatitis has become an infrequent cause of FHF in the USA, currently making up about ~10 % of cases (hepatitis B ~7 % and hepatitis A 3 %) (Ostapowicz et al. 2002). The role of nucleos(t)ide analogues in the management of FHF due to hepatitis B in the absence of immunosuppression is debated. Although several articles have suggested, based on case reports or historical controls, that nucleoside analogues are of value, a recent controlled trial by Seremba et al. (2007) has disputed this thought (Reshef et al. 2000; Teo et al. 2001; Tillmann et al. 2006; Kumar et al. 2007b; Liaw et al 2012).

Hepatitis B carriers undergoing immunosuppressive or cancer chemotherapy may experience reactivation of hepatitis B virus (HBV) replication, and this can lead to FHF. Prophylactic antiviral therapy is recommended for HBV carriers at the onset of cancer chemotherapy or for a finite course of immunosuppressive therapy (Liaw et al 2012). A high viral load at baseline is the most important risk factor for HBV reactivation.

In an endemic area such as Russia, Pakistan, Mexico, or India, hepatitis E remains an important cause of hepatic failure, particularly in the context of pregnancy (Jayanthi and Udayakumar 2008). The overall case fatality rate for hepatitis E is 0.5–3 % with mortality rate rising to 15–25 % in pregnant women (CDC 1987). Moreover, vertical transmission of hepatitis E from women with acute infection results in FHF in more than half of neonates. Certain hepatitis E genotypes have also been associated with more severe disease. Fortunately, HEV has not been an important cause of fulminant hepatitis in healthy individuals in the USA. From recent studies in the USA, it has been noted that infections with HEV can lead to hepatic decompensation in patients with preexisting liver disease and recipients of solid organ transplants and cause the development of infection (Hamid et al 2002; Kumar et al. 2007a; Kamar et al. 2008; Khuroo and Khuroo 2008). Therefore, pathogens like HEV should be considered early in the workup as potential viral syndromes in FHF and transplant recipients.

Herpes viruses, Epstein-Barr virus, varicella zoster virus, and others occasionally cause FHF usually in the setting of immunosuppression. Pregnancy has been implicated previously as increasing the risk that herpes virus infection will have a fulminant course (Peters et al. 2000). Obtaining a liver biopsy can be helpful in making a diagnosis in these cases. Treatment should be initiated with acyclovir in suspected or documented cases.

Acetaminophen-Related Injury

No prescription drug is known to have caused as many deaths and near-fatal episodes as acetaminophen. Over the past two decades, the number of cases reported in the USA has increased as a percentage of the number of overall cases of FHF. While this may reflect a decline in the incidence of viral hepatitis A and B, it probably represents an increase in the number of cases as well. Acetaminophen overdose is the number one cause of FHF in the USA, Great Britain, and most of Europe, accounting for nearly 50 % of all cases of US acute liver injury. Fortunately, the prognosis for acetaminophen-induced liver failure is somewhat better than for most other causes but still carries 30 % mortality, making it linked to more deaths in the US Acute Liver Failure Registry than any other etiology (Ritt et al. 1969; Lee 2008). Liver injury due to acetaminophen is generally more commonly seen after unintentional than intentional overdose (Wolf et al. 2012).

The development of liver failure from acetaminophen is dose dependent; hepatic failure is more likely with ingested dosages >150 mg/kg. Various risk factors increase the probability of acute liver damage even at therapeutic doses of acetaminophen. These factors include: alcoholic abuse, malnutrition, and concurrent use of narcotic analgesics compounded with acetaminophen. Liver damage from acetaminophen leads to a characteristic pattern of pericentral necrosis due to cytochrome P450-mediated oxidative metabolism of acetaminophen to the highly reactive, intermediate metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI) (Moyer et al. 2011). Accumulation of NAPQI leads to cell death and hepatocellular necrosis. *N*-Acetylcysteine (NAC) is established as a treatment for acetaminophen-induced hepatotoxicity (Heard and Green 2012). NAC acts by replenishing glutathione that is depleted and detoxifies NAPQI. In addition, excessive NAC also provides substrates for hepatic ATP synthesis, thus supporting mitochondrial energy metabolism. The latter pathway may be particularly important in delayed administration of NAC. The administration of NAC should be given as early as possible but still may be of value 48 h or more after ingestion (Harrison et al 1990). Allergic reactions may be treated with antihistamines or epinephrine (Vale and Proudfoot 1995).

Establishing the diagnosis of acetaminophen poisoning is often easy if a clear history can be obtained. Obstacles that often delay the correct diagnosis include failure of the first medical contact to not elicit the correct history, the patient's altered mentation at the time of interview, covering up detail by the patient because of embarrassment, and simply ignorance of any risk involved from an over-the-counter preparation. The parent compound, acetaminophen, can readily be measured by several different methods, and these tests are available in most hospital laboratories. Despite this, acetaminophen levels are often undetectable at the time of presentation with liver failure due to delay in presentation. A characteristic pattern of very high enzyme elevations is observed in most cases in association with a low bilirubin, the classic hyperacute injury pattern which can suggest acetaminophen as the etiology (Lee 2008).

Drug Reactions

Unlike FHF due to acetaminophen, which is dose related, FHF due to idiosyncratic drug reactions (known as drug-induced liver injury [DILI]) is dose independent. DILI usually occurs within six months of drug initiation (O'Grady et al. 1993). Idiosyncratic drug reaction results in ~12 % of FHF cases (Lee 2012). Drugs commonly implicated in cases of DILI include antibiotics, nonsteroidal anti-inflammatory drugs, and anticonvulsants. Herbal medications and dietary supplements have also been associated with acute liver failure. Idiosyncratic drug reactions are likely the result of a specific alteration (genetic polymorphisms) in the metabolizing enzymes leading to a toxic by-product. The reaction is further enhanced by the patient's own innate immune response (Kaplowitz 2002,2005; Navarro and Senior 2006; Chang and Schiano 2007). In general, DILI cases evolve with a subacute course with lower aminotransferase levels than acetaminophen and much higher bilirubin. There are a few exceptions, particularly the quinolone antibiotics such as ciprofloxacin (Fuchs et al. 1994; Clay et al. 2006). Establishing the diagnosis is equally, if not more, difficult with DILI in comparison to acetaminophen. Unfortunately, DILI-induced FHF cases carry a much poorer prognosis with less than 30 % spontaneous survival as compared with >65 % spontaneous survival following acetaminophen-induced FHF.

Cardiovascular Causes

Hypoperfusion of the liver can result in ischemic hepatitis and FHF in extreme cases. Hypoperfusion can result from systemic hypotension due to cardiac dysfunction, sepsis, Budd-Chiari syndrome (hepatic vein thrombosis), veno-occlusive disease, or the use of vasoconstricting drugs such as cocaine or methamphetamine. Documented hypotension is not always found. Simultaneous onset of renal dysfunction and muscle necrosis may be noted (Kisloff and Schaffer 1976; Hoffman et al. 1990; Silva et al. 1991; Taylor et al. 2012). Aminotransferase levels will be markedly elevated and respond rapidly to stabilization of the circulatory problem. Cardiovascular support is the treatment of choice in this setting.

The Budd-Chiari syndrome (acute hepatic venous outflow tract obstruction) is an uncommon cause of FHF accounting for about 1 % of cases (Menon et al. 2004; DeLeve et al. 2009). Right upper quadrant pain, hepatomegaly, and fluid retention characterize the initial clinical picture and may help distinguish this syndrome from other forms of FHF in which the liver parenchyma is collapsed and not tender. Therapeutic strategies have included anticoagulation, use of transjugular intrahepatic portocaval shunting, or transplantation (Kuo et al. 1996; Shrestha et al. 1997; Ryu et al. 1999). The ability to manage the cause of ischemia will determine the outcome for these patients as transplantation is rarely needed (Taylor et al. 2012).

Metabolic Causes

Metabolic disorders like Wilson disease (WD), HELLP (hemolysis, elevated liver enzymes, low

platelets) syndrome, acute fatty liver of pregnancy, Reye's syndrome, galactosemia, hereditary fructose intolerance, and tyrosinemia may also cause FHF.

WD accounts for 6–12 % of all patients with FHF who are referred for emergency liver transplantation. FHF due to WD occurs predominantly in young women at a ratio of about 4:1 (EASL 2012). Diagnostic tests for WD should include ceruloplasmin, serum and urinary copper levels, total bilirubin/alkaline phosphatase ratio, slit lamp examination for Kayser-Fleischer rings, and quantitative hepatic copper levels obtained by liver biopsy when possible (Roberts and Schilsky 2008). High bilirubin (>20 mg/dL) and low alkaline phosphatase levels (including undetectable levels) due to profound hemolytic anemia help with its recognition. Liver transplantation is the only effective option for those with WD who present with FHF. One-year survival following liver transplantation ranges from 79 % to 87 %, with good long-term survival (Roberts and Schilsky 2008).

When a pregnant woman presents with FHF, some specific etiologies must be considered. The hepatic damage of HELLP syndrome is proposed to result from disordered placentation, leading to either the circulation of antiangiogenic factors and endothelial dysfunction, or cytokine production causing the characteristic periportal hemorrhage and fibrin deposition (Sánchez-Bueno et al. 2012). Acute fatty liver of pregnancy is a sudden catastrophic illness occurring most frequently in the third trimester, when mitochondrial dysfunction due to maternal and fetal fatty acid β-oxidation defects resulting in microvesicular fatty acid accumulation in hepatocytes (Song et al. 2012). There is an overlap of these two clinical syndromes, and they play a major role in the pathogenesis of preeclampsia and proteinuria. Early recognition of these syndromes and prompt delivery of care are critical in achieving good outcomes. Failure to recover from the illness should prompt urgent listing for liver transplantation (Bacq 2011).

Miscellaneous Causes

Some rare causes of FHF include heat shock, protracted seizures, amatoxin-containing mushroom poisoning, autoimmune hepatitis, and malignant infiltration (Broussard et al. 2001; Chavez-Tapia et al. 2007; Garcin et al. 2008; Magdalan et al. 2010).

Amatoxins are found in a variety of poisonous mushrooms (e.g., *Amanita phalloides*, *Amanita virosa*, and *Galerina autumnalis*) and are responsible for more than 90 % of fatalities caused by mushroom poisoning worldwide. The onset of signs and symptoms >6 h after mushroom consumption should increase suspicion for amatoxin-containing mushroom poisoning. The natural history of amatoxin poisoning has been grouped into three phases: gastrointestinal phase (vomiting and diarrhea), latency phase, and FHF phase (48–72 h after ingestion). In addition to urgent evaluation for liver transplant, therapy with amatoxin uptake inhibitor therapy such as intravenous silibinin or continuous infusion of penicillin G with oral silymarin should be started (Broussard et al. 2001; Magdalan et al. 2010).

FHF occurs in a small fraction of autoimmune hepatitis patients. The clinical picture is in the form of a subacute presentation, with intermediate elevation of enzyme levels and high bilirubin concentrations. Presence of autoantibodies and a compatible picture on biopsy help to confirm the diagnosis. Some cases of autoimmune hepatitis may respond well to steroid therapy, and others may still require transplantation (Chavez-Tapia et al. 2007).

The most common forms of malignant infiltration implicated in FHF are lymphoma, breast cancer, and melanoma (Dellon et al. 2006). It must be remembered that this is an extremely rare cause of FHF. Diagnosis should be made by imaging and biopsy, and treatment appropriate for the underlying malignant condition is indicated.

Indeterminate Causes

About 15–20 % of FHF occurs without a cause being determined. These cases can include unrecognized idiosyncratic drug toxicity, non-A–E viral hepatitis, and possibly unrecognized metabolic and genetic diseases. The reasons for this misdiagnosis may include

failure to obtain an adequate history, failure to perform the definitive diagnostic tests, or simply due to some other rare diagnoses. About 20 % of FHF of indeterminate cause is related to obscure acetaminophen toxicity as found through detection of acetaminophen-protein adducts, the by-products of the toxic reaction (Khandelwal et al. 2011).

Clinical Features and Management

As described previously in this chapter, the causes of FHF are variable; however, they all share the common mechanism of acute hepatocyte death and its resulting sequel. In most cases, FHF will result in multisystem organ failure with the development of coma. The general management of a patient with FHF includes ensuring the patient is being cared for in an intensive care setting at a center with an active liver transplantation program, monitoring for worsening liver failure, treating complications, and providing nutritional support (Fig. 1) (O'Grady et al. 1993). The mortality rate of FHF is as high as 40–50 %, depending on the cause and therapeutic management (Wang et al. 2013). In this section the various complications of FHF and their management will be reviewed.

Encephalopathy and Cerebral Edema

Cerebral edema presents clinically as hepatic encephalopathy and may vary from subtle changes in affect, insomnia, and difficulty with concentration (stage 1) to deep coma (stage 4)

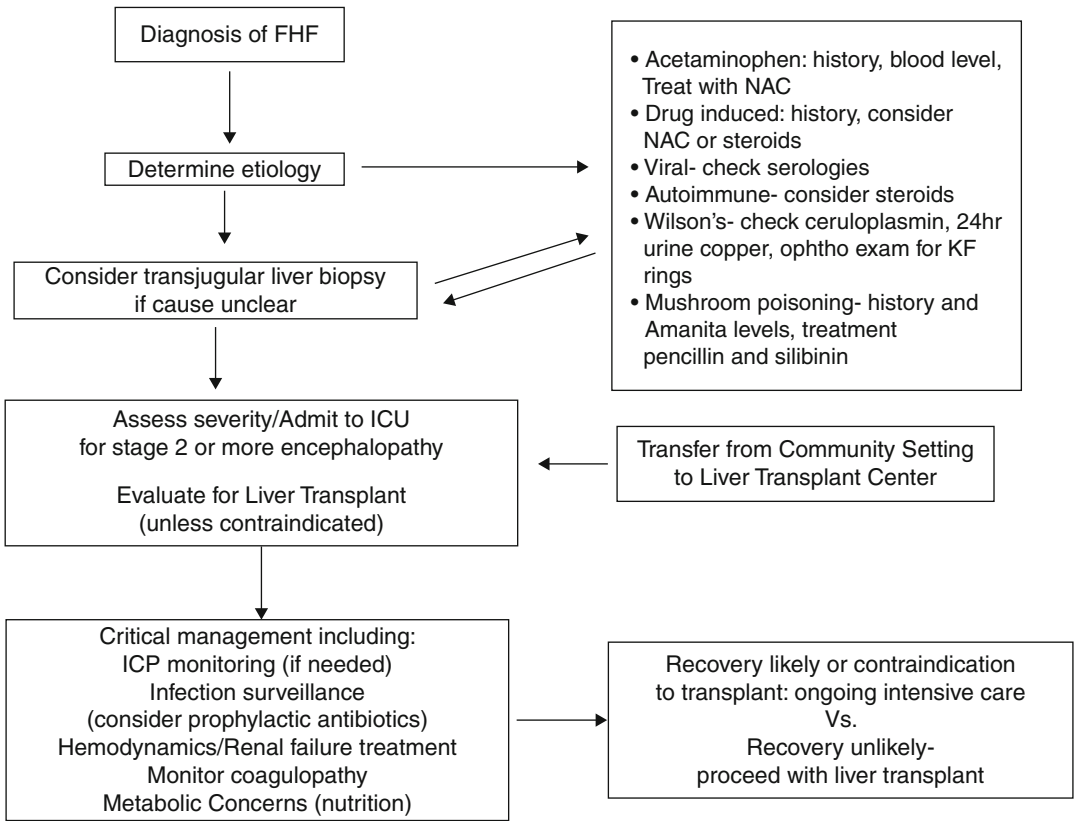

Fig. 1 Algorithm for management of FHF. *Abbreviations: FHF* fulminant hepatic failure, *ICP* intracranial pressure, *KF* Kayser-Fleischer

Table 1 Stages of hepatic encephalopathy

Stage	Mental status	Tremor	EEG
I	Euphoria; occasionally depression; fluctuant mild confusion; slowness of mentation and affect; untidy; slurred speech; disorder in sleep rhythm	Slight	Usually normal
II	Accentuation of stage I; drowsiness; inappropriate behavior; able to maintain sphincter control	Present (easily elicited)	Abnormal; generalized slowing
III	Sleeps most of the time but is arousable; speech is incoherent; confusion is marked	Usually present if patient can cooperate	Always abnormal
IV	Not arousable; may or may not respond to painful stimuli	Usually absent	Always abnormal

Adapted from Sass and Shakil (2003) and Trey and Davidson (1970)

(Ede and Williams 1986; Hoofnagle et al. 1995). Cerebral edema is a common neurologic component of FHF with the vast majority of cases progressing to stage 4 (Table 1) (Ede and Williams 1986). Cerebral edema leading to intracranial hypertension (ICH) is one of the major causes of morbidity and mortality in patients with FHF, accounting for the cause of death in the majority of patients due to brain herniation (Gazzard et al. 1975; Ede and Williams 1986; Pathikonda and Munoz 2010). The pathogenesis of cerebral edema and ICH in FHF appears to be multifactorial. Ammonia is converted in brain white matter to active glutamine, which osmotically causes cerebral edema (Bjerring et al. 2009). Other factors such as impaired cerebral blood flow, impaired autoregulation, systemic inflammatory response, and ischemic injury have also been proposed as a mechanism for the formation of cerebral edema.

Basic interventions for the management of cerebral edema should be applied universally in patients with high-grade hepatic encephalopathy. These interventions include elevation of the head of the bed to 30°, maintenance of a neutral neck position, endotracheal intubation, minimizing painful stimuli, and control of arterial hypertension (Frontera and Kalb 2011; Wang et al. 2013). Propofol is a reasonable choice for sedation because it may protect from worsening ICH. Intracranial pressure (ICP) monitoring by placement of epidural, subdural, or parenchymal catheter should be considered in FHF patients with high-grade hepatic encephalopathy, in centers with expertise in ICP monitoring, as well as in patients awaiting liver transplantation (Lidofsky et al. 1992). ICP monitoring can detect elevations in ICP to direct interventions, which may preserve brain perfusion and prevent cranial herniation. Generally, the goal of therapy in FHF is to maintain ICP less than 20 mmHg and cerebral perfusion pressure (CPP) more than 60 mmHg. CPP less than 40 mmHg for more than 2 h indicates reduced neurological blood flow to maintain intact brain function and could lead to poor posttransplantation prognosis (Hoofnagle et al. 1995). There are also several tools available for *indirect* measurement of cerebral blood flow, including jugular bulb catheter, transcranial Doppler, and xenon-enhanced computed tomography (Sundaram and Shaikh 2011). Factors that increase ICP need to be avoided and include hypercapnia, hyponatremia, frequent movements, neck vein compression, fluid overload, fever, hypoxia, coughing, sneezing, seizures, and endotracheal suctioning.

In patients with persistently elevated ICP, osmotic therapy with mannitol can be considered. Mannitol reduces ICP by osmotically drawing water from the brain parenchyma into the intravascular space (Larsen and Bjerring 2011). Hypothermia, although controversial, is thought to have some benefit in reducing ICP as it lowers brain energy metabolism, reduces arterial ammonia concentration and extraction of ammonia by the

brain, and reverses systemic inflammatory reactions therefore reducing cerebral edema (Jalan et al. 1999). In addition to its neurological effect, studies have shown that hypothermia results in significant improvement of cardiovascular hemodynamics, as manifested by increased mean arterial pressure (MAP) and systemic vascular resistance, and reduction in noradrenaline requirements (Jalan et al. 1999; Vaquero and Blei 2004). Potential hazards include cardiac arrhythmias, infection, and bleeding complications (Stravitz and Larsen 2009). Therapeutic hypothermia (cooling to a core temperature of 34–35 °C) is probably well tolerated and effective, but randomized, controlled trials are needed to confirm the benefits of hypothermia before it is recommended routinely. Additionally, there may be challenges with the re-warming of patients.

Cardiovascular Dysfunction

FHF is characterized by a hyperdynamic circulation with high cardiac output, low mean arterial pressure (MAP), and low systemic vascular resistance (Siniscalchi et al. 2010). Due to poor oral intake, transudation of fluid into the extravascular space, and possibly gastrointestinal bleeding, most patients are volume depleted and require initial fluid resuscitation. The initial treatment of hypotension should involve intravenous infusion of normal saline and a volume challenge is recommended (Stravitz and Kramer 2009; Stravitz and Larsen 2009; Siniscalchi et al. 2010; Lee et al. 2011). With progressive renal failure and pulmonary edema, a Swan-Ganz catheter may be required to guide further management. The MAP should be maintained in a narrow range to achieve a CPP of 60–80 mmHg to prevent cerebral hypoperfusion and further cerebral hyperemia. Noradrenaline, with fewer β-adrenergic side effects, could increase hepatic blood flow in parallel with minimizing tachycardia and is often the preferred vasopressor (Stravitz and Kramer 2009). Patients with uncorrectable hypotension after volume repletion and vasopressor administration should be evaluated for adrenal insufficiency, which occurs frequently in the setting of liver failure (O'Beirne et al. 2007). Adrenal insufficiency can be corrected with stress doses of corticosteroids.

Renal Failure

The incidence of acute renal failure in FHF is as high as 50–70 %. Direct drug nephrotoxicity, hepatorenal syndrome, and acute tubular necrosis due to ischemia from hypotension are among the most important associated disease entities (Bihari et al. 1986). Management includes avoidance of nephrotoxic agents, treatment of infection, maintenance of adequate renal perfusion, and renal replacement therapy. Early targeted volume replacement and vasoactive agent administration are essential to avoid arterial hypotension and ensure adequate renal perfusion. Worsening renal failure needs to be addressed with renal replacement therapy. Continuous renal replacement therapy is recommended, as most patients with FHF tolerate intermittent hemodialysis poorly because of circulatory instability, precipitous fluid shifts, and a rise in ICP (Davenport et al. 1993).

Coagulopathy

The liver plays a central role in the synthesis of the majority of coagulation factors and many inhibitors (Pereira et al. 1996). The principal hematologic abnormalities seen in FHF include platelet dysfunction and reduced levels of anticoagulant proteins (protein C/S or antithrombin III) and procoagulation factors (II, V, VII, IX, and X) due to failure of synthesis and consumption (Pereira et al. 1996). This causes a prolongation in the prothrombin time, as well as a tendency to develop thrombotic events such as disseminated intravascular coagulation (Langley and Williams 1992).

Bleeding generally occurs from superficial mucosal lesions, especially gastric erosions. Administration of proton pump inhibitors can decrease the risk of gastric mucosal bleeding. In general, infusion of fresh frozen plasma is

indicated only for control of active bleeding or during invasive procedures. Cryoprecipitate is recommended in patients who have significant hypofibrinogenemia (<1 g/L). Platelet transfusion is indicated only to aid in controlling active bleeding or during invasive procedures if the count is $<50 \times 10^9$/L or prophylactically if $<20 \times 10^9$/L (Munoz et al. 2009). Finally, vitamin K (5–10 mg subcutaneously) should be considered in all patients with FHF, because its deficiency can occur in >25 % of patients.

Metabolic Abnormalities

Metabolic abnormalities in FHF include hypoglycemia, lactic acidosis, and electrolyte derangements. Patients are prone to develop hypoglycemia because hepatocyte necrosis causes glycogen depletion and defective glycogenolysis and gluconeogenesis. Rapid development of hypoglycemia can confound hepatic encephalopathy and contribute to poor ICP control (Schneeweiss et al. 1993). Serum phosphate, potassium, and magnesium are frequently low, requiring repeated supplementation. Owing to the hypercatabolic state of FHF, nutrition is vital and enteral feedings should be initiated early. If enteral feeding is contraindicated, parenteral nutrition may be considered on a case-by-case basis (Montejo González et al. 2011).

Infections and Sepsis

Infections, particularly bacterial respiratory and urinary tract, develop in as many as 80 % of patients with FHF (Wyke et al. 1982; Sass and Shakil 2005). FHF patients have enhanced susceptibility to infection because of the presence of indwelling lines and catheters, dysfunction of monocytes, impaired complement system, and impaired neutrophil and Kupffer cell function (Leber et al. 2012). Infectious organisms are mainly Gram-negative enteric bacilli, Gram-positive cocci, and *Candida* species (Rolando et al. 1996). In addition to infection inhibiting hepatic regeneration, it is associated with progression of hepatic encephalopathy and renal failure, reduces successful rate of liver transplantation, and increases mortality in FHF (Rolando et al. 1996). One must have a high index of suspicion for infection and obtain surveillance cultures in addition to chest radiographs if there is any unexpected deterioration in the patient's status. Empirical antibiotics should be considered upon presentation (Leber et al. 2012).

Role of Liver Transplantation

Liver transplantation (OLT) remains the only definitive treatment for patients with FHF and irreversible liver injury (Starzl et al. 1982). Before the use of OLT in the 1960s, approximately 15 % of patients with FHF survived. With continued surgical refinement and better immunosuppressive agents, OLT for FHF offers about a 65 % survival but has been reported as high as 80 % (Ascher et al. 1993; Sass and Shakil 2005). In light of this, rapid evaluation for transfer to a transplantation center and consideration for liver transplantation are mandatory before contraindications develop. All patients meeting criteria for OLT may be listed as United Network for Organ Sharing Status 1A immediately upon arrival to the transplant center. Contraindications to OLT include: extrahepatic malignancy, uncontrolled extrahepatic sepsis, multisystem organ failure, irreversible brain damage, and unresponsive cerebral edema with a sustained elevation of ICP (>50 mmHg) and a decrease in CPP (<40 mmHg) (Sass and Shakil 2005).

The key factors affecting post-OLT survival are the severity of the pretransplantation illness of the recipient and the quality of the graft used (Bernal and Wendon 2004; Barshes et al. 2006). The more severe the encephalopathy at the time of surgery or severity of multisystem organ failure, the less likely that the surgery will be successful. Several risk factors have been associated with a decreased likelihood of patient survival after OLT, including history of life support, recipient age >50 years old, recipient BMI $> =30$ kg/m^2, and serum creatinine >2.0 mg/dL (Schiodt et al. 1999; Farmer

et al. 2003). The additional risk to post-OLT patient survival posed by each of these risk factors was additive in terms of etiology; acetaminophen toxicity tends to have a more favorable outcome than do viral hepatitis or drug reactions (Farmer et al. 2003). The main causes of death in the posttransplantation period are sepsis and multiorgan failure (Farmer et al. 2003).

Role of Experimental Therapies and Liver Support Systems

Due to the low incidence and high mortality of FHF, few therapies have been evaluated in a controlled study. Besides the few etiologies of FHF with immediate and specific treatment [i.e., acetaminophen (NAC), HSV (acyclovir), Amanita (silibinin)], most other liver-focused therapies have proven ineffective. In this section, the two therapies which have shown the most promise, NAC and liver replacement therapy, will be reviewed.

Use of *N*-Acetylcysteine

It is well studied and known that NAC when given within the first 24 h after acetaminophen overdose can prevent or minimize liver damage (Hamlyn et al. 1978; Prescott and Critchley 1983). Promising research has found that treatment with NAC may benefit patients with other forms of acute liver failure, by improving systemic hemodynamics, tissue oxygen delivery, and other favorable effects on the acutely injured liver (Harrison et al. 1991; Walsh et al. 1998; Rank et al. 2000).

The US Acute Liver Failure Study Group reported the result of their experience with intravenous NAC in 2009 to treat acute liver failure due to etiologies other than acetaminophen. In this prospective, double-blind trial, patients with acute liver failure (nonacetaminophen), at 24 medical centers across the USA between 1998 and 2006, were randomized to receive NAC or placebo infusion for 72 h (Lee et al. 2009). Acute liver failure caused by DILI ($n = 45$) represented the single largest group among 173 patients who were randomized. Although the overall survival at 3 weeks was not significantly different between the groups, the transplant-free survival was significantly better among those patients randomized to NAC (40 vs. 27 %, $P = 0.043$). The benefits of transplant-free survival were confined to the 114 patients with coma grades I–II who received NAC (52 % compared with 30 % for placebo; 1-sided $P = 0.010$), while those with coma grades III–IV receiving NAC had a 9 % transplant-free survival versus 22 % in the placebo group (1-sided $P = 0.912$). When the overall and transplant-free survival of the four largest etiologic groups was considered, patients with DILI and hepatitis B virus (HBV) showed improved outcome in comparison with the AIH and indeterminate groups. In the DILI patients, transplant-free survival was 58 % for those receiving NAC compared with 27 % for those receiving placebo (Lee et al. 2009). This study suggests that therapy with intravenous NAC should be considered in patients with early stage acute liver failure due to or thought to possibly be due to idiosyncratic DILI. Nausea and vomiting were the symptoms more frequent during treatment with NAC. Along with its excellent safety profile, NAC is easy to administer, does not require intensive care monitoring, and can be given in community hospitals.

Liver Support Systems

Extracorporeal supportive devices have been studied and developed to replace the liver function in FHF patients. Unfortunately, the complexity of liver metabolic, synthetic, detoxifying, and excretory functions makes the development of extracorporeal hepatic support extremely difficult. Currently available liver support systems are comprised of nonbiological (detoxification) systems and bioartificial systems. The most common techniques of nonbiological systems are the molecular adsorbent recirculating system (MARS) and Prometheus therapy. These systems are useful methods of removing the accumulated water-soluble/insoluble, protein-bound, and metabolic waste products in patients with FHF (Rademacher

et al. 2011). Unfortunately, no survival benefit could be demonstrated compared with standard medical therapy (Oppert et al. 2009). Bioartificial liver systems rely on the use of actual liver cells to perform detoxification and secretion of hepatocyte-derived factors. To date, the C3A line, a subclone of the HepG2 hepatoblastoma cell line, is the only human-based cell line that has been tested clinically in a bioartificial liver device named ELAD™ (Millis et al. 2002; Duan et al. 2007). Of note, a multicenter, randomized trial of the ELAD device is ongoing to assess the safety and efficacy of this system in FHF. Preliminary data on the use of bioartificial devices suggest some improvement in encephalopathy. A systematic review that pooled 12 randomized controlled trials (with a total of 483 patients) using various bioartificial support systems concluded that overall they had no significant effect on mortality compared with standard medical therapy (Kjaergard et al. 2003; Liu et al. 2004).

Table 2 The King's college criteria for liver transplantation

Acetaminophen	Nonacetaminophen
pH < 7.3 (irrespective of grade of encephalopathy)	PT > 100 s (INR > 6.5) (irrespective of grade of encephalopathy)
Or all three of the following	Or any three of the following
Grade III–IV encephalopathy	Age <10 or >40 years
PT > 100 s (INR > 6.5)	Etiology: (non-A, non-B hepatitis, halothane, idiosyncratic drug reaction, Wilson disease)
Serum creatinine >300 μmol/L (3.4 mg/dL)	Period of jaundice to encephalopathy >7 days
	PT > 50 s (INR > 3.5)
	Serum bilirubin >300 μmol/L (17.5 mg/dL)

Adapted from O'Grady et al. (1989)
Abbreviations: INR international normalized ratio, *PT* prothrombin time

Prognosis

The prognosis of FHF varies greatly with the underlying cause of liver injury and patient related factors. Limited organ availability and potential complications to lifelong immunosuppression make an accurate prognosis in FHF a major goal. Predicting the outcome of a patient with FHF is key and must be recognized early for the possibility of liver transplant if required (Sass and Shakil 2003). Several models have been developed for predicting the outcome in patients with FHF.

The King's College Criteria are the most widely used for selecting patients for liver transplantation (Table 2) (O'Grady et al. 1989). It was developed in a cohort of 588 patients with FHF who were managed medically between 1973 and 1985 (O'Grady et al. 1989). The predictors differ based on the etiology of FHF (acetaminophen vs. other causes). In patients with acute liver failure due to acetaminophen, recovery may be observed even in patients who have evidence of severe hepatocellular necrosis and synthetic dysfunction. In acetaminophen-induced acute liver failure, there are two broad criteria for referral for orthotopic liver transplantation: arterial pH of less than 7.30, irrespective of grade of encephalopathy or grade III or IV encephalopathy with both a prothrombin time (PT) greater than 100 s, and a serum creatinine concentration greater than 3.4 mg/dL. For other causes of FHF, poor prognosis predictors include PT greater than 100 s, irrespective of the grade of encephalopathy or any three of the following: age less than 10 or greater than 40 years, unfavorable disease etiology (such as non-A, non-B viral hepatitis, idiosyncratic drug reactions, Wilson disease), duration of jaundice before development of encephalopathy greater than seven days, PT greater than 50 s, or serum bilirubin greater than 18 mg/dL.

The accuracy of the King's College Criteria has been evaluated in several studies. These studies have shown positive predictive values ranging from just below 70 % to nearly 100 % (Anand et al. 1997; Shakil et al. 2000; Bernal et al. 2002; Schmidt and Dalhoff 2002). Recently, the addition of arterial lactate levels in patients with APAP-induced FHF has been proposed to improve sensitivity of the criteria

and identifies patients in need for OLT earlier (Bernal et al. 2002). The Clichy criteria are widely used in Northern Europe for FHF and takes into consideration coagulation factor V concentrations and patient age (Bernuau et al. 1986).

The model for end-stage liver disease (MELD) score has been used since 2002 by the United Network for Organ Sharing for allocation of grafts to adult patients with cirrhosis awaiting transplantation in the USA (Freeman et al. 2002). MELD is a severity score derived from the transformation of three biochemical parameters in a logarithmic formula, i.e., total serum bilirubin, prothrombin time, and creatinine. Studies have examined the MELD score at listing as a predictor of pretransplant and posttransplant survival in United Network for Organ Sharing Status 1 patients and compared survival among four diagnostic groups within the Status 1 designation (Kremers et al. 2004 and Yantorno et al. 2007). The four groups were comprised of FHF due to acetaminophen, FHF without acetaminophen toxicity, primary graft nonfunction within 7 days of transplantation, and hepatic artery thrombosis within 7 days of transplantation. They found, using Cox regression methodology, that the FHF-nonacetaminophen group had the poorest survival probability while awaiting OLT. This was negatively correlated with MELD score ($P = 0.0001$), which translated into the best survival benefit associated with OLT. The authors concluded that liver allocation within the Status 1 designation may need to be further stratified by diagnosis and that MELD score may be useful in prioritizing the FHF-nonacetaminophen group (Kremers et al. 2004 and Yantorno et al. 2007).

Liver histology (Fig. 2) and liver volume are often used by clinicians when trying to determine prognosis. There are a few limitations due to risk of bleeding with liver biopsy, a small potential for sampling error, and the fact that they can be overall misleading (Hanau et al. 1995). A small or shrinking liver on radiologic assessment can be of some value as this demonstrates collapse of the liver parenchyma (Hanau et al. 1995; Itai et al. 1997).

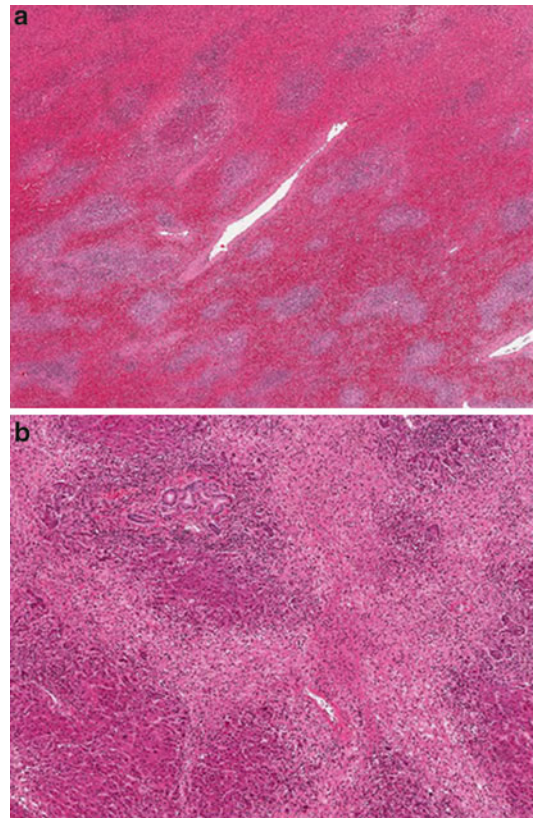

Fig. 2 Liver biopsy from a patient with FHF due to herbal supplement hepatotoxicity. (**a**) Low power: confluent hepatic necrosis (hematoxylin and eosin staining). (**b**) High power: centrilobular necrosis

Conclusion

FHF is a very challenging and serious medical condition. It tests our best clinical and surgical skills because of its rarity, rapid progression, and frequently poor outcomes. Early identification of FHF and the administration of etiology-specific treatment are crucial in its management. Patients with FHF are particularly vulnerable to infection, bleeding, and cerebral edema. The technique of liver transplantation has reduced the mortality rate associated with FHF. Rescue therapies that provide temporary liver support or other treatments short of transplantation may be of some benefit. Increased knowledge on the mechanisms of liver cell injury, hepatic regeneration, and the pathogenesis of encephalopathy and extrahepatic organ

failure is needed. The greatest benefits in terms of reduced mortality and morbidity from FHF will result from public health measures to control drug-induced liver injury.

Cross-References

- ▶ Artificial Liver Treatment: When and Which One?
- ▶ Orthotopic Liver Transplantation: Complications
- ▶ Orthotopic Liver Transplantation: Indications and Contraindications
- ▶ Orthotopic Liver Transplantation: Surgical Techniques

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Hepatitis C Virus Infection: A New Era

13

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Contents

Abstract

Rapid and dramatic advances in development of the modern generation of direct antiviral agents specific for hepatitis C have occurred over the last 3 years. In this chapter, we discuss the applications of the new antiviral agents to patients with hepatitis C infection relevant to liver transplantation, namely, those with compensated and decompensated cirrhosis, patients with hepatocellular carcinoma (HCC) related to HCV, and in liver transplant recipients with recurrent HCV. The limits of applicability of the new direct antiviral agents (DAAs) are reviewed, as well as the new issues raised by the high rates of HCV cure. The global impact of high cure rates of HCV has not yet been fully appreciated. Access to the new antiviral agents and diagnosing the large numbers of patients currently unaware of this infection are clearly now the major challenges, rather than discovering new agents to optimizing cure rates. Liver transplantation for HCV and HCV-related HCC is likely to remain at current levels for the rest of the decade, but recipients and allografts are likely to enjoy a much longer useful life following HCV eradication with DAAs.

Keywords

Hepatitis • Transplantation • Cirrhosis • Antiviral • Hepatocellular carcinoma • Ascites • Childs • MELD • DAAs • Hepatitis C

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Introduction

The relationship between chronic hepatitis C virus infection (HCV) and liver transplantation (LTx) has rapidly evolved through several stages over the last three decades. When LTx first reached clinical medicine and became an accepted therapeutic modality for irreversible liver failure in the early 1980s, the viral etiology of HCV was unknown; most patients transplanted had cirrhosis caused by autoimmune liver disorders such as primary biliary cirrhosis, autoimmune hepatitis, and primary sclerosis cholangitis. Nonetheless, it was noted that some patients had cryptogenic cirrhosis preceded by chronic hepatitis, which was provisionally called chronic "non-A, non-B" hepatitis. Eventually, the hepatitis C virus was identified, and it became apparent that many patients previously diagnosed with cirrhosis of unknown cause were indeed infected with this new hepatotropic flavivirus virus. The life-saving effect of LTx for decompensated HCV cirrhosis was rapidly apparent on thousands of transplanted patients and soon this procedure became standard care for HCV-related cirrhosis. In the USA, about 35 % of LTx is performed in patients with liver failure due to HCV cirrhosis, and in some geographical areas, the majority of the wait-list is accounted for patients with HCV cirrhosis or HCC caused by HCV. Indeed, HCC has risen from a relatively uncommon malignancy in the 1980s to an aggressive neoplasm of nearly epidemic proportions. HCC is currently the fastest rising cause of cancer-related mortality in the USA (El Serag 2011).

The HCV quasispecies nature with highly conserved genomic areas results in several genotypes of worldwide distribution. The most common genotypes in the USA are 1, 2, and 3. For many years, genotype 1 was the most difficult to cure with interferon-based therapies, although it was believed that the severity was not particularly worse for any of the HCV genotypes. Within the last few years, several of these concepts have dramatically changed. The historic events of the late twentieth century in viral hepatitis discovery and causality of various syndromes of liver disease have been reviewed elsewhere (Alter 2014).

It is now clear that the majority of patients infected with HCV were born between 1945 and 1965. Consequently, many of them have now had the disease for more than 50 years. Since the risk of progression to cirrhosis is directly related to disease duration, a striking increase in cirrhosis due to HCV and associated complications, including hepatocellular carcinoma (HCC), has been observed over the last decade. Conservative predictions suggest that the peak frequency of decompensated cirrhosis due to HCV is still to come and may occur during the midpoint of the next decade.

The current antiviral therapy of HCV-chronic hepatitis cures the viral infection and halts the progression to cirrhosis and associated complications. For the last three decades, antiviral therapy was limited to variants of interferon-based combinations. Such therapies had severe adverse events, poor tolerability, and achieved a cure of the HCV infection only in a minority of cases. The use of interferon reached maximal intolerance and adverse events when it was combined with the first generation of direct-acting antiviral agents (DAAs) in 2011. Although cure rates climbed to the 60–80 % range, systemic toxicity was much worse, sometimes even fatal, resulting in substantial dropout rates during therapy (Hezode et al. 2014; Saxena et al. 2014).

Nevertheless, the introduction of DAAs in the medical therapy of HCV constitutes a true revolution in the management of HCV, not only in hepatology but also in the realm of infectious diseases and medicine at large. Within only 2 years from their introduction, the new generation of DAAs have now entirely displaced interferon from the therapy of HCV. The current DAAs induce a cure of HCV at nearly universal rates in the absence of interferon (Shiffman et al. 2015; Zeuzem et al. 2014, 2015; Lawitz et al. 2013, 2014; Afdhal et al. 2014a, b; Poordad et al. 2014; Feld et al. 2014; Sulkowski et al. 2014; Jacobson et al. 2013; American Association for the Study of Liver Diseases, IDSA, IAS-USA). Very high cure rates are now routinely achieved for genotypes 1 and 2 HCV. HCV genotype 3 is now associated with the "lowest" success rate at only 80 % and 60 % in treatment-

experienced cirrhotics (Nelson et al. 2015). Additionally, it is now clear that genotype 3 is associated with more severe liver disease and greater progression to cirrhosis (Nkontchou et al. 2011).

This review summarizes the currently approved DAAs (and advanced clinical trials) in settings directly related to liver transplantation, namely in patients with cirrhosis, liver transplant candidates (decompensated cirrhosis and patients with HCC), and in the post-transplant management of HCV recurrence in liver transplant recipients.

Types of Direct-Acting Antiviral Agents for Hepatitis C Virus Infection

The three major classes of DAAs include HCV-specific protease inhibitors (NS3/4 inhibitors), polymerase inhibitors (NS5B nucleotide and non-nucleotides inhibitors), and replication complex inhibitors (NS5A inhibitors). In contrast to α-interferon, these agents are orally administered and have a much better tolerance and adverse event profile. At present, 3 of the 4 DAAs programs of treatment for HCV approved by the Food and Drug Administration do not contain ribavirin, an agent with weak antiviral potency, but associated with reduced relapse rates. It is almost certain that ribavirin is destined to be replaced by DAAs in the near future as well.

Use of DAAs Prior to Liver Transplantation

Compensated HCV Cirrhosis

The patient with compensated HCV cirrhosis has an advanced form of HCV infection and is at risk of developing complications that may require LTx. As the necroinflammatory activity driven by ongoing HCV infection continues to cause apoptosis and fibrosis, decompensation of the cirrhosis eventually occurs and/or HCC develops. For both of these late complications of end-stage cirrhosis, liver transplantation is the only curative therapy at the present time. Therefore, antiviral therapy with DAAs is considered a high priority for patients with compensated HCV cirrhosis, as the cure of a cirrhotic patient has the greatest impact on patient's life expectancy and on consumption of health care resources. It is now clear that patients who are cured from HCV have substantially improved survival due to reduction in liver- and non-liver-related causes of death (van der Meer et al. 2012).

Although the presence of cirrhosis was a negative predictor of response in the interferon era, the effect of cirrhosis on response rates to DAAs is greatly diminished. In fact, in most of the DAAs large clinical trials, patients with cirrhosis responded equally well compared to those with early disease (Nelson et al. 2015; Zeuzem et al. 2014; Lawitz et al. 2013, 2014; Afdhal et al. 2014; Poordad et al. 2014; Feld et al. 2014; Sulkowski et al. 2014; Jacobson et al. 2013). Thus, cirrhosis has now essentially vanished as a predictor of response in the DAA era, just as ethnicity, HIV coinfection, and obesity have also proved to be no longer predictors of lower response to DAA therapy. A notable exception remains that of genotype 3 cirrhosis, in which response rates with the currently approved therapy are only 60 %. However, noncirrhotic patients with genotype 3 currently enjoy very high cure rates, as shown in recent studies (Nelson et al. 2015).

A large, recent clinical trial enrolled only compensated cirrhotic patients, who were treated with 3 DAAs plus or minus ribavirin depending on the subtype of genotype 1 (1a or 1b) for durations between 3 and 6 months (Poordad et al. 2014). Between 90 % and 100 % of patients achieved a cure (SVR12), a rate similar to those with early, noncirrhotic disease. The response to modern DAA therapy in patients with HCV cirrhosis can be summarized by stating that over 90 % of these patients are now able to achieve a cure, with the exception of HCV genotype 3 patients, who achieve a cure in 60–80 % of cases (Poordad et al. 2014).

Antiviral Therapy in Decompensated Cirrhosis

The onset of ascites, hepatic encephalopathy, jaundice, or variceal hemorrhage in a patient

with HCV cirrhosis signals the final stages of the disease, commonly referred as decompensation. The onset of decompensation is associated with markedly decreased survival at 1 and 2 years and constitutes a clinical indication to determine if the patient is a viable liver transplant candidate. Antiviral treatment with alpha-interferon of patients with decompensated HCV cirrhosis was fraught with risks and frequent severe complications, on occasion fatal. The allure of inducing sustained virological response (SVR) in patients with decompensated cirrhosis lies in the potential to avoid liver transplantation. One of the first DAA developed was the nucleoside analog lamivudine for hepatitis B virus infection back in 1995. Although not very potent and limited by frequent emergence of resistant variants, lamivudine had a profound impact on transplantation for HBV cirrhosis, decreasing the frequency of HBV by approximately 70 %. Refractory ascites, encephalopathy, and other manifestations of decompensated HBV cirrhosis often substantially improved on lamivudine, leading to removal of many patients from the transplant waiting list. In the case of HCV cirrhosis, the introduction of safe and very effective DAA antiviral therapy has raised the hopes that a similar phenomenon could potentially be observed. In this regard, a multicenter study of sofosfuvir/ledipasvir and ribavirin in decompensated Childs B and C cirrhotics recently reported SVR rates of nearly 90 % (Charlton et al. 2015a).

In this groundbreaking study, 108 patients with decompensated cirrhosis Child B/C were treated with 12–24 weeks of ledipasvir, sofosfuvir, and ribavirin. Limits were imposed on the severity of the decompensation by capping serum bilirubin level at 10 mg/dl and excluding patients with CPT scores of 13–15 points. Entry MELD score was 20 or lower in all except 1 patient. Nonetheless, nearly 60 % of Childs B patients had ascites, whereas 96 % of Childs C patients had ascites. Similarly, hepatic encephalopathy was present in 60 % and 90 % of Child's B and C patients, respectively. The antiviral DAA combination was well tolerated and caused a SVR12 in 87–89 % of patients, with no apparent benefit observed in the 24-week arm. Virological response was associated with improvement in serum bilirubin, albumin, CTP score, and MELD reduction of approximately 2.5 points in response to DAA therapy. Thus, this study demonstrates the feasibility, safety, and surprisingly high efficacy of DAA therapy in decompensated patients (Charlton et al. 2015a). The proportion of patients who will exhibit continued improvement in MELD following a virological cure is not yet known. Encephalopathy, ascites, and edema improved in many patients but more information is necessary on the reversibility of the ascites, encephalopathy and other clinical manifestations of decompensation in patients who achieved and SVR in this study. Will SVR in decompensated patients be followed by resolution of signs and symptoms of decompensation, thus dissipating the need for liver transplantation? Of course, many questions remain on the critical issue of curing patients with decompensated cirrhosis. For instance, we need to find the limits of reversibility of ascites, encephalopathy, malnutrition, and esophagogastric varices. Patients with these symptoms may be cured of the HCV infection, but if patients remain disabled by these symptoms, the value of the cure would be questionable. At the present time, a decrease in MELD score induced by the DAA therapy is viewed by some as potentially detrimental to patients by decreasing the probability of organ allocation. A recent single-center study, however, did not show an impact of SVR on the probability of transplantation (Dugum et al. 2014). The hope is that the new DAA therapy for decompensated cirrhosis will re-create the events observed when lamivudine and adefovir were introduced for HBV nearly two decades ago.

Hepatocellular Carcinoma Due to HCV

The first development in this area occurred in 2013, when the combination of sofosfuvir/ribavirin administered to HCV patients waiting for liver transplantation due to HCC induced a high rate of cure following the liver transplantation procedure (Curry et al. 2015). The beneficial effect was pronounced enough that it became standard care for patients wait-listed for HCC related to HCV

infection. More recently, the new generations of DAAs sofosfuvir/ledipasvir, and the 3Ds, have shown even better cure rates in compensated cirrhotics, making either of these options better than sofosfuvir/ribavirin for patients listed for HCC with otherwise compensated cirrhosis.

Overall, the anticipated effect of the new DAAs on the incidence of hepatocellular carcinoma (HCC) is likely to be substantial. However, this effect will take much longer to be apparent as it depends on first arresting progression to cirrhosis via SVR in large numbers of patients, subsequently leading to a gradual diminution of the risk of HCC.

DAA Therapy for HCV Recurrence After Liver Transplantation

Although LTx is a life-saving treatment for patients with liver failure and/or HCC caused by HCV infection, intraoperatively the liver allograft becomes immediately HCV infected and all recipients remain chronically infected with HCV after LTx. Furthermore, it has been clearly established that the recurrence of the HCV in the liver allograft is characterized in most cases by an accelerated progression of fibrosis, reaching cirrhosis level in the allograft in 25–40 % of recipients at the 5th postoperative year. In some recipients, decompensated cirrhosis can develop as early as 2–3 years post-LTx. The severity of the HCV recurrence is extreme in 3–5 % of cases, with onset within a few months of LTx and characterized by typical histological findings with rapid progression to a cholestatic form of fatal liver failure (fibrosing cholestatic hepatitis, FCH).

The interferon-based antiviral therapies rarely proved effective in eradicating HCV after LTx, and intolerance limited greatly the applicability to liver transplant recipients. The off-label addition of the first generation DAAs (telaprevir, boceprevir) to pegylated interferon and ribavirin in 2012 brought about a moderate increase in response rates but at the cost of even greater severe adverse events and marked drug-to-drug interactions (DDIs) with both immunosuppressant agents tacrolimus and cyclosporine.

A breakthrough in therapy of post-LTx recurrence only occurred with the introduction of the NS5B polymerase sofosfuvir in 2013, which in conjunction with ribavirin yielded 70 % of HCV eradication in liver transplant recipients with genotypes 1 or 4 (Charlton et al. 2015b; Curry et al. 2015; Price and Terrault 2014). Due to the weak antiviral effect of ribavirin, this dual therapy amounted to near ribavirin-free monotherapy with sofosfuvir, explaining the moderate response rate (by comparison with today's expectations). The absence of interferon and protease inhibitors made this dual antiviral therapy much better tolerated than the previous interferon-based triple therapy, and in fact it remains the preferred therapeutic modality for genotype 2 or 3 HCV recurrence. However, the life span of the above successful dual therapy for genotype 1 recurrence was quite short, as the following year, superior regimens for HCV recurrence were approved by the regulatory agencies. Specifically, sofosfuvir plus ledipasvir with or without ribavirin for 12 or 24 weeks, respectively, in genotype 1 or 4 HCV recurrence, including cirrhosis, caused a cure in 96–98 % (Charlton et al. 2015b). Additionally, the combination of three ritonavir-boosted DAA antivirals (paritaprevir, ombitasvir, dasabuvir) plus ribavirin for 24 weeks in genotype 1 HCV recurrence with moderate fibrosis ($F \leq 2$) induced a cure of HCV recurrence in 97 % (Kwo et al. 2014). Lastly, a third treatment option for genotype 1 HCV recurrence is that of sofosfuvir in combination with the second generation NS5A inhibitor daclatasvir with or without ribavirin, which results in substantial rates of HCV recurrence eradication even in recipients with the aggressive recurrence of fibrosing cholestatic hepatitis (FCH) (Pellicelli et al. 2014).

Thus, in the span of only 2 years, the treatment of post-LTx recurrence dramatically changed from a combination with maximal severe adverse events and poor efficacy, to four DAA regimens with very high cure rates and much better tolerance. Given the high cost of the newer DAAs, limited access, and other barriers to widespread use, several questions remain, including optimal timing of treatment of the recurrence. Some liver transplant programs are now starting DAA

therapy as early as the sixth postoperative month in all HCV recipients (hoping, among other objectives, to essentially eliminate the potential for the FCH variant of recurrence), while other programs are following liver recipients closely during the first postoperative year, attempting to identify and proactively treat those with clinically significant early recurrence.

Of note, the above clinical trials with the new DAAs have not included the most severe cases of recurrence, namely, the FCH variant. The prognosis of FCH is so poor that even with the new potent DAAs, very early identification of FCH and initiation of potent DAA antiviral therapy is crucial in the management of this variant of recurrence (Pellicelli et al. 2014). These investigators found that once serum bilirubin is greater than 18 mg/dl in FCH, antiviral therapy with DAAs may not be able to rescue the allograft from failing in spite of rendering the recipient nonviremic. The practical implication is that in the presence of early allograft dysfunction (1st to 3rd postoperative month), FCH should be strongly considered, and after biliary and vascular complications are ruled out, a liver biopsy should be performed to look for the characteristic diagnostic histology of FCH.

Finally, the relatively easy eradication of HCV after LTx will likely have some effects on the immunosuppressive management of these recipients. Traditionally, the intensity of immunosuppressive therapy has been lower than utilized in non-HCV recipients, hoping to slow down the aggressive recurrence of HCV. Corticosteroid usage, in particular, has been greatly decreased in HCV liver recipients and, in many programs, altogether eliminated from the immunosuppression protocol for HCV recipients. Likewise, tacrolimus and cyclosporine levels have been generally targeted to lower levels in HCV recipients. With the current DAA-induced eradication of HCV both prior and after LTx, the liver recipient will no longer have the intrinsic immunosuppressive effect of HCV recurrence. If the conventional (lower) level of net immunosuppressive therapy is maintained, an environment may be created that may favor increased risk for allograft rejection in HCV-cured recipients. These and many additional new questions prompted by the rapid advances of DAA therapy will require prospective targeted studies.

Potential Impact of DAAs on Liver Transplantation, Organ Allocation, and Distribution

At first glance, the effect on liver transplantation of DAAs achieving universal cure of HCV would suggest a potentially dramatic reduction in annual transplant procedures for HCV. However, a rapid decline in transplantation for HCV cirrhosis is unlikely to occur due to several factors. These include the fact that at least two million (or more) of persons infected with HCV are not currently diagnosed. With the increasing awareness of the high cure rates of DAAs, excellent tolerance and demise of interferon, and over ten million newly insured patients under the expanded health insurance policies, the programs to identify HCV-infected persons not yet diagnosed are likely to uncover at least one million, and perhaps more, new HCV patients. A substantial proportion of the newly diagnosed patients may have either compensated or decompensated cirrhosis, resulting in a paradoxical increase in the number of patients with advanced liver disease due to HCV. On the other hand, if studies such as SOLAR and others determine and confirm that patients with decompensated cirrhosis may satisfactorily re-compensate, and no longer require transplantation, the impact of DAAs on liver transplantation for HCV could be substantial. Our own simulation modeling based on the above preliminary data would suggest that a sizable number of wait-list patients may improve to MELD scores lower than 15 points following DAA therapy, and reach MELD values no longer associated with transplant benefit (Munoz et al. 2015). This, in turn, could affect organ allocation and distribution by shifting organs to other etiologies of cirrhosis, lowering the overall MELD scores at transplantation, and decreasing the gap between the waiting list size and available organs.

New issues are raised by the easy cure of HCV in liver transplant candidates, for instance, at what

point a virological cure is no longer associated with clinical recovery and resolution of ascites, encephalopathy, portal hypertension, and other manifestations of end-stage cirrhosis (placing the patient in the so called "MELD purgatory"). In liver transplant recipients, we will need to determine whether the easy cure of HCV will require intensification of immunosuppression, which has traditionally been lesser in HCV recipients compared to nonviral etiologies. Additionally, the success of HCV cure with the new DAAs are also likely to result in increased usage of liver and kidney donors previously excluded due to HCV infection (Reese et al. 2015).

Conclusion

The rapid and dramatic advances in curing HCV-related liver disease both before and after liver transplantation are unparalleled in the history of medicine. The formidable pace of progress over the last 3 years holds the promise for this disease eventually becoming a rare condition. The yearly leaps in efficacy and safety observed since 2012 have forced professional societies (AASLD, IDSA) to issue frequent updates in recommendations, and even often fall behind the most current data. The global impact of high cure rates of HCV has not yet been fully appreciated. Accessing and diagnosing the large numbers of patients currently unaware of this infection are clearly now the major challenges, rather than discovering new agents to optimizing cure rates.

Liver transplantation for HCV and HCC-related HCC is likely to remain at current levels for the rest of the decade, but recipients and allografts will enjoy a much longer useful life following HCV eradication with DAAs.

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Infections and Sepsis After Liver Transplantation

14

Erika D. Lease

Contents

Abstract

Despite recent advances, infectious complications remain a significant contributor to morbidity and mortality after liver transplantation, affecting both patient and graft survival. Following transplantation, one third to one half of liver transplant recipients experience an infectious complication with over 80 % of infections occurring within the first 6 months following transplant. Infectious complications are the cause of death in over 15–25 % of all liver transplant recipients but are responsible for over half of deaths in the first year following transplant. Infection remains the most common cause of death for the first 3 years after liver transplant. Bacterial infections predominate and include presentations such as bloodstream, abdominal, wound, or biliary tract infection. Liver transplant patients are also particularly susceptible to fungal infections, predominantly candidemia, invasive aspergillosis, and cryptococcal infection. As with other high-risk populations, multidrug-resistant (MDR) organisms are becoming more prevalent after liver transplantation with an increased mortality than with drug-susceptible infections. With targeted pre-transplant and posttransplant prevention, prophylaxis, and monitoring, many infections may be prevented or identified early allowing for prompt initiation of appropriate therapy.

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Introduction

Since 2004, over 6,000 liver transplants have been performed in the United States each year with reported survival following transplant reaching approximately 88 % at 1 year, 80 % at 3 years, and 75 % at 5 years (www.unos.org). Despite improvement in overall survival, however, infectious complications remain a significant contributor to morbidity and mortality after liver transplantation, affecting both patient and graft survival. Recent studies have found that 35–55 % of liver transplant recipients experience an infectious complication at some point (Kalpoe et al. 2012; Kim et al. 2013b; Rubin 2002; Vera et al. 2011) with up to 83 % of infections occurring within the first 6 months after transplant (Vera et al. 2011). Infection has been found to cause over 15–25 % of deaths of all liver transplant recipients, second only to malignancy of non-hepatic causes of death. Infectious complications are responsible for over half of deaths in the first year, remaining the most common cause of death during the first 3 years following transplant (Avkan-Oguz et al. 2013; Kim et al. 2013; Vera et al. 2011; Watt et al. 2010).

In the initial month after liver transplant, most infections are related to technical or surgical issues and complications or exposure to infectious agents through prolonged hospitalizations before and after transplant (Blair and Kusne 2005). Other risk factors for infectious complications after liver transplant include prolonged intensive care unit stay, need for parenteral nutrition, perioperative blood transfusion requirements, surgical technique, level of immunosuppression, other underlying immune deficiencies such as neutropenia, comorbidities such as diabetes mellitus, and immunomodulating activity of certain viruses such as cytomegalovirus (CMV) (Vera et al. 2011). There are several infectious complications unique to recipients of liver transplants, different from other surgical patients and even other recipients of solid organ transplants that must be taken into consideration when evaluating these patients. The emergence of multidrug-resistant (MDR) pathogens has also become a great concern in the management of liver transplant recipients.

Efforts toward the prevention of infection can begin in the pre-transplant period through the use of donor and recipient screening as well as through recipient vaccine administration. Following liver transplant, targeted prophylaxis in certain patients and close monitoring are the most commonly used methods to prevent infectious complications. With targeted pre-transplant and posttransplant prevention, prophylaxis, and monitoring, many infections may be prevented or identified early allowing for prompt initiation of appropriate therapy.

Pre-transplant Evaluation, Treatment, and Prevention of Infections

Comprehensive guidelines for donor and recipient screening as well as recipient vaccine administration have been published previously (Fischer et al. 2013; Danzinger-Isakov et al. 2013). Pre-transplant evaluation begins primarily with serologic screening which when combined with donor serologic screening, can help determine the risk of infection following transplantation. Viruses, such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV), can all affect the outcome following liver transplantation if present in the donor or recipient prior to transplant. For some infections, such as CMV and EBV, the combined serologic status of the recipient and donor can be an important predictor for infection in the posttransplant period and may indicate the need for prophylactic treatment in high-risk individuals.

Recipients should be screened and tested when clinically appropriate for infections that have the potential for reactivation in the setting of immunosuppression. Information regarding previous infections, locations of travel or residence, and

exposures to environmental pathogens through animals or activities can help direct targeted screening for infections. *Treponema pallidum* (the bacteria responsible for syphilis), *Strongyloides stercoralis*, *Mycobacterium tuberculosis* (TB), and endemic fungi such as *Histoplasma capsulatum*, *Coccidioides immitis*, and various *Cryptococcus* species are a few examples of infections for which a provider may screen and test in a potential liver transplant recipient. Active infections that are found generally require initiation of treatment and possibly completion of therapy prior to transplantation.

Limiting the transmission of infections through the donated organ is also crucial to the success after liver transplant. Unexpected disease transmission through the donor can lead to significant morbidity and mortality. As discussed by Ison et al. (2013), risk of donor disease transmission can be mitigated by a three-pronged approach: (1) use of donor medical and social history for risk stratification, (2) physical assessment of the donor and donor organs, and (3) laboratory screening of the donor for infection. If a donor-derived infection is suspected, coordination of care with the local organ procurement organization (OPO), if in the United States, or other national organ procurement authorities is essential so that quality control is ensured and that the providers of other organ recipients from the same donor may be notified and begin appropriate evaluation and treatment if needed.

Vaccine administration is an important part of the prevention of infectious complications after transplant. As vaccines are generally less effective in end-stage organ failure and while on immunosuppression after transplant, early administration of vaccines prior to transplant is preferred. If needed, inactive vaccines are safe after transplant and generally felt to be most effective once recipients have achieved a baseline level of immunosuppression, usually 3–6 months after transplant. Live vaccines are considered contraindicated after transplant due to the immunosuppressed state; thus, vaccines such as MMR (measles, mumps, and rubella) and varicella should be administered prior to transplant if needed.

Bacterial Infections

Characterization of Post-Liver Transplant Bacterial Infections

Bacterial infections are the most common infectious complication after liver transplant, comprising 69–78 % of all posttransplant infections (Chen et al. 2011; Kim et al. 2013; Kim 2014; Vera et al. 2011) with nearly half of all bacterial infections occurring within the first 2 months following liver transplant (Kim 2014). Early in the postoperative phase (<1 month), posttransplant infections are frequently healthcare associated caused by bacteria that are routinely seen with nosocomial infections (Kim 2014). Risk factors for the development of a bacterial infection after liver transplant include pre- or posttransplant renal replacement therapy, operation-related or biliary complications, graft rejection, reoperation including re-transplantation, perioperative blood transfusion requirements, or prolonged time spent in the intensive care unit (Chen et al. 2011; Kim et al. 2013).

While the spectrum of infection varies regionally and among centers, infections caused by gram-negative bacteria are generally most common, causing 50–70 % of bacterial infections (Kalpoe et al. 2012; Kim et al. 2013; Shi et al. 2009; Vera et al. 2011; Zhong et al. 2012), although nearly a third of infections may be polymicrobial (Kalpoe et al. 2012). Common organisms include *Escherichia coli*; various species of *Pseudomonas*, *Klebsiella*, *Acinetobacter*, and *Enterobacter*; as well as gram-positive organisms such as *Staphylococcus aureus* and *Enterococcus* species.

As the worldwide prevalence of multidrug-resistant (MDR) organisms has increased, the prevalence has also increased among liver transplant recipients (Bert et al. 2010; Mrzljak et al. 2010; Shi et al. 2009). An estimated 52 % of all organisms and up to 56–66 % of gram-negative infections after liver transplant are resistant to more than one antibiotic (Dganga et al. 2012; Kalpoe et al. 2012; Zhong et al. 2012). With this increased incidence of multi-drug resistance comes an increased risk mortality due to infections. Kalpoe et al. (2012) studied carbapenem-resistant *Klebsiella*

pneumonia (CRKP) infections in liver transplant recipients and found the mortality following CRKP infections was 71 % versus 14 % of non-CRKP infections. Of liver transplant recipients with CRKP infections, 86 % had a bloodstream infection, and 79 % had an intra-abdominal infection or peritonitis, with 82 % having both an intra-abdominal infection and peritonitis in conjunction with a bloodstream infection. CRKP infections occurred on average 12 days following liver transplantation with 93 % of infections occurring within 1 month and were associated with a 64 % mortality within 30 days of developing the infection. An increased mortality is not with CRKP infections alone. Shi et al. (2009) found a mortality of 39 % in liver transplant recipients with any gram-negative MDR infection as opposed to 15 % of patients without a gram-negative MDR infection.

Specific Bacterial Infections After Liver Transplant

Intra-Abdominal and Surgical Site Infections

Intra-abdominal and surgical site infections are the most common infection after liver transplant, comprising over half of all infections (Kim et al. 2013) and occurring in 18–51 % of all liver transplant recipients (Freire et al. 2013; Hellinger et al. 2009; Kim et al. 2013; Kim et al. 2008). The infections range from superficial and deep incisional infections to peritonitis, cholangitis, and intra-abdominal abscesses. Posttransplant intra-abdominal and surgical site infections are associated with longer hospital stays and higher medical costs (Hollenbeak et al. 2001) as well as increased death and graft loss (Hellinger et al. 2009).

Risk factors for the development of intra-abdominal and surgical site infections include a higher model for end-stage liver disease (MELD) score at the time of transplant, duration of transplant surgery, Roux-en-Y biliary anastomosis, need for renal replacement therapy following transplant, extended postoperative intensive care unit (ICU) stay, need for reoperation, or extended preoperative hospital stay (Avkan-Oguz et al. 2013).

The biliary tract is a common source for intra-abdominal infections, contributing to the development of cholangitis, abscess, or bilomas. Risk factors for the development of biliary complications in particular, specifically biliary necrosis, strictures, and leaks, include hepatic artery thrombosis, hepatic artery stenosis, Roux-en-Y biliary anastomosis, and T-tube placement (Safdar et al. 2004). As surgical techniques have improved, so too has the incidence of biliary tract complications following liver transplantation. Greif et al. (1994) reported an initial biliary complication rate at their institution of 19 % in 1983 which had fallen to 11.5 % in 1994. Other studies have shown an incidence of 5–25 % (Akamatsu et al. 2011; Chen et al. 2011; Gastaca 2012; Safdar et al. 2004). Of all biliary complications, strictures and leaks are most common, occurring predominantly in the first 3 months after transplant (Akamatsu et al. 2011; Chen et al. 2011; Safdar et al. 2004).

The presentation of intra-abdominal and surgical site infections can range from erythema and pain of the incisional site to fever, abdominal pain, elevated white blood cell (WBC) count and/or liver enzymes, or sepsis. At times, laboratory abnormalities may be the only presenting sign of an intra-abdominal infection. Infections can be caused by a spectrum of bacteria most commonly including *Staphylococcus aureus* (both methicillin sensitive and methicillin resistant), enterococci, anaerobic bacteria, *Escherichia coli*, *Pseudomonas* sp., *Enterobacter* sp., *Klebsiella* sp., and *Acinetobacter* sp. Most infections are managed by surgical or interventional procedures as needed and drainage if a fluid collection is present. Broad-spectrum antibiotics should be initiated immediately and tailored once microbiologic data is available. Treatment should extend for at least 2 weeks once any necessary drainage has occurred.

Bloodstream Infections

Bloodstream infections are the second most common infection following liver transplant, occurring in 17–30 % of liver transplant recipients, with

mortality reaching 28–36 % (Chen et al. 2011; Kalpoe et al. 2012; Kim et al. 2013; Lee et al. 2011; Singh et al. 2000, 2004). Most bloodstream infections occur within the first 60 days following transplant, although they can occur at any time (Dganga et al. 2012). There are conflicting reports of the predominant bacteria causing bloodstream infections following liver transplant, likely due to center-specific epidemiology, with some documenting primarily gram-negative bacteria (Dganga et al. 2012; Kim et al. 2013; Singh et al. 2004) and others reporting a predominance of gram-positive bacteria (Lee et al. 2011). The timing of bacteremia following liver transplant may play a role, however, as shown by Lee et al. (2011). They found over 92 % of gram-positive bloodstream infections occurred within the first 30 days following transplant, whereas over 41 % of gram-negative bloodstream infections occurred after the first 30 days. For episodes of bacteremia occurring within the first 30 days after transplant, nosocomial bacteria were more common than in episodes of bacteremia occurring after 30 days. Polymicrobial bloodstream infections may also be common, occurring in up to 28 % of liver transplant recipients, primarily comprised of staphylococci, enterococci, and *Candida* (Kim et al. 2013).

Patients with bloodstream infections may present with a variety of signs and symptoms including fever, rigors, elevated WBC count, sepsis, or localizing symptoms of the primary source. Risk factors for developing bloodstream infections include extended postoperative ICU stay, an MELD score of greater than 20 at the time of transplant, preoperative albumin level of less than 2.8 g/dL, and the need for reoperation (Avkan-Oguz et al. 2013; Singh et al. 2000).

The primary sources of bloodstream infections include intra-abdominal or biliary tract infections, pneumonia, urinary tract infection, intravascular catheter-related infection, or wound infection. Kim et al. (2013) found the primary sources for bacteremia include the biliary tract in 36 %, abdominal or wound in 28 %, and intravascular catheters in 19 % of liver transplant recipients. In patients who developed biliary complications, 42 % developed a concurrent bloodstream infection (OR 2.91 (95 % CI)). Bloodstream infections were found to be an independent risk factor for death with 1 year survival being 60 % in patients who developed a bloodstream infection and 90 % in those who did not (HR 3.93 (95 % CI)). Among patients who developed a bloodstream infection, the risk factors for death included hepatocellular carcinoma (HCC) (HR 3.82), candidemia (HR 3.71), polymicrobial bacteremia (HR 3.18), and posttransplant need for renal replacement therapy (HR 2.44).

Treatment for bloodstream infections involves identification and management of the primary source if possible, removing any indwelling catheters that may be involved and providing broad-spectrum antibiotic coverage that may be tailored once microbiologic data is available. Initial antimicrobial coverage should take into consideration the prevalence of MDR bacteria at each individual institution.

Prevention

Beyond the use of routine antibacterial prophylaxis, perioperative antibiotics may also be used to minimize the risk of postoperative bacterial infections. Perioperative antibiotics in the first 48 h after transplant are a widely used practice; however, more tailored therapy can be considered for patients in whom there is a previously documented donor or recipient bacterial infection. While active infection in a recipient is generally considered a contraindication for transplant, no consensus has been reached regarding the optimal timing of transplant after initiation of treatment and/or resolution of the infection (Kim 2014). Screening for bacterial infection should be performed in both the donor and recipient prior to transplantation; however, laboratory limitations often prevent full information to be available at the time of transplant (Fischer and Avery 2009). As such, close follow-up of outstanding laboratory studies and microbiologic cultures is essential so that appropriate therapy may be given as soon as possible if an infection is identified. Recipients of organs from a donor with a documented infection will also need to be monitored closely as

infection may recur despite appropriate antibacterial therapy (Coucette 2013).

Fungal Infections

Fungal infections are the third most common infection following liver transplant with an estimated incidence of 7–9 % (Chen et al. 2011; Fung 2002; Vera et al. 2011). The incidence has decreased significantly over time, from 42 % at a single center between 1981 and 1983 falling to 7 % between 1989 and 1992 (Fung 2002; Wajszczuk et al. 1985). Fungal infections in liver transplant recipients are generally due to *Candida* (33–73 %), followed by *Aspergillus* (16–33 %) and *Cryptococcus* (16–33 %). Mortality is high following a fungal infection, reaching 55–69 % (Fung 2002; Wajszczuk et al. 1985).

Risk factors for the development of a fungal infection after liver transplant include a choledochojejunostomy anastomosis, serum creatinine >3 mg/dL, prolonged transplant operative time, re-transplantation, early fungal colonization, and development of cytomegalovirus (CMV) infection or disease (Collins et al. 1994; George et al. 1997; San-Juan et al. 2011). In liver transplant recipients without any of these risk factors, the incidence of fungal infection has been found to be 1–2 %, whereas in recipients with two or more risk factors, the incidence is 67 % (Collins et al. 1994; San-Juan et al. 2011).

Prophylaxis for fungal infection can be considered in liver transplant recipients, particularly those who are at high risk; however, universal prophylaxis is likely not warranted. San-Juan et al. (2011) found an incidence of fungal infection in low-risk liver transplant recipients to be 1.9 % in those who received prophylaxis and 1 % in those who do not receive prophylaxis. The MELD score may be a helpful predictor for the need of antifungal prophylaxis. Saliba et al. (2013) found a twofold increased risk for fungal infection in liver transplant recipients who had a pre-transplant MELD score between 20 and 30 and an over fourfold increased risk in those with a pre-transplant MELD score of greater than 30. Current recommendations for fungal prophylaxis include fluconazole or liposomal amphotericin B for 4 weeks or until resolution of the risk factors predisposing for fungal infection (Silveira and Kusne 2013). A recent study has reported that an echinocandin, anidulafungin, may also have a similar efficacy as fluconazole for the prevention of fungal infection following liver transplant (Winston et al. 2014).

Candida

Candidal infections are the most common fungal infection following liver transplantation with the highest incidence within the first 30 days and nearly all episodes occurring within the first 6 months following transplant (Vera et al. 2011). The mean onset of *Candida* infections has been found to be 12 days after transplant (Kime et al. 2013). Risk factors for the development of invasive candidal infections include a prolonged operative time, need for early reoperation, choledochojejunostomy anastomosis, need for more than 40 units of blood products during surgery, need for renal replacement therapy, early colonization with *Candida* or previously documented colonization, and acute fulminant liver failure (Fagiuoli et al. 2014). *Candida albicans* is the most common infecting organism; however, non-*albicans* species are becoming more frequent, some of which are inherently resistant to fluconazole (Romero and Razonable 2011).

The most common presentation of a *Candida* infection is mucocutaneous candidiasis; however, invasive candidiasis is the more worrisome infection in liver transplant recipients and usually presents as candidemia related to an intravascular catheter or an intra-abdominal infection (Huprikar 2007). Caution should be used when starting empiric treatment for invasive candidiasis due to the increasing resistance of certain *Candida* species, particularly to fluconazole. An echinocandin may be preferred in a hemodynamically unstable liver transplant recipient, particularly if there has been prior azole exposure (Fagiuoli et al. 2014). Liposomal amphotericin is an alternative as empiric treatment, although its use may be limited in patients with renal dysfunction. Once the

organism has been identified, sensitivity testing and local epidemiology may help guide targeted treatment choices. Management of a potential source of the candidal infection (i.e., infected intravascular catheter, abdominal abscess, etc.) is also crucial in the resolution of the infection.

Prophylaxis for infections caused by *Candida* in high-risk individuals is currently recommended by the American Society of Transplantation (Silveira and Kusne 2013). A recent meta-analysis showed antifungal prophylaxis reduced the rates of colonization and infection with *Candida albicans* and reduced the mortality due to *Candida albicans* infection but did not reduce overall mortality (Cruciani et al. 2006).

Aspergillus

Invasive aspergillosis is the second most common fungal infection in liver transplant recipients but has the highest rates of mortality. Invasive aspergillosis occurs in 1–9 % of patients following liver transplant with mortality reaching 33–100 % (Barchiesi et al. 2014; Brown et al. 1996; Singh et al. 2003). In a literature review by Barchiesi et al. (2014), the median diagnosis of invasive aspergillosis was found to be 25 days following transplant, and the primary site of infection was the lung (66 %), followed by the central nervous system (39 %) and osteoarticular infections (29 %). *Aspergillus fumigatus* caused the majority of infections (73 %), followed by *Aspergillus flavus* (14 %), and *Aspergillus terreus* (8 %). The mortality in this study was 66 %, with a large proportion of those who did not survive having pulmonary infection or infection in unusual sites such as in the kidney, heart, liver, eye, thyroid, muscles, or pancreas. Survival was improved in those who were transplanted after the year 2000, in those diagnosed with invasive aspergillosis more than 30 days after transplant, in patients who did not have renal failure, and in those who received voriconazole. Although data would suggest that the majority of infections with *Aspergillus* following liver transplant occur early posttransplant, other reports indicate an increasing number of infections beyond 6 months posttransplant and even 1 year posttransplant (Singh et al. 2006).

Risk factors for post-liver transplant invasive aspergillosis include need for dialysis, re-transplantation, CMV infection, prior colonization with *Aspergillus*, and acute fulminant liver failure (Fagiuoli et al. 2014). Diagnosis occurs with identification of the mold in a clinical specimen and/or clinical signs or symptoms consistent with the disease. There has been an attention on the use of *Aspergillus* antigens such as galactomannan in the diagnosis of invasive aspergillosis; however, there is a data to suggest that this test does not perform well in solid organ transplant recipients (Pfeiffer et al. 2006).

Preferred treatment for *Aspergillus* species is voriconazole followed by amphotericin B as second-line therapy (Romero and Razonable 2011). While antifungal prophylaxis is recommended following liver transplant in individuals with identifiable risk factors (Singh et al. 2013), there is evidence to suggest that antifungal prophylaxis has no effect on the incidence of invasive aspergillosis (Cruciani et al. 2006).

Cryptococcus

Cryptococcus neoformans is the third most common fungal infection in liver transplant recipients with a reported incidence of 2.4 % and mortality of up to 40 % (Husain et al. 2001). While cryptococcal infection following solid organ transplantation generally occurs 16–21 months following transplant, early cases have been reported that may be related to unrecognized cryptococcal disease in the recipient or due to a donor-derived infection (Sun et al. 2010). These early cryptococcal infections have been found to occur primarily in liver transplant recipients with the infection presenting in the allograft or at the surgical site (Sun et al. 2010). Risk factors for cryptococcal infection include the administration of corticosteroids or antilymphocyte antibodies (Patel and Hhuprikar 2012).

Diagnosis of cryptococcal infection is made with either identification of the organism on

culture or biopsy or with the use of serum and/or cerebrospinal fluid (CSF) antigen assay. Liver transplant recipients may develop cutaneous involvement with *Cryptococcus* at the surgical site or other cutaneous sites and present with a non-resolving skin infection unresponsive to standard therapy for cellulitis. A skin biopsy may be needed for the diagnosis of cryptococcal cellulitis, which likely represents a disseminated disease. A lumbar puncture should be performed to exclude CNS involvement, particularly as liver transplant recipients are more likely to present with disseminated disease than other solid organ transplant recipients (Singh et al. 2007).

Per the Infectious Diseases Society of America, recommended treatment for disseminated cryptococcosis includes liposomal amphotericin plus flucytosine or amphotericin B lipid formulation (Perfect et al. 2010). Consolidation may be accomplished with fluconazole for 8 weeks followed by maintenance fluconazole for 6–12 months. Cryptococcal infection limited to the lungs may be managed with fluconazole therapy alone for 6–12 months.

Viral Infections

Following bacterial infections, viral infections are the second most common infection in liver transplant recipients, occurring in 12–19 % of patients (Chen et al. 2011; Vera et al. 2011). Cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella-zoster virus (VZV) are the most common viral agents to cause infection after liver transplant, although numerous other viruses can also cause significant morbidity and mortality after transplantation (Ison 2005).

Cytomegalovirus (CMV)

CMV will be discussed in full detail elsewhere. Briefly, CMV can occur following liver transplant as either new primary infection or reactivation of latent infection. Nearly two thirds of CMV episodes occur between 2 and 6 months posttransplant (Vera et al. 2011). Clinical presentations can range from asymptomatic viremia, CMV syndrome with fever, leukopenia and/or thrombocytopenia, or CMV disease with end-organ disease such as hepatitis, pneumonitis, and/or gastritis/colitis. The highest-risk patient for the development of CMV reactivation or disease is a CMV seronegative recipient of a CMV seropositive donated organ. Antiviral agents are key for the treatment of CMV infection and may be considered for the posttransplant prophylaxis of CMV infection.

Herpes Simplex Virus (HSV)

Herpes simplex virus can appear as either a new primary infection, reactivation of latent infection, or as a donor-derived infection with clinical presentations of orolabial, genital, or perianal lesions. More severe disease can present as fulminant hepatitis, pneumonitis, or keratitis. A recent review of liver transplant recipients who developed HSV hepatitis found the average presentation to be 20 ± 12 days following transplant (Côté-Daigneault et al. 2014) with 67 % of cases occurring within the first 30 days (Vera et al. 2011). Mortality from HSV hepatitis reaches 55 % following liver transplantation (Côté-Daigneault et al. 2014). Fever, leukopenia, elevated liver enzymes, and/or abdominal pain are the most common presenting signs and symptoms. Treatment involves administration of antiviral therapy, supportive care, and reduction of immunosuppression when feasible. It is recommended that liver transplant recipients receive a period of antiviral prophylaxis with HSV coverage for at least 1 month following transplant given the high rate of HSV infection during times of significant immunosuppression (Wilck et al. 2013).

Varicella-Zoster Virus (VZV)

Varicella-zoster virus can occur in liver transplant recipients either as a new primary infection, reactivation of latent infection, or as a donor-derived infection. Following liver transplantation, the incidence of herpes zoster has been reported to be 1.2–12 % (Ignacio Herrero et al. 2004;

Gourishankar et al. 2004; Levitsky et al. 2005). While most patients present with herpes zoster, or shingles, there have been reports of fulminant liver failure due to the infection (Roque-Alfonso et al. 2008). Treatment includes antiviral therapy, supportive care, and reduction of immunosuppression when feasible. Key preventative measures for herpes zoster are the pre-transplant administration of a varicella-zoster virus vaccine as well as consideration of antiviral prophylaxis for a period of time following transplant.

Adenovirus

Adenovirus is a double-stranded, non-enveloped DNA virus that primarily causes self-limited conjunctival, respiratory, and gastrointestinal infection in immunocompetent hosts. In immunocompromised patients such as liver transplant recipients, adenovirus can lead to hepatitis and acute liver failure, pneumonitis and respiratory failure, hemorrhagic cystitis, and disseminated disease (disease in more than two end organs). Infection can occur via new infection, including nosocomial infection, as well as reactivation of latent infection (Ison 2006). Of adult solid organ transplant recipients, adenoviral infection occurs most commonly following liver transplantation, with a reported incidence of 6 % and mean time to disease of 55 days after transplant (McGrath et al. 1998). There is no definitive treatment of adenoviral infections; however, management includes supportive care, reduction of immunosuppression when feasible, and consideration of antiviral therapy and/or intravenous immunoglobulin in severe cases.

Parasitic Infections

Toxoplasma gondii

Toxoplasma gondii is a parasitic protozoan transmitted to humans through the ingestion of contaminated food or water. Following liver transplant, infection can occur as reactivation of latent disease or as a donor-derived infection. While toxoplasmosis is well described following cardiac transplantation, a number of cases in noncardiac solid organ transplant recipients have also been reported (Gourishankar et al. 2008; Wendum et al. 2002). Clinical presentations can range from a nonspecific syndrome of fever, myalgias, lymphadenopathy, rash, and/or hepatosplenomegaly to central nervous system (CNS) lesions, pneumonitis, or chorioretinitis. While little data exists regarding treatment in solid organ transplant recipients, treatment recommendations generally follow those for patients with human immunodeficiency virus (HIV) which includes pyrimethamine plus leucovorin and sulfadiazine. Prophylaxis for *Pneumocystis jirovechii* (PJP) with trimethoprim-sulfamethoxazole also provides prophylactic coverage for *Toxoplasma* (Schwartz et al. 2013).

Strongyloides stercoralis

Strongyloides stercoralis is an intestinal helminth which is found worldwide, predominantly in tropical or subtropical regions. Infection occurs via direct inoculation by larvae in the soil, and infection in the host is perpetuated by an autoinfective cycle. Following liver transplant, strongyloidiasis occurs primarily by reactivation of latent infection or as a donor-derived infection. Liver transplant patients, as with all immunosuppressed patients, are at risk for the development of hyperinfection and disseminated disease which have a mortality rate up to 85 % (Le et al. 2014). Treatment in immunocompromised patients is not well established but may include ivermectin and/or albendazole (Rodriguez-Hernandez et al. 2009). The American Society for Transplantation recommends serologic screening for *Strongyloides* in at-risk recipients, living donors, and at-risk deceased donors whenever possible so appropriate therapy may be given prior to or just following transplantation (Schwartz et al. 2013).

Conclusion

Despite recent advances, infectious complications remain a significant contributor to morbidity and mortality after liver transplantation. Infection is

the most common cause of death for the first 3 years after liver transplant and limits both patient and graft survival. Bacterial infections predominate; however, liver transplant recipients are also particularly susceptible to fungal infections. As with other high-risk populations, multidrug-resistant (MDR) organisms are becoming more prevalent after liver transplantation with increased mortality than with drug-susceptible infections. With targeted pre-transplant and posttransplant prevention, prophylaxis, and monitoring, many infections may be prevented or identified early allowing for prompt initiation of appropriate therapy.

Cross-References

- ▶ Liver Transplantation in the Third Millennium in North America: The Strategy for Success
- ▶ Orthotopic Liver Transplantation: Complications
- ▶ Orthotopic Liver Transplantation: Surgical Techniques

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Liver Transplantation for HCC: The Milan Criteria

15

Jesse M. Civan

Contents

Abstract

Liver transplantation represents a potentially curative intervention for patients with hepatocellular carcinoma and in fact is an important indication for transplant evaluation. However, early experiences with liver transplantation for this indication were characterized by dismal outcomes, mediated by high rates of posttransplant cancer recurrence. Based on these early experiences, the role of liver transplant for HCC patients was in serious doubt. This chapter reviews the importance of, and the substantial challenges confronting, the *Milan Criteria*. These criteria are currently used by the global transplant community to determine transplant candidacy of HCC patients. It was the development of these criteria which allowed identification of a subset of HCC patients who are predicted to have good outcomes after liver transplantation. This in turn ensured the continued role of liver transplantation as a lifesaving therapeutic intervention for this group of patients. This chapter reviews the data leading to the development of the Milan Criteria and their validation and discusses some current challenges to the application of these criteria to patients under consideration for liver transplant today.

Keywords

Hepatocellular carcinoma • Liver transplantation • Milan criteria

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Abbreviations	
AASLD	American Association for the Study of Liver Disease
APASL	Asian Pacific Association for the Study of the Liver
BCLC	Barcelona Clinic Liver Cancer
EASL	European Association for the Study of the Liver
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
LI-RADS	Liver Imaging Reporting and Data System
NIH	National Institutes of Health
OPTN	Organ Procurement and Transplantation Network
UNOS	United Network for Organ Sharing

Introduction

Hepatocellular carcinoma (HCC) is a significant cause of mortality, ranked as the third leading cause of cancer-related death worldwide, accounting for approximately 10,000 deaths annually in the United States (El-Serag 2004, 2011). Chronic infection with the hepatitis B virus (HBV) is the underlying risk factor accounting for the development of HCC in approximately 50 % of cases worldwide (Sanyal et al. 2010). However, it is chronic infection with the hepatitis C virus (HCV) in the setting of cirrhosis which carries the highest annual risk of developing HCC and which is the most important single risk factor for developing HCC in the United States (Sanyal et al. 2010).

Liver transplantation can be a curative intervention for HCC patients with cirrhosis (Bruix et al. 2011; EASL/EORTC 2012). However, early experiences with liver transplant for HCC were deeply disappointing, as detailed in the following section, with very high rates of recurrent HCC and poor overall survival. It became clear with time that some criteria were needed to stratify on the one hand patients with good prospects for cure and long-term survival and on the other hand those with prohibitively high risk for death from recurrence of HCC who should not be offered liver transplantation. Although the exact nature of an optimal set of such criteria remains a matter of some debate, at present, the most important set of criteria used in clinical practice around the world to determine liver transplant candidacy remain the *Milan Criteria*. In the United States, the Milan Criteria are endorsed by the American Association for the Study of Liver Disease (AASLD) to guide management decisions for HCC patients and are used by the United Network for Organ Sharing (UNOS) and the Organ Procurement and Transplantation Network (OPTN) to guide allocation of priority for liver transplant (Bruix et al. 2011; HRSA/OPTN a). The Milan Criteria are likewise incorporated into the practice guidelines of the European Association for the Study of the Liver (EASL) (EASL/EORTC 2012) and the Asian Pacific Association for the Study of the Liver (APASL) (Omata et al. 2010).

Central to the concept of the Milan Criteria is the quantification of HCC "tumor burden," i.e., the number of discrete masses and the maximal diameter(s) of each lesion. The Milan Criteria are defined by the absence of extrahepatic metastases, absence of macrovascular invasion, and limitation of hepatic parenchymal tumor burden to either a single HCC mass not exceeding 5 cm or alternatively up to three masses none of which exceeds 3 cm (see Fig. 1). Currently, outcomes for patients undergoing liver transplant with HCC meeting the Milan Criteria are excellent, with 1-year survival rates of 89 % and 5-year survival rates of 61 %, which are comparable to outcomes for patients transplanted without HCC (Pelletier et al. 2009).

Unfortunately, due to advanced stage at initial diagnosis, only a minority of patients diagnosed with HCC will meet the Milan Criteria and be candidates for curative intervention (see Fig. 2). Although only a minority of HCC patients may be eligible for liver transplant, HCC falling within the Milan Criteria remains an important indication for liver transplant. In 2013, HCC was the primary indication for just under 20 % of liver transplants performed in the United States (Kim et al. 2015).

This chapter traces the disappointing early experiences with liver transplantation for HCC patients and the development of the Milan

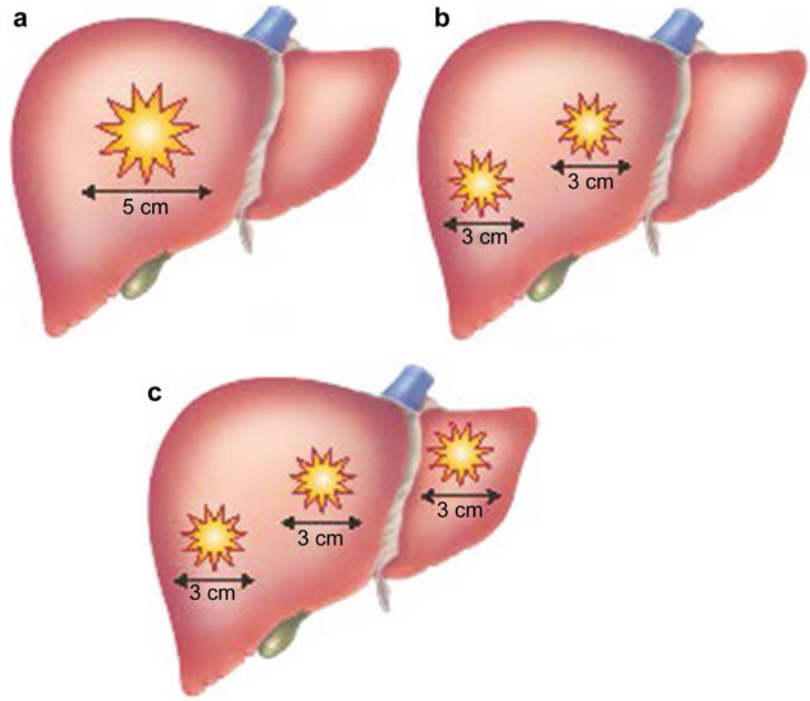

Fig. 1 The Milan Criteria are currently the most important criteria to determine candidacy of patients with HCC for curative intervention with liver transplantation. Patients meeting the Milan Criteria do not have extrahepatic metastases and do not have macrovascular invasion. Patients may have either a single HCC tumor up to 5 cm in maximal diameter (**a**) or may alternatively have either two (**b**) or three (**c**) tumors so long as none exceeds 3 cm in maximal diameter

Criteria. Data on the validation of the Milan Criteria is reviewed, and issues and challenges are discussed on how the lessons learned from the development of the Milan Criteria might best be applied to patients undergoing evaluation for liver transplant today.

Early Experiences with Liver Transplant for HCC

The first successful liver transplant surgery was performed in 1963 by the pioneering surgeon Thomas Starzl. However it was not until the advent of cyclosporine and its introduction into clinical practice in the late 1970s and 1980s that adequate 1-year survival could be achieved and liver transplant became truly viable as a therapeutic intervention (Starzl et al. 1981). Initially, advanced HCC was thought to be a good indication for liver transplant. Although the volume of liver transplants performed in the 1980s for the indication of HCC varied by center, in at least one German transplant program, 37 % of patients underwent transplant for the primary indication of HCC (Scharschmidt 1984).

Unfortunately, early experiences with liver transplantation for HCC were notable for poor survival rates. For example, a 1984 multicenter analysis reported an overall 1-year posttransplant survival on the order of 40 % for HCC patients (see Fig. 3) (Scharschmidt 1984). Rates of recurrent HCC after transplant were high, ranging from 53 % to as high as 82 % (Koneru et al. 1988; Iwatsuki et al. 1985).

Based on these early experiences, in 1984, a National Institutes of Health (NIH) conference on liver transplant was convened. The consensus statement from this conference concluded that although survival data were limited at the time, "results to date indicate a strong likelihood of recurrence of the malignancy" but that "the procedure may achieve significant palliation" (Anonymous 1984). Indeed, in a 1985 paper, Starzl's group wrote that "it has been tempting during the acquisition of this experience to conclude that liver replacement for malignant hepatic neoplasms is conceptually unsound, except for

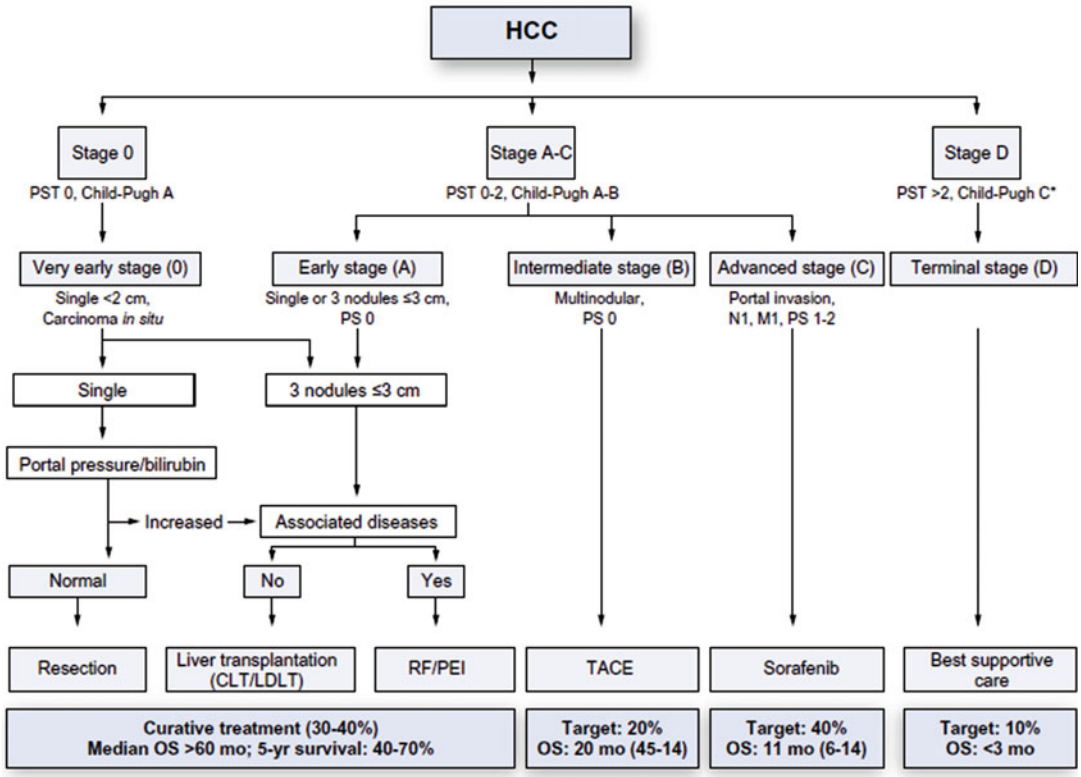

Fig. 2 The Barcelona Clinic Liver Cancer (BCLC) algorithm for management of HCC. Liver transplantation is a curative option for patients with HCC. However the role of liver transplantation is limited to patients with a limited degree of tumor burden, defined by the Milan Criteria. Unfortunately, due to advanced stage at initial diagnosis, the majority of patients diagnosed with HCC are not candidates for curative liver transplant (Reproduced from the European Association for the Study of Liver Disease (EASL)- European Organisation for Research and Treatment of Cancer (EORTC) guidelines on management of HCC (European Association For The Study Of The Liver and European Organisation For Research And Treatment Of Cancer 2012)

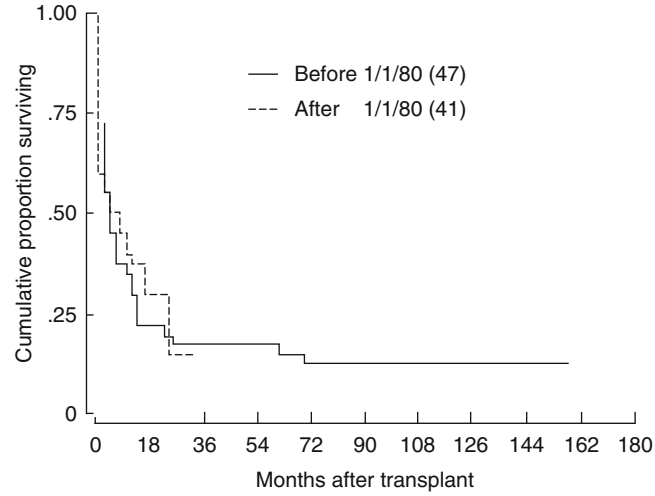

Fig. 3 Early experiences with liver transplantation for HCC were marked by poor outcomes, as exemplified by this 1984 multicenter study reporting approximately 40 % one-year survival for a series of 88 patients transplanted for HCC (Scharschmidt 1984) (Reproduced with permission from John Wiley and Sons)

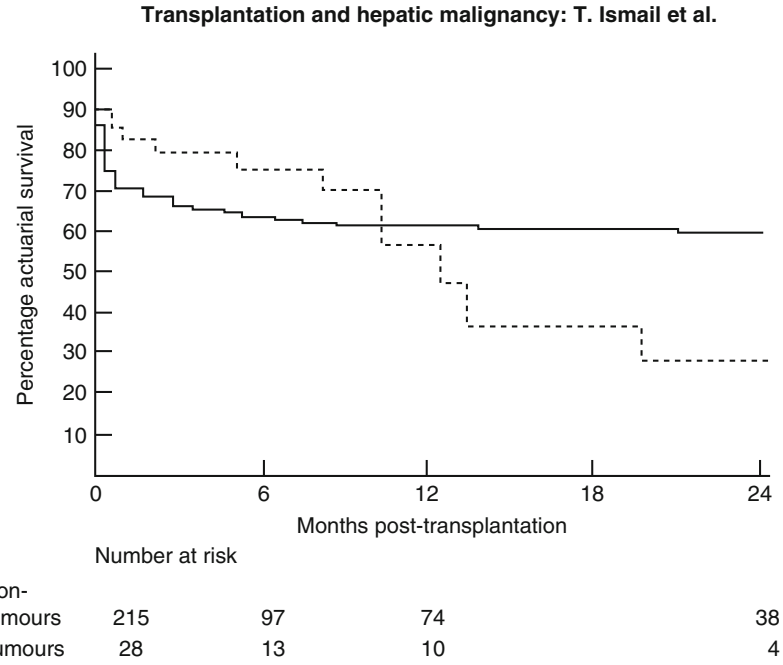

Fig. 4 Through the 1980s and early 1990s, outcomes for liver transplant patients overall improved, thanks to advances in surgical technique and immunosuppression; however, relative outcomes for patients transplanted with HCC (*dashed line*) remained poor in comparison to patients transplanted without malignancy (*solid line*), as exemplified in this 1990 study (Ismail et al. 1990) (Reproduced with permission from John Wiley and Sons)

fibrolamellar hepatomas, and to abandon such efforts" (Iwatsuki et al. 1985). The authors even went so far as to speculate that total body irradiation and chemotherapy might be necessary adjuvant therapies to make liver transplant a curative intervention for HCC (Iwatsuki et al. 1985). Likewise, in a 1987 commentary, Bismuth noted "it is in this group [primary liver cancer] that the long-term results for transplantation are poorest due to the appearance of recurrent disease" (Bismuth 1987). The increasing demand for donor organs for use in patients with superior anticipated outcomes soon precluded the use of liver transplantation with palliative intent.

Throughout the 1980s and early 1990s, additional reports confirmed the observation that patients transplanted for HCC did poorly, with high rates of recurrent HCC and limited overall survival (O'Grady et al. 1988; Jenkins et al. 1989; Ismail et al. 1990). In the most heartening of these early reports, Haug et al. reported in a 1992 paper a 25 % rate of recurrent HCC in patients surviving at least 3 months after transplant, which was good compared to other reports of the time, but which is still high by current standards (Haug et al. 1992). Although overall outcomes for liver transplant patients in general were improving during this time period, due to advances in surgical technique and immunosuppression, outcomes for HCC patients remained poor in comparison to those without HCC (see Fig. 4).

In this era, attempts to stratify patients into groups at acceptably low risk for recurrent HCC versus unacceptably high risk met with limited success. For example, some studies examined using size and number of HCC masses as a predictor of outcome, but did not find this to be helpful (O'Grady et al. 1988; Olthoff et al. 1990). These early findings, which are contrary to our current understanding of the relationship between tumor burden and risk for recurrent HCC, were likely in large part due to the fact that so many of the patients included in these analyses had tumor that was very advanced by current standards. Because so many patients in these early studies already had quite significant tumor burden, well beyond the Milan Criteria, and were already at quite high risk for recurrent HCC posttransplant, quantification of tumor within this group was of limited utility. The one exception was that patients found to have HCC as an incidental finding on explant, as compared to

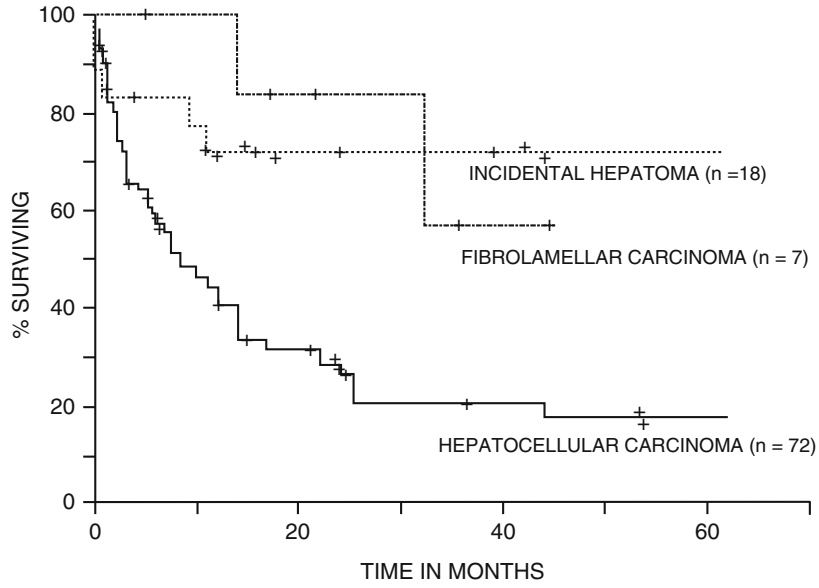

Fig. 5 Although high rates of recurrent HCC limited survival in early experiences of liver transplant, it was noted that patients with HCC identified incidentally on explant had substantially better outcomes in comparison to those with known HCC at the time of transplant, as exemplified in this 1989 study. Likely, those patients with incidentally found HCC were comfortably within the Milan Criteria, and many of those with known HCC prior to transplant were beyond the Milan Criteria. Reproduced with permission from Springer

having a known HCC diagnosis prior to transplant, did substantially better in terms of HCC recurrence and overall survival (Iwatsuki et al. 1985; Jenkins et al. 1989) (see Fig. 5). Indeed, in a 1989 paper, Ringe et al. noted that "at present, the factors playing a major prognostic role – being either especially advantageous or disadvantageous – are virtually unknown, and it is impossible to predict those patients who are most likely to have prolonged survival without tumor recurrence. Obviously there are only two known exceptions to the generally poor prognosis in cancer patients: incidental hepatomas arising in livers with other diseases, and the fibrolamellar variant of hepatocellular carcinoma" (Ringe et al. 1989). Today this observation can be understood in terms of "incidental hepatoma" serving as a surrogate for HCC staged comfortably within the Milan Criteria.

Interpretation of these early data is confounded by several factors. First, many of these early papers combined HCC patients together with cholangiocarcinoma patients and even with cases of metastatic cancer of non-hepatic primary. Second, quantification of tumor burden, if reported at all, was done in a rudimentary fashion. Third, many of the patients undergoing transplant with HCC were non-cirrhotic, in contrast to the situation at present in the United States. Additionally, some patients in these early series underwent embolization therapy, further complicating understanding of tumor burden (Moreno Gonzalez et al. 1992; Pichlmayr 1988; Olthoff et al. 1990). However, the clear historical lesson from these early experiences with liver transplantation for HCC is that the availability of liver transplantation as a therapeutic option for HCC patients was in jeopardy. The option of liver transplantation was in danger of being closed to HCC patients unless some method could be developed to identify at least a subset of HCC patients with a reasonable expectation of adequate long-term survival to justify the use of scarce donor organs.

Staging Evolution

Initial observations that small incidental HCCs identified on explant carried less ominous prognosis in comparison to known large HCC led to a more refined appreciation of the relationship between tumor burden and risk of posttransplant recurrence in the ensuing period. However, before

reviewing these data in detail in the following section, it is important to note the absence of any one uniform staging system used to quantify the degree of HCC tumor burden.

In fact, a multitude of HCC staging systems is available. Although pathologists do routinely use the standardized "TNM" (tumor-node-metastasis) system for describing findings in surgical specimens, there is no such uniform standard used by hepatologists, surgeons, and clinical researchers. Therefore, studies assessing the relationship between tumor burden and clinical outcomes use the language of the TNM system, the BCLC, Cancer of the Liver Italian Program (CLIP), Okuda, and others. These staging systems generally incorporate measures of the degree of underlying liver disease in addition to quantification of tumor burden. It is beyond the scope of this chapter to detail these various alternative staging systems, but suffices to state that analysis of the relationship between tumor stage and clinical outcome has been made more complex by this proliferation of competing clinical staging systems. Additionally, the TNM system itself has undergone a series of significant changes over time, notably including the introduction of TNM staging for primary hepatobiliary cancer in the 2nd edition of the American Joint Committee on Cancer (AJCC) staging manual, and a major change to the staging system in the 6th edition in 2002. The evolution of the TNM staging system as defined by the AJCC from its origins in 1977 to the current 7th edition released in 2010 is detailed below (Table 1).

In the early editions of the AJCC TNM staging system, T1 stage indicated a small solitary tumor without vascular invasion, whereas after 2002 in the 6th and 7th editions, T1 took on an entirely different meaning, encompassing solitary tumors of any size as long as vascular invasion was not present. It is important for the present-day reader to keep in mind the changing meaning of TNM staging over time when considering publications assessing the relationship between tumor burden and clinical outcomes. It is of particular note that in none of the various versions of the AJCC TNM system did a particular TNM stage correlate with the Milan Criteria. For example, at the time of publication of Mazzaferro's 1996 paper, patients who fell within the Milan Criteria could have tumor staged by then-current 4th edition of TNM anywhere from T1 to T4, and patients with HCC beyond Milan could be staged by TNM anywhere from T2 to T4. Similarly using the now-current 7th edition of TNM, a patient falling within the Milan Criteria could have HCC staged by TNM either T1 or T2, and patients beyond the Milan Criteria could be staged by TNM anywhere from T1 to T4.

In light of the adoption of the Milan Criteria, a new staging system initially entitled the "American Liver Tumor Study Group-Modified TNM Staging System" was defined (see Table 2). Critically, this new staging system was developed for clinicians and was discordant with the AJCC TNM system used by pathologists. The "American Liver Tumor Study Group-Modified TNM Staging System" has since been variously referred to as "UNOS stage," "Milan stage," and/or "clinical stage" and is the basis of pretransplant radiographic staging of HCC under current UNOS/OPTN policy (Befeler et al. 2005; Schlansky et al. 2015).

In summary, the reader is cautioned when encountering "T1," "T2," etc., phraseology in the literature cited in this chapter. The meaning of such classification is dependent not only on which staging system is employed but, in the case of the AJCC TNM system, also on the edition of the staging manual.

Refining the Relationship Between Tumor Burden and Posttransplant Outcome

Although some earlier studies, as noted above, failed to detect an association between quantification of tumor burden and clinical outcomes, in the late 1980s and through the 1990s, a number of studies did begin to detect a correlation between clinical outcome and TNM stage of HCC assessed

on the explanted liver (Pichlmayr et al. 1995; Iwatsuki et al. 1991; Ringe et al. 1991; Selby et al. 1995). Higher degrees of tumor burden were associated with worse clinical outcomes.

Independent of studies using the established TNM system, other groups assessed novel cutoffs in terms of number and size of HCC masses and similarly reported better clinical outcomes for

Table 1 Evolution of the AJCC TNM staging system. In the years leading up to Mazzaferro's seminal 1996 paper defining the Milan Criteria, and the subsequent years during which these criteria were validated, the TNM system has undergone significant changes. It is important when considering literature assessing relationship between HCC tumor burden as measured by TNM stage and clinical outcomes, to keep in mind these changing definitions of TNM stage for HCC

Version	1	2	3	4	5	6	7
Year	1977	1983	1988	1992	1997	2002	2010
T1	–	Solitary mass <2 cm	Solitary mass $\leq$ 2 cm without vascular invasion	Unchanged	Unchanged	Solitary tumor of any size without vascular invasion	Unchanged
T2	–	2a: Solitary mass >2 cm confined to one major lobe 2b: Multiple masses of any size confined to one major lobe	Solitary mass $\leq$ 2 cm with vascular invasion *or* Multiple tumors limited to one major lobe, all $\leq$ 2 cm without vascular invasion *or* Solitary mass $>$ 2 cm without vascular invasion	Unchanged	Unchanged	Solitary tumor of any size with vascular invasion *or* Multiple tumors, all $\leq$ 5 cm	Unchanged
T3	–	3a: Solitary mass involving both major lobes 3b: Multiple masses of any size involving both major lobes	Solitary mass >2 cm with vascular invasion *or* Multiple masses limited to one major lobe, all $\leq$ 2 cm, with vascular invasion *or* Multiple masses limited to one major lobe with any mass $>$ 2 cm	Unchanged	Unchanged	Multiple tumors, any $>$ 5 cm *or* Tumor involving the major branch of the portal or hepatic vein	3a: Multiple tumors, any $>$ 5 cm 3b: Tumor involving the major branch of the portal or hepatic vein

(*continued*)

Table 1 (continued)

Version	1	2	3	4	5	6	7
T4	–	Invasion of adjacent organ(s)	Multiple masses involving both major lobes *or* Tumor involving the major branch of the hepatic or portal vein	Same as prior	Multiple masses involving both major lobes *or* Tumor involving the major branch of the hepatic or portal vein *or* Invasion of adjacent organ (s) other than gallbladder or perforation of the visceral peritoneum	Invasion of adjacent organ other than the gallbladder or perforation of the visceral peritoneum	Unchanged

Adapted from: Manual for Staging of Cancer, 1977; Beahrs, Myers, Editors: Manual for Staging of Cancer (2nd Edition), J.B. Lippencott, 1983; Beahrs, Henson, Hutter, Myers, Editors: Manual for Staging of Cancer (3rd Edition), J.B. Lippencott, 1988; Beahrs, Hensen, Hutter, Kennedy, Editors: Manual for Staging of Cancer (4th Edition), J.B. Lippencott, 1992; Fleming, Cooper, Henson, Hutter, Kennedy, Murphy, O'Sullivan, Sobin, Yarbro, Editors: AJCC Cancer Staging Manual (5th Edition), Lippincott-Raven, 1997; Greene, Page, Fleming, Fritz, Balch, Haller, Morrow, Editors: AJCC Cancer Staging Manual (6th Edition), Springer, 2002; Edge, Byrd, Compton, et al., Editors: American Joint Committee on Cancer Staging Manual (7th Edition), Springer, 2010

Table 2 The American Liver Tumor Study Group Modified TNM staging system, a.k.a. "UNOS stage" or "Milan stage." Note: this clinical staging system is discordant with the AJCC TNM system used by pathologists (see Table 1)

Stage I	Solitary mass < 2 cm
Stage II	Solitary mass ≥ 2 cm and ≤ 5 cm *or* 2 or 3 masses, all ≤ 3 cm
Stage III	Solitary mass > 5 cm *or* 2 or 3 masses, any > 3 cm
Stage IV	IVA_1: four or more masses IVA_2: intrahepatic involvement of the portal or hepatic vein IVB: extrahepatic metastases or extrahepatic involvement of the portal or hepatic vein

Adapted from Befeler et al. (2005), *Gastroenterology* 2005; Wiesner et al. (2004), *Gastroenterology* 2004

patients with more limited tumor burden. For example, Yokoyama et al. reported that the rate of posttransplant recurrence of HCC was 64 % in all HCC patients, but was reduced to 37 % in those patients with maximal tumor diameter of 5 cm or less (Yokoyama et al. 1990). McPeake et al. observed significantly better overall survival for patients classified into a low-risk group characterized by having solitary tumor no more than 4 cm, as compared to a high-risk group with multifocal disease or solitary tumor in excess of 8 cm and also as compared to the intermediate risk group comprised of the remaining patients (McPeake et al. 1993) (see Fig. 6). Similarly, Bismuth et al. observed a trend toward better outcomes for a low-risk group of patients with tumors less than 3 cm, as compared to a moderate risk with tumor between 3 and 5 cm, and a high-risk group with tumor in excess of 5 cm (Bismuth et al. 1993). Although this relatively small study involving 60 HCC patients undergoing transplant was not powered to demonstrate statistical

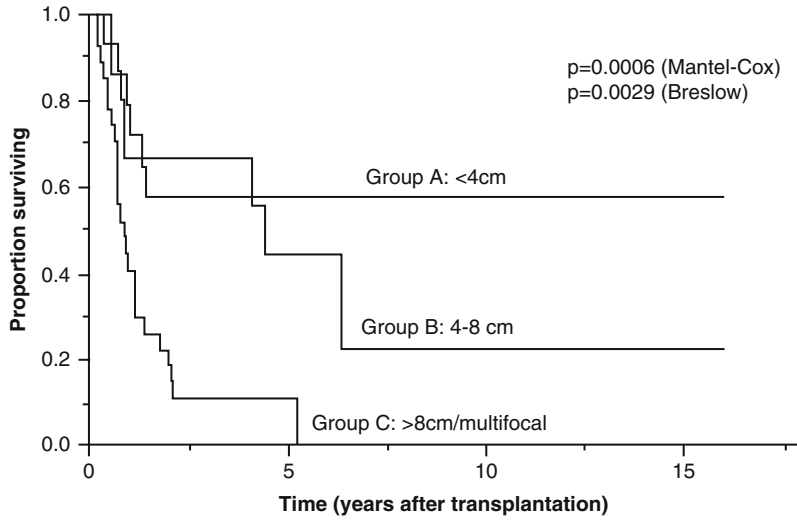

Fig. 6 Increasingly evidence accumulated of a relationship between burden of HCC tumor and post-operative clinical outcome, as exemplified in this 1993 report by McPeake et al. Those patients with solitary tumor no more than 4 cm (*group A*) had better overall survival compared to those with solitary tumor between 4 and 8 cm (*group B*) or those in the highest risk group with multifocal HCC or solitary tumor in excess of 8 cm (McPeake et al. 1993) (Reproduced with permission from Elsevier)

significance of this three-tiered stratification of risk, they were able to demonstrate with statistical significance that patients with either one or two tumors no more than 3 cm in diameter had better outcomes in comparison to those with higher degrees of tumor burden (Bismuth et al. 1993). Tan et al., in a 1995 paper, reported that when transplant was restricted to patients with tumors less than 8 cm in diameter, recurrence rates were held to 15 %, in a small patient cohort with a minimum of 18 months of clinical follow-up (Tan et al. 1995).

In the context of growing evidence of a relationship between tumor burdens measured in terms of number and size of HCC masses, Figueras et al. reported in a 1997 paper that outcomes of patients with HCC can equal those transplanted without HCC (Figueras et al. 1997). In this study, 89 % of patients with HCC had maximal tumor diameter less than 5 cm and 66 % had either one or two masses. Actuarial survival was equivalent between this group of patients and a group undergoing transplant without HCC (Fig. 7). Of note, the great majority of HCC patients in this study did undergo transarterial chemoembolization prior to transplant.

Similarly, in their 1998 paper, Llovet et al. report very good outcomes for HCC patients undergoing transplant when tumor burden was restricted to patients with solitary HCC tumors smaller than 5 cm, such that rate of posttransplant HCC recurrence was 3.5 %, 1-year survival was 84 %, and 5-year survival was 64 % (Llovet et al. 1998). These outcomes were excellent.

To summarize, once the relationship between HCC tumor burden and risk of posttransplant recurrence became understood, it was possible to justify continued access of HCC patients to liver transplant as a lifesaving therapeutic option. The next step was to develop a uniform set of criteria which could serve as an accepted standard to define transplant candidate on the basis of quantification of tumor burden.

Mazzaferro's Seminal Paper: Introduction of the Milan Criteria

Mazzaferro et al.'s seminal paper published in the *New England Journal of Medicine* in 1996 (Mazzaferro et al. 1996) laid out what became known as the *Milan Criteria*, which remain the

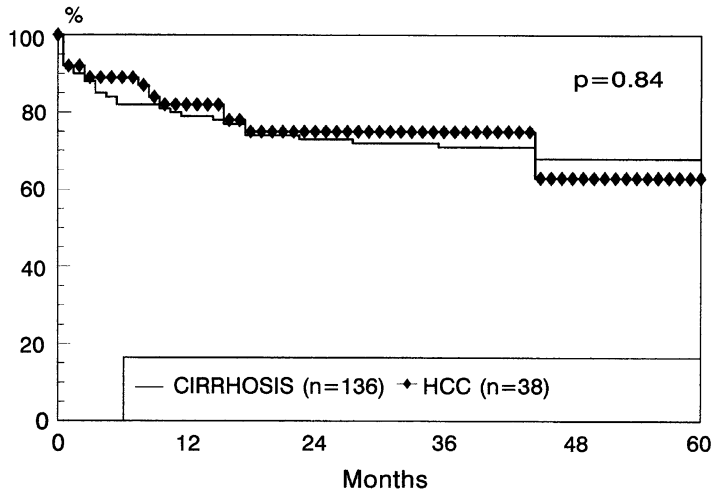

Fig. 7 Whereas the earliest experiences with liver transplant for HCC were associated with dismal outcomes with very poor survival driven by very high rates of posttransplant recurrence of HCC, Figueras et al. in a 1997 study demonstrated that equivalent outcomes could be achieved for patients transplanted with HCC compared to those without HCC. In this study, almost all HCC patients had maximal tumor diameter less than 5 cm, and two thirds had at most two HCC masses (Figueras et al. 1997) (Reproduced with permission from John Wiley and Sons)

cornerstones of determining candidacy of HCC patients for transplant to this day. This paper has been enormously influential, referenced in the transplant literature over one thousand times (OVID MEDLINE search, December 2015).

The authors included 48 patients with known HCC and cirrhosis in their analysis (Mazzaferro et al. 1996). As inclusion criteria, all patients had tumor restricted to what are now called the Milan Criteria as assessed radiographically prior to transplant, and none were considered candidates for resection. Pretransplant radiographic staging was performed at a median of 143 days prior to transplant (range 2–294 days) (Mazzaferro et al. 1996). Twenty-eight (58 %) of the patients underwent trans-arterial chemoembolization while awaiting liver transplant (Mazzaferro et al. 1996).

At the time of transplant, 35 patients (73 %) were found histologically to be within the Milan Criteria and 13 patients (27 %) were beyond. For those patients within criteria on explant, overall survival was 85 % at 4 years (Mazzaferro et al. 1996). For those patients beyond criteria on explant, overall survival was 50 % at 4 years (Mazzaferro et al. 1996) (Fig. 8).

This study was of great importance because it demonstrated that a subset of HCC patients could be identified with very good prospects for long-term survival, comparable to that expected for patients undergoing transplant without HCC at the time.

However, a number of factors need to be considered when interpreting the results of this paper. First, Mazzaferro et al. applied quantification of tumor using their newly proposed criteria to *explant pathology*. Today, the Milan Criteria are used primarily to determine candidacy for transplant and therefore by definition must be applied to pretransplant imaging and not explant pathology findings. In fact, every one of the patients in Mazzaferro et al.'s paper was thought to be within the Milan Criteria radiographically. Complicating our understanding of the relationship between pretransplant radiographic staging and explant pathology staging in this paper are confounding factors such as the relatively long time interval between radiographic staging and pathology staging for many patients and the use of trans-arterial therapy while awaiting transplant.

Nonetheless, this study helped prove that liver transplant for HCC patients was conceptually

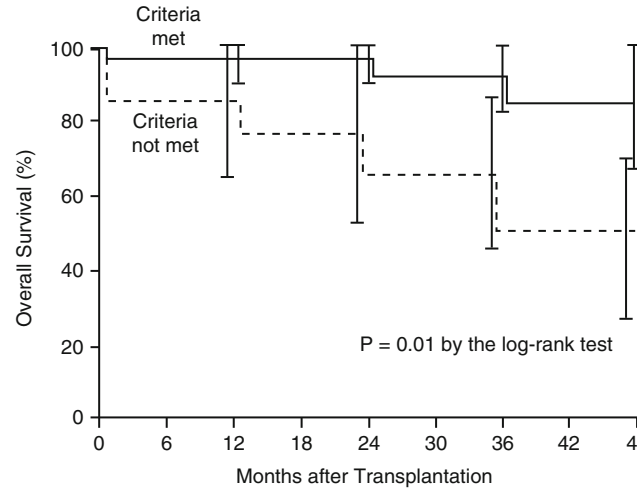

Fig. 8 Relationship between tumor burden, assessed by application of the Milan Criteria to explant pathology, and overall posttransplant survival. In the seminal 1996 *New England Journal of Medicine* paper, Mazzaferro et al. demonstrated the power of what would come to be called the "Milan Criteria" to stratify risk for death after transplant, largely mediated by risk of recurrent HCC (Mazzaferro et al. 1996)

sound and helped justify the candidacy of HCC patients for transplant from a societal perspective as regards the allocation of scare donor organs. This paper provided a set of objective criteria which could be used to guide determination of transplant candidacy of individual patients in a rational and evidence-based manner, consistent with adoption by the major international hepatology societies and incorporation into UNOS/OPTN policy.

Validation of the Milan Criteria

Since Mazzaferro's 1996 paper, the Milan Criteria have been extensively validated. For patients within the Milan Criteria, reported rates of recurrent HCC after transplant range for the most part from 1.4 % to 15 % (Ravaioli et al. 2004; Shah et al. 2006; Kneteman et al. 2004; Sotiropoulos et al. 2007; Herrero et al. 2008; Todo et al. 2004; Zavaglia et al. 2005). Two studies did report significantly higher rates of recurrent HCC after transplant. First, Decaens et al. noted a 20.2 % recurrence rate, notably in a quite large multicenter study involving 279 patients transplanted with HCC within the Milan Criteria (Decaens et al. 2006). Importantly, in the Decaens study, the assessment of whether or not the patients were within Milan was assessed based on pretransplant imaging, rather than explant pathology. This distinction may explain the relatively high rate of posttransplant HCC recurrence and is discussed in greater detail in the following section. Second, Vakili et al. in a 2009 paper also reported a high posttransplant recurrence rate of 23 % in a small series of patients undergoing living donor transplant for HCC (Vakili et al. 2009). The high rate of vascular invasion, in just under half of the patients, may in part explain the relatively high rate of posttransplant recurrence in Vakili et al.'s study. It is possible that the fact that living donors rather than cadaveric donors were used in Vakili et al.'s study could have biased the study toward a higher-risk patient population. Although both the Decaens and Vakili papers reported relatively high rates of posttransplant recurrence of HCC in comparison to other papers validating the Milan Criteria, they still found that the Milan Criteria predicted a lower rate of posttransplant recurrence in comparison to the even higher rates observed in patients found to be beyond the Milan Criteria in these particular studies of 43 % and 52.6 %(Decaens et al. 2006; Vakili et al. 2009).

In terms of overall survival, Mazzaferro et al.'s findings have been validated as well. Reported 1-year survival rates for patients within the Milan Criteria range from 78.1 % to 94.3 % (Shah et al. 2006; Todo et al. 2004; Merli et al. 2005; Pelletier et al. 2009; Yao et al. 2002;

Table 3 Overall survival for patients within versus beyond the Milan Criteria, from an analysis of data on over 3,000 HCC patients from the UNOS/OPTN database. This was an intention-to-treat analysis, with assessment of the Milan Criteria based on pretransplant radiographic staging (Adapted from Pelletier et al. 2009)

	1-year survival (%)	3-year survival (%)	5-year survival (%)
Within Milan	89	75	65
Beyond Milan	82	65	38

Zheng et al. 2008) and 3 years from 65 % to 88.4 % (Todo et al. 2004; Pelletier et al. 2009; Xiao et al. 2009; Yao et al. 2002; Zheng et al. 2008). A 2009 study by Pelletier et al. is of particular note, due to its very large sample size, based on analysis of data from the UNOS/OPTN database assessing outcomes of over three thousand patients transplanted with HCC (see Table 3) (Pelletier et al. 2009). Mazzaferro et al. in a similar fashion reported results in a 2009 paper of a large, multicenter, international database study and found superior 5-year survival of 73.3 % for those within the Milan criteria as compared to 53.6 % for those beyond the criteria (Mazzaferro et al. 2009).

Other reports confirmed superior overall survival (Adler et al. 2008) and recurrence-free survival for patients transplanted within the Milan Criteria as compared to those beyond (Shetty et al. 2004; Zimmerman et al. 2007). Additionally, in several single-center experiences, clinical outcomes improved when comparing cohorts prior to, versus after, implementation of the Milan Criteria for the purpose of determining transplant candidacy (Ravaioli et al. 2004; Onaca et al. 2009). Other studies validated the finding that patients transplanted within the Milan Criteria had outcomes comparable to those transplanted without HCC (Leung et al. 2004).

Mazzaferro and colleagues produced a meta-analysis in 2011, which included 19 original studies, confirming superior outcomes for HCC patients if transplanted with tumor restricted to within the Milan Criteria (Mazzaferro et al. 2011) (see Fig. 9).

Radiographic Versus Histological Staging

The Milan Criteria were introduced in Mazzaferro et al.'s seminal 1996 *New England Journal of Medicine* article and demonstrated a relationship between clinical outcome and tumor burden *as assessed on pathology of the explanted liver* (Mazzaferro et al. 1996). It is self-evident that in order to use the Milan Criteria for the purpose of determining transplant candidacy, reliance on explant pathology is not possible. Therefore, the Milan Criteria can only be clinically useful in this regard if radiographic staging can serve as a reasonable surrogate for pathological staging. Although the Milan Criteria have been extensively validated in studies assessing tumor burden on explant pathology, data assessing the relationship between tumor burden assessed on pretransplant imaging and clinical outcomes are more limited. Indeed, a large intention-to-treat study reported a posttransplant recurrence rate of 20.2 % for patients *radiographically* within the Milan Criteria (Decaens et al. 2006), which is higher than the rates generally reported in studies validating the Milan Criteria based on explant pathology (see "Validation of the Milan Criteria" section above).

In studies assessing agreement of pretransplant radiographic staging versus pathological staging specifically as regards the question of meeting the Milan Criteria, 14.2–43 % of patients thought to be within Milan radiographically were actually beyond Milan on explant (Mazzaferro et al. 1996; Shah et al. 2006; Zavaglia et al. 2005; Wiesner et al. 2004; Todo et al. 2004). In fact, assessing the broader question of agreement of pretransplant radiology compared to explant pathology, Freeman et al. in an influential 2006 paper demonstrated that staging as gauged by the UNOS clinical criteria was accurate in only 44.1 % of cases (Freeman et al. 2006).

The accuracy of pretransplant imaging as regards meeting the Milan Criteria in comparison to explant pathology is influenced by a number of factors, including the sensitivity/specificity of imaging technique (including both attributes of

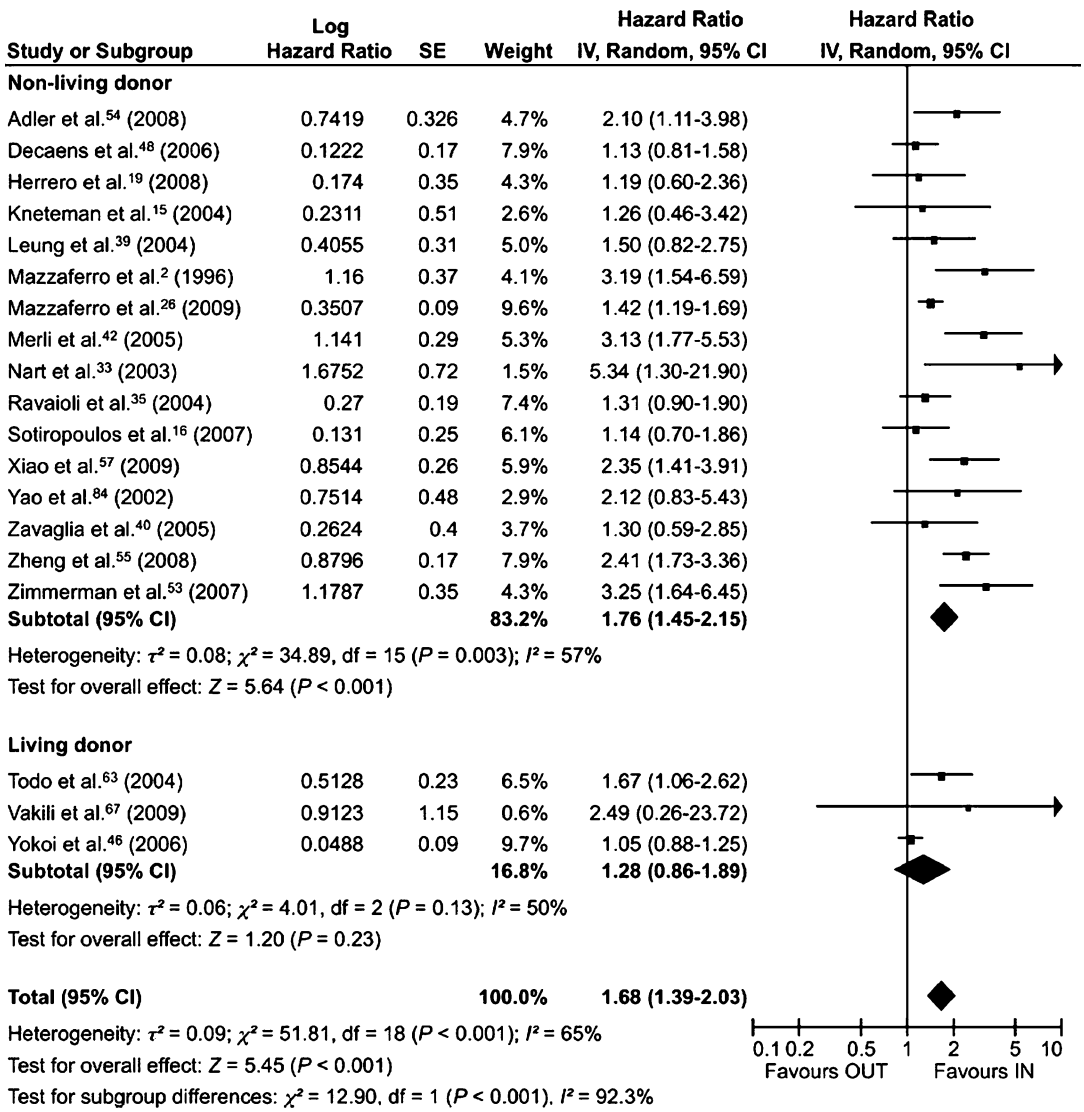

Fig. 9 Validation of the superior clinical outcomes for patients transplanted within the Milan Criteria, in meta-analysis performed by Mazzaferro et al. (2011) (Reproduced with permission from John Wiley and Sons)

the hardware generating an image and the radiographic criteria used by the radiologist to interpret that image), time interval between imaging and transplant, biological behavior/aggressiveness of the cancer, and any interval tumor-directed therapy.

There is a substantial body of literature available regarding the sensitivity and specificity of cross-sectional imaging techniques for the detection of HCC in general, including several meta-analyses, the largest of which included over 200 original publications (Chou et al. 2015; Chen et al. 2014; Kierans et al. 2015; Junqiang et al. 2014). Based on these studies, the sensitivity of cross-sectional imaging for the detection of HCC has been estimated to range from 30 % to 99 % and specificity to range from 80 % to 95 %. Some of this variation is explained by technical

advancements over time with higher-resolution machines, resulting in better diagnostic accuracy. However, the radiographic criteria used to interpret a given image as either demonstrating the presence of HCC or not have been changing over time as well.

In addition to demonstrating limitations on the accuracy of pretransplant radiographic staging of HCC, the abovementioned paper by Freeman et al. from 2006 also showed that an alarmingly high proportion of patients – 21 % – undergoing transplant for the primary indication of HCC, and with adjusted transplant priority on the basis of the HCC diagnosis, actually had no evidence of HCC on explant (Freeman et al. 2006). Importantly, patients with a history of tumor-directed therapy prior to transplant were excluded from that analysis. In large part as a response to Freeman's findings, the transplant community determined it necessary to develop new radiographic criteria, designed to maximize specificity and positive predictive value. The reason for prioritizing positive predictive value in developing new radiographic criteria for detecting HCC was to allow more confident decision-making regarding allocation of transplant priority for HCC patients (Pomfret et al. 2010). Driven by this effort, the Liver Imaging Reporting and Data System (LI-RADS) and most recently the OPTN-5 designation were developed (Mitchell et al. 2015; Wald et al. 2013).

At present, UNOS/OPTN considers only lesions meeting OPTN-5 criteria (LI-RADS 5 criteria) in radiographic staging, a policy which went into effect in 2013 (HRSA/OPTN a). Although there is a large body of literature regarding the diagnostic accuracy of cross-sectional imaging, data on the diagnostic accuracy of pretransplant imaging specifically using these particular criteria are sparse. One study validating the OPTN-5 criteria found low sensitivity for the detection of HCC lesions between 1 and 2 cm of 26–34 % (Fowler et al. 2013). Indeed, the authors of this study concluded that "The improved specificity comes necessarily at the expense of sensitivity, especially in the 1–2 cm subset. . ." (Fowler et al. 2013). Overall, it remains unknown how the 2013 UNOS/OPTN policy change of staging only OPTN-5/LI-RADS 5 lesions will affect diagnostic accuracy of pretransplant imaging assessed in comparison to explant pathology.

The LI-RADS classification system and the OPTN-5 designation do not apply to HCC tumors which have been treated with any form of locoregional therapy. In fact, there is no standardized approach to staging previously treated lesions from either a radiology or pathology standpoint. Increasingly, patients awaiting transplant with HCC are undergoing some form of "bridging" tumor-directed therapy. In Freeman's 2006 analysis of UNOS data, 61.5 % of patients awaiting transplant with HCC between 2003 and 2005 had some form of tumor-directed therapy. In a more recent study by Schlansky, Naugler, and this author, published so far only in abstract form, 79.0 % of patients awaiting transplant between 2013 and 2014 had some form of tumor-directed therapy (Anonymous 2015). The most recent change in UNOS/OPTN policy added a waiting period between when a patient is deemed a candidate for adjustment of priority on the transplant list on the basis of having HCC and when the adjusted priority score is actually allocated (HRSA/OPTN b). A likely consequence of this policy change is that an even smaller proportion of patients going to transplant for HCC will do so without some pretransplant tumor-directed therapy, making rigorous assessment as to whether these patients actually meet the Milan Criteria either radiographically or pathologically difficult.

Beyond the Milan Criteria: The Metroticket Concept

The Milan Criteria have proved to be critical in stratifying HCC patients into relatively low-risk and high-risk groups for having bad outcomes after transplant mediated by risk of recurrent HCC. However, these particular criteria are to a degree arbitrary. Since the adoption of the Milan Criteria by the international transplant community, a number of alternative criteria have been proposed, under the hypothesis that modestly easing these criteria might allow access for more patients to a curative intervention, without significantly compromising outcomes. To date, the

most influential such alternate criteria have been the "UCSF Criteria" (Yao et al. 2001, 2002). In addition to such expanded criteria, another approach to patients with HCC tumor exceeding the Milan Criteria is to attempt "downstaging" treatment. A comprehensive discussion of the topics is beyond the scope of this chapter. Please see related chapters "▶ Downstaging Hepatocellular Carcinoma for Liver Transplantation" and "▶ HCC: The San Francisco Criteria."

- Suffice to say that rather than a Boolean relationship between tumor burden and outcome, such that a line can be drawn between patients with likely good or bad outcomes after transplant, it may be that there is a continuous relationship between the degree of tumor burden and risk of posttransplant HCC recurrence. In a 2009 paper, Mazzaferro et al. laid the groundwork for the Metroticket concept, by compiling data on 1,556 patients who underwent liver transplant for HCC beyond the Milan Criteria, with data contributed from 36 centers internationally (Mazzaferro et al. 2009). They found that there was a continuum in the relationship between number and size of tumors (assessed on explant pathology) and survival. By plotting the number of HCC tumors and the diameter of the largest tumor on a nomogram, the Metroticket provides an estimate of 5-year survival (see Fig. 10). The Metroticket concept has been subsequently validated (Raj et al. 2011).

The concept of a continuous relationship between tumor burden and risk of poor outcome mediated by posttransplant HCC recurrence makes transplant candidacy more of an ethical question or at least one of social utility. What degree of risk is acceptable? Do HCC patients necessarily need to have the same outcomes as non-HCC patients? If not, then to what degree might poorer outcomes for HCC patients be tolerated? This question is perhaps most relevant to HCC patients who are living donor transplant candidates. For living donor candidate, a more nuanced approach to risk stratification regarding risk of posttransplant HCC recurrent might be tolerated, in comparison to the needs of a national policy regarding fair allocation of cadaveric donor organs.

Conclusion

In summary, liver transplant for patients with HCC has come a long way. Initial experiences suggested that transplant might have some limited benefit for palliation of advanced HCC, which would not have been sustainable as demand for a scarce supply of donor organs increased. Since the advent of the Milan Criteria, the role of liver transplant as a curative intervention for a subset of HCC patients has been assured. However, challenges remain. In particular, it remains unresolved how to determine with confidence whether patients who have undergone "bridging" locoregional therapy while awaiting transplant are actually within the Milan Criteria, at a time when increasingly an overwhelming majority of patients do undergo such therapy. Additionally, recent UNOS/OPTN policy changes have resulted in the use of new radiographic criteria for the pretransplant staging of HCC, and the impact of these new criteria on accuracy of staging as compared to explant pathology is not yet known. In particular how these new criteria might affect the relationship between pretransplant radiographic staging and risk of recurrent HCC or overall survival remains to be seen. Because the new criteria were designed specifically to maximize positive predictive value in the detection of HCC, at the likely cost of decreased negative predictive value, the new criteria might lead to a higher degree of radiographic under-staging of HCC. The Milan Criteria will need to be re-validated in the future in light of these questions, using modern radiographic technology and modern radiographic criteria. In a hypothetical future, in which an adequate supply of donor organs were to be available (perhaps through advances in biotechnology), the Milan Criteria would no longer be necessary. However, for the foreseeable future in which donor organs remain a scarce resource, and

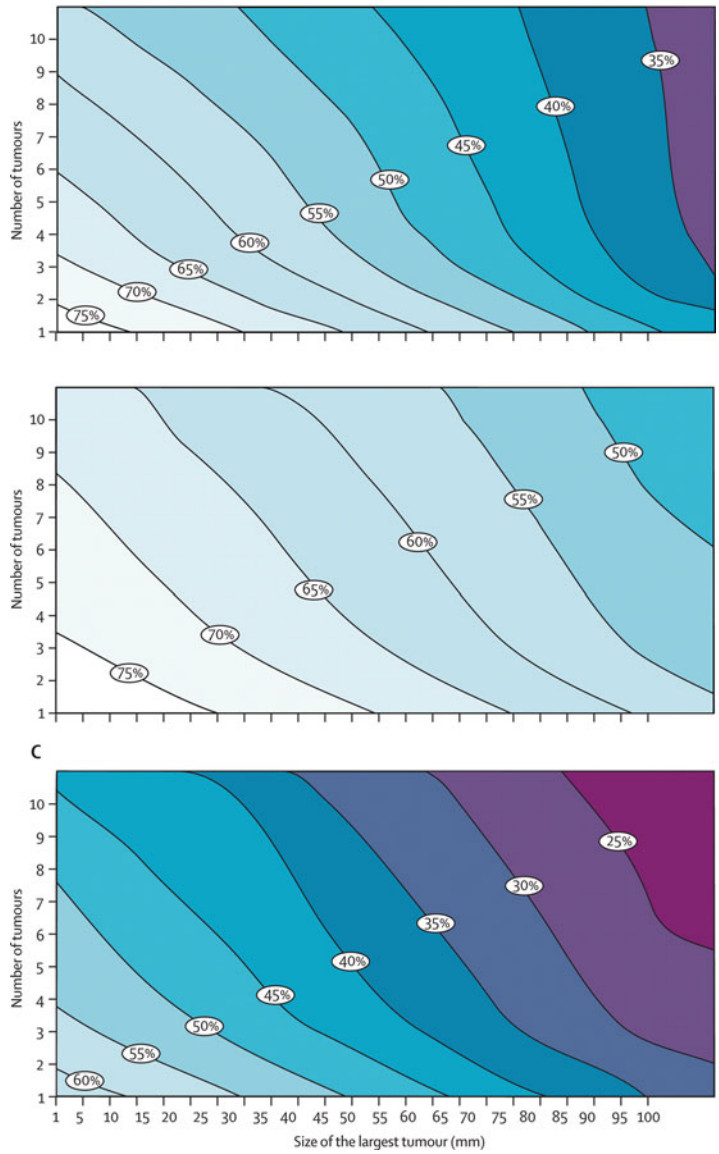

Fig. 10 The Metroticket concept of a continuous relationship between the extent of HCC tumor burden and outcome mediated by risk of recurrent HCC. The number of HCC tumors is plotted on the Y-axis, and the diameter of the largest tumor is plotted on the X-axis. For a given patient, the region on the graph at the intersection of these parameters provides an estimate of 5-year posttransplant survival (Mazzaferro et al. 2009) (Reproduced with permission from Elsevier)

thousands of people die annually for want of an available graft, the Milan Criteria remain a cornerstone in assessing the transplant candidacy of HCC patients.

Cross-References

- ▶ Downstaging Hepatocellular Carcinoma for Liver Transplantation
- ▶ HCC: The San Francisco Criteria

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HCC: The San Francisco Criteria

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Thomas Byrne and Hugo Vargas

Contents

Abstract

Hepatocellular carcinoma (HCC) is one of the most common human malignancies and a leading cause of cancer-related mortality. The incidence of HCC has dramatically increased in recent decades. Cirrhosis is a major risk factor for HCC development, and because the diseased liver itself is a nidus for cancer formation, liver transplantation (LT) has emerged as a widely utilized therapy for patients with HCC.

Because it was recognized early in the LT experience that patients with large and/or multicentric cancers fared poorly, criteria based on tumor size and number have emerged to govern which patients with HCC are eligible for LT. The most common criteria have been referred to as the "Milan criteria" and are associated with favorable outcomes after LT. But some groups have advocated expanding those criteria to include patients slightly outside of Milan criteria, whose tumor burden may become reduced back to within Milan criteria through a process known as "downstaging." In the United States one such downstaging pathway comprises what is known as the University of California San Francisco (UCSF) criteria.

Herein we review the UCSF criteria. We describe the downstaging process, its rationale, and the outcomes associated with the expanded LT criteria. Concerns and controversies are acknowledged.

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Keywords
Downstaging • Hepatocellular carcinoma (HCC) • Liver transplantation (LT) • Milan criteria

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common human cancer with a historically poor prognosis (Bosch et al. 1999). Meaningful improvement in treatment outcomes has only occurred in recent decades, with the incidence-to-mortality ratio for HCC approaching one prior to this (El-Serag 2001). Cirrhosis of the liver appears to be the single most common risk factor for HCC and is present in the vast majority of cases. The incidence of HCC in developed nations has approximately tripled during the last four decades, almost certainly due to the hepatitis C virus (HCV) epidemic (El-Serag and Mason 1999). Furthermore, the incidence of HCC is likely to continue to increase at least for several more years as the HCV epidemic persists and nonalcoholic fatty liver disease (NAFLD) continues to provide a background for HCC occurrence.

Rationale for Liver Transplantation for HCC

Although radiofrequency ablation (RFA) may achieve 5-year survival rates comparable to resection for patients with Stage I HCC ($\leq$2 cm single lesion) (Lau and Lai 2009) including achieving "cure" in some cases, surgical removal of all tumor tissue is considered the only curative option for most patients. This is likely because most patients present with a more advanced stage of HCC and/or are cirrhotic with the attendant risk of ongoing hepatocarcinogenesis in the diseased liver.

Surgical resection of HCC remains a highly utilized therapy with relatively favorable survival rates, particularly for noncirrhotic patients (or highly selected cirrhotic patients) with unifocal or unilobar tumor burden (Iwatsuki et al. 1991). However, even with favorable survival, recurrence of HCC after resection is common, in some series exceeding 60 % at 3 years (Bismuth et al. 1993). Unrecognized micrometastases in the unresected liver or in the case of cirrhotic patients, de-novo tumor formation in the diseased remnant liver parenchyma, likely account for the high recurrence rates associated with resection.

Early experience with liver transplantation (LT) for HCC was quite poor (Ismail et al. 1990; Ringe et al. 1989). However, in this era there were no standardized eligibility criteria regarding tumor size or number. Furthermore, imaging capability was relatively limited. Thus the initial low rates of long-term survival were likely driven by the inclusion of patients with large and/or multiple tumors. Mortality in such patients was driven largely by aggressive tumor recurrence after LT. In many centers HCC was considered a contraindication to LT.

At the same time, there were observations that patients with small, incidental hepatomas discovered at explant experienced low rates of HCC recurrence and fared well (Pichlmayr et al. 1994). This led to consideration of LT for patients with small HCCs. Ultimately, Mazzaferro's seminal report of successful LT for patients meeting certain criteria to limit tumor burden for LT eligibility transformed the previous pessimism about LT in the setting of HCC (Mazzaferro et al. 1996). The so-called Milan criteria (single lesion $\leq$ 5 cm or up to 3 lesions none $>$ 3 cm, no macrovascular invasion or extrahepatic spread) have since served as the most widely accepted eligibility standards for patients with HCC seeking LT in the United States. Since implementation of the Model for End-Stage Liver Disease (MELD) prioritization system for organ allocation in 2002, selected patients with HCC have been able to receive artificially increase MELD scores via MELD exception points. This policy was driven by awareness of long waiting times that led to HCC progression and waitlist "dropout" before the current system

(Wiesner et al. 2004). The Milan criteria are the most commonly utilized to determine which patients are eligible for MELD exception points in the setting of HCC. As a result, HCC has become one of the most common indications for LT, being present in as much as 1/3 of transplant recipients in some UNOS regions.

Rationale for Expanded HCC Criteria and the Role of Pretransplant HCC Therapy

Due to concerns about increasing waiting time on the transplant list, as demand for LT has grown, most transplant centers have utilized some form of locoregional therapy (LRT) in an effort to prevent growth and spread of HCC for patients awaiting LT. Although data showing that LRT confers a survival advantage after LT has been limited, LRT is widely utilized as a bridge to transplantation. The goal of LRT in this setting is to preserve patients' eligibility for LT by preventing waitlist dropout that could result from unchecked tumor progression. Transarterial chemoembolization (TACE) and RFA have been the most commonly utilized LRTs in patients awaiting LT. Increasingly, intra-arterial delivery of drug-eluting beads (DEBs) impregnated with doxorubicin and Yttrium-90 microspheres (radioembolization) have been employed.

In 2001, Yao and colleagues reported experience with 70 patients transplanted over a 12-year period, most of whom had undergone TACE (Yao et al. 2001). Patients whose tumor burden exceeded Milan criteria but fell within an expanded domain – (A) solitary tumor $\leq$ 6.5 cm or (B) $\leq$ 3 nodules with largest lesion $\leq$ 4.5 cm and (C) total tumor diameter $\leq$ 8 cm – had 1- and 5-year survival rates of 90 % and 75.2 %, versus only a 50 % 1-year survival in patients exceeding these thresholds (Yao et al. 2001). Limitations of this study included its retrospective nature and the fact that a third of the cohort had incidentally discovered HCC at explant. Nonetheless, this report and others (Duffy et al. 2007; Decaens et al. 2006) led to advocacy for the expansion of eligibility for LT to include patients with HCC that exceeded Milan criteria.

"Downstaging" is a term used to describe the use of LRT in an effort to decrease the amount of active tumor burden in patients with HCC who are being considered for LT. The excellent posttransplant survival for HCC patients meeting Milan criteria has been widely validated. Advocates of expanded HCC criteria suggest that patients whose HCC burden initially exceeds Milan, but whose tumor burden is reduced to Milan parameters after LRT, should achieve the same favorable survival after LT.

This argument assumes that the amount of visible, measurable tumor by conventional imaging is predictive of posttransplant outcome. Increasingly however, underlying tumor biology – its natural aggressiveness or lack thereof – is believed to be a key determinant of post-LT outcome, as opposed to measured tumor diameter at a single time point. Observation of HCC behavior over time – by mandating a certain minimum amount of time where transplantation is delayed – has therefore been proposed as a way to assess tumor biology. By observing for downstaging success or failure at a future time point (as opposed to immediately after LRT), the underlying aggressiveness of tumor biology is revealed: less aggressive tumors are more likely to be successfully downstaged. In contrast, those patients whose tumor biologies are inherently more aggressive are less likely to be downstaged and theoretically less likely to benefit from LT.

Expanded HCC Criteria Outcomes: The UCSF Experience

Since 2002, UCSF has utilized a specific downstaging protocol for patients with HCC tumor burden exceeding Milan criteria but falling within a broader set, commonly referred to as "UCSF criteria." In this scheme, patients must have their active viable tumor burden as measured by imaging downstaged via LRT to within Milan criteria, after which they are eligible for MELD exception points to become competitive for

LT. The results of this protocol on an Intention-to-treat basis have been reported in 2008 (Yao et al. 2008) and more recently in 2015 (Yao et al. 2015).

Eligibility criteria for the downstaging protocol include: (A) single lesion $\leq$ 8 cm or (B) 2 or 3 lesions each $\leq$ 5 cm, with the sum of maximum tumor diameters $\leq$ 8 cm, or (C) 4 or 5 lesions each $\leq$ 3 cm, with the sum of maximum tumor diameters $\leq$ 8 cm, and (D) absence of vascular invasion on imaging. Success of downstaging with LRT (such that the viable remaining tumor burden is within Milan (UNOS T2) criteria) is determined by imaging, with a minimum of 3 months required between LRT and LT.

Reported 5-year Intention-to-treat survival in the downstaging cohort of 118 patients was 56.1 % (Yao et al. 2015). This compares similar to patients initially meeting Milan criteria at the same institution (5-year survival 63.3 %, $p = 0.29$) (Yao et al. 2015). Patients in the downstaging cohort had a higher frequency of waitlist dropout at 1 and 2 years (24.1 %/34.2 %) compared to UNOS T2 patients (20.3 %/25.6 %, $p = 0.04$), and pre-LRT alpha-fetoprotein $\geq$ 1,000 ng/mL was associated with substantially higher risk of dropout (Yao et al. 2015).

Concerns in a Time of Organ Shortage and Future Directions

Several concerns exist regarding whether the expanded UCSF HCC criteria for patients successfully downstaged should become adopted regionally or nationally. HCC recurrence is a key factor in determining patient and graft survival after LT, and there is a lack of standardized reporting of HCC recurrence nationally (Bittermann et al. 2014). In addition, the choice of which LRT to employ to achieve downstaging is haphazard, often related to institution or individual physician preference. At present there is no evidence to designate an optimal type of LRT for a given tumor burden and/or location within the liver. Inherent tumor biology may be more important in predicting outcome than which type of LRT is employed. Accordingly, any effort to expand HCC criteria on a widespread basis should have a mandatory surveillance period where LT is not offered, in order to observe tumor behavior and thus identify patients who are most likely to benefit from LT.

There is also obvious concern that HCC criteria expansion disadvantages patients with advanced liver failure but no HCC. With the demand for LT expected to increase in the coming years and the supply of organs relatively stable, exacerbation of the already-dire organ shortage problem can be expected. Transplant societies, patient groups, and ultimately policy-makers will need to engage in continuous appraisal of evidence to inform decision-making on HCC and MELD exception criteria. Ultimately, with no practical near-term way to meet the expected demand for donor organs, there is a pressing need for therapies that will reverse liver disease itself, along with strategies to prevent it at a public health level.

Conclusion

Selected transplant centers – prominently UCSF in the United States – have advocated LT in a population of patients whose initial HCC burden falls slightly outside of Milan criteria, but who may be successfully downstaged to within Milan criteria with locoregional therapy. Outcomes data from this approach – from an intention-to-treat standpoint – are roughly equivalent to patients meeting traditional Milan criteria. However, these expanded criteria have not become universally accepted, and there are concerns about the potential exacerbation of an already-severe shortage of organs for patients awaiting LT.

Cross-References

- ▶ Downstaging Hepatocellular Carcinoma for Liver Transplantation
- ▶ Liver Transplantation for HCC: The Milan Criteria

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Downstaging Hepatocellular Carcinoma for Liver Transplantation

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Contents

Abstract

The incidence of hepatocellular carcinoma (HCC) has been on the rise in the United States in the past few decades. Liver transplantation is considered the treatment of choice for patients who present with stage II HCC and fall within the MILAN criteria with a 5-year overall survival of 65–70 %. Unfortunately, most of the patients present with advanced disease and only 10–20 % are eligible for orthotopic liver transplant (OLT). In an attempt to help patients meet the criteria for OLT, several modalities are being used to decrease tumor load and downstage patients, namely, radiofrequency ablation (RFA) and transarterial chemoembolization (TACE). The main problems with the concept of downstaging reside in identifying patients who should undergo downstaging, defining the end points of successful downstaging and deciding on a reasonable time frame before listing for transplant. Several reports have been published that show good results with downstaging. The percentage of patients who were successfully downstaged in published series ranged from 24 % to 70 %. Overall survival after downstaging and OLT was approximately 65 % at 5 years in most of the series. This supports the idea that downstaging is a reasonable method for treatment of patients who present with unresectable HCC that do not fit the criteria for initial liver transplantation. It is also useful in selecting patients with favorable biology that would

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otherwise not receive OLT. There is currently no evidence in the literature to suggest that patients who are downstaged and receive OLT do worse than patients that present within MILAN transplant criteria, a notion that should drive surgeons and hepatologists to aggressively treat stage III HCC patients with the goal of downstaging.

Keywords

Downstaging hepatocellular carcinoma (HCC) • Liver transplant • Transarterial chemoembolization (TACE) • Radiofrequency ablation (RFA)

Introduction

Hepatocellular carcinoma (HCC) is considered to be the fifth most common malignancy worldwide and is ranked third in mortality (Gordon-Weeks et al. 2011). The incidence in the United States has been on the rise in the past few decades from 3.1 to 5.1 per 100,000 persons based on data analyzed from the SEER database (Altekruse et al. 2014). Orthotropic liver transplant (OLT) is currently recognized as the treatment of choice for patients presenting with low-volume unresectable HCC who fulfill restricted criteria (1 tumor less than 5 cm, 3 tumors each less than 3 cm, absence of distant metastasis, absence of vascular invasion, also known as MILAN criteria) with a low recurrence rate of 10 % and a 5-year survival of 70 % (Mazzaferro et al. 1996). Unfortunately most of the patients present with advanced stage disease and do not fit the aforementioned criteria resulting in OLT being attempted in only 10–20 % of the patients with HCC (Llovet et al. 1999; Toso et al. 2009). Tumor rupture and elevated alpha-fetoprotein levels (AFP) greater than 10,000 have also been considered contraindications for transplant (Gordon-Weeks et al. 2011). Untreated patients have a median survival of 6–9 months, while those who receive locoregional therapy have a 5-year survival of 30 % (Yeung et al. 2005; Signoriello et al. 2012). Use of sorafenib alone results in a median survival of 11 months in patients with advanced HCC (Llovet et al. 2008). In an attempt to overcome the shortcomings of the MILAN criteria, several investigators proposed the concept of expanding these criteria which resulted in the extended UCSF criteria (1 tumor less than 6.5 cm, three tumors with the largest diameter being less than 4.5 cm, total sum of tumor diameter that does not exceed 8 cm) (Yao et al. 2001). Nevertheless, many patients continued to be excluded and the concept of "*downstaging*" hepatocellular carcinoma was introduced.

Downstaging is defined as any treatment modality that results in successful decrease of tumor load (size or number) to allow for patients to meet defined criteria for OLT, namely, MILAN (Sharr et al. 2014). This should be contrasted from the concept of "bridging" where patients already meet the criteria for OLT; however, treatment is given to prevent progression of disease and drop-out from transplant waiting lists. Downstaging also offers the theoretical advantage of selecting patients with favorable biology that will benefit from OLT with a low rate of recurrence (Yao et al. 2008). Despite the fact that several groups around the world have reported their experience with patients who underwent downstaging of HCC before transplant, no unified criteria are present at this point to govern this emerging practice (Yao et al. 2008; Barakat et al. 2010; DeLuna et al. 2009; Lewandowski et al. 2009; Ravaioli et al. 2008; Chapman et al. 2008; Otto et al. 2006; Graziadei et al. 2003; Bova et al. 2013; Jang et al. 2010; Lei et al. 2013a). The issue of downstaging HCC was discussed in the international consensus conference on liver transplantation for HCC held in Zurich, Switzerland, in December 2010. The goal of downstaging was identified as the use of any method (TACE, alcohol injection, radioembolization, or RFA) in an attempt to decrease the size and number of tumors in patients who present with HCC that do not fit the standard criteria used for transplantation (Clavien et al. 2012). The committee concluded that (1) the criteria for successful downstaging should include the size and number of viable tumors, (2) alpha-fetoprotein level before and

after downstaging may provide more information and should be collected, and (3) there is no evidence that one method of locoregional therapy is better than others in achieving downstaging of HCC (Clavien et al. 2012).

The main problems with the concept of downstaging reside in identifying patients who should undergo downstaging, defining the end points of successful downstaging and deciding on a reasonable time frame before listing for transplant. There is no consensus in the literature regarding selection of patients for downstaging HCC. This is clearly reflected in the inclusion criteria in the abovementioned series. Most of the series did not have an upper limit regarding selection (Barakat et al. 2010; DeLuna et al. 2009; Chapman et al. 2008; Otto et al. 2006; Graziadei et al. 2003; Jang et al. 2010). Others like Yao et al. and Ravaioli et al. used a combination of tumor size and number of tumors as selection criteria for inclusion (Yao et al. 2008; Ravaioli et al. 2008). Recently Pomfret et al. suggested that patients who had one tumor less than or equal 8 cm or 2–3 tumors each less than or equal to 5 cm with a total tumor diameter less than or equal to 8 cm should be eligible for downstaging (Pomfret et al. 2010). Others have suggested total tumor volume of less than or equal to 250 cc to be the only criterion for inclusion (Toso et al. 2010). The major caveat in these selection criteria is the fact that they do not address tumor biology as a factor. Neither tumor differentiation nor AFP level was included as selection criteria. This might result in denying patients who have good biology from receiving treatment based on morphology alone. Another topic that is important when addressing downstaging protocols is defining the meaning of successful downstaging. To date, most of the series used MILAN criteria as the sole marker for successful downstaging (Yao et al. 2008; DeLuna et al. 2009; Ravaioli et al. 2008; Chapman et al. 2008; Jang et al. 2010). Others reported a 30–50 % decrease in size of the lesions as adequate response (Graziadei et al. 2003). This was mainly dependent on amount of viable tumor left. Lesions that were rendered avascular and did not show contrast enhancement on CT scan were not considered viable and did not affect selection. The time frame used before enlisting patients who underwent successful downstaging for transplant is another topic of debate. Most of the reports use 3 months as a minimum period of observation before enlisting patients. In reality, however, patients wait an average of 6 months before being transplanted according to most series (Sharr et al. 2014). Patients who develop recurrence or distant metastasis during that time are not listed. This allows for further selection of patients with favorable biology.

As a conclusion, patients who have tumors less than or equal to 8 cm in maximum diameter or a total tumor volume of less than 250 cc should undergo downstaging based on the present data. Those who respond to treatment and subsequently fall within the MILAN criteria should be listed for liver transplant after they complete a 6-month period without progression of disease.

Methods Used for Downstaging

Several treatment modalities can be used as downstaging procedures for hepatocellular carcinoma. These include transarterial chemoembolization (TACE), transarterial radioembolization (TARE), radiofrequency ablation (RFA), ethanol alcohol injection, high-intensity focused ultrasound, and surgical resection. The two most common procedures used in the literature are TACE and RFA. RFA has replaced the use of ethanol alcohol injection at most large centers; the use of a particular method is dependent on several factors including tumor size, tumor number, tumor location, and the degree of liver function and cirrhosis. Risks and benefits are taken into account when suggesting one form of treatment over the other including risk of liver failure.

TACE is the most common method utilized in downstaging in the literature (Sharr et al. 2014; Yao et al. 2008; Otto et al. 2006). It includes transarterial injection of cisplatin or Adriamycin along with embolization with gel particles to the side of the liver that suffers from HCC. It is

relatively contraindicated in the setting of portal vein thrombosis. It allows for treatment of patients who have large tumor size or multiple tumors within the same lobe or different lobes. Its use is however restricted to patients who have adequate liver function due to increased risk of liver failure especially when treating a large area of the liver. Post-chemoembolization syndrome has been described where patients present with abdominal pain and fever due to a large area of necrosis.

RFA uses radiofrequency energy for hyperthermic ablation. It is usually best used for lesions that are less than or equal to 3 cm in largest dimensions. It results in 90 % tumor necrosis and has replaced ethanol alcohol injection recently. RFA is usually avoided when tumors are at the surface of the liver due to risk of rupture and when lesions are close to biliary structures due to risk of heat-induced injury (Rossi et al. 1996; Buscarini et al. 2001). Ascites should be drained before the use of RFA (Rossi et al. 1996; Buscarini et al. 2001).

Transarterial radioembolization (TARE) is another method used for downstaging of HCC. It is performed using insoluble glass beads coated with the beta-emitter Yttrium-90 (Y-90). The beta particles cause local necrosis of the tumor (Salem et al. 2002). It is well tolerated and can lead to early discharge of patients post procedure. Patients usually complain of flu-like symptoms and fatigue. The main advantage is that it can be performed in the setting of portal vein thrombosis. Before undergoing TARE, excessive intrahepatic blood shunting should be ruled out to avoid radiation injury to the patient's lungs. Complications associated with TARE are similar to those seen with TACE with biliary strictures and hepatic failure being rare but serious problems.

A very interesting concept is the use of surgical resection as a downstaging modality before LT for patients suffering from advanced HCC (Majno et al. 2000; Belghiti et al. 2003; Adam et al. 2003; Adam and Azoulay 2005; Gamblin and Geller 2005). This concept has been popularized by Poon et al. who noted that 80 % of patients who recur after resection continue to be eligible for liver transplantation (Poon et al. 2002). It is usually proposed for patients with reserved liver function. This allows for utilization of liver transplant as a "salvage" treatment. Its main advantage is that it allows to compensate for the prolonged time on waiting lists and the shortage of organs. It also allows for the selection of patients who will benefit the most from LT, i.e., patients with better biology. The main argument against this strategy is the fear that prior liver resection will affect the morbidity of the transplant operation and decrease the survival post liver transplant. Adam reported his series of 358 patients with HCC who underwent liver resection ($n = 163$) or transplantation ($n = 195$) (Adam et al. 2003). He first compared the outcomes of patients who received secondary LT (salvage) for recurrence ($n = 17$) with those who underwent primary LT ($n = 195$). Second, he compared the outcomes of patients who were originally transplantable but underwent liver resection ($n = 98$) with those who underwent LT directly ($n = 195$). He reported that operative mortality for secondary LT was higher than primary LT (29 % vs 2 %, $p < 0.001$). Posttransplant disease-free survival and a 5-year overall survival were lower with secondary LT versus primary LT, respectively (29 % vs 58 % $p = 0.003$; 41% vs 61 % $p = 0.03$). On the contrary, Belghiti et al. reported their experience with 80 patients who underwent primary LT for HCC and compared them to 18 patients who underwent LT after resection (secondary LT or salvage LT) (29). Perioperative outcomes including operative time, operative blood loss, hospital stay, morbidity, and mortality were comparable between both groups (Belghiti et al. 2003). Three- and five-year survival after LT was similar in both groups (82 % vs 82 % and 59 % vs 61 %, respectively). He concluded that in selected patients liver resection prior to LT does not increase morbidity of the transplant procedure itself or decrease long-term survival after it. One of the major disadvantages of liver resection followed by salvage LT in the setting of recurrence is that patients who receive liver resection will lose the bonus points on the MELD score that are allocated to patients with stage II HCC and thus their priority on the waiting list (Sala et al. 2004).

Results

Several authors have reported their experience with downstaging patients with HCC outside current transplant criteria (Table 1). Most of the authors included patients who were beyond the MILAN criteria for downstaging (Barakat et al. 2010; DeLuna et al. 2009; Lewandowski et al. 2009; Chapman et al. 2008; Otto et al. 2006; Graziadei et al. 2003; Bova et al. 2013; Jang et al. 2010). Methods used for downstaging included RFA, TACE, TARE, ethanol alcohol injection, or a combination of treatments, with TACE being the most commonly used method. In most series, the goal of downstaging was to shrink the tumor to within the MILAN criteria. Two series, Otto et al. and Graziadei et al., used a decrease in size between 30 % and 50 % as reflection of adequate downstaging. In all series, only viable tumor was considered after downstaging (Otto et al. 2006; Graziadei et al. 2003).

The percentage of patients who underwent successful downstaging in the previously mentioned

Table 1 Selected series on downstaging HCC before OLT

References	Pts	Inclusion criteria	Exclusion criteria	Downstaging treatment	Criteria to downstage
Lei et al. (2013)	112	Beyond MC, within UCSF	NS	CE, RFA, resection, HIFU	To within MC
Bova et al. (2013)	48	Beyond MC	>65 years, metastasis	TACE, TAE	To within MC + AFP <100 ng/mL
Barakat et al. (2010)	32	Beyond UCSF (18pts), beyond MC (14pts)	Macrovascular invasion, metastasis	TACE, TARE, RFA, resection	To within UNOS T2 criteria
Jang et al. (2010)	386	Beyond MC	Bilirubin >3 mg/dL, albumin <2.8 g/dL, PT >50 %, macrovascular invasion, metastasis	TACE	To within MC
Lewandowski et al. (2009)	86	UNOS T3	Portal vein thrombosis, metastasis	TACE	To within MC
DeLuna et al. (2009)	27	Beyond MC	>70 years, metastasis, portal vein thrombosis, tumor burden > 8 cm	TACE	To within MC
Chapman et al. (2008)	76	Beyond MC	NS	TACE	To within UNOS T2 criteria
Yao et al. (2008)	61	1 HCC 5–8 cm; 2 HCCs 3–5 cm, total diameter ≤8 cm; 4–5 HCCs ≤3 cm, total diameter ≤8 cm	Single lesion >8 cm, >5 lesions, total tumor diameter >8 cm, macrovascular invasion	TACE, RFA, resection	To within UNOS T2 or total tumor necrosis
Ravaioli et al. (2008)	48	1 HCC 5–8 cm; 2 HCCs 3–5 cm, total diameter ≤8 cm; 3–5 HCCs ≤4 cm, total diameter ≤12 cm	Macrovascular or biliary invasion	TACE, RPEI, RFA, resection	To within MC + AFP <400 ng/mL
Otto et al. (2006)	62	Beyond MC	Metastasis	TACE	Decreased size ≥30 %
Graziadei et al. (2003)	36	HCC ≥5 cm	Macrovascular invasion, metastasis	TACE	Decreased size ≥50 %

Table 2 Outcomes of OLT after downstaging for HCC

References	Pts	Downstaged pts (%)	Transplanted pts (%)	Recurrence-free survival after LT	Absolute survival after LT
Lei et al. (2013)	112	58 (52)	58 (100)	64 % at 5 years	70 % at 5 years
Bova et al. (2013)	48	19 (39)	9 (47)	Recurrent HCC: 1 pt (11 %)	NS
Barakat et al. (2010)	32	18 (56)	14 (78)	Recurrent HCC: 2 pts (14 %)	75 % at 2 years
Jang et al. (2010)	386	160 (41)	37 (23)	66 % at 5 years	55 % at 5 years
Lewandowski et al. (2009)	86	36 (42)	20 (56)	TACE 73 % at 1 year, TARE 89 % at 1 year	N/A
De Luna et al. (2009)	27	17 (63)	15 (88)	N/A	79 % at 3 years
Chapman et al. (2008)	76	18 (24)	17 (94)	50 % at 5 years	94 % at 5 years
Yao et al. (2008)	61	43 (70)	35 (81)	92 % at 2 years	92 % at 2 years
Ravaioli et al. (2008)	48	32 (67)	32 (100)	71 % at 3 years	62 % at 3 years
Otto et al. (2006)	62	34 (55)	27 (79)	68 % at 5 years	73 % at 5 years
Graziadei et al. (2003)	36	15 (42)	10 (67)	Recurrent HCC: 3 pts (30 %)	41 % at 4 years

series ranged between 24 % and 70 % (Table 2). The proportion of patients who were downstaged and then transplanted ranged from 23 % to 100 %. The average wait period from initiation of downstaging to OLT ranged between 2 and 11 months. Recurrence-free survival after downstaging and OLT was approximately 65 % at 5 years in most of the series. The overall survival rate ranged from 79 % to 90 % and from 55 % to 94 % at 3 and 5 years, respectively. Four studies (DeLuna et al. 2009; Chapman et al. 2008; Otto et al. 2006; Lei et al. 2013) did not report any significant difference in overall or disease-free survival in patients who were transplanted after downstaging and those who received transplant directly. Chapman et al. reported on 76 patients with stage III/IV HCC who received TACE as a downstaging modality before OLT. 18 patients were downstaged to within the MILAN criteria and of those 17 patients underwent OLT. 94 % of patients were alive at a median of 19.6 month. Only one patient sustained a recurrence in the lungs that was resected and was alive 63 months after OLT. They concluded that patients with advanced HCC that are successfully downstaged have excellent midterm and disease-free survival after OLT and are similar to stage II HCC (Chapman et al. 2008).

Yao et al. reported on 61 patients with HCC who did not meet traditional criteria for transplantation. Patients were treated with TACE, RFA, ethanol injection, or a combination of those modalities. Patients were considered to be eligible for OLT if after treatment they had either one tumor greater than 5 cm but less than 8 cm or two to three tumors with one lesion greater than 3 cm but less than 5 cm and total tumor diameter not exceeding 8 cm or four to five lesions with none greater than 3 cm with a total tumor diameter not exceeding 8 cm. All patients had to be observed for 3 months before OLT. 43 patients (70 %) were successfully downstaged. Of those, 35 patients (81 %) underwent LT. The posttransplant 1- and 4-year survival was 96 % and 92 %, respectively. At a follow-up period of 25 months, no patients had posttransplant recurrence. The authors concluded that in selected patients downstaging of HCC can be achieved and is associated with excellent posttransplantation outcomes (Yao et al. 2008).

Along the same line of thought, DeLuna et al. in 2009 studied 122 patients with HCC who received transarterial chemo-infusion either as a bridge or as a downstaging modality before OLT. 27 patients did not meet the MILAN criteria and were considered for downstaging with TACI.

17 patients (63 %) were successfully downstaged to meet the MILAN criteria. Of those, 15 patients (88 %) underwent LT. The overall survival after LT was 79 % at 3 years. There was no difference in post LT outcomes between patients who originally met the MILAN criteria and those who did not. No factors associated with downstaging were identified in this series (DeLuna et al. 2009).

In an attempt to identify factors that successfully predict downstaging in patients with advanced HCC, Barakat et al. studied 32 patients with advanced HCC who underwent locoregional therapy as a method of downstaging including TACE, radioembolization, RFA, or a combination of those modalities. 18 (56 %) patients were successfully downstaged and 14 (78 %) of them were transplanted. 92 % and 75 % of the patients were alive at 1 and 2 years, respectively, after OLT. After a median follow-up period of 35 months, only 2 patients had tumor recurrence after OLT. He concluded that the only factor that predicts successful downstaging and improved outcome in patients with advanced HCC on both univariate and multivariate analyses is the presence of non-infiltrative expanding type of HCC (Barakat et al. 2010). Similarly, Bova et al. attempted to identify factors that predict successful downstaging. He studied 227 patients who received intra-arterial chemotherapy for treatment of HCC. He was able to identify 80 patients who originally did not meet criteria for transplantation. He excluded patients with infiltrative-type HCC, hypovascular HCC, and portal vein thrombosis. 48 patients were included in the final analysis. Reduction in the number and size of viable tumors within the MILAN criteria and presence of serum AFP level of 100 ng/ml for 6 months were considered as criteria for successful downstaging. 19 (39 %) patients were successfully downstaged, of which 9 (47 %) underwent LT. At a median follow-up of 40 months, 8 of the 9 patients did not have HCC recurrence. When identifying factors that were associated with successful downstaging, only a serum AFP level of 100 ng/ml and a high 3-year calculated survival using the "Metroticket" calculator were good predictors of response after intra-arterial chemotherapy in patients with advanced HCC (Bova et al. 2013).

Lewandowski et al. in 2009 reported his series of 86 patients who underwent downstaging of HCC with either transarterial chemoembolization (TACE) or transarterial radioembolization with Y-90 (TARE) (Lewandowski et al. 2009). Downstaging was successful in 36 (42 %) patients using either modality. 20 (55 %) of the downstaged patients underwent liver transplant. When comparing TACE to TARE, they found that the number of patient who were successfully downstaged was higher with TARE than TACE (58 % vs 31 % $p = 0.023$). For TACE patients, overall survival censored to radical therapies (transplantation/resection) at 1, 2, and 3 years was 73 %, 28 %, and 19 %, respectively (median: 18.7 months); it was 77 %, 59 %, and 45 % for TARE-Y-90 (median: 35.7 months) ($p = 0.18$). For TACE, overall survival without censoring to radical therapies (transplantation/resection) at 1, 2, and 3 years was 75 %, 42 %, and 19 % (median: 19.2 months); it was 81 %, 69 %, and 59 % for TARE-Y-90 (median: 41.6 months) ($p = 0.008$) (Lewandowski et al. 2009). The author concluded that TARE seems to "outperform" TACE as a method for downstaging of patients from UNOS T3 to UNOS T2 stage (Lewandowski et al. 2009).

Only one series showed worse survival in downstaged patients after liver transplant when compared to patients who fit the MILAN criteria on presentation (Graziadei et al. 2003). The actuarial survival rate of the group who had successful downstaging was significantly lower in the intention to treat as well as the post-OLT analyses with a 1-, 2-, and 5-year survival rate of 93 %, 78 %, 31 % vs 97.8 %, 97.8 %, and 94 % in patients who fit the MILAN criteria ($p < 0.001$), respectively (intention to treat), and 82 %, 55 %, 41 % versus 97.2 %, 93.8 %, and 93.8 % (post-OLT), respectively ($p < 0.001$) (Graziadei et al. 2003).

Discussion

Management of HCC has undergone multiple developments over the past few years with OLT being the most durable option at this time for small unresectable HCC (Mazzaferro

et al. 1996). Selection criteria for OLT are currently very strict (MILAN) and result in several patients being disapproved for transplant. These also do not take into consideration the biology of the tumor as a critical factor in affecting outcome. When analyzing the landmark article by Mazzaferro et al. that established OLT as a valid and durable option for management of small HCC, 27 % of patients were found to have a tumor load greater than MILAN criteria upon pathologic review. Furthermore, 40 % had microvascular invasion and 14 % had poorly differentiated tumors (Mazzaferro et al. 1996). Downstaging allows for patients who do not fit the MILAN criteria to be considered for transplant if they sustain a good response. It also allows for selection of those patients who carry a favorable biology but poor morphology. Currently there is no evidence in the literature that patients who respond to downstaging protocols do worse than patients who originally where eligible for transplant without any intervention. Actually in most of the reported series, the posttransplant outcomes are similar between both groups with a 5-year overall survival reaching up to 94 % and a 5-year disease-free survival up to 75 % (Chapman et al. 2008; Otto et al. 2006; Jang et al. 2010). Lie et al. further suggested that patients who undergo liver resection after downstaging have comparable outcomes to patients who undergo liver transplant after downstaging with overall patient survival rates at 1, 3, and 5 years of 87.1 %, 80.6 %, and 77.4 %, respectively, after LT and 91.4 %, 77.1 %, and 68.6 %, respectively, after LR ($P = 0.498$) (Lei et al. 2013). The overall 1-, 3-, and 5-year tumor recurrence-free rates were also comparable ($P = 0.656$). The only factors associated with higher tumor recurrence were poorer tumor differentiation and a post-downstaging AFP of greater than 400 ($p = 0.041$ and $p = 0.015$, respectively) (Lei et al. 2013).

Conclusion

Downstaging is a reasonable method for treatment of patients who present with unresectable HCC that do not fit the criteria for initial liver transplantation. It is useful in selecting patients with favorable biology that would otherwise not receive OLT. There is currently no evidence in the literature to suggest that patients who are downstaged and receive OLT do worse than patients that present within transplant criteria, a notion that should drive surgeons and hepatologists to invest more time and effort in exploring this topic and the underlying concept of favorable tumor biology as a factor that predicts outcome. Standard criteria for selection, definition of downstaging, and time to enlistment should be developed.

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Systemic Chemotherapy in Orthotopic Liver Transplantation

18

Jascha Rubin and Ashwin Sama

Contents

Abstract

The management of hepatocellular carcinoma (HCC) is complex, requiring a multidisciplinary approach with surgeons, hepatologists, medical oncologists, radiation oncologists, and interventional radiologists. Patients with HCC often have concurrent liver disease, further complicating their management. Options for therapy range from potentially curative resection and orthotopic liver transplantation (OLT), local ablative therapies, trans-arterial embolization, and systemic therapy. A number of treatment algorithms have been developed to aid in the management of HCC, including the Barcelona Clinic Liver Cancer (BCLC) staging system. This model incorporates liver function, performance status, and tumor characteristics. It also includes treatment recommendations based on BCLC stage. Included in the algorithm is OLT for eligible patients with early stage disease, and sorafenib as systemic therapy for advanced stage disease. It does not, however, include recommendations about the combination of these two treatments. This chapter will review literature for the use of systemic therapy combined with OLT for HCC, as well as for the use of systemic therapy in the event of relapse after OLT. Additionally, a review of systemic therapy in combination with OLT for cholangiocarcinoma and neuroendocrine tumors is included.

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Introduction

Compared with surgical excision and local therapies, OLT for HCC is associated with improved overall survival and long term disease-free survival (Bismuth et al. 1993). OLT has the added benefit of restoring normal liver function and replacing the cirrhotic liver which is predisposed to formation of new tumors. While this approach is promising, it does have a number of limitations. First and foremost, the eligibility is limited to a highly selected population, as defined by the Milan Criteria. The vast majority of patients with HCC do not qualify for OLT, and the ones who do often progress beyond the Milan criteria while on the waiting list for a donor liver. Furthermore, the rate of HCC recurrence after OLT has been estimated to be between 15 and 20 percent (Welker et al. 2013). This may be a result of surgical manipulation of cancer cells during transplantation, or the presence of micro-metastatic disease at the time of transplantation. The risk of recurrence is compounded by immunosuppression required after OLT which favors tumor growth. In a case-control study that reviewed HCC tumor doubling time (TDT), patients on immunosuppressive medications had a TDT as much as three times quicker than those with intact immune systems (Yokoyama et al. 1991). Currently the most commonly utilized algorithm for the management of HCC is the Barcelona Clinic Liver Cancer (BCLC) staging system, which is endorsed by American Association of Study of Liver Disease (AASLD) (European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer 2012) and European Association for the Study of the Liver (EASL) (Llovet et al. 2008a). This model incorporates liver function determined by the Child-Pugh score, the Eastern Cooperative Oncology Group (ECOG) performance status, and tumor characteristics including size, number, portal invasion, nodal status, and metastasis. It also includes treatment recommendations based on BCLC stage (Forner et al. 2010). Absent from this model are clear recommendations for the use of systemic therapy as an adjunct to OLT. Clearly, further risk reduction of recurrent HCC after transplantation is desirable. More aggressive approaches using the combination of systemic therapy and OLT have been investigated, and are reviewed here.

Hepatocellular Carcinoma

Neoadjuvant chemotherapy – that is, treatment given prior to surgery – is an approach used in a variety of cancers, with the aim of reducing tumor burden prior to surgery, lowering the risk of intraoperative spread of tumor and reducing recurrence rates. On the other hand, adjuvant chemotherapy is the chemotherapy given shortly after a surgical resection of a tumor, with the sole purpose of reducing recurrence rates by treating any micrometastatic disease. Together, these modalities of treatment are integral in medical oncology and both have advantages and disadvantages. Neoadjuvant therapy can be started right away, but its side effects could potentially affect transplant eligibility. Adjuvant therapy has to be held until patients recover from the transplant. This section will explore the role of neoadjuvant and adjuvant chemotherapy in the setting of OLT for HCC, as well as treatment options for HCC recurrence after OLT, with the focus primarily on the tyrosine-kinase inhibitor sorafenib.

Chemotherapy

Systemic chemotherapy offers the potential benefit of shrinking a tumor, decreasing recurrence rates, and improving survival without the risks

of an invasive procedure. Unfortunately, the results of studies using cytotoxic chemotherapy for HCC have been disappointing. Response rates in clinical trials have rarely exceeded 20 %, and none have demonstrated a significant survival benefit. Multiple theories account for this lack of efficacy, including a high degree of multidrug resistance, the presence of underlying chronic liver disease limiting treatment options, and impaired hepatic function resulting in the toxicity of standard drug doses (Nowak et al. 2004). Despite this lack of success, systemic chemotherapy has often been used for lack of a better option. Cytotoxic chemotherapy can also variably cause bone marrow suppression and other unwanted side effects, but as these are manageable and rarely fatal, cytotoxic chemotherapy is still widely used (Schwartz and Beutler 2004). A number of small trials prior to 2008 evaluated the use of systemic chemotherapy in the setting of liver transplant, before the approval of targeted therapy for HCC.

The first neoadjuvant trials for HCC prior to OLT implemented various localized therapies to HCC tumors as a means of down-staging patients and achieving transplant eligibility. These methods include transarterial chemoembolization (TACE), radiofrequency ablation, and transarterial radioembolization. Though multiple studies reported favorable outcomes, results of randomized trials have been mixed and have not demonstrated a survival benefit when performed prior to OLT (Huang et al. 2013). These local therapies are often used as bridging and down-staging strategies for HCC. These strategies will not be discussed in this chapter. Studies of chemotherapy have yielded similarly disappointing results. The only neoadjuvant chemotherapy to be studied for patients undergoing OLT for HCC was doxorubicin, an anthracycline that intercalates with DNA. A phase II study, published in the early 1990s assigned 27 patients to receive doxorubicin in three phases: while on the OLT wait list, intraoperatively, and postoperatively (Stone et al. 1993; Holman et al. 1995). The authors noted a 15–20 % objective response rates in prior studies in HCC as their rationale for using doxorubicin. At 6, 12, and 24 month follow up after OLT, survival was 74 %, 61 %, and 49 %, with a 33 % overall recurrence rate. The regimen was well tolerated, with some mild leukopenia and thrombocytopenia. Two subsequent prospective, randomized trials, conducted in Austria and Sweden compared a similar regimen to OLT alone (Pokorny et al. 2005; Soderdahl et al. 2006). These two studies, together, assigned 53 patients to receive pre-, intra-, and postoperative low dose doxorubicin. Both of these studies were not able to demonstrate an improvement in disease-free survival or overall survival. Patients with tumors exceeding 5 cm did exceedingly poor, despite the attempt to down-stage the tumors. Thus, low dose doxorubicin cannot be considered a reasonable option for perioperative therapy for HCC undergoing liver transplant, and the Milan criteria remain the ultimate predictor of survival.

Adjuvant chemotherapy alone for HCC following OLT is widely given but has only been evaluated in a handful of small, uncontrolled studies, with mixed results (Table 1). Each trial varied significantly in the type of chemotherapy it implemented. Three studies reported favorable outcomes with adjuvant chemotherapy (Olthoff et al. 1995; Cherqui et al. 1994; De la Revilla et al. 2003). The first of these studies used a combination of 5-fluorouracil, doxorubicin, and cisplatin in 25 patients who had advanced disease. The next study gave mitoxantrone postoperatively to nine patients, though this study included upfront TACE and radiotherapy prior to OLT in its protocol. The last of these studies used doxorubicin alone in ten patients after OLT. All of these studies show better outcomes compared to historical controls. Unfortunately, there have not been any randomized controlled studies confirming these promising results. Two additional studies using different regimens did not demonstrate improved outcomes (Bernal et al. 2006; Hsieh et al. 2008). One study used cisplatin and doxorubicin in 12 patients and the other cisplatin and gemcitabine in 17 patients, all of whom had tumors exceeding the Milan criteria prior to OLT. There did seem to be a slightly improved disease-free survival amongst these patients compared to those with those who underwent OLT for

Table 1 Adjuvant chemotherapy trials for HCC after OLT

Adjuvant trials		
Positive trials	Patients (n)	Outcome
5-fluorouracil + doxorubicin + cisplatin (Olthoff et al. 1995)	25	Survival %: 1 year – 78, 2 years – 55, 3 years – 46
Mitoxantrone (+ TACE before OLT) (Cherqui et al. 1994)	9	3 years survival %: 64
Doxorubicin (De la Revilla et al. 2003)	10	28 month survival %: 68
Negative trials		
Cisplatin + doxorubicin (Bernal et al. 2006)	12	Recurrence in 7 of 12 patients
Cisplatin + gemcitabine (Hsieh et al. 2008)	17	2 years DFS: 56 %

tumors beyond the Milan Criteria, but the overall survival was still poor. A separate study raised questions about the harmful effects of chemotherapy on recurrence of HCV, a common comorbidity in this population (Bassanello et al. 2003). The study showed that HCV recurrence-free survival rates at 12 months was zero percent among those who received chemotherapy with 5-fluorouracil and carboplatin, as compared to 25 % when no chemotherapy was given. Given the lack of prospective, controlled studies, and the concerns of unnecessary toxicity, the addition of adjuvant chemotherapy after OLT should not be considered outside of a clinical trial. It is not known if modern chemotherapy regimens, like pegylated liposomal doxorubin, FOLFOX, S1 or Gemcitabine plus oxalipatin, used with currently available, highly effective, oral HCV therapies can improve outcomes in high risk patients after transplant, and randomized studies are needed.

There have been encouraging results reported from a randomized, phase I/II study in China using the radioimmunologic agent Licartin (Xu et al. 2007). This molecule is a 131-I-radiolabeled murine monoclonal antibody that targets an HCC-specific molecule, HAb18G/CD147. The study assigned 60 patients who had positive immunohistochemical expression of HAb18G/CD147 present on their HCC biopsies to receive three monthly doses of Licartin or a placebo starting 4 weeks after OLT. At 12 month follow up, Licartin significantly lowered the risk of recurrence by 30 %, (27 % vs. 57 %) and improved overall survival by 21 % (83 % vs. 62 %), while maintaining a tolerable side effect profile. Licartin has not yet been studied in phase III clinical trials and further details are not available on its development.

When HCC recurs after OLT, the prognosis is dismal, with an overall survival of only 6 months (Roayaie et al. 2004). No controlled clinical trials have been conducted for patients with recurrence after transplantation. Chemotherapy has been offered for lack of alternative options, though the choice of therapy has been widely variable and mostly arbitrary. A retrospective review of 24 patients who received any form of chemotherapy showed that, while generally tolerable, chemotherapy did not improve any meaningful endpoints (Lee et al. 2009). There remains an unmet need for patients with recurrent HCC after OLT. Sorafenib is commonly used, as discussed below. For patients ineligible to receive sorafenib or who progress on sorafenib, cytotoxic chemotherapy is often used with minimal benefit. These patients are often excluded from clinical trials due to their posttransplant status, although they tend to do well if surgical resection of recurrence can be performed and if the time to recurrence is greater than 24 months (Kornberg et al. 2010). In addition, patients with good synthetic liver function may do well with treatment on clinical trials, although there is no available data to support this.

Immunotherapy has been studied in patients with advanced HCC with conflicting results. A number of controlled trials have evaluated interferon alfa (IFNa) as a monotherapy. The earliest of these was a Chinese study that randomized 75 patients to IFNa or doxorubicin. The study demonstrated slightly improved response rates

and better tolerability of IFNa (Lai et al. 1989). A later trial that randomized 75 patients to IFNa or best supportive care suggested a possible survival benefit for IFNa (Lai et al. 1993). However, a subsequent study was not able to replicate these results, and found IFNa to be associated with significant toxicity (Llovet et al. 2000). IFNa was later studied in combination with chemotherapy. The PIAF regimen cisplatin, IFNa, doxorubicin, and 5-fluorourocil – was found to have moderate activity in HCC, and achieved durable, complete responses in a number of patients (Leung et al. 1999, 2002). PIAF was later studied in a multinational trial in which 188 patients with unresectable HCC were randomized to receive PIAF or doxorubicin monotherapy. This study was not able to detect a significant survival difference, and PIAF was associated with unacceptable toxicity (Yeo et al. 2005). The combination of IFNa and 5-fluorouracil has also been studied with mixed results. This regimen was first evaluated in a phase II study of 43 patients, and an objective response was achieved in 14 patients (Patt et al. 2003). In a separate report of ten patients treated with a similar regimen, there were no measurable responses, but toxicity was considerably high (Stuart et al. 1996). However, the patients in this series received nearly twice as much IFNa as did the patients in the initial study, suggesting that the efficacy and toxicity of this regimen may be dosedependent. Interferon has been used to treat HCV recurrence after transplant although its use is decreasing due to availability of better tolerated oral regimens. The use of immunotherapy has not been evaluated as an adjuvant therapy after OLT to prevent recurrence of HCC or in treatment of relapsed HCC after OLT. Therefore, this therapy should only be used after OLT in the setting of a clinical trial.

Targeted Therapy

The use of targeted therapies heralded a new era in the management of hepatocellular carcinoma. As mentioned above, cytotoxic chemotherapies have rarely yielded response rates of greater than 20 % and no trial has demonstrated a survival benefit for chemotherapy (Nowak et al. 2004). Sorafenib, an oral inhibitor of VEGFR and Raf, is the only systemic treatment that confers a statistical survival advantage, and has dramatically changed the management of HCC (Hollebecque et al. 2015). To date, it is the only targeted therapy approved by the FDA for HCC, despite multiple phase III trials targeting different pathways including VEGF, PDGFR, FGFR, EGFR, and mTOR (Table 2) (Abou-Alfa and Venook 2013; Harding and Abou-Alfa 2014). There are other targeted therapies currently under clinical trials exploring a host of cellular targets, including MET, MEK, arginine, and immune checkpoint inhibitors target (Table 3) (Hollebecque et al. 2015).

Sorafenib was studied in the SHARP trial in patients with advanced HCC (Llovet et al. 2008b). In this phase III study, 602 patients were treated with sorafenib plus placebo or placebo alone. The use of sorafenib improved survival by 30 %, translating to an overall survival of nearly 3 months. This survival was most pronounced in patients with HCV-related cirrhosis. The trial excluded patients with Child-Pugh B and C, raising questions about its efficacy and tolerability in patients with poor liver function. However, The Gideon registry showed that sorafenib could be used safely is subsets of patients with Child-Pugh B cirrhosis (Lencioni et al. 2014). In 2007, Sorafenib was approved by the FDA for systemic therapy for unresectable HCC. The benefit of sorafenib was replicated in the Asia-Pacific study although the magnitude of difference was smaller (Cheng et al. 2009). Several reasons have been postulated including ethnicity, population, etiology of HCC, and underlying liver function (Di Marco et al. 2013). Common side effects of sorafenib include anorexia, diarrhea, weight loss, hand foot skin reaction, hoarse voice and hypertension (Llovet et al. 2008b; Cheng et al. 2009).

The use of sorafenib in the setting of OLT for HCC has not been studied at length. Given its efficacy in unresectable HCC, a number of studies have been conducted exploring the role of

Table 2 Completed Trials in Targeted Therapy for HCC

Trial	Targets	Trial phase	Line of treatment	Patients (*n*)	TTP (in months)	OS (in months)
Sorafenib versus placebo (SHARP) (Llovet et al. 2008b)	VEGFR, PDGFR Raf kinases	III	1st	Sorafenib (n = 299) Placebo (n = 303)	5.5 versus 2.8; HR = 0.58 (95 % CI, 0.45–0.74); $p > 0.001$	10.7 versus 7.9; HR = 0.69 (95 % CI, 0.55–0.87); $p = 0.00058$
Sorafenib versus placebo (Asia–Pacific) (Cheng et al. 2009)	VEGFR, PDGFR Raf kinases	III	1st	Sorafenib (n = 150) Placebo (n = 76)	2.8 versus 1.4; HR = 0.57 (95 % CI, 0.42–0.79); $p = 0.0005$	6.5 versus 4.2; HR = 0.68 (95 % CI, 0.50–0.93); $p = 0.014$
Brivanib versus sorafenib (Johnson et al. 2013)	VEGFR-2	III	1st	Brivanib (n = 577) Sorafenib (n = 578)	4.1 versus 4.2; HR = 1.01 (95 % CI, 0.88–1.16); $p = 0.8$	9.5 versus 9.9; HR = 1.05 (95 % CI, 0.94–1.23); $p = 0.31$
Sunitinib versus sorafenib (Cheng et al. 2013)	PDGFR, VEGFR, CD117, RET	III	1st	Sunitinib (n = 530) Sorafenib (n = 544)	3.8 versus 4.1; HR = 1.13 (95 % CI, 0.98–1.31); $p = 0.16$	7.9 versus 10.2; HR = 1.30 (95 % CI, 1.13–1.5); $p = 0.001$
Linifanib versus sorafenib (Cainap et al. 2015)	RTK, VEGF, PDGF	III	1st	Linifanib (n = 517) Sorafenib (n = 518)	5.4 versus 4.0; HR = 0.76 (95 % CI, 0.64–0.89); $p > 0.001$	9.1 versus 9.8; HR = 1.04 (95 % CI, 0.89–1.22); p = NS
Dovitinib versus sorafenib (Cheng et al. 2015)	FGFR VEGFR and PDGFR	II	1st	Dovitinib (n = 82) Sorafenib (n = 83)	17.6 weeks versus 17.9 weeks	34.6 weeks versus 36.7 weeks HR = 1.27 (95 % CI, 0.89–1.80)
Ramucirumab versus placebo (Zhu et al. 2014b)	VEGFR-2	III	2nd	Ramucirumab (n = 283) Placebo (n = 282)	HR = 0.59 (95 % CI, 0.49–0.72); $p = 0.0001$	9.2 versus 7.6; HR = 0.866 (95 % CI, 0.72–1.05); $p = 0.14$
Brivanib versus placebo (Llovet et al. 2013)	VEGFR-2	III	2nd	Brivanib (n = 263) Placebo (n = 132)	4.2 versus 2.7; HR = 0.56 (95 % CI, 0.42–0.78); $p = 0.001$	9.4 versus 8.2; HR = 0.89 (95 % CI, 0.69–1.15); $p = 0.33$
Everolimus versus placebo (Zhu et al. 2014a)	mTOR	III	2nd	Everolimus (n = 362) Placebo (n = 184)	3.0 versus 2.6; HR = 0.93 (95 % CI, 0.75–1.15); p: NA	7.6 versus 7.3; HR = 1.05 (95 % CI, 0.86–1.27); $p = 0.67$
Sorafenib + erlotinib versus sorafenib + placebo (Zhu et al. 2015)	VEGFR, EGFR	III	1st	Sorafenib + erlotinib (n = 362) Sorafenib + placebo (n = 358)	3.2 versus 4.0; HR = 1.13 (95 % CI, 0.94–1.36); $p = 0.91$	9.5 versus 8.5; HR = 0.92 (95 % CI, 0.78–1.1); $p = 0.2$
Tivantonib versus placebo (Santoro et al. 2013)	MET	II	2nd	Tivantonib (n = 71) Placebo (n = 36)	2.7 versus 1.4; HR = 0.43; p = 0.03)	7.2 versus 3.8; HR = 0.38; p = 0.01)
Selumetinib (O'Neil et al. 2011)	MEK	II	2nd	n = 17	Median 8 weeks	

sorafenib prior to OLT as a "bridging therapy," postoperatively as an adjuvant therapy to decrease recurrence rates and in the salvage setting of recurrent HCC after OLT.

Though sorafenib clearly improves survival in transplant-ineligible patients with HCC, as shown in two large randomized phase III studies, it does not have dramatic response rates in the form of

Table 3 Ongoing Trials in Targeted Therapy for HCC

Ongoing trials	Target	Line	Trial phase
Lenvatinib versus sorafenib (NCT01761266)	VEGFR-2,3	1st	III
Sorafenib + doxorubicin versus sorafenib (CALGB80802, NCT01015833)	VEGFR, PDGFR, Raf	1st	III
Regorafenib versus placebo (NCT01774344)	VEGFR2, PDGFR, KIT, RET,TIE2 and others	2nd	III
Tivantinib versus placebo (Metiv-HCC, NCT01755767)	MET	2nd	III
Cabozantinib versus placebo (CELESTIAL, NCT01908426)	cMET, VEGFR2	2nd	III
ADI-PEG20 versus placebo (NCT01287585)	Arginine	2nd	III
Refametenib	MEK	1st	II
Ipilumumab	CTLA 4	2nd	I
Nivolumab	PD1	2nd	I

tumor shrinkage. The SHARP and Pan-Asia study had response rate by RECIST to be less than 5 %. Using standard RECIST may not be ideal, in part because of its cytostatic properties, as well as due to necrosis causing tumors to appear larger (Abou-Alfa et al. 2006). In fact, modifications to conventional RECIST have been developed, resulting in the modified RECIST (mRECIST), for a more appropriate assessment of response in HCC trials. mRECIST has been accepted and endorsed by the European Association for Study of the Liver and by the American Association for the Study of Liver Diseases. Using mRECIST in assessing response increases the amplitude of the observed tumor shrinkage and thus a better assessment of a therapeutic effect (Lencioni and Llovet 2010; Edeline et al. 2012). However, response rates with sorafenib are still low despite using mRECIST, and thus sorafenib is not an ideal candidate for neoadjuvant therapy as a monotherapy to downstage tumors prior to OLT. There have been case reports of transplant-ineligible patients initially treated with sorafenib who achieved a rare reduction in tumor burden, allowing them to be listed (Vagefi and Hirose 2010; Adair and Wigmore 2013). However, this is an uncommon outcome. Its most promising use is expected to be seen when used in combination with locoregional therapy, such as TACE, and TARE, and external beam radiation. In patients treated with conventional bridging therapies to the tumor locally, dropout rates from the transplant list can be as high as 50 % (Maddala et al. 2004). The combination is likely to have synergistic effects and is currently being actively studied (Fujiki et al. 2014). There is an ongoing prospective, phase III study entitled HeiLivCa, evaluating this hypothesis. Over 200 patients on the transplant list for HCC are randomized to receive TACE plus sorafenib or TACE alone prior to OLT, with the primary outcome as time-to-progression (Hoffmann et al. 2008). The results of this study are not yet available.

Generally, the goal of neoadjuvant therapy is to achieve tumor shrinkage prior to surgical resection, so as to improve surgical outcomes and limit residual disease. Tumors beyond Milan Criteria, exceeding 5 cm, do benefit from down-staging with TACE or TARE followed by OLT (Huang et al. 2013). As mentioned above, sorafenib does not generally shrink tumors, but it may improve outcomes by lowering the rate of dropout from the transplant list due to progression. An explorative, cost-benefit analysis was performed looking at the potential for improvement in rates of OLT for eligible patients should they receive sorafenib as a bridge to transplant. The authors determined that sorafenib has the potential to increase probability of receiving OLT by 5 % (Vitale et al. 2010). However, the safety of sorafenib prior to OLT has not fully been studied. The criticism of the analysis was that it did not take into consideration the potential for poor surgical outcomes for patients taking sorafenib, which has the potential to complicate wound healing during and after surgery (Finn 2012). A cohort study was performed comparing posttransplant outcomes in ten patients who received sorafenib prior to OLT. Death rates were similar to control patients, but a significantly higher incidence of acute graft rejection and biliary complications were noted in the

treatment group (Truesdale et al. 2011). Conflicting results were reported in a later study that compared 15 patients treated with sorafenib prior to OLT to 64 controls. This study demonstrated no increase in the rate of surgical complications or overall survival (Frenette et al. 2013). At this time there is no convincing data that sorafenib is an effective "bridging therapy" for patients with HCC prior to OLT. There is evidence that it may be safe to transplant patients after having received sorafenib, but data is conflicting. Results from the HeiLivCa study are certainly anticipated.

Limited attention has been given to using targeted therapies after OLT as adjuvant therapy to lower the risk of recurrence in high risk patients. The first study to analyze sorafenib in the adjuvant setting was a retrospective case–control analysis of eight patients who were treated with sorafenib after OLT (Saab et al. 2010). Only one of the eight patients developed recurrent HCC, while four out of eight matched controls recurred. There was a non-statistical 1-year survival advantage for the sorafenib group compared to the control group of 87.5 % and 62.5 % respectively. A subsequent retrospective study in Taiwan found similar positive results (Teng et al. 2012). In this case–control study, five of 17 patients received adjuvant sorafenib within 6 weeks after OLT. The disease-free survival for patients with or without adjuvant sorafenib were 100 % versus 37.5 % at 6 months, 66.7 % versus 9.4 % at 12 months, and 66.7 % versus zero percent at 18 months. Though these studies were small, they did suggest a potential role for sorafenib in the adjuvant setting. A prospective study enrolled seven patients to receive sorafenib after OLT for HCC if their explanted livers revealed tumor burden exceeding the Milan criteria. These patients were compared to 12 similar historical controls who received no adjuvant therapy. Two of seven patients who received sorafenib developed HCC recurrence, as compared to nine of 12 patients in the control group. Sorafenib was determined to be safe as well (Shetty et al. 2014). Larger prospective trials will be necessary to determine whether sorafenib is safe and effective as an adjuvant therapy after OLT for HCC. A large randomized phase II trial is ongoing for high risk patients following liver transplantation (Busuttil 2015).

Another area of concern is the use of sorafenib for recurrent HCC after OLT. As mentioned above, there is an unmet need for therapy these patients. The universal requirement for immunosuppression in this population raises questions about the applicability of the SHARP trial in this setting. A considerable amount of data exists on the safety and of sorafenib while patients are receiving immunosuppressive medicines, with mixed results. The first such study, conducted in Japan, retrospectively analyzed 13 patients who were treated with sorafenib for recurrent HCC (Yoon et al. 2010). Only ten patients were included in the final evaluation. Six of these ten patients achieved stable disease. The median time-to-progression was 2.9 months and OS was 5.4 months. These results are comparable to those found in the SHARP study. Subsequently there have been multiple small studies that have yielded similar results (Teng et al. 2012; Sposito et al. 2013; Pfeiffenberger et al. 2013; Waghray et al. 2013). The first of these studies was a case–control study in China, wherein sorafenib was used to treat six patients with recurrent HCC after OLT. OS rates for patients in the palliative and control groups were 66.7 % versus 40 % ($p = 0.248$) at 6 months, 66.7 % versus 40 % ($p = 0.248$) at 12 months, and 50 % versus 20 % ($p = 0.17$) at 18 months, respectively. Another study from Italy compared a cohort 15 patients treated with sorafenib and 24 patients who received the best supportive care. There was a significant difference in median survival after HCC recurrence in the group that received sorafenib with respect to historic controls (21.3 vs.11.8 months: $p = 0.0009$). In a separate retrospective study, 18 patients from Italy and Germany with HCC recurrence were analyzed, eight of whom received sorafenib. There was a slight survival advantage in the sorafenib group. Lastly, a study in America prospectively compared 17 patients who received sorafenib for HCC relapse against 17 patients who were not treated. Survival at 3 and 12 months from recurrence was 100 % and 63 %, respectively, in patients on sorafenib group, and 73 % and 23 %, respectively, in the control group.

A larger prospective cohort study of 26 patients with HCC recurrence after OLT was conducted in Spain (Gomez-Martin et al. 2012). The selected patients were not suitable for surgical resection or locoregional therapy, and their immunosuppressive medication was switched to a mTOR inhibitor. Patients were then treated with sorafenib alone. The rate of disease control was 54 %, the time-to-progression was 6.8 months, and overall survival was more than 18 months. Moreover, the therapy was well tolerated, with expected side effects of sorafenib and mTOR inhibitors.

Despite these promising results, there have been multiple conflicting reports with respect to the safety profile of sorafenib in combination with calcineurin inhibitors (Staufer et al. 2012; Kim et al. 2010; Zavaglia et al. 2013). In a study of 13 patients with recurrent HCC after OLT that received sorafenib, nine patients had to switch their immunosuppressive medication to an mTOR inhibitor, and ten had to stop sorafenib due to significant toxicity. Interestingly, among those who switched to an mTOR inhibitor, one patient achieved a partial response and four achieved stable disease (Staufer et al. 2012). From this, an argument could be made for the use of sorafenib plus and mTOR inhibitor for all patients who recur, though more data is necessary.

Overall, sorafenib is a potentially effective therapy for the treatment of HCC recurrence after OLT. However, if used it must be under close supervision with an experienced oncologist who is equipped to monitor for severe side effects. Randomized studies are needed to confirm safety and efficacy in patients with recurrence posttransplant but are unlikely to be undertaken.

Cholangiocarcinoma

OLT for unresectable cholangiocarcinoma (CCA) offers a potential cure for an otherwise fatal disease. OLT is only indicated for localized, node-negative hilar CCA and CCA arising in the setting of Primary Sclerosing Cholangitis (PSC). Intrahepatic CCA and extrahepatic CCA arising below the bifurcation of the common hepatic duct are not eligible for MELD exception (Gores et al. 2006). Cholangiocarcioma is sometimes found incidentally in patients undergoing OLT for PSC (Meyer et al. 2000). These patients have poor outcomes compared to those without incidental CCA (Patkowski et al. 2014). Patients with CCA and PSC who undergo an OLT may have better outcomes than those without PSC, although data is conflicting.

The use of OLT for known CCA has been evaluated in a number of referral centers, with mixed results. Initial attempts at improving using OLT for CCA were disappointing, with 1, 2, and 5 year survivals of 72 %, 48 %, and 23 %, and a recurrence rate of over 50 % (Meyer et al. 2000). However, the addition of neoadjuvant chemoradiation – that is, radiation given concomitantly with a radio-sensitizing chemotherapy with infusional 5-fluorouracil – prior to OLT in subsequent studies were more successful. The first published experience was of a pilot study of 17 patients at the University of Nebraska (Sudan et al. 2002). Highly selected patients were given continuous daily intravenous 5-fluorouracil while receiving local radiation therapy. Patients then underwent an exploratory laparotomy when a compatible liver became available. Laparotomy was followed by OLT if there was no evidence of advanced disease outside the hepatobiliary system. 11 of the 17 patients qualified for OLT. The median survival of the 11 patients who underwent OLT was 25 months, and five patients were alive and free of any tumor recurrence 2.8–14.5 years after long-term follow up. By far the largest experience using neoadjuvant chemoradiation with OLT was published by the Mayo Clinic (Rea et al. 2005; Rosen et al. 2008; Panjala et al. 2012). Using a similar approach in 148 patients over more than a decade, favorable results were achieved, with 1, 3, and 5 year survival rates of 82 %, 63 %, and 55 %, respectively. This approach was later adopted by a number of referral centers in the United States. After chemoradiation, some centers also give brachytherapy and maintenance chemotherapy until OLT. In a retrospective analysis of the experience at 12 centers, with 193 of the 287 patients coming from the Mayo Clinic, 2 and 5 year survival rates were 68 % and 53 %, respectively. Patients with

tumor mass of 3 cm, transperitoneal tumor biopsy, metastatic disease at transplantation, or a prior malignancy had significantly shorter survival, with tumor size greater than 3 cm being the worst predictor of survival. When stratified by center, results were not as pronounced in patients not treated at the Mayo Clinic, but were still favorable (Darwish Murad et al. 2012). Neoadjuvant therapy with 5-fluorouracil and radiation, with or without brachytherapy followed by oral capecitabine, and exploratory laproscopy to rule out metasatic disease prior to OLT may be a reasonable option for selected patients with unresectable perihilar CCA. However, it should only be offered at highly experienced tertiary centers, with vigorous screening protocols and data collection so that results could be generalizable to other transplant centers as a randomized clinical trial is unlikely to be initiated.

Neuroendocrine Tumors

Metastatic neuroendocrine tumor (NET) to the liver is the only metastatic malignancy for which OLT may be a treatment option. Treatment options for metastatic NET to the liver only include surgical resection, locoregional therapies including ablation, TACE, TARE, chemotherapy, somatostatin analogs, systemic peptide receptor radionuclide therapy, and molecular targeted therapies. OLT is not considered a standard of care and has been studied in only a limited number of patients. Strict criteria have been proposed to determine eligibility for liver transplant (Mazzaferro et al. 2007; Pavel et al. 2012). The largest reported series described 213 patients who received OLT for NET in 35 centers throughout the European countries between 1982 and 2009. At a median follow-up of 5 years, the 1, 3, and 5-year overall survival rates were 81 %, 65 %, and 52 %, respectively. Moreover, disease-free survival rates were 65 %, 40 %, and 30 %, respectively (Le Treut et al. 2013). A later report from the United Network for Organ Sharing (UNOS) database described 137 patients who received OLT for NET between 1988 and 2008. The 1, 3, and 5-year survival rates were 81 %, 65 %, and 49 %, respectively (Gedaly et al. 2011). However, the majority of patients who do undergo OLT for NET will have disease recurrence (Florman et al. 2004). This raises the question of whether OLT is a reasonable treatment for this disease. Immunosuppression to prevent rejection also increases the risk of NET recurrence after OLT. There are no studies evaluating the use of systemic therapy for NET as an adjuvant therapy after OLT or for treatment of recurrent disease after OLT. In the case of recurrence after OLT, care should be taken when extrapolating from literature in the nontransplant setting. Many of the treatments are immunosuppressive and extreme caution should be used when these treatments are given after OLT. There are a number of systemic therapies used for metastatic NET, including somatostatin analogs octreotide and lanreotide, mTOR inhibitor everolimus, VEGF inhibitor sunitinib, alkylator temozolomide, and systemic chemotherapy like streptozocin, doxorubicin, and capecitabine (Strosberg et al. 2011). There is no published data on the best treatment for recurrence of NET after an OLT and treatment has to be individualized.

Conclusion

Systemic chemotherapy and targeted therapy have the potential to improve outcomes in OLT for malignancies by decreasing rates of progression while on the transplant list and by decreasing the rates of recurrence after OLT. Furthermore, systemic therapy may be a reasonable option for relapsed cancer after OLT. The limited available data on the use of such therapy in this setting does not conclusively demonstrate a survival benefit, though the approach is likely safe, with a strong suggestion for benefit. Larger studies are required to demonstrate a significant benefit with the use of systemic therapy before or after OLT, and for relapsed cancer. It is critical that patients who might benefit from adjuvant chemotherapy should be referred for clinical trial at a tertiary center with expertise in such practices.

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Combined Transplantations

19

Pooja Singh and Jerry McCauley

Contents

Abstract

The numbers of simultaneous liver and kidney (SLK) transplantation have increased since introduction of Model for End-Stage Liver Disease (MELD) score for allocation of orthotropic liver transplant (OLT) in February 2002. For OLT candidates with concurrent end-stage kidney failure, SLK transplantation is a well-established indication for suitable candidates. However, there is lack of evidence-based guidelines to determine at what threshold a kidney transplant should be offered simultaneously to those who have chronic kidney disease (CKD) or prolonged acute kidney injury (AKI) while awaiting a liver transplant. Accurate assessment of the degree of existing renal dysfunction can be difficult and estimating progression of established CKD and likelihood of renal function recovery in those with AKI can be challenging. Etiology of renal dysfunction in liver failure patients, burden of CKD after liver transplantation, and usual indications for SLK transplantation are presented in this review. Finally, the UNOS (United Network for Organ Sharing) initiatives to formalize the SLK listing indications are also discussed.

Keywords

Simultaneous Liver kidney transplantation • Acute Kidney Injury • Chronic Kidney Disease • Hepatorenal syndrome

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Introduction

Simultaneous or subsequent renal transplantation in patients with other transplanted organs is becoming progressively common. In 2012, 8.4 % of all deceased donor liver transplants were part of multiorgan transplants with 92 % of these being simultaneous liver and kidney (SLK) transplants as shown in (Fig. 1a, b) (SRTR Annual Report 2012). The transplant community has been motivated to attempt these options due to improvements in immunosuppression possibilities, patient and graft survival. A growing number of patients with previous liver, heart, and bone marrow transplants have subsequently required kidney transplants due to primary renal diseases, glomerular disease associated with viral hepatitis, and most importantly the result of nephrotoxic calcineurin inhibitor-based immunosuppression. This is reflected in Organ Procurement and Transplantation Network (OPTN) data where the kidney listings after liver transplant alone have increased from an average of 200 every year in 2005–2006 to about 250 in the most recent years (Fig. 2) (OPTN data 2014). Annually, about 100–130 subsequent kidneys after liver transplants are being performed (Fig. 3) (OPTN data 2014). Many possible insults to renal function are routinely encountered in patients awaiting vital organ transplantation and in those who are successfully transplanted. Functional renal failure such as hepatorenal syndrome or cardiorenal syndrome is generally expected to improve after transplantation of the primary organ. Likewise, patients with acute kidney injury (AKI) without preexisting renal insufficiency can be expected to regain normal renal function after transplantation but many variables such as duration of AKI, dialysis dependency, recurrent renal insults, and a tumultuous perioperative course can introduce uncertainties and lead to permanent loss of renal function. Based on United Network for Organ Sharing (UNOS) data analysis, the median time to kidney transplant after liver transplantation was 10 years when etiology for renal failure was calcineurin nephrotoxicity, 7 years for hypertensive nephrosclerosis, 6 years for type 2 diabetes, and 2 years for hepatorenal syndrome (OPTN/UNOS Kidney Transplantation Committee Report 2014). The decision to offer a

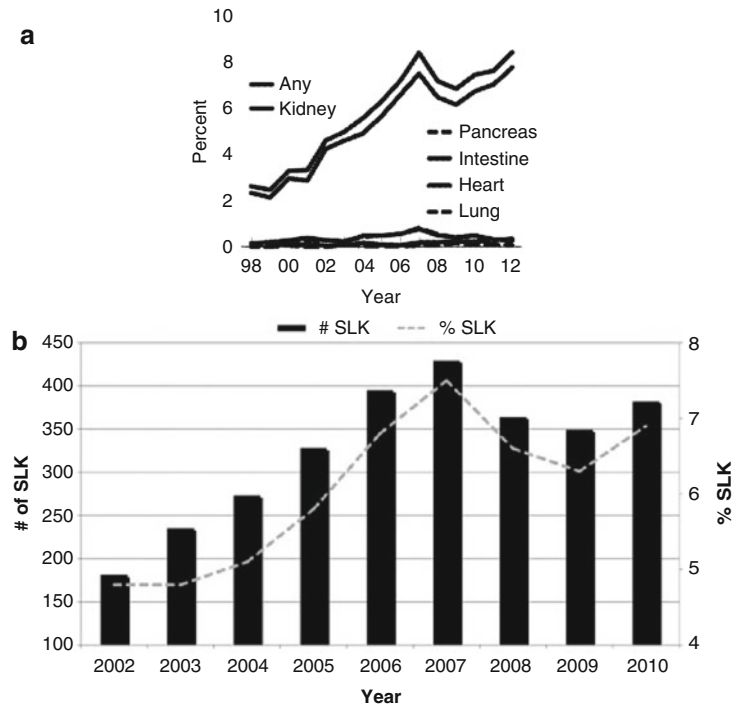

Fig. 1 (**a**) Liver transplants done as part of combined organ transplants (Data from http://srtr.transplant.hrsa.gov/annual_reports/2012/. slide 34 SRTR report liver slides). (**b**) Total number and percentage of simultaneous liver–kidney transplantation (*SLK*) of all deceased donor, adult liver transplantation. Model of the end-stage liver disease (*MELD*) score was implemented in February 2002. Original reference is Data from Organ Procurement and Transplantation Network (*OPTN*) as of June 2011 (http://optn.transplant.hrsa.gov) (This figure is adapted from Nadim et al. 2012)

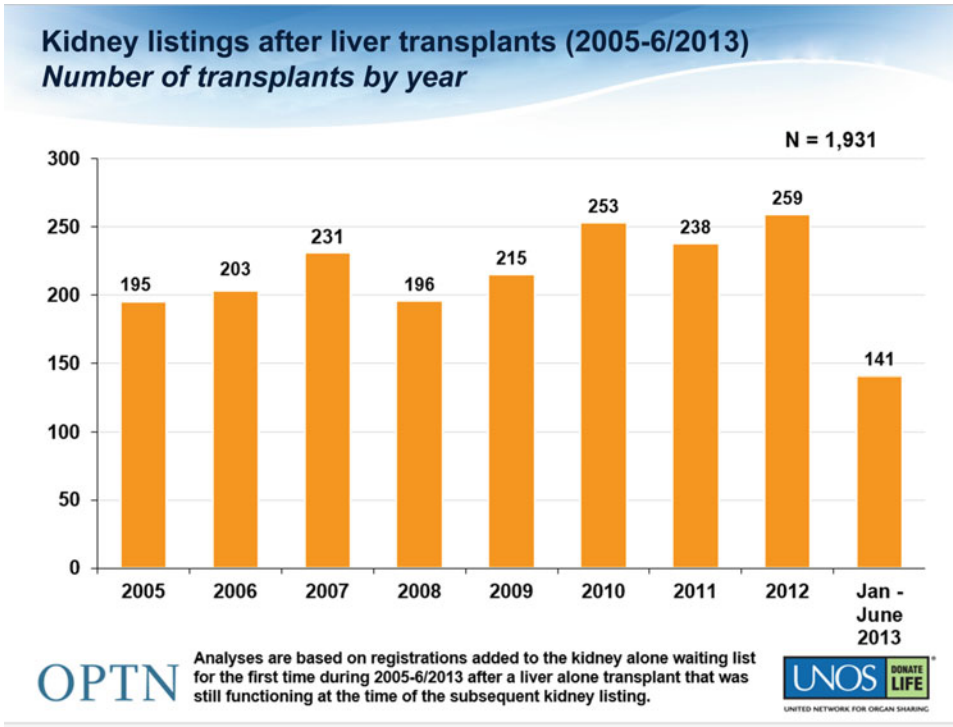

Fig. 2 Kidney listings after Liver Transplants (Data from United network for organ sharing)

simultaneous renal transplant to these patients may vary from a spectrum of being straightforward to quite complex. A thorough investigation into the patient's baseline renal function, chronic kidney disease (CKD) risk factors aided by clinical and radiological investigations can provide some guidance to establishment of permanent renal impairment. However, this can be a challenging exercise since these patients often have reduced muscle mass. The use of serum and urine creatinine-based methods to assess baseline renal function introduces inaccuracies due to underproduction and increased renal tubular secretion of creatinine. The decision to do a renal biopsy to delineate chronicity is not straightforward. Coagulopathy from liver failure or use of anticoagulation in heart failure patients with atrial fibrillation or ventricular assist device (VAD) may increase the risk of complications. Ultimately, determining which patients will require simultaneous renal transplantation in this setting can be difficult.

Estimating Renal Function

The preoperative evaluation of renal function in candidates being considered for simultaneous renal and nonrenal solid organ transplantation should emphasize assessment for a past history of AKI including duration and prior reversibility, risk factors and stage of CKD, and best estimates about anticipated rate of progression of CKD to end-stage renal disease after nonrenal solid organ transplantation. This starts with a detailed history and physical examination, an accurate measure of kidney function, urine studies including urinalysis and urine protein/creatinine ratio, and renal ultrasonography. Based on these results, a renal biopsy and other studies may be considered. If dual listing is pursued, waiting time for both organs is determined primarily by liver or heart allocation algorithm. Therefore, the decision to list for a combined nonrenal and renal transplant should be made very carefully given the profound kidney organ shortage coupled with an increased demand

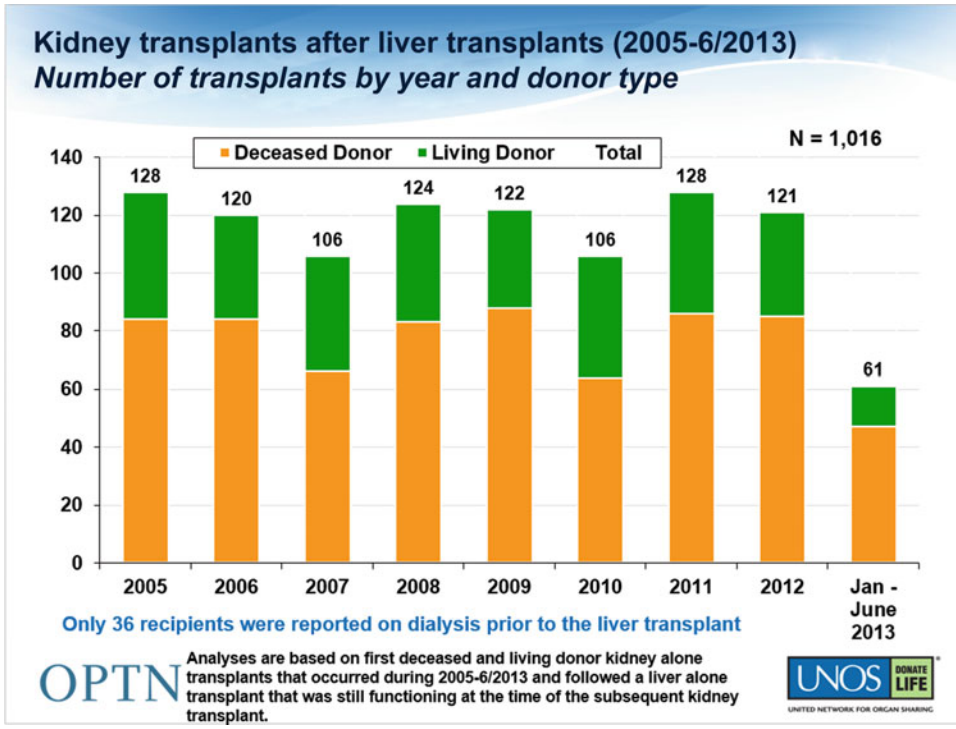

Fig. 3 Kidney transplants after liver transplants (Data from United network for organ sharing)

with already more than 100,000 patients awaiting a renal transplant alone.

Candidates for liver, heart, or small bowel transplantation typically have reduced muscle mass due to underlying advanced organ failure and consequently, low serum creatinine values. Creatinine is derived from the metabolism of creatine produced by skeletal muscle and from dietary meat intake. It is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney. However, approximately 10–40 % of urinary creatinine is derived from tubular secretion by the organic cation secretory pathways in the proximal tubule (Shemesh et al. 1985). Creatinine excretion is usually a good clinical marker of renal function since its reabsorption and secretion as well as total production and excretion are equal under steady state. For normal females, creatinine excretion is 15–25 mg/kg of lean body weight/day and for males it is 20–30 mg/kg of lean body weight per day (Rose 1989). These values are helpful to determine if 24 h urine collections are accurate.

Estimation of glomerular filtration rate (GFR) using 24 h urine creatinine clearance is the most commonly available method used clinically with the caveat that certain prerequisite criteria are met to ensure accuracy: (1) Patients have normal muscle mass for their gender. (2) Serum creatinine is stable. (3) Absence of agents which affect creatinine reabsorption or excretion. (4) The 24 h urine collection is complete. (5) Creatinine is equally reabsorbed and secreted. These criteria are frequently violated in patients awaiting a liver, heart, or small bowel transplant since they have underlying sarcopenia. Therefore a near normal serum creatinine value may not necessarily reflect normal kidney function, especially in states of heart or liver failure where affected patients frequently have poor nutritional status, low muscle mass, weight loss, and edema. Values for urine creatinine less than the lower limit for the patient's gender on a 24 h urine collection usually suggests an undercollection. However, for liver and heart failure patients, it is unusual to find values at or above the lower limit for creatinine excretion due

to reduced creatinine generation. To overcome this problem and increase accuracy, repeat 24 h urine collections should be done and total creatinine excretions that are similar on repeated collections suggest that the collections are at least complete (McCauley 1997). Estimation of GFR is most commonly done in clinical practice based on estimation equations utilizing serum creatinine. Some examples of these include Cockcroft-Gault equation, the Modification of Diet in Renal Disease (MDRD) study equations, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. A recent study using iohexol clearance as the gold-standard measure of GFR in 300 liver transplant candidates confirmed that the six-variable MDRD equation had superior accuracy to the abbreviated MDRD-4 as well as to the CKD-EPI equations in identifying patients with GFR <30 mL/min (Francoz et al. 2014). The OPTN Kidney and Liver Intestinal Organ Transplantation Committees have also recommended using the six-variable MDRD equation for GFR estimation. The *six-variable MDRD equation* is highlighted below:

$$\begin{aligned}\text{eGFR} = {} & 170 \times \text{Serum Creatinine}^{-0.999} \\ & \times \text{Age}^{-0.176} \times [0.762 \text{ if Female}] \\ & \times [1.180 \text{ if Black}] \times \text{BUN}^{-0.170} \\ & \times \text{Albumin}^{+0.318}\end{aligned}$$

(Creatinine and BUN in mg/dl and Albumin in gm/dl)

There are some limitations to using creatinine clearance or serum creatinine-based equations. Overestimation of GFR is commonly encountered in end-stage heart or liver failure since serum creatinine value is falsely low due to underproduction. Overestimation can also happen in chronic kidney disease as the contribution of tubular secretion of creatinine to total creatinine clearance is increased. Some have suggested competitively inhibit creatinine secretion by the administration of cimetidine which blocks the renal tubular secretion, however wide variability in its blocking effect may make interpretation difficult (van Acker et al. 1992). Finally, overestimation is also encountered due to extrarenal creatinine elimination from increased gastrointestinal bacterial overgrowth and increased creatininase activity in advanced kidney failure when estimated GFR falls below ≤15 mL/min/1.73 m^2 (Dunn et al. 1997). Therefore, it is reasonable to conclude that creatinine clearance represents an upper limit of what the true GFR may be in these scenarios. In other scenarios, underestimation of GFR is seen due to spuriously elevated serum creatinine levels. Transient increase in serum creatinine acutely as a result of volume depletion or excessive intake of animal protein intake are the most common circumstances when this happens.

More precise methods of estimating GFR rely on the renal clearance of various radionuclide markers, like 99mTc-labeled diethylene triamine penta-acetic acid (DTPA), 51Cr-labeled ethylenediaminetetraacetic acid (EDTA), and 125I-labeled iothalamate (Tanriover et al. 2008) but have restricted application outside of research protocols due to limited availability and cost.

Defining Acute Kidney Injury and Causes of Renal Disease in Liver Failure Patients

Establishing the cause, severity, and chronicity of pretransplant renal dysfunction is important in patients with liver failure. After liver transplantation, analyzing perioperative events and their influence on renal recovery are equally important. These are some of the questions that need to be answered to help develop selection criteria for SLK candidates. Definitive conclusions regarding long-term outcomes in patients undergoing liver transplantation with or without kidney transplantation with pretransplant renal dysfunction are lacking due to lack of standardized definition of AKI. Accordingly, some have adopted the modified RIFLE (Risk, Injury, Failure, Loss, End stage)/AKIN criteria (Acute Kidney Injury network) in cirrhotic patients (Table 1) to complement research initiatives to define patient outcomes (Mehta et al. 2007). The RIFLE criterion has been validated in over half a million

Table 1 Modified RIFLE/AKIN criteria for definition and classification of acute kidney injury

AKI stage	Serum creatinine criteria	Urine output criteria
1 (Risk)	Increase Scr of ≥0.3 mg/dL within 48 h or a 1.5- to 2-fold increase from baseline	>0.5 mL/kg/h for >6 h
2 (Injury)	Increase Scr >2- to 3-fold from baseline	>0.5 mL/kg/h for >12 h
3 (Failure)	Increase Scr >3-fold from baseline or Scr ≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL or initiation of renal replacement therapy	>0.3 mL/kg/h for 24 h or anuria for 12 h

Original reference for table: Mehta et al. (2007)
Above adapted from Nadim et al. (2012)
RIFLE risk, injury, failure, loss, end stage, *AKI* acute kidney injury, *Scr* serum creatinine

Table 2 Differentiating factors for most common causes of AKI in patients with liver disease

Laboratory parameter	Prerenal azotemia	Hepatorenal syndrome	Acute tubular necrosis
Urinary sodium	<10	<10	>30
Urine/plasma creatinine	>30:1	>30:1	<20:1
Urine/plasma osmolarity	U Osm > P Osm	U Osm > P Osm	U Osm = P Osm
Urine sediment	normal	Unremarkable except bile pigmented casts	Muddy brown casts, cellular debris

Modified from Epstein (1994)

critically ill patients including patients with ESLD and has demonstrated strong concordance for mortality predictions with worsening RIFLE class (Jenq et al. 2007; O'Riordan et al. 2007; Ferreira et al. 2010).

The etiology for AKI is variable in patients with liver disease ranging from prerenal etiology, hepatorenal syndrome, and acute tubular injury before liver transplantation to post-transplant events like CNI-induced nephrotoxicity and tubular injury related to the procedure itself (Table 2). Increased severity of liver failure is marked by increased renal vasoconstriction. Many potential mechanisms are implicated in causing this predisposition such as activation of renal angiotensin system, sympathetic overactivity, and a decrease in vasodilators like prostaglandins and kinins. Hepatorenal syndrome is usually difficult to differentiate from prerenal azotemia but lack of improvement after fluid challenge in hepatorenal syndrome is a differentiating factor. Finally, other postrenal causes such as obstruction can be easily ruled out by obtaining a kidney ultrasound to rule out hydronephrosis. This may also provide information about the size, echogenicity of the kidneys to assess if CKD is present and a Doppler study will rule out renal artery stenosis (McCauley 1997).

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) represents the end stage of a sequence of reductions in renal perfusion induced by increasingly severe liver injury. This is marked by arterial vasodilation in the splanchnic circulation due to overproduction of nitric oxide triggered by portal hypertension. However, the changes in the renal bed are the opposite marked by increase in renal vascular resistance as a result of renin angiotensin activation in response to systemic hypotension (Ginès and Schrier 2009, Wadei et al. 2006). This leads to a reduction in glomerular filtration rate (GFR) as a result of decreased renal perfusion with a concomitant decrease in renal sodium excretion (often to less than 10 meq/day in advanced cirrhosis). Based on the rapidity of onset, two forms of HRS have been described (Ginès and Schrier 2009). *Type 1 hepatorenal syndrome* has a rapid onset, fast progression, characterized by oliguria and twofold increase in serum creatinine to a level greater than 2.5 mg/dL in less than 2 weeks. *Type 2 Hepatorenal* has slower onset, less severe renal impairment, and is clinically marked by diuretic resistant ascites. Often precipitants of this syndrome are gastrointestinal bleeding and spontaneous bacterial peritonitis. Hepatorenal syndrome is a diagnosis of exclusion after other etiologies such as prerenal azotemia, acute tubular injury,

glomerulonephritis, and obstruction are ruled out first. There should also be absence of hematuria and proteinuria in these patients and a lack of improvement in renal function in response to normal saline infusion and/or Albumin administration. Since hepatorenal syndrome is considered a functional form of renal failure, patients will usually recover renal function after liver transplantation; however, they do tend to be sicker than non-HRS patients and may have a greater overall risk of developing ESRD (Gonwa et al. 1995).

Acute Tubular Injury or Necrosis

Usage of nephrotoxic medications, intra-arterial or intravenous iodinated contrast-based studies, and hemodynamic instability from bleeding or sepsis can result in acute tubular injury or necrosis (ATI/ATN). Traditional laboratory parameters used to distinguish ATI/ATN from prerenal azotemia such as fractional excretion of sodium above 2 % in tubular injury and <1 % in prerenal azotemia may not be accurate since it is possible this value may be <1 % in cirrhotic patients who have persistent renal ischemia as a result of hepatic disease (Diamond and Yoburn 1982). The urinalysis also may be misrepresentative since granular and epithelial cell casts may be seen with marked hyperbilirubinemia alone and not necessarily representative of ATN. Post liver transplantation, recovery of ATN can often be delayed due to recurrent renal injury during perioperative period and use of calcineurin inhibitors which promote persistent renal vasoconstriction especially in native kidneys with intact autonomic regulation and therefore lead to delayed regeneration of renal epithelial cells. CNI usage has also been incriminated in inhibiting proliferation of renal epithelial cells in dose-dependent manner (McCauley et al. 1991). Dialysis-dependent acute tubular necrosis pre or post liver transplantation may also be complicated by the bouts of intermittent hypotension occurring during hemodialysis which may impede renal recovery. It is therefore important to maintain mean arterial pressures above 60–65 mmHg and avoid aggressive volume removal over short periods of time on dialysis.

Glomerular Disease and Liver Failure

Many liver transplant patients have liver diseases which may be associated with glomerulonephritis (GN) and chronic renal insufficiency (Table 3). Hepatitis B has been associated with membranoproliferative GN (MPGN), membranous GN, and polyarteritis nodosa (Johnson and Couser 1990, Lai and Lai 1991). Glomerular diseases associated with Hepatitis C virus infection include Mixed cryoglobulinemia, membranous nephropathy, and Polyarteritis nodosa (PAN) (Davis et al. 1994, Misiani et al. 1992). Finally, in liver failure, secondary Ig A nephropathy due to impaired removal of Ig A containing complexes by the Kupffer cells predisposes to Ig A deposits in the kidney (Amore et al. 1994) with deposits also noted in skin and hepatic sinusoids (Van de Wiel et al. 1988). Adults usually have no clinical manifestations of glomerular disease (Pouria and Feehally 1999) while up to one third children may have asymptomatic hematuria or proteinuria (Noble-Jamieson et al. 1992). It is postulated that the lack of symptomatic presentation may be

Table 3 Common causes of AKI and chronic kidney disease in liver failure patients

Glomerular/vascular (acute or chronic)	Hepatitis B and C resulting in membranous or MPGN Type II mixed cryoglobulinemia Secondary Ig A nephropathy Hemochromatosis, sickle cell disease Polyarteritis nodosa
Other causes of acute kidney injury	Prerenal azotemia Acute tubular necrosis (hypotension, sepsis, mushroom poisoning, myoglobin, hemoglobin, bilirubin cast nephropathy, contrast agent) Hepatorenal syndrome
Non cirrhotic liver diseases with CKD	Methylmalonic aciduria Familial non-neuropathic amyloidosis Primary oxalosis Atypical hemolytic uremic syndrome (HUS)
Un related CKD with liver disease	Hypertension Diabetes mellitus

AKI acute kidney injury, *MPGN* membranoproliferative glomerulonephritis

due to absence of concomitant IgG deposition which may minimize activation of complement and other inflammatory mediators (Emancipator 1990). Apparently, restoration of normal hepatic function after liver transplantation is adequate to allow dissipation of these deposits from the kidney and other sites and therefore IgA deposits on renal biopsies before liver transplantation can generally be viewed as a relatively benign finding.

Noncirrhotic Liver Disease and Chronic Kidney Disease

These include metabolic disease such as methylmalonic aciduria, familial non-neuropathic amyloidosis, primary oxalosis, and atypical hemolytic uremic syndrome (HUS). These patients are usually referred for simultaneous liver and kidney transplantation with MELD exception. Primary oxalosis and Atypical HUS are outlined below.

Primary Oxalosis

Primary hyperoxaluria (PH) is a rare autosomal recessive inborn error of glyoxylate metabolism characterized by overproduction of oxalate, which is deposited as calcium oxalate in various organs. The kidney is a principal target for oxalate deposition resulting in recurrent stones and progressive nephrocalcinosis which may progress to ESRD. Type 1 PH accounts for 80 % of all cases and is characterized by decreased or absent activity of hepatic peroxisomal enzyme: alanine glyoxylate aminotransferase (AGT) which leads to increased glyoxalate pool and production of oxalate. When the GFR falls below 30–40 mL/min/1.73 m^2, combination of oxalate overproduction and reduced urinary oxalate excretion results in systemic oxalosis with deposition in the heart, blood vessels, joints, bone, and retina. Combined liver and kidney transplantation has increasingly become the treatment used in patients with PH type 1 with progressive renal disease (Bergstralh et al. 2010) since the transplanted liver provides the missing enzyme. The outcome of simultaneous transplantation is probably best when the procedure is performed as the glomerular filtration rate (GFR) falls to 25 mL/min/1.73 m^2 and prior to marked tissue oxalate deposition.

Atypical Hemolytic Uremic Syndrome

Atypical hemolytic uremic syndrome is often associated with mutations in genes encoding complement regulatory proteins like CFH, CFI, CFB, and C3, which are synthesized in the liver. Progression to kidney failure and recurrence with graft loss after kidney transplantation are frequent. The most common mutation is in the gene encoding complement factor H. Combined liver-kidney transplantation may correct this complement abnormality and prevent recurrence when the defect involves genes encoding circulating proteins that are synthesized in the liver, such as factor H or I (Saland et al. 2009). Good outcomes have been reported when surgery is combined with a regimen for complement regulation such as plasma therapy or use of Eculizumab (Saland 2014). The decision for combined liver-kidney transplantation to provide a permanent cure should be based on an assessment that cautiously weighs the risks and benefits for the individual patient.

Preexisting Chronic Kidney Disease

Patients with end-stage liver disease may develop CKD from causes unrelated to their liver disease. Preexisting CKD is common before liver transplantation (McCauley et al. 1990, Gonwa et al. 1995). Diabetic nephropathy, hypertensive nephrosclerosis, and glomerular diseases not associated with viral hepatitis probably occur at the same frequency as the general population. It is imperative to consider the natural history of specific CKD etiology when deciding to offer a concomitant renal transplant. For those with moderate to severe CKD, kidney transplants should ideally be offered only to patients who are projected to require some form of renal replacement therapy within 3 years of liver transplant (Davis et al. 2002; Pham et al. 2005). It is usually customary that patients with CKD and an eGFR <30 mL/min be listed for combined liver and kidney transplant (Davis et al. 2007; Pham and

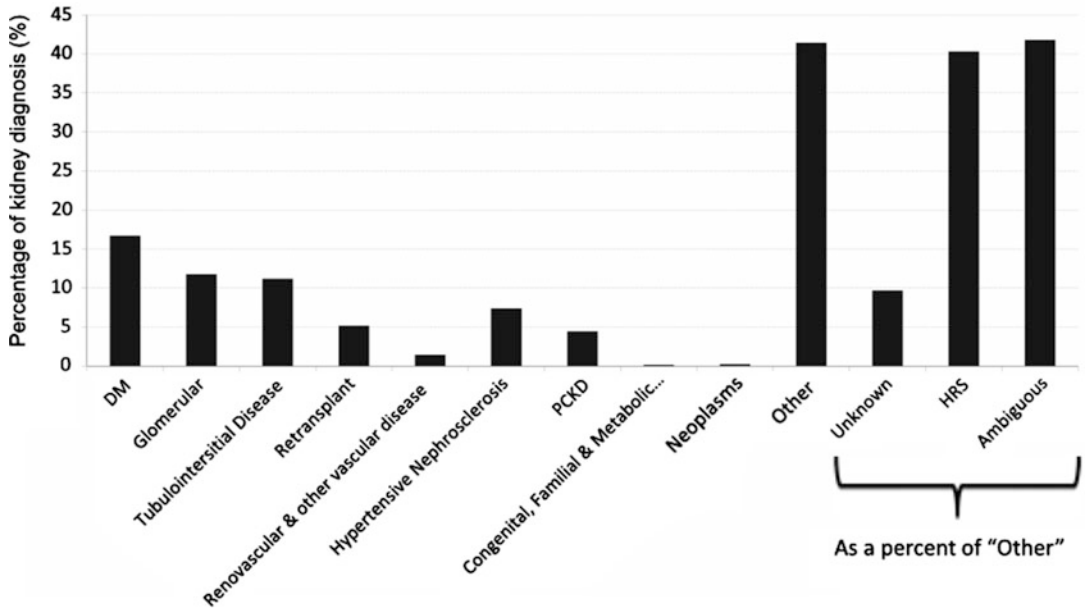

Fig. 4 Most commonly reported etiology for kidney disease in patients receiving simultaneous liver and kidney transplant from 2002 to 2010. Data from Organ Procurement and Transplantation Network (*OPTN*) as of June 2011 (http://optn.transplant.hrsa.gov) (Figure adapted from Nadim et al. 2012)

Wilkinson 2008). Ruebner et al. (2012) provided support for this recommendation by evaluating 4997 liver recipients without known ESRD who were transplanted from 2002 to 2008. The serial eGFRs were calculated from the MELD score in the 90 days prior to transplant. Among recipients whose eGFR were consistently <30 mL/min/1.73 m^2, the proportion of patients with ESRD by 3 years was 31 %, versus less than 10 % for other groups. Figure 4 shows the most commonly reported kidney diagnosis as indication for dual liver and kidney transplantation.

Indications for Combined Liver-Kidney Transplantation

After the first combined Liver-kidney transplantation reported by Magreiter et al. 1984, renal failure was no longer considered a contraindication to Liver transplantation. Liver transplant done singly or as SLK is believed to shield the kidney from rejection. There are many mechanisms postulated for this effect. This could be due to secretion of soluble class I HLA antigens which have the ability to block HLA antibodies and inhibit cytotoxic T lymphocytes (McMillan et al. 1997). Additionally, Kupffer cells have been implicated in phagocytosis of HLA antibodies (Starzl et al. 1994). This immunoprotective effect has helped to overcome both ABO and positive crossmatch incompatibility barriers in liver and SLK (Flye et al. 1990; Fung et al. 1988). For this reason, pretransplant cytotoxic crossmatches are not routinely used for liver transplantation. A report by Fung et al. (1987), suggested that the liver is capable of converting a positive crossmatch to negative in a patient with preformed donor-specific antibodies thereby allowing successful renal transplantation 8 h after completion of liver transplantation. Additionally, multiple studies have concluded that renal rejection and graft loss is lessened after SLK in presensitized recipients (Gonwa

Table 4 Most common indications for combined liver and kidney transplantation

Diseases synchronously affecting both organs	Hepatitis B or C causing cirrhosis and MPGN/ membranous nephropathy/ cryoglobulinemia
Un related liver and kidney disease	Primary renal diseases (hypertension, diabetes) Primary liver diseases (alcoholic liver disease, PBC, etc.)
Non cirrhotic diseases with origin/involvement of liver and kidney	Primary oxalosis, atypical HUS, familial amyloidotic polyneuropathy, end stage polycystic liver kidney disease
ESLD of any etiology with prolonged AKI	Most commonly acute tubular injury or hepatorenal syndrome with dialysis dependency of $\geq$6 weeks duration

MPGN membranoproliferative glomerulonephritis, *PBC* primary biliary cirrhosis, *HUS* hemolytic uremic syndrome, *ESLD* end stage liver disease, *AKI* acute kidney injury

et al. 1988; Shaked et al. 1993; Vogel et al. 1988; Gil-Vernet et al. 1992). With greater technical expertise and improvements in immunosuppression, the indications for combined liver and kidney transplantation have evolved. A summary of indications are highlighted in Table 4.

Burden of CKD After Nonrenal Organ Transplant

Calcineurin inhibitor (CNI) therapy remains the foundation of immunosuppression in most solid organ transplant recipients. Therefore, calcineurin inhibitor nephrotoxicity is the primary cause of post-transplantation CKD (Ojo et al. 2003). There are other contributing causes to CKD development and progression post solid nonrenal organ transplantation. The key factor is preexisting chronic kidney damage that predates the transplant and often under recognized in the setting of organ failure where serum creatinine correlates poorly with GFR. Specific immunosuppressive regimens post transplantation with CNI and mammalian target of rapamycin (m TOR) inhibitor such as sirolimus combination may also result in synergistic nephrotoxicity. Based on the type of nonrenal transplantation, differential CNI trough goals are targeted with higher trough levels maintained in intestinal transplants thus resulting in higher incidence of post-transplant CKD. Finally preexisting CKD risk factors like hypertension, diabetes, advanced age, as well as perioperative acute kidney injury contributes to the burden of CKD in the post-transplantation setting.

The best long-term data on incidence of CKD in nonrenal solid organ transplantation patients is provided by Ojo et al. (2003) from his study involving 69,321 people who received nonrenal transplants (heart, lung, liver, and intestine) in the United States between 1990 and 2000. The use of CNI was documented in 88 % of these patients. Approximately 16.5 % developed stage 4 or 5 CKD (glomerular filtration rate [GFR] $<$30 mL/min/1.73 m^2 of body surface area) during a median follow-up of 36 months. Renal replacement therapy in the form of dialysis or renal transplantation was needed in 29 % of those who developed stage 4 or 5 CKD. The highest incidence of CKD 4 or 5 at 5 year follow-up was seen in intestinal transplant recipients at 21.3 %.

Although both patient and graft survival has improved post liver transplantation, calcineurin inhibitor-induced nephrotoxicity is the main cause for CKD in these patients. The nephrotoxicity of these drugs is similar in native and transplanted kidneys. These include vascular obliteration, tubular atrophy, interstitial fibrosis, arteriolar hyalinosis, and focal and global glomerulosclerosis. The effect of pretransplant kidney function on patient and graft survival after liver transplantation has been studied using UNOS database (Nair et al. 2002) by Nair et al. who noted that about 33 % of patients undergoing liver transplantation had some renal impairment defined as estimated gfr $<$ 70 cm^3/min. It was noted that patients with pretransplant renal impairment had higher incidence of graft nonfunction and 30-day mortality rates. Creatinine clearance was the sole variable associated with post-transplant mortality prediction in liver transplant recipients.

OPTN/UNOS Initiatives: Background and Future Directions for Listing Criteria for Simultaneous Liver-Kidney Transplantation

The **Model for End-Stage Liver Disease**, or **MELD**, is a scoring system used for assessing the severity of chronic liver disease. It incorporates serum bilirubin levels, serum creatinine, INR value, and dialysis dependency. It was initially developed to predict death within 3 months of surgery in patients who had undergone a transjugular intrahepatic portosystemic shunt (TIPS) procedure (Malinchoc et al. 2000). Since its adoption in 2002 for liver allocation, the proportion of transplant recipients undergoing combined liver-kidney transplantation has increased from less than 3 % in the pre-MELD era to almost 5 % in 2009 (Papafragakis et al. 2010) and have averaged around 400 transplants/year. This is likely a result of substantial priority given to liver transplant candidates with renal dysfunction in the MELD era (Locke et al. 2008). The criteria for SLKT listing is evolving. The proceedings of a consensus conference on simultaneous liver-kidney transplantation were published in 2008 which recommended that SLK be automatically approved for (i) cirrhotic patients with symptomatic portal hypertension and end-stage renal disease, (ii) liver failure and CKD with glomerular filtration rate (GFR) $\leq$30 mL/min, (iii) acute kidney injury or HRS with creatinine level 2.0 mg/dL or higher and dialysis 8 weeks or more, (iv) liver failure and known CKD with biopsy demonstrating greater than 30 % glomerulosclerosis or 30 % fibrosis (Eason et al. 2008). Currently, OPTN/UNOS Policy does not include listing criteria for candidates who require a simultaneous liver-kidney transplant (SLK). A proposal has been released for public comment in August 2015 by UNOS at the time of writing this chapter to set forth listing criteria for SLK transplantation (Table 5). This policy proposal currently incorporates dual listing criteria for both patients with CKD and/or AKI specifying GFR cutoffs, duration of dialysis dependency, or a combination of both irrespective of etiology. Additionally, MELD exceptions for systemic metabolic diseases needing dual transplantation will also be incorporated.

The rationale for formalizing these criteria is based on the premise that the kidneys are being allocated to liver candidates who likely would have regained native kidney function following a liver transplant alone. The use of Kidney Donor Profile Index (KDPI) based on 10 donor characteristics to define deceased donor kidney quality was introduced in December 2014 as part of the

Table 5 UNOS policy proposal for simultaneuos liver kidney transplant

If the candidate's transplant nephrologist confirms a diagnosis of	Then the transplant program must document in the candidate's medical record
Chronic kidney disease (CKD) with a measured or calculated glomerular filtration rate (GFR) less than or equal to 60 mL/min for greater than 90 consecutive days	At least one of the following 1. That the candidate has begun regularly administered dialysis as an end-stage renal disease (ESRD) patient in a hospital based, independent non-hospital based, or home setting 2. That the candidate's most recent measured or calculated creatinine clearance (CrCl) or glomerular filtration rate (GFR) is less than or equal to 35 mL/min at the time of registration on the kidney waiting list
Sustained acute kidney injury	At least one of the following 1. That the candidate has been on dialysis for at least 6 consecutive weeks 2. That the candidate has a measured or calculated CrCl or GFR less than or equal to 25 mL/min for at least 6 consecutive weeks and this is documented in the candidate's medical record every 7 days beginning with the date of the first test with this value 3. That the candidate has any combination of #1 and #2 above for 6 consecutive weeks
Metabolic disease	An additional diagnosis of at least one of the following 1. Hyperoxaluria 2. Atypical HUS from mutations in factor H and possibly factor I 3. Familial non-neuropathic systemic amyloid 4. Methylmalonic aciduria

New Kidney allocation system with a lower score translating into a better-quality kidney with superior kidney allograft survival (Rao et al. 2009). Review by OPTN has shown that almost half of SLK recipients received a kidney with a KDPI <35 % based on allocation priority of the lifesaving organ such as liver or heart. This essentially means that some of the best-quality kidneys were allocated in conjunction with dual transplantation thus diverting these kidneys from other patients on the kidney list. Another important component of this proposed policy is to introduce the concept of **safety net** to impart kidney transplant priority for those Liver transplant recipients with renal dysfunction and dialysis dependency post liver transplant who did not meet the listing criteria for dual transplantation. The idea here is that attaching some precedence under safety net provision may deter overzealous dual listing and hopefully will provide a realistic chance of minimizing SLK in those who may regain native renal function post liver transplantation.

Conclusion

In the era of organ shortage, the use of kidneys in the setting of combined liver and kidney transplantation should be done prudently. Suitable risk stratification of patients with AKI and/or CKD is crucial to differentiate patients with good renal prognosis from those with poor prognosis in whom SLK transplantation is warranted. There are variable practices for SLK transplant listing at transplant centers. This adds complexity to robust data collection and hampers generation of evidence-based guidelines. Currently, UNOS is working toward developing a policy for SLK transplant which will help to streamline listing practices across transplant centers.

Cross-References

- ▶ History of Liver and Other Splanchnic Organ Transplantation
- ▶ Regulatory Agencies in Transplantation

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Part V

Immunology and Pathology of Liver Transplant

Immunology of Liver Transplantation 20

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Contents

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Abstract

Immunosuppression has allowed the liver transplant recipient to have prolonged graft survival in the modern era. Graft loss from acute and chronic rejection has greatly declined, allowing clinicians to focus more on disease recurrence rather than rejection. The use of induction regimens in liver transplant has increased over the last decade to approximately 30 % of liver transplant recipients, and their main role is to decrease the short- and long-term renal effects of calcineurin inhibitors. Today, the mainstay of maintenance immunosuppression includes a calcineurin inhibitor, an antimetabolite agent, and in certain circumstances the addition of low-dose corticosteroids. Newer agents such as the mammalian target of rapamycin inhibitors may be viable options to diminish the renal effects of calcineurin inhibitors and may have a role in preventing hepatocellular carcinoma recurrence. Given the potent systemic effects of all immunosuppressive medications, they have long-term complications that need to be managed, as well as high potential for drug-drug interactions. The incidence of acute cellular rejection has decreased in the modern era. A single episode of rejection does not portend worse survival, with the exception of patients with hepatitis C virus. Lastly, the incidence of chronic rejection is extremely low, and early recognition and treatment may improve overall graft survival.

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Keywords
Liver transplantation • Transplantation immunology • Graft rejection • Acute rejection • Chronic rejection • Antibody-mediated rejection • Immunosuppressive agents • Drug monitoring • Induction therapy • Antibody induction • Maintenance immunosuppression

Introduction

Since the first liver transplant was performed by Thomas Starzl in 1963, the art of liver transplant immunosuppression has undergone a magnificent transformation. An era that began with steroids, a drug with a myriad of side effects, has now evolved to include multidrug regimens that are well tolerated and prolong graft survival well beyond 10 years while minimizing adverse reactions. In the modern era of liver immunosuppression, rejection is no longer the main reason for graft loss. In special circumstances, grafts can maintain operational tolerance, and immunosuppression can be withdrawn altogether.

The practicing clinician should focus more on disease recurrence in the transplant and the long-term consequences of immunosuppression rather than rejection. More so than ever, immunosuppression is both an art and a science. Unfortunately, there are few overall markers of overall immunosuppression, biochemical liver tests correlate poorly with the level of immunosuppression, and many drugs have narrow therapeutic ranges with high potential for drug-drug interactions. One must be able to balance these multidrug regimens, know there potential for systemic toxicity, and implement preemptive measures to minimize the long-term side effects of immunosuppression.

Overview of Transplant Immunology

The role of the immune system is to protect an individual from incursion by foreign pathogens and to identify self-nonself discrimination. A coordinated immune response will recognize a foreign pathogen and activate the innate immune cells and soluble mediators of immunity (Martinez and Rosen 2005). Whereas the innate immune system is responsible for the speed component, the humoral immune response plays a central role in organ rejection.

Hepatic allograft rejection is a multistep process of the recipient's immunological response that includes alloantigen recognition, lymphocyte activation, clonal expansion, and graft inflammation.

Alloantigen Recognition

The first signal of rejection is alloantigen recognition, when the host immune system detects same species, nonself antigens (Game and Lechler 2002). This is precipitated by donor-recipient mismatching of the major histocompatibility complex (MHC) which leads to an alloimmune response (Wiesner et al. 1998). There are two pathways in which recipient T lymphocytes can recognize donor alloantigen, the direct and indirect pathways. In both pathways, the end result is an antigen, bound to an MHC molecule, and binds to the T-lymphocyte receptor (TCR) which activates a signal required for T-lymphocyte maturation (Fig. 1).

In the direct pathway, the hepatic allograft and its surrounding tissue will express dendritic cells; these are professional antigen-presenting cells (APC). MHC molecules are expressed on APCs, which are recognized by host T lymphocytes. The indirect pathway involves a similar process; however, in this pathway, host T lymphocytes recognize processed donor alloantigen peptides expressed on host APCs and MHC molecules. There is evidence that both of these pathways occur as part of the immunologic response in the liver transplant recipient (Martinez and Rosen 2005). In the early posttransplant period, it is likely the direct pathway predominates and is a major factor in acute rejection. This stage can be aborted by antilymphocyte antibodies.

In contrast, the amount of T lymphocytes responding in the indirect pathway is low;

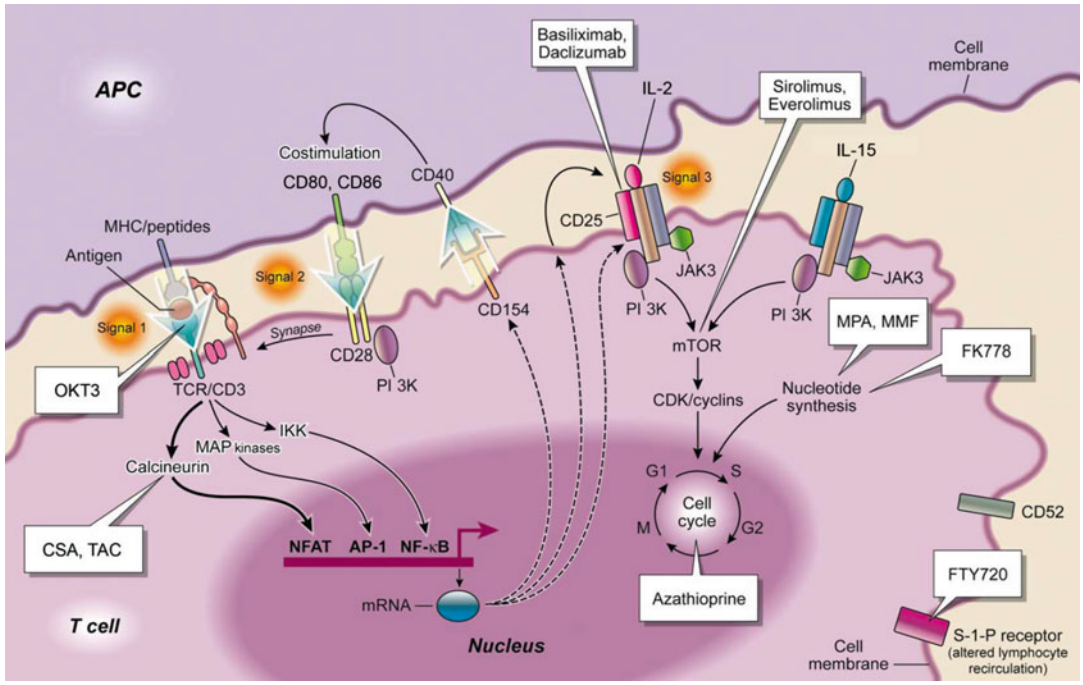


Fig. 1 Model of T-lymphocyte activation and sites of action for immunosuppressive agents (Reprinted with expressed permission from Russell H. Wiesner) (Wiesner and Fung 2011)

compared to the direct pathway, they make up only 5–10 % of the total alloresponse (Valujskikh et al. 2001; Heeger and Dinavahi 2012). Despite this, indirectly primed T lymphocytes are integral to the rejection process and play an important role in chronic allograft dysfunction (Heeger and Dinavahi 2012).

Lymphocyte Activation

Signal two is lymphocyte activation, also known as costimulation, a process in which ligands on the APC cell bind to T-lymphocyte receptors. CD80 and CD86 markers on dendritic cells engage CD28 receptors on T lymphocytes (T-lymphocyte receptor, TCR); the receptor complex is then internalized and activates signal transduction pathways (Wiesner and Fung 2011). The TCR complex binds immunophilin; this stimulates calcineurin which activates nuclear factor of T-lymphocyte activation (NFAT). NFAT then translocates to the cell nucleus and signals IL-2 transcription (Fig. 1). Two immunosuppressive drugs target immunophilin, and cyclophilin and FK-binding protein (FKBP) are targets of cyclosporine and tacrolimus.

Clonal Expansion

Signal three is clonal expansion; transduction pathways from signal two activate numerous molecules, including IL-2 and other cytokines. Newly synthesized IL-2 is produced by T lymphocytes and binds to IL-2 receptors on the T-lymphocyte surface in a paracrine and autocrine fashion. This stimulates the downstream pathway of the mammalian target of rapamycin (mTOR) which is the trigger for cell proliferation (Fig. 1) (Martinez and Rosen 2005). Immunosuppressive drugs target multiple steps at this process, both basiliximab and daclizumab are monoclonal antibodies against the IL-2 receptor, and sirolimus and everolimus are mTOR inhibitors that block cell proliferation.

Graft Inflammation

The last step in the immunological rejection response is graft inflammation. Activated T lymphocytes precipitate differentiation in their ability to mediate effector functions (i.e., secrete cytokines and kill) and by modifying an array of cell surface molecules, including L-selectin (lymph node homing receptor) and chemokine receptors. This allows cells to migrate from lymphoid organs and circulate throughout the periphery. Activated T lymphocytes express a multitude of chemokine receptors which attract various immune cells to the site of inflammation, the allograft. The result is an inflammatory milieu with toxic and vasoactive mediators. Effector T lymphocytes reencounter their specific alloantigens on the graft and initiate effector mechanisms leading to cytolysis (Heeger and Dinavahi 2012).

Phases of Immunosuppression

Liver transplant immunosuppression can be classified into two distinct phases: induction and maintenance. Induction immunosuppression usually refers to a period of intense immunosuppression given in the first 30 days after transplant when the risk of organ rejection is highest (Kirk 2006). Maintenance immunosuppression refers to the immunosuppressive regimen an organ transplant recipient is continued on after the initial 30 days; in liver transplant recipients, there is usually a decrease in the number of drugs and dosages needed to prevent rejection (Wiesner and Fung 2011). With the exception of autoimmune liver disease and hepatitis C virus, most LTRs may receive similar regimens with steroid induction with or without adjunctive antibody therapy, followed by two maintenance agents and eventual steroid withdrawal (Fig. 2).

Induction

Induction regimens in the USA have typically referred to the use of antilymphocyte-depleting agents; this is only used in a small percentage of liver transplant recipients, but in the past decade, the use of induction has increased. In 2003, the overall use of induction immunosuppression regimens was approximately 20 %; in 2013, nearly

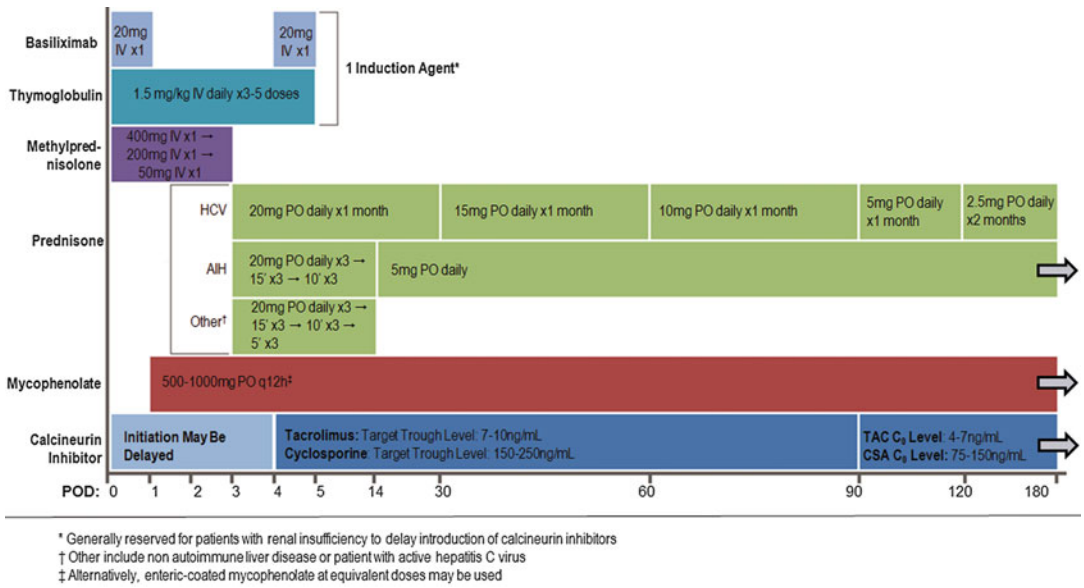
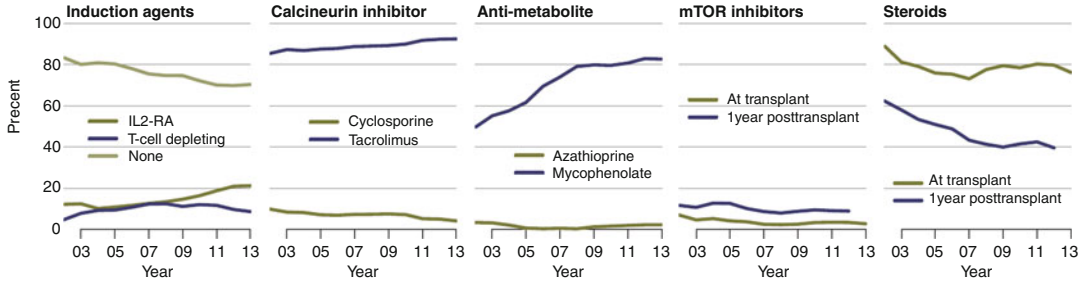


Fig. 2 Example of induction and maintenance immunosuppression regimens in liver transplant recipients



Immunosuppression in abult liver transplant recipients

One-year posttransplant data are limited to patients alive with graft function at 1 year posttransplant. Mycophenolate includes mycophenolate mofetil and mycophenolate sodium. IL2-RA, interleukin-2 receptor antagonist; mTOR, mammalian target of rapamycin.

Fig. 3 Immunosuppression in adult liver transplant recipients (Kim et al. (2015))

30 % of liver transplant recipients were given induction therapy (Fig. 3). More commonly peri- and postoperatively, these patients are started on a common drug regimen that includes high-dose corticosteroids with a rapid taper, a calcineurin inhibitor, and an antimetabolite agent such as mycophenolate (Wiesner and Fung 2011).

The role of antilymphocyte-depleting agents has been clearly defined in other organ transplants such as kidney transplant; however, in liver transplant recipients, the data is not as clear. Traditionally, induction therapy has been given as an adjunct to conventional immunosuppression to prevent the risk of rejection, to delay or minimize calcineurin exposure to prevent renal dysfunction, or to facilitate steroid avoidance and decrease the risk of HCV recurrence.

Induction therapy as an adjunct to conventional immunosuppression refers to adding a lymphocyte-depleting or a nonlymphocyte-depleting agent as an adjunct to a conventional calcineurin-based regimen. The most commonly used lymphocyte-depleting agent in the USA is antithymocyte globulin (Thymoglobulin); this is a polyclonal rabbit, derived antibody preparation which targets multiple epitopes on T lymphocytes. The result is nonspecific T-lymphocyte depletion with a dose-dependent lymphopenia that suppresses T lymphocytes for up to 90 days post administration (Boillot et al. 2009). (*A more in-depth explanation of pharmacology and monitoring will be explained in the section "Immunosuppressive Drugs".*)

Antithymocyte globulin induction to prevent rejection in liver transplantation has been evaluated in two small, randomized controlled trials. Boillot et al. evaluated antithymocyte globulin induction added to conventional maintenance therapy with tacrolimus/mycophenolate/prednisone vs. conventional therapy without induction, in 93 patients (Boillot et al. 2009). The primary outcome of rejection at 5 years was not different between groups. Bogetti et al. evaluated antithymocyte globulin induction added to maintenance of tacrolimus/prednisone in 22 patients (Bogetti et al. 2005). Compared to tacrolimus/prednisone alone, induction did not improve rejection rates at 3 months. Neither study showed differences in safety outcomes, including infection and malignancy. This limited data suggests that adding antithymocyte globulin induction therapy does not reduce rejection risk in liver transplant recipients.

Alemtuzumab (Campath) is a monoclonal antibody that targets the CD52 T-lymphocyte receptor that depletes mature lymphocytes for up to 1 year post administration. Experience using alemtuzumab in liver transplantation is limited. An NIH-sponsored study showed that alemtuzumab induction permits weaning to spaced tacrolimus monotherapy with comparable efficacy outcomes as conventional immunosuppression in de novo liver transplant recipients (Marcos et al. 2004). However, despite comparable outcomes between groups in the subgroup with hepatitis C virus, a large number of those exposed to alemtuzumab

experienced complications or graft loss related to hepatitis C virus reactivation. Similar trials evaluating alemtuzumab induction followed by tacrolimus monotherapy in liver transplant yielded similar efficacy results, but excluded patients with hepatitis C virus (Tzakis et al. 2004; Tryphonopoulos et al. 2005). A recent retrospective case-controlled study of 140 patients without hepatitis C virus found that alemtuzumab followed by tacrolimus monotherapy, compared to conventional therapy, was associated with comparable efficacy outcomes, less hypertension and fewer cases of rejection, but a 43.6 % relative risk increase for infections, particularly viral infections (Levitsky et al. 2011). Overall, while alemtuzumab appears to permit less intense maintenance immunosuppression in liver transplantation, its increased risk of infection and hepatitis C reactivation remains concerning.

The lymphocyte-nondepleting agents, basiliximab (Simulect) and daclizumab (Zenapax), selectively target the activated T-lymphocyte IL-2 receptor, CD25, which stops downstream signaling of T-lymphocyte proliferation and activation, and effects are sustained for 1–2 months post administration. Several studies have evaluated interleukin-2 receptor antagonists (IL2RAs) as induction agents to prevent acute rejection in liver transplantation. A meta-analysis including 12 randomized controlled trials and 3,251 patients showed that IL2RA induction was associated with significant reduction in rejection at 1 year (23 % vs. 28 %) (Wang et al. 2010). The difference was significant for the subgroup of eight studies of daclizumab, but not for the four studies of basiliximab. Regardless of IL2RA, the overall improvement in rejection rates did not translate to an improvement in graft or patient survival. A recent Cochrane review comparing any antibody induction therapy to no induction found induction to be associated with statistically significantly less acute rejection (RR 0.85, CI 0.75–0.96), but nonsignificant differences in death or graft loss (Penninga et al. 2012).

Induction therapy has been used to facilitate calcineurin inhibitor minimization. It is known that calcineurin inhibitors cause renal dysfunction. Studies have shown that there is an 8 % incidence of chronic renal failure at 1 year post-OLT and 18 % at 5 years posttransplant. Also, an elevated creatinine 1 month posttransplant carries an increased risk of developing chronic renal failure (Gonwa et al. 2001). The presence of renal dysfunction is associated with significant morbidity and mortality after liver transplant.

The use of antithymocyte globulin induction to delay the initiation of calcineurin inhibitors has been evaluated in two retrospective studies. Tchervenkov et al. showed that antithymocyte globulin induction and delayed CNI introduction were associated with a modest, yet significantly improved, serum creatinine at 6 months (1.39 vs. 1.56 mg/dL) (Tchervenkov et al. 2004). Similarly, Soliman et al. showed modest improvements in serum creatinine and estimated glomerular filtration rates at 1 year (1.26 vs. 1.37 mg/dL and 81 vs. 75 mL/min) with antithymocyte globulin induction (Soliman et al. 2007). Both studies found reduced rejection rates with antithymocyte globulin induction, suggesting that antithymocyte globulin may permit the safe delay of CNI introduction in an attempt to improve short- to midterm renal function.

The use of IL2RAs to delay CNI has also been evaluated. The ReSpECT study was a prospective, randomized controlled trial comparing three arms: daclizumab with delayed reduced-dose tacrolimus/mycophenolate/prednisone, delayed reduced-dose tacrolimus/mycophenolate/prednisone, or standard-dose tacrolimus/prednisone ($n = 517$) (Neuberger et al. 2009). At 26 weeks, the estimated GFR was significantly improved in the group that received daclizumab (difference of 14.5 mL/min) compared to standard-dose tacrolimus, without differences in other efficacy or safety endpoints. Furthermore, a meta-analysis subgroup including six randomized controlled trials, with durations ranging 3–24 months, showed that the addition of IL2RAs to delayed or reduced CNIs was associated with improved renal function (estimated GFR difference 6.29 mL/min, 3 studies, $n = 641$) and lower rates of renal dysfunction (RR 0.46; CI 0.27–0.78, 5 studies, n = 778) (Goralczyk et al. 2011). A recent Cochrane review showed that any antibody induction was associated with higher serum creatinine (0.04 mg/dL; CI 0.003–0.08 mg/dL), although GFR was not significantly affected (Penninga

et al. 2012). These data suggest that IL2RAs can be used to safely delay the initiation of CNIs, and this strategy is associated with improved short- to midterm renal function.

Last, induction regimens have been employed as a strategy to facilitate steroid avoidance. Along with the numerous metabolic effects of steroids, they have been associated with recurrence of hepatitis C, a major cause of liver transplantation and graft failure. Antithymocyte globulin and IL2RAs have been successful in steroid-free induction with no difference in acute cellular rejection; however, a difference in hepatitis C recurrence or adverse metabolic effects of steroid use has not been shown (Eason et al. 2001; Turner and Knechtle 2013). The use of alemtuzumab as an induction agent to minimize steroid use is not recommended because it has been associated with an increased incidence of hepatitis C recurrence (Turner and Knechtle 2013).

Maintenance Immunosuppression

Maintenance immunosuppression typically refers to the immunosuppressive regimen a liver transplant recipient (LTR) is started on after the first 30 days. However, one should think of a maintenance regimen in the immediate postoperative state. Early initiation of CNI regimens has shown to prevent acute rejection and prolong graft survival. The addition of antimetabolite agents confers additional immunosuppression while augmenting the long-term side effects of CNIs. The clinician must also take into account a recipient's underlying liver disease. For instance, LTRs transplanted for autoimmune hepatitis will require higher doses of immunosuppression, often with the complement of low-dose steroids indefinitely. In contrast, patients transplanted for alcoholic cirrhosis and steatohepatitis will require lower doses of immunosuppression and can often be maintained low-dose dual-drug regimens or monotherapy. In rare instances, LTRs can maintain operational tolerance, whereas they have good graft function off all immunosuppression. Figure 3 shows the current immunosuppressive regimens in the USA. An in-depth review of the available immunosuppressive medications and their use in maintenance of the liver transplant recipient, as well as therapeutic monitoring and short- and long-term side effects, will be explored in the following section on "Immunosuppressive Drugs."

Immunosuppressive Drugs

Corticosteroids

Given the abundance of glucocorticoid receptors throughout the body, corticosteroids have numerous pharmacologic actions. The most important immunosuppressive mechanism of corticosteroids occurs via steroid-receptor complex binding to DNA sequences (*glucocorticoid response elements*, *GRE*), which subsequently inhibit transcription of cytokine-encoding genes. Through inhibition of nuclear translocation of nuclear factor-κB (NF-κB), the expression of numerous cytokines, including IL-1, IL-2, IL-3, IL-6, TNF-α, and IFN-γ a, is inhibited.

Adverse effects of corticosteroids include short-term and long-term effects. Short-term adverse effects include hyperglycemia, hypertension, gastrointestinal discomfort, psychiatric disturbances, insomnia, increased appetite, and transient leukocytosis. Long-term adverse effects include infection, diabetes, hypertension, dyslipidemia, weight gain, Cushing's syndrome, insomnia, depression, osteopenia/osteoporosis, glaucoma/cataracts, and cosmetic changes to skin and hair. A comparison of the adverse effects of maintenance immunosuppressants, including corticosteroids, is shown in Table 1.

Corticosteroids have been the cornerstone of immunosuppression since the advent of liver transplantation. They are almost universally administered preoperatively. Despite its antirejection benefit, numerous studies have been performed to evaluate the impact of steroid minimization on reducing their numerous adverse effects. A meta-analysis of 21 trials, including 2,590 patients, demonstrated that steroid-free maintenance regimens were associated with similar rejection rates and patient and graft survival,

Table 1 Adverse drug reactions of maintenance immunosuppressive agents

	Steroids	TAC	CSA	MPA	AZA	mTORi	Belatacept
Nephrotoxicity		++	++				
Proteinuria						++	
Infection	+	+	+	+	+	+	+
Malignancy		+	+	+	+		+
Diabetes	++	++	+			+	
Dyslipidemias	++	+	++			++	
Hypertension	++	+	++				
Weight gain	++						
Osteopenia	++						
Bone marrow suppression				++	++	+	
Impaired wound healing	+					++	
GI disturbances	+	+		++	+	+	
Cosmetic changes	+	+	+		+		
Neurotoxicity		+					
Glaucoma/cataracts	+						
Infusion reactions							+
PTLD	+	+	+	+	+		++

+ indicates common adverse drug reactions
++ indicates significant or severe adverse drug reactions

when compared to conventional steroid-based immunosuppression (Sgourakis et al. 2009). Overall, steroid minimization was associated with a more favorable safety profile, including reduced posttransplant diabetes, CMV infection, and serum cholesterol. Of note, rejection rates were lower in patients that received antibody induction in place of steroid maintenance; however, protocols that employed steroid withdrawal without replacement favored maintenance steroids to reduce rejection. In sum, steroid minimization is safe in liver transplantation, especially when replaced with antibody induction.

The role of steroids in liver recipients with hepatitis C virus (HCV) remains controversial. Data is conflicting on whether steroid-free regimens, early steroid withdrawal, or late steroid withdrawal is best for HCV recurrence rates. Humar et al. showed that when steroids were withdrawn on postoperative day 6, HCV recurrence rates were 30 % lower at 1 year than when compared to conventional immunosuppression with steroid withdrawal at 6 months (Humar et al. 2007). The THOSIN study showed that a steroid-free regimen was associated with fewer liver biopsies with grade 4 portal inflammation or grade 3 or 4 fibrosis through 2 years, when compared to a regimen which withdrew steroids at 90 days (Lladó et al. 2008). Conversely, Vivarelli et al. compared steroid withdrawal at 3 months vs. slow tapering over 24 months (Vivarelli et al. 2007). In this trial, slow tapering of steroids was associated with a lower incidence of advanced fibrosis and improved advanced fibrosis-free survival. Surprisingly, in a large randomized trial enrolling 295 patients, the HCV-3 study found no significant difference in HCV outcomes with the steroid-free regimen when compared to the conventional therapies (Klintmalm et al. 2011). Despite the controversial findings of these studies, the bulk of the data, including a meta-analysis subgroup of a 14 trials, supports safe and beneficial steroid withdrawal in liver transplant recipients with HCV (Sgourakis et al. 2009).

Calcineurin Inhibitors

The calcineurin inhibitors, cyclosporine (CSA) (Neoral, Sandimmune, Gengraf) and tacrolimus

(TAC) (Hecoria, Prograf, Astagraf XL, common name: FK506), bind to intracellular receptor proteins, cyclophilin and FK-binding protein (FKBP), respectively. The resulting CNI-receptor complex binds to calcineurin, a protein phosphatase responsible for the dephosphorylation and translocation of nuclear factor of activated T lymphocytes (NFAT). NFAT is a gene transcription factor integral to the expression of cytokines. Specifically, IL-2 expression is suppressed and T-lymphocyte activation is inhibited.

Cyclosporine is available in an intravenous formulation and two different oral formulations. The bioavailability of conventional CSA is more dependent on food intake, gastrointestinal motility, and bile for absorption than the CSA microemulsion [modifed] dosage form. Tacrolimus is available in an intravenous formulation, as well as an immediate release and extended release oral capsules. Intravenous formulations of CNI can be given in a 1:3 dosage ratio to oral formulations. Pharmacokinetic similarities of the CNI include their variable bioavailability, high protein binding, and metabolism by gastrointestinal and hepatic P-glycoprotein (PGP) and CYP3A4/5 isoenzymes. The elimination half-lives (t½) of CNI are similar, with CSA t½ ~8 h and TAC t½ ~8–12 h.

The most serious adverse effect of CNI is their dose- and duration-dependent nephrotoxicity. Acutely, CNIs lead to vasoconstriction of afferent arterioles mediated by an increase in vasoconstrictors (endothelin and thromboxane) and reduction of vasodilators (prostacyclin, prostaglandin E2, and nitric oxide) (Naesens et al. 2009). Chronically, irreversible tubular atrophy, interstitial fibrosis, arteriolar hyalinosis, and glomerulosclerosis may be observed on biopsy. In one series, more than 25 % of patients show histologic evidence of CNI-induced nephrotoxicity (CIN) after 1 year on therapy, and CIN was almost universal after 10 years (Nankivell et al. 2003). The incidence of chronic renal failure has been reported at 22 % 5 years after liver transplant (Sharma et al. 2009). Additionally, due to their vascular effects, CNIs are associated with systemic hypertension, with a higher incidence reported with CSA than TAC. Electrolyte abnormalities such as hyperkalemia, hypomagnesemia, hypocalcemia, and hyperuricemia are also common. Thrombotic microangiopathy (TMA) resembling thrombotic thrombocytopenic purpura (TTP) has been reported with CNI use.

Nonrenal adverse effects of CNI include diabetes, dyslipidemia, neurotoxicity, and cosmetic effects. Both CNIs are toxic to pancreatic islet cells and may lead to posttransplant diabetes mellitus (PTDM), although this is observed in a higher frequency with TAC than CSA. Dyslipidemia is more often associated with CSA. Neurotoxic effects occur more frequently with TAC and range from headache and tremors to seizures and reversible posterior leukoencephalopathy syndrome (RPLS). Cosmetic effects of CSA include gingival hypertrophy and hirsutism, whereas TAC is associated with hair loss and alopecia. Both CNIs are associated with an increased risk of infection and malignancies including posttransplant lymphoproliferative disorder (PTLD).

Given the wide inter-patient and intra-patient variability of CNI, therapeutic drug monitoring is integral to their safe and effective use. Trough (C_0) levels of TAC are strongly correlated with area under the curve ($AUC_{0–12}$) and may be used to assess treatment (Schiff et al. 2007). Unfortunately, CSA C_0 levels are poorly correlated to $AUC_{0–12}$, and pharmacokinetic data suggests that monitoring abbreviated $AUC_{0–4}$ or C_2 levels (i.e., concentration 2 h post-dose) may be preferable (Keown et al. 1996; Cantarovich et al. 1998). Despite this, owing to the logistic difficulty of obtaining AUC or C_2 levels, coupled with a lack of data to demonstrate clinical superiority of C_2 vs. C_0 levels, C_0 level monitoring remains the most commonly employed method in practice. Target levels of CNI are not universally accepted, but should take into consideration time from transplant, cause of liver disease, infection risk, and concomitant immunosuppression. Earlier studies utilized high initial target levels for CSA (e.g., C_0 250–400 ng/mL); however, more modern studies utilize more modest targets (e.g., C_0 150–250 ng/mL), with later targets as low as 75–100 ng/mL. Likewise, initial TAC targets in earlier studies were more aggressive (e.g., C_0 10–20 ng/mL) than more modern targets (e.g., 7–12 ng/mL), with later targets as low as 4–6 ng/mL.

Cyclosporine

Prior to the approval of cyclosporine in 1983, 1-year survival after a liver transplant was approximately 30 % under immunosuppression with azathioprine and corticosteroids (Starzl et al. 1974). The earliest reports of CSA use, while small in size and duration, showed survival rates greater than 70 % in 1 year when used in conjunction with steroids (Starzl et al. 1981). Longer-term data supported these findings and led to the more than decade-long "cyclosporine" era of liver transplantation. Today, cyclosporine remains a reasonable alternative for patients intolerable of tacrolimus.

Tacrolimus

Since its FDA approval in 1994, tacrolimus eventually replaced cyclosporine as the first-line CNI in liver transplantation. The registry study was an open-label randomized trial of 478 de novo liver recipients comparing TAC to CSA, with concomitant azathioprine and corticosteroids. At 1 year, patient and graft survival rates were comparable, but a 10 % relative risk reduction in rejection, and more profound reductions in steroid-resistant and refractory rejections, was observed with TAC (US Multicenter FK506 Liver Study Group 1994). These results were echoed by the comparable European registry study of 545 patients, which found an 18 % relative risk reduction in rejection at 1 year (European FK506 Multicentre Liver Study Group 1994). The TMC study was an open-label randomized trial in 606 de novo liver recipients, comparing TAC-based to CSA-based regimens. The primary composite endpoint of transplantation, death, or refractory rejection occurred less frequently with TAC vs. CSA at 1 year (RR 0.63, CI 0.48–0.84) and 3 years (RR 0.75, CI 0.6–0.95) (O'Grady et al. 2002; O'Grady et al. 2007). Furthermore, a meta-analysis of 16 trials ($n = 3{,}813$) found that TAC was associated with significantly more favorable outcomes with regard to patient survival, graft survival, rejection, and steroid-resistant rejection, albeit with a higher risk for diabetes (Haddad et al. 2006).

Antimetabolites

Mycophenolic Acid

Mycophenolic acid (MPA) (CellCept, Myfortic) is a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), a critical enzyme in de novo purine synthesis. It is available as mycophenolate mofetil (MMF) which undergoes rapid hydrolysis to MPA and enteric-coated mycophenolate sodium (EC-MPS) which is equivalent to active MPA. Peak MPA levels are observed 0.9–1.3 and 2.0–2.5 h after MMF and EC-MPS administration, respectively. Food reduces absorption of MPA and is best taken on an empty stomach. Mycophenolate undergoes hepatic glucuronidation to inactive mycophenolic acid glucuronide (MPAG), a portion of which is converted back to MPA and reabsorbed, leading to second peaks in the concentration-time curve approximately 5–6 h after administration. MPA is excreted renally; however, dose adjustment in renal impairment is not necessary.

The main dose-limiting toxicities of MPA are gastrointestinal in nature and include nausea, vomiting, dyspepsia, and diarrhea. Leukopenia, anemia, and thrombocytopenia are also frequently observed and may require dose reduction or interruption. Importantly, MPA is associated with congenital malformations when taken during pregnancy. In patients electing to become pregnant, MPA should be withheld at least 6 weeks prior to conception. All pregnancies occurring in patients on or previously exposed to MPA should be reported to the Mycophenolate Pregnancy Registry.

Therapeutic drug monitoring of MPA is possible, though not commonly utilized. Studies of kidney recipients in the early posttransplant period have shown that calculating the area under the curve ($AUC_{0–12}$) predicts the risk of rejection and toxicity (van Gelder et al. 1999). Trough (C_0) levels are poorly correlated with AUC and do not accurately predict rejection or toxicity (Mardigyan et al. 2005). A target $AUC_{0–12}$ of 30–60 mg h/L has been suggested to prevent rejection; however, the logistic difficulty in obtaining multiple accurate levels and its

paucity of supporting data have deterred its widespread use (van Gelder et al. 2006).

Since its approval in 2000, mycophenolate has largely replaced azathioprine. The superiority of MMF over AZA as an adjunctive agent was determined by a randomized, double-blind trial of 565 patients (Wiesner et al. 2001). In part of combination therapy with CSA and steroids, 6-month acute rejection rates in the MMF arm were 38.5 % compared to 47.7 % in the AZA arm. Patient survival, graft survival, and adverse events were comparable between groups. Of note, the MMF dose studied (3 g/day) is higher than what is typically employed in clinical practice. A smaller randomized trial of 63 patients found lower rejection rates with MMF 2 g/day compared to AZA, though the study may have been too small to detect a significant difference (Fischer et al. 2000; Sterneck et al. 2000).

The use of enteric-coated mycophenolate sodium in liver recipients has not been compared to mycophenolate mofetil in a randomized controlled trial; however, several small open-label studies have shown comparable outcomes after conversion for gastrointestinal adverse effects (Cantisani et al. 2006; Dumortier et al. 2006). Doses of EC-MPS 720 mg are considered therapeutically equivalent to MMF 1000 mg.

Azathioprine

Azathioprine (AZA) (Azasan, Imuran) is a purine analog prodrug. After administration, AZA is rapidly hydrolyzed to 6-mecaptopurine (6MP), which is then converted to active 6-thioguanine (6TGN) which incorporates into DNA to inhibit nucleotide synthesis. A portion of 6-mercaptopurine is also converted to 6-thiouric acid, an inactive metabolite, by xanthine oxidase. The main toxicity of AZA is bone marrow suppression. Pancreatitis has also been rarely reported. Despite its pregnancy category, AZA may be safely used in pregnant transplant recipients.

While azathioprine has been largely replaced by mycophenolate, the quality of the data demonstrating a clinical benefit has been called into question (Germani et al. 2009). At most centers, azathioprine is reserved for patients intolerant to mycophenolate.

Mammalian Target of Rapamycin Inhibitors

Mammalian target of rapamycin inhibitors (mTORi) include sirolimus (SRL) (Rapamune) and everolimus (ERL) (Zortress). Sirolimus is a macrolide antibiotic, also known as rapamycin, and everolimus is an SRL derivative. Both bind to FK-binding protein and subsequently inhibit mTOR, inhibiting downstream kinase activation and arresting cell cycle progression. Pharmacokinetic similarities include low bioavailability and high protein binding, whereas differences include the effect of food on exposure and elimination half-life. A high-fat meal increases SRL exposure but decreases ERL exposure. Both should be taken consistently with regard to meals. The half-life of SRL is ~62 h, whereas ERL is ~30 h. Like CNI, both are substrates of P-glycoprotein and CYP3A4.

Adverse effects of mTORi include proteinuria, dyslipidemia, cytopenias, impaired wound healing, peripheral edema, and hyperglycemia. While mTORi are not intrinsically nephrotoxic, numerous studies have suggested that mTORi may potentiate the nephrotoxic effects of CNI. Despite this, some studies have demonstrated improved renal function when mTORi was given in regimens containing reduced-dose CNI. Proteinuria is common and nephrotic syndrome has been reported with mTORi use. As such, patients should have urinary protein evaluated at baseline and periodically while on treatment with mTORi. Up to 50 % of patients on mTORi will experience some level of hypertriglyceridemia or hypercholesterolemia; however, their influence on cardiovascular outcomes is not known. Some data suggests an overall cardioprotective effect of mTORi (McKenna et al. 2013). Other less common but potentially serious adverse effects of mTORi include reversible azoospermia in males and interstitial pneumonitis. Notably, due to antiangiogenic effects, mTORi have been implicated

with a low risk of malignancies, and some forms are approved for use in treating cancers.

Trough (C_0) levels of mTORi are strongly correlated with area under the curve (AUC) and may be used to ensure safe and effective therapy (Kahan et al. 2000; Rostaing et al. 2014). Given the long half-lives of mTORi, levels should be assessed less frequently than CNI. Sirolimus levels reach steady state in approximately 13 days, and everolimus in approximately 6 days. Based on the registry studies, FDA labeling recommends that everolimus C_0 levels should be maintained within 3–8 ng/mL (De Simone et al. 2012). Sirolimus has never received FDA approved for liver transplantation; however, pharmacokinetic data suggests that C_0 levels less than 5 ng/mL predict rejection, and levels greater than 15 ng/mL correlate with adverse effects (Kahan et al. 2000).

Sirolimus

Sirolimus was FDA approved in 1999 for use in kidney transplantation; however, it was never approved for use in de novo liver transplantation owing to an increased risk for hepatic artery thrombosis, graft loss, and death (Asrani et al. 2014). Despite the boxed warning for these adverse events, SRL has been studied in liver transplant recipients as a replacement for CNI to preserve renal function. A meta-analysis evaluated three randomized controlled trials and eight observational studies to determine if there is a renal protective benefit to converting from CNI to SRL, in patients with renal insufficiency (Asrani et al. 2010). The analysis of the controlled trials concluded that SRL was associated with an improvement in glomerular filtration rate (10.35 mL/min; CI 3.98–16.77; $n = 86$); however, the difference was not statistically significant in the total cohort. Sirolimus use was not associated with an increased risk of death or graft loss, but infectious complications, oral ulcers, and discontinuation due to adverse event were more likely in sirolimus-treated patients. A more recent trial including 607 patients, the largest to date, failed to find any significant difference in renal function 12 months after conversion to SRL, but did demonstrate that it was associated with an increased risk of rejection and treatment discontinuation due to adverse events (Abdelmalek et al. 2012). At this time, the data to support the use of sirolimus as a conversion agent to preserve renal function is unclear.

Owing to its antitumor properties, sirolimus has been studied in liver transplant recipients with hepatocellular carcinoma (HCC). A meta-analysis of five trials, including 2,950 patients, demonstrated that SRL-based regimens had lower rates of HCC recurrence posttransplant (OR 0.42; CI 0.21–0.83) (Liang et al. 2012). The analysis showed that SRL-based regimens had improved patient survival at 1 year (OR 4.53; CI 2.31–8.89), 3 years (OR 1.97; CI 1.29–3.00), and 5 years (OR 2.47; CI 1.72–3.55). There were no differences in hepatic artery thrombosis or acute rejection. These data suggest that sirolimus-based regimens are safe and may provide a benefit to patients with pre-transplant HCC.

Everolimus

Everolimus was FDA approved in 2013 following the results of a prospective, randomized, open-label study in de novo liver transplant recipients (H2304 Study). In this study of 719 patients, everolimus with reduced-exposure tacrolimus was shown to be non-inferior to standard-exposure tacrolimus with regard to the primary composite endpoint of 12-month rejection, graft loss, and death (De Simone et al. 2012). The estimated glomerular filtration rate at 12 months was superior (8.50 mL/min/1.73 m^2 higher) in the everolimus group compared to the tacrolimus group. A third arm, which assigned patients to everolimus with tacrolimus elimination, was terminated early owing to higher rates of rejection. The PROTECT study was a 12-month prospective, randomized, open-label study in de novo liver transplant recipients which demonstrated comparable efficacy outcomes with everolimus and CNI withdrawal at 8 weeks vs. continued CNI therapy (Fischer et al. 2012). At 12 months, the estimated glomerular filtration rate was 7.8 mL/min higher in the everolimus group than the CNI maintenance group, using the Modification of Diet in Renal Disease (MDRD) equation. These studies suggest that everolimus may be

employed in strategies to minimize nephrotoxicity of CNIs via adjunctive CNI dose reduction or eventual CNI replacement.

Costimulatory Blocking Agents

Belatacept

Belatacept (Nulojix) is a fusion protein of human immunoglobulin and cytotoxic T-lymphocyte antigen-4 (CTLA-4-Ig), which binds to CD80 and CD86 on antigen-presenting cells, blocking CD28-mediated costimulation of T lymphocytes. It is an intravenous infusion, which following more frequent dosing for the first 3 months, continues as a monthly maintenance infusion. The risk for posttransplant lymphoproliferative disorder (PTLD) was significantly higher with belatacept when compared to CSA, particularly in patients that were Epstein-Barr virus serostatus negative. Notably, belatacept does not cause nephrotoxicity.

Belatacept was approved for use in kidney transplant recipients in 2011. A phase II study in comparing three belatacept regimens to two tacrolimus regimens in de novo liver transplant recipients demonstrated higher rates of the primary composite endpoint (acute rejection, graft loss, and death) at 6 months in the low-dose belatacept group (Klintmalm et al. 2014). The long-term extension of the study was terminated in its second year when patient and graft survival was shown to be worse in another belatacept arms. The future of belatacept use in liver transplantation is uncertain.

Antibody Therapies

Antithymocyte Globulin

The immunosuppressive mechanism of antithymocyte globulin is not fully understood. It is a polyclonal preparation which includes antibodies to numerous T-lymphocyte markers such as CD2, CD3, CD4, CD8, CD11a, CD18, CD44, CD45, HLA-DR, HLA class I heavy chains, and ß2 microglobulin. Following administration of antithymocyte globulin, a profound T-lymphocyte depletion occurs within a day and lasts for months and in some cases more than a year. The depletional activity of antithymocyte globulin is thought to be due to complement-dependent lysis of T lymphocytes or the opsonization and phagocytosis of T lymphocytes by macrophages. Monitoring absolute lymphocyte count or the CD3+ lymphocyte subset is recommended.

Antithymocyte globulin is given as an intravenous infusion preoperatively, followed by 2–4 postoperative doses. Studies have typically used doses of 1.5 mg/kg/day to a total of 4.5–7.5 mg/kg. Given the high potential for infusion reactions, including anaphylaxis and cytokine release syndrome, premedication with an antihistamine, corticosteroid, and acetaminophen is recommended. Additionally, patients should be monitored for severe adverse reactions including leukopenia, thrombocytopenia, infection, and malignancy.

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody which binds to the CD52 receptor of T and B lymphocytes, resulting in antibody-dependent T-lymphocyte-mediated lysis. It is usually given as a one-time intravenous infusion, although it may also be administered subcutaneously. The half-life of alemtuzumab after a single 30 mg dose is 11 h; however, the lymphocyte-depleting effect is prolonged, lasting as long as 1–3 years. The main adverse effects of alemtuzumab are cytopenias, infections, and potentially severe infusion reactions. Premedication with an antihistamine and acetaminophen is suggested to minimize infusion reactions. Coagulopathy has been rarely reported with alemtuzumab use, including disseminated intravascular coagulopathy, intraoperative surgical bleeding, and abnormal coagulation parameters.

Interleukin-2 Receptor Antagonists

The interleukin-2 receptor antagonists (IL2RA) include basiliximab, a chimeric monoclonal antibody, and daclizumab, a humanized monoclonal antibody. Both bind to the IL-2 receptor α-chain

(CD25) of T lymphocytes, inhibiting the IL-2-mediated lymphocyte proliferation pathway. Basiliximab is a 20 mg intravenous infusion given 2 h prior to transplantation, with a subsequent dose given on postoperative day 4. Daclizumab, which is no longer marketed in the USA, was an intravenous infusion given preoperatively, followed by 1–4 doses postoperatively. Both IL2RA are well tolerated, and clinical studies showed that the incidence of adverse effects, including infection and malignancy, was not different than placebo.

Drug-Drug Interactions of Immunosuppressants

Drug-drug interactions are frequently encountered in the posttransplant setting. CNI and mTORi are substrates for hepatic and gastrointestinal CYP3A4. As such, concomitant administration of potent inhibitors and inducers of CYP3A4 will result in increased and decreased CNI and mTORi levels, respectively. Table 2 lists frequently encountered agents that interact with CYP3A4. Often times, coadministration of these drugs is unavoidable, and increased monitoring and empiric dose adjustment may be necessary. Since CNI and mTORi are substrate for the gastrointestinal P-glycoprotein efflux pump, drugs inhibiting or inducing this system will influence the bioavailability of orally administered CNI and mTORi. Cyclosporine significantly increases the levels of mTORi when administered simultaneously. The product labeling for sirolimus recommends administering it 4 h after cyclosporine; however, everolimus labeling recommends administering everolimus and cyclosporine simultaneously.

Table 2 Drugs which interact with CNI or mTORi

CYP3A4 inhibitors (will increase CNI/mTORi exposure)	CYP3A4 inducers (will decrease CNI/mTORi exposure)
Azole antifungals[a] (e.g., *fluconazole*, *voriconazole*, *posaconazole*)	Antiepileptic drugs (e.g., *phenytoin*[b], *carbamazepine*, *phenobarbital*)
Macrolide antibiotics (e.g., *erythromycin*[a], *clarithromycin*)	Rifamycins (e.g., *rifampin*[b], *rifapentine*, *rifabutin*)
Protease inhibitors (e.g., *ritonavir*[a], *paritaprevir*, *telaprevir*, *boceprevir*)	Non-nucleoside reverse transcriptase inhibitors (e.g., *efavirenz*, *nevirapine*)
Non-dihydropyridine calcium channel blockers[a] (*verapamil*, *diltiazem*)	CNS stimulants (*modafinil*, *armodafinil*)
Dietary, herbals (*grapefruit juice*)	Dietary, herbals (*St. John's wort*[b])

[a]Agent also inhibits intestinal P-glycoprotein
[b]Agent also induces intestinal P-glycoprotein

Mycophenolate is not metabolized by CYP3A4, nor is it a substrate for P-glycoprotein. The main interactions with mycophenolate are with drugs that may reduce its bioavailability, such as antacids, ferrous sulfate, and sevelamer. Recently, proton pump inhibitors have been identified as leading to significant reductions in MPA exposure; however, the clinical impact of this interaction is unknown. Given that mycophenolate undergoes enterohepatic recirculation, drugs that inhibit this process lead to reductions in MPA exposure. Cyclosporine is a known inhibitor of enterohepatic recirculation, as are the bile acid sequestrants, cholestyramine, colestipol, and colesevelam. Notably, tacrolimus does not inhibit the enterohepatic recirculation of MPA, and patients on this combination have comparatively higher MPA concentrations than those on cyclosporine. Azathioprine is not affected by the aforementioned agents; however, xanthine oxidase inhibitors, such as allopurinol, should be avoided as they inhibit the conversion of its active metabolite 6-MP to an inactive metabolite, increasing its risk for hematologic toxicity.

Evaluation for drug-drug interactions should include consideration for drugs that result in overlapping or augmented toxicity. For example, administering concomitant nephrotoxins (e.g., aminoglycosides, NSAIDs, IV contrast, etc.) with CNI may result in a higher risk for renal toxicity, and alternative options should be employed whenever possible. Agents which are

associated with myelosuppression (e.g., co-trimoxazole and valganciclovir) may worsen the cytopenic effects of MPA, AZA, or mTORi.

Rejection

Acute Cellular Rejection

Traditionally, the liver has been thought of as an immunologically privileged organ, requiring less immunosuppression than other organ transplants with fewer episodes of acute and chronic rejection while being less susceptible to antibody-mediated rejection. Some liver transplant recipients are able to sustain operational tolerance, where they can maintain good graft function off all immunosuppression. However, in the liver transplant recipient in the early postoperative course, there will be biochemical abnormalities; these can be dysfunctional for a number of reasons including reperfusion/ischemic injury, vascular abnormalities, biliary complications, disease recurrence, and drug injury, to name a few. The astute clinician must also be able to recognize acute cellular (ACR) rejection as a cause because failure to promptly diagnosis and treat ACR can have devastating consequences.

The frequency of ACR in the modern era has been greatly reduced with the advent of calcineurin-based immunosuppressive regimens, especially tacrolimus. Earlier studies by Wiesner and colleagues with a large cohort ($n = 762$) found an incidence of ACR of 64 % within 1 year using random protocol biopsy in patients treated with a cyclosporine-based regimen (Wiesner et al. 1998). In a more recent 2010 meta-analysis ($n = 3{,}251$) with variable use of induction regimens and a tacrolimus-based CNI regimen in conjunction with prednisone and MMF, the incidence of ACR was between 23 % and 28 % (Wang et al. 2010). Interestingly, as opposed to other organ transplants, ACR is not associated with decreased graft or patient survival, and it is theorized that ACR can promote immunologic tolerance (Wiesner et al. 1998). In addition, a single episode of ACR within 6 weeks of transplant is associated with increased long-term patient survival (Charlton 2013). The exception to this is a patient with HCV where rejection and repeated steroid exposure can lead to worse outcomes.

Various risk factors have been identified that predispose the liver transplant recipient to ACR, and this is an area where there is a potential to adjust immunosuppressive regimens based on different patient characteristics. Younger recipient age has been a well-established risk factor for ACR that has been validated in numerous studies. Additional risk factors include preserved renal function (creatinine level <2.0 mg/dL without dialysis), lack of edema, higher AST levels (>200U/L), fewer HLA-DR matches, longer cold ischemic times, and older donors (≥ 30 years) (Wiesner et al. 1998; Wang et al. 2012; Charlton 2013).

The diagnosis of ACR is mainly based upon histological criteria. As stated previously, serum biochemical tests do not accurately reflect degree of immunosuppression and can be abnormal because of a number of other etiologies. Serum biomarkers of ACR have been studied, but to date none has been validated nor are they commercially available. Physical symptoms are nonspecific; patients can be completely asymptomatic or exhibit nonspecific symptoms such as fever, malaise, abdominal pain, hepatosplenomegaly, jaundice, or in rare, severe cases ascites. In the absence of a highly plausible alternative explanation for elevated liver enzymes in the LTR, these patients require liver biopsy.

On liver biopsy, the histological hallmarks of ACR are portal inflammation, bile duct inflammation, and venous inflammation. (*A more in-depth explanation of liver histology and pathology will be reviewed in another chapter.*) At least two of these three features are needed to make a histopathological diagnosis of acute cellular rejection. Once there is a firm diagnosis of acute cellular rejection, the liver pathologist will grade the severity of rejection using the Banff criteria. According to these criteria, three specific features are evaluated: portal inflammation, bile duct inflammation/damage, and venular inflammation.

They are semiquantitatively scored on a scale of 0–3 based on severity (mild, moderate, severe), and then the final scores are added together to arrive at a final rejection activity index (RAI). Mild rejection is an RAI score ≤4, moderate 4–6, and severe rejection ≥6 (Demetris et al. 1997). See Tables 3 and 4.

Table 3 Grading of acute liver allograft rejection

Global assessment*	Criteria
Indeterminate	Portal inflammatory infiltrate that fails to meet the criteria for the diagnosis of acute rejection
Mild	Rejection infiltrate in a minority of the triads that is generally mild and confined within the portal spaces
Moderate	Rejection infiltrate, expanding most or all of the triads
Severe	As above for moderate, with spillover into periportal areas, and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis

Global assessment of rejection grade mode on a review of the biopsy and after the diagnosis of rejection has been established

*Verbal description of mild, moderate, or severe acute rejection could also be labeled as grades I, II, and III, respectively

As discussed above, the consequence of ACR is variable; therefore, the clinical context of the patient must be taken into account before treatment is considered. There is no universal protocol for treating ACR and most institutions utilize individual protocols. For cases of mild acute rejection found on random or routine liver biopsies without corresponding biochemical abnormalities, often no treatment is required as these cases usually resolve without an increase in immunosuppression. For moderate to severe rejection, high-dose corticosteroids remain the mainstay of therapy. Methylprednisolone is usually given in doses of 500–1000 mg for one to five days depending on center-specific protocols. Some centers will then administer a gradual steroid taper. Histological and biochemical improvement should be observed in three to five days when steroid therapy is successful.

Special consideration should be given to liver transplant recipients with ACR and hepatitis C. High-dose intravenous methylprednisolone is

Table 4 Rejection activity index

Category	Criteria	Score
Portal inflammation	Mostly lymphocytic inflammation involving, but not noticeably expanding, a minority of the triads	1
	Expansion of most or all of the triads, by a mixed infiltrate containing lymphocytes with occasional blasts, neutrophils, and eosinophils	2
	Marked expansion of most or all of the triads by a mixed infiltrate containing numerous blasts and eosinophils with inflammatory spillover into the periportal parenchyma	3
Bile duct inflammation damage	A minority of the ducts are cuffed and infiltrated by inflammatory cells and show only mild reactive changes such as increased nuclear/cytoplasmic ratio of the epithelial cells	1
	Most or all of the ducts infiltrated by inflammatory cells. More than an occasional duct shows degenerative changes such as nuclear pleomorphism, disordered polarity, and cytoplasmic vacuolization of the epithelium	2
	As above for 2, with most or all of the ducts showing degenerative changes or focal luminal disruption	3
Venous endothelial inflammation	Subendothelial lymphocytic infiltration involving some but not a majority of the portal and/or hepatic venules	1
	Subendothelial infiltration involving most or all of the portal and/or hepatic venules	2
	As above for 2, with moderate or severe perivenular inflammation that extends into the perivenular parenchyma and is associated with perivenular hepatocyte necrosis	3

Total score = sum of components. Criteria that can be used to score liver allograft biopsies with acute rejection, as defined by the World Gastroenterology Consensus Document

associated with a transient elevation of HCV RNA levels 10–100fold (Gane et al. 1996; Magy et al. 1999). Multiple studies have shown more severe recurrence results from repeated corticosteroid boluses used to treat ACR and increased risk for mortality (Samonakis et al. 2012). Confounding the picture is the histological occurrence of hepatitis C which can have overlap features of ACR (Petrovic 2006). Since there does not appear to be an increased risk of mortality from mild rejection per se, it is recommended that mild rejection in HCV liver transplant recipients should not be treated (Burton and Rosen 2006). With the advent of new interferon-free HCV treatment with >90 % sustained virological response rates, this may no longer be a clinical conundrum.

Approximately 5–15 % of LTR with an episode ACR will develop steroid-resistant rejection (SRR) (Volpin et al. 2002). In the past, a polyclonal antilymphocyte preparation was given to patients; if they did not respond, their only option was urgent retransplantation. Muromonab (OKT3), a murine monoclonal antibody that binds to the CD3 receptor on mature lymphocytes, results in rapid clearance of circulating T lymphocytes. This was one of the first agents to be used and show effectiveness in the treatment of SRR (Colonna et al. 1987; Solomon et al. 1993). However, the manufacturer voluntarily withdrew this agent from the market in 2009 because of its safety profile. Antithymocyte globulin has been well studied in SRR in kidney transplant recipients, and data in liver transplant is small, but it has shown to be effective and is the first-line agent in many US centers for SRR. The IL2RA basiliximab has been studied in small series for liver SRR with success and is a viable treatment option (Fernandes et al. 2005; Orr et al. 2005).

Chronic Rejection

Chronic rejection (CR) in the LTR is defined as "immunologic injury to the allograft, which usually evolves from severe or persistent acute rejection and results in potentially irreversible damage to the bile ducts, arteries, and veins" (Demetris et al. 2000). In the modern era of calcineurin inhibitor-based regimens, the incidence of CR has dramatically decreased, from 15–20 % in the 1980s to 3–5 % in current liver allograft recipients. Chronic rejection should be suspected in LTRs who have a history of acute rejection and develop progressive cholestasis with a preferential elevation of gamma-glutamyl transpeptidase and alkaline phosphatase (Wiesner et al. 1999; Demetris et al. 2000).

The development of CR is usually seen in three typical clinical scenarios. Early (less than 6 weeks) is usually seen within the first month posttransplant. The presentation is similar to that of ACR with a rapid rise in liver biochemistries and biopsy with features of rejection cholangitis. The episode fails to respond to additional immunosuppression therapy, and subsequent follow-up liver biopsy reveals persistent rejection cholangitis and bile duct destruction. The disease process continues to progress with loss of portal bile ducts and arteries; eventually, portal tracts become fibrotic and inflammatory infiltrates subside. Liver biochemistries continue to worsen, and ultimately, the patient develops graft failure requiring retransplantation. Delayed CR (6 weeks to 6 months) is the most common presentation. Typically, the patient will develop CR after one or more episodes of ACR that fail to respond to maximal immunosuppressive therapy. The biochemical and histological pattern is similar to early CR. The third and least common presentation is late CR (greater than 6 months). Often this condition is seen in combination with a late ACR episode that fails to respond to therapy, or alternately, it can develop in an LTR with previously unrecognized episodes of ACR. Again, these patients will have slow progression to cholestatic graft failure. This scenario is unusual and occurs in patients who are noncompliant with immunosuppressive therapy (Wiesner et al. 1999).

A number of risk factors have been identified for chronic rejection. Younger recipient age, donor-recipient sex disparity, black and non-European recipients, CMV infection, insufficient immunosuppression, and the histologic severity as well as the number of episodes of ACR are all known risk factors for chronic rejection (Wiesner et al. 1999; Thurairajah et al. 2013).

Histologically, in chronic rejection, the perivenular areas and portal tracts are most severely affected. The portal tracts show damage and eventual loss of small bile ducts and small branches of the hepatic artery. The damage to the bile ducts is caused by a combination of mechanisms: direct immunological damage from the rejection process, obliterative arteriopathy causing indirect ischemic insult resulting in small artery/arteriolar loss, and destruction of the peribiliary capillary plexus (Demetris et al. 2000). Since the human liver biliary system is exclusively supplied by the hepatic artery, once small hepatic arterioles are destroyed, there is irreversible bile duct loss.

Typically, the clinical course of the LTR with chronic rejection is poor, and these patients ultimately require retransplantation. Fortunately with newer tacrolimus-based CNI regimens, the incidence of CR is very low. If less than 50 % of the bile ducts in the allograft are preserved, the recipient has an improved chance of survival if interventions are performed. There is no universal protocol for the treatment of CR. Generally, if the patient is not on a tacrolimus-based regimen, they should be switched to one. Labs and tacrolimus levels should be checked frequently. If tolerated, higher tacrolimus levels then are used for maintenance immunosuppression should be targeted.

Conclusion

Overall transplant immunosuppression has allowed the LTR to have prolonged graft survival, and graft loss from rejection no longer remains a clinical concern. Induction therapy allows for reduced doses of calcineurin inhibitors, thereby reducing renal side effects. Maintenance regimens consist of CNI, MPA, and, depending on the underlying liver disease, low-dose corticosteroids. MTORi may be employed in strategies to minimize nephrotoxicity of CNIs via adjunctive CNI reduction or eventual CNI replacement. Patients must be monitored for the long-term side effects of immunosuppressive medications, and preemptive healthcare screening should be employed to prevent complications.

Cross-References

- Hepatitis C Virus Infection: A New Era
- History of Liver and Other Splanchnic Organ Transplantation
- Infections and Sepsis After Liver Transplantation
- Orthotopic Liver Transplantation: Complications
- Pathology of Liver Transplantation

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Pathology of Liver Transplantation 21

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Abstract

Liver biopsy is an integral part of the clinical management of liver transplant patients. In most cases, it provides essential information for diagnosis, assessment of disease activity and extent, and further guidance in treatment. In this chapter, the liver pathology of the most common disease entities in the post-transplant setting are reviewed, including early complications, rejection, and recurrent disease. For pathologists, it is crucial to recognize the pattern of injury on histopathology, and communication with the clinical team is important to arrive at a definitive diagnosis.

Keywords

Liver transplantation • Pathology • Donor biopsy • Preservation/reperfusion injury • Biliary complications • Rejection • Acute cellular rejection • Chronic rejection • Recurrent disease • Recurrent hepatitis C • Fibrosing cholestatic hepatitis • Plasma cell-rich hepatitis • Recurrent autoimmune hepatitis • Recurrent primary biliary cirrhosis • Recurrent primary sclerosing cholangitis • Recurrent non-alcoholic steatohepatitis • CMV hepatitis

Introduction

Liver transplantation is a standard therapy for many end-stage liver diseases (ESLDs), acute liver failure, selected hepatic neoplasms, and metabolic diseases with systemic manifestations (Martin et al. 2014). The most common indication for liver transplantation in the USA is hepatitis C cirrhosis, while other indications include hepatitis B, alcohol-induced liver disease (ALD), autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis, etc. With the advancement of surgical techniques, optimization of immunosuppressive therapy, and prevention of complications, the 1-year post-transplant survival rate after liver transplant is approaching 90 %, and the 5-year survival rate is approximately 75 % (Martin et al. 2014).

The pathologic processes that occur in the liver allograft include primary non-function, preservation/reperfusion injury, surgical complications, rejection, infections, recurrent disease, and de novo disease. During the different time periods following transplantation, certain processes predominate (Table 1); for example, most life-threatening complications occur in the peri-operative period, whereas long-term

Table 1 Liver allograft complications

Time period	Common complications	Less likely complications
Perioperative	Donor liver diseases (e.g., steatosis)	
	Preservation injury	
	Hyperacute rejection	
	Primary non-function	
Within the first week	Preservation/ reperfusion injury	Hyperacute rejection
	Hepatic artery thrombosis	Recurrent viral hepatitis
	Portal vein thrombosis	Sepsis
	Bile duct leak	
	Acute cellular rejection	
1 Week to 2 months	Acute cellular rejection	Chronic rejection
	Recurrent viral hepatitis	Opportunistic infections
	Preservation/ reperfusion injury	
	Biliary complications	
	Drug reactions	
More than 2 months	Acute cellular rejection	Persistent preservation/ reperfusion injury
	Chronic rejection	Post-transplant lymphoproliferative disorder
	Recurrent liver diseases	
	De novo liver diseases	
	Biliary complications	
	Drug reactions	

complications mainly include recurrent disease, chronic rejection, and effects of chronic immunosuppressive therapy. Histopathologic assessment of a liver biopsy is often very helpful, and in some cases is the 'gold standard' in establishing a specific diagnosis. Thus, liver biopsy is an integral part of the clinical management of liver transplant patients.

Evaluation of Donor Biopsies

Histologic evaluation of donor biopsies is not routinely performed in most centers. A liver biopsy is requested when the gross appearance of the liver is of concern (e.g., fatty liver), when the donor is known to have pre-existing disease (e.g., hepatitis C infection), or when an extended criteria donor graft is to be used. Examples of the extended criteria donor include advanced donor age (>60 years), donation after cardiac death (DCD), increased cold ischemia time (>12 h), moderate to severe macrovesicular steatosis (>30 %), hypernatremia, hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, and a history of malignancy (Harring et al. 2011).

For frozen section evaluation of the donor liver, at least two tissue core biopsies (one from the right lobe and one from the left lobe) should be collected. A third wedge biopsy from the subcapsular right lobe may also be added in some centers. To avoid preparation and freezing artifacts, the fresh liver tissue should be moistened in preservation solution and transported immediately to the frozen section laboratory. Air drying and storage in physiologic saline should be avoided because they can cause hepatocytes to appear shrunken or necrotic. Absorbent substrates and dry tissue paper should also be avoided because they can cause the extent of steatosis to be underestimated.

Histologic findings that usually disqualify an organ for transplantation include hepatic necrosis involving >10 % of the hepatocytes, significant macrovesicular steatosis (>30 %), moderate or severe atherosclerosis of intrahepatic artery branches, and at least bridging fibrosis. Of these factors, the most commonly assessed is steatosis. There are three types of hepatic steatosis (Fig. 1): macrovesicular steatosis is defined as a single intracytoplasmic fat droplet greater than the nuclear diameter that displaces the nucleus; small droplet steatosis is defined as multiple, small fat droplets less than the nuclear diameter with a centrally placed nucleus; and true microvesicular steatosis is defined as numerous tiny lipid droplets surrounding the nucleus and imparting a foamy appearance to the cytoplasm. Many studies have shown that moderate to severe macrovesicular steatosis (>30 %) is associated with an increased risk of early graft dysfunction and failure (Briceño et al. 2009; Spitzer et al. 2010; Gabrielli et al. 2012; Chu et al. 2015). However, several recent reports question this notion, particularly when other risk factors such as cold ischemia time are absent (McCormack et al. 2007; Westerkamp et al. 2015). Small droplet steatosis is often the result of a short period of warm ischemia or other insults, and does not affect outcome (Fishbein et al. 1997). Oil red O stain may be utilized to evaluate fat content; however, the extent of steatosis can be estimated reliably by hematoxylin and eosin (H&E) stains alone, provided that all care is given to eliminating possible artifacts.

Post-Transplant Needle Biopsies

Histologic assessment plays an important role in determining the cause of allograft failure/dysfunction, evaluating disease progression, and assessing the effects of therapy, thereby providing guidance for further clinical management. Similar to the guidelines for native liver provided by the American Association for the Study of Liver Diseases, in order to ensure sufficient tissue for diagnosis, an adequate transplant biopsy is best attained by two passes with a 16-gauge needle. This is especially relevant at later time periods when fibrosis can be present, since small biopsies (much smaller than 20 mm in length or <11 total portal tracts) can be subject to sampling error (Rockey et al. 2009).

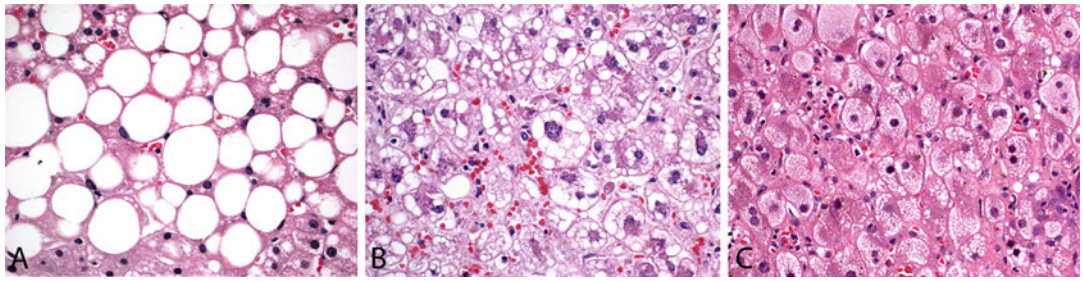

Fig. 1 Three types of steatosis in liver: (**a**) macrovesicular steatosis; (**b**) small droplet steatosis; and (**c**) microvesicular steatosis

Preservation/Reperfusion Injury

Preservation/reperfusion injury is a major cause of primary non-function or dysfunction of the allograft. Preservation injury occurs in two phases. The initial cold ischemia lasts less than 12 h, and occurs when the donor organ is stored in preservation fluid and placed in an ice bath. The second phase, a shorter period of warm ischemia (<120 min), results from suboptimal perfusion of the liver at body temperature before and during harvesting. Studies have demonstrated that cold ischemia mainly affects sinusoidal endothelial cells, whereas warm ischemia primarily damages hepatocytes (Schön et al. 1998). Other cell types, including bile duct cells, Kupffer cells, and Ito cells, are also very sensitive to cold and warm ischemia (Wang et al. 2011). The duration and severity of the ischemia determines the degree and type of injury. Several predisposing factors are especially important in preservation/reperfusion, including macrovesicular steatosis and DCD.

The hallmark of preservation/reperfusion injury is centrilobular (zone 3) hepatocyte ballooning, scattered acidophil bodies, and hepatocyte dropout (Fig. 2). Surgical hepatitis (perivenular sinusoidal neutrophilia without necrosis), perivenular cholestasis, and macrovesicular steatosis may also be evident. Severe preservation/reperfusion injury manifests as confluent hepatocellular necrosis, either centrilobular or panlobular, which usually results in graft failure (Fig. 2). A lack of significant portal or lobular inflammation is also characteristic.

Repair from preservation/reperfusion injury usually starts in 1–2 days and it is resolved within 2–4 weeks. Histologically, the resolving injury manifests as hepatocyte binucleation and repopulation of the perivenular areas, if dropout has occurred. In grafts with severe injury, brisk mitosis may be seen. Zone 3 hepatocyte ballooning and cholestasis may persist for several weeks. The differential diagnosis of preservation/reperfusion injury includes ischemia as a result of hepatic artery occlusion and hyperacute rejection.

Complications

A recent comprehensive meta-analysis of postoperative complications after liver transplantation reviewed 74 studies published between 2002 and 2012 including a cohort of 29,227 deceased donor liver transplant recipients in western countries (McElroy et al. 2014). The most common complications found include biliary complications (biliary leak and biliary stricture), vascular complications (hepatic artery thrombosis [HAT] and hepatic artery stenosis), and hemorrhage/thrombosis (portal vein thrombosis, hemorrhage, and pulmonary embolus).

Vascular Complications

Although vascular complications following liver transplantation rarely occur, they are the most feared complications due to the associated high incidence of graft loss and mortality (McElroy et al. 2014). The overall incidence of vascular

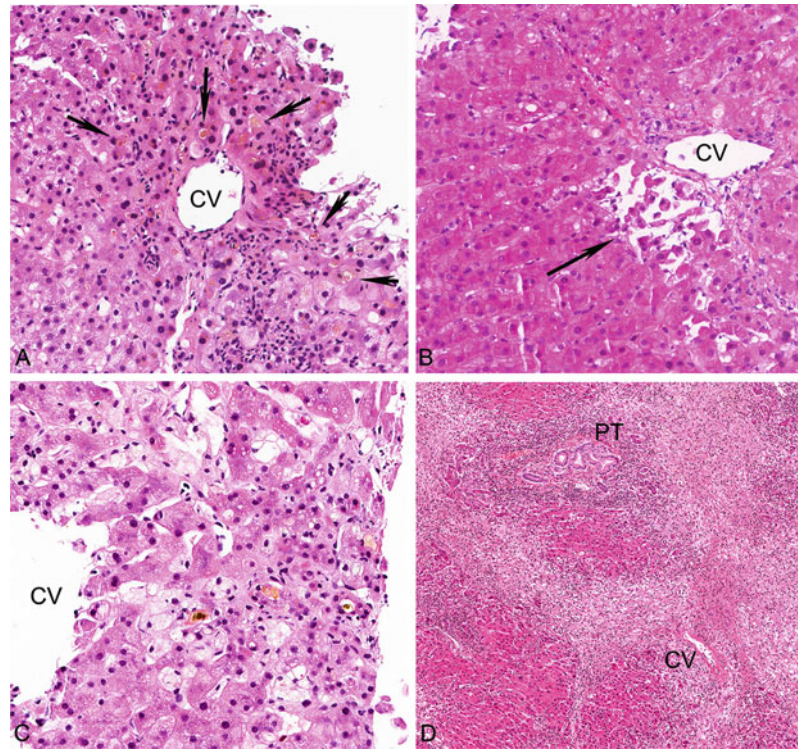

Fig. 2 Preservation/reperfusion injury: (**a**) centrilobular cholestasis (*arrows*); (**b**) centrilobular hepatocyte rounding and dropout (*arrow*); (**c**) centrilobular cholestasis and hepatocyte ballooning; and (**d**) confluent necrosis may be seen in severe cases, causing graft failure. *CV* central vein, *PT* portal tract

complications in adults is around 7 % in orthotopic liver transplantation (OLT) and 13 % in living donor liver transplants (McElroy et al. 2014). It often occurs within the first several months post-transplantation (Pawlak et al. 2003; Piardi et al. 2016).

Hepatic Artery Thrombosis

HAT is the most common vascular complication of liver transplantation. It is associated with a high rate of graft failure (>50 %) and high mortality rate (>50 %) in the absence of revascularization and retransplantation (Piardi et al. 2016). HAT is classified into two types: early HAT (within 30 days of liver transplantation) and late HAT (30 days or more after liver transplantation). The incidence of early HAT varies from 0 % to 12 % in adults, whereas the incidence of late HAT is around 7.5 % (Piardi et al. 2016). Risk factors for HAT include surgical causes at the anastomosis, a hypercoagulable state, extended cold ischemia time, donor positivity for cytomegalovirus (CMV) in a CMV-negative recipient, retransplantation, etc.

The hepatic artery supplies the biliary tree of the transplant. Therefore, biliary complications are frequently encountered in HAT and manifest as ischemic cholangitis/cholangiopathy. The structures most susceptible to ischemic injury include perihilar soft tissue and large bile ducts, which are most often not sampled in needle biopsies, thereby make these biopsies unreliable. The peripheral biopsies show ischemic injury, such as centrilobular (zone 3) hepatocyte swelling, dropout, and frank necrosis. Ischemic hepatitis is occasionally seen with spotty hepatocyte necrosis/acidophil bodies. Biliary changes, such as ductular reaction and acute cholangitis, may also be present. When a failed explant is examined grossly, hepatic artery thrombus with occlusion is observed and the liver parenchyma shows segmental collapse and necrosis. Other possible findings include bile duct epithelial damage/necrosis, acute cholangitis, and biliary abscesses.

The differential diagnosis includes primary biliary complications alone and acute viral hepatitis (in the case of ischemic cholangitis). Doppler ultrasound and computed tomography (CT) angiogram/angiography are important imaging modalities to confirm a suspected diagnosis of HAT.

Portal Vein Complications

Portal vein complications include thrombosis, stricture, and poor flow. They are relatively uncommon, occurring in 1–3 % of transplants (Piardi et al. 2016). Portal vein complications are associated with high morbidity and graft loss and are more common in split liver, living donor transplantations, and pediatric transplantations. The clinical presentation of these complications depends on the severity of the venous flow compromise, ranging from small infarcts, seeding bacteremia, and recurrent fever to massive necrosis and fulminant hepatic failure. Diagnostic tools include Doppler ultrasound, contrast-enhanced ultrasound, and contrast-enhanced CT.

Pathologically, complete portal vein thrombosis causes massive necrosis. Partial obstruction due to smaller thrombi, strictures, kinks, or persistent collateral circulation can cause periportal or zone 2 hepatocyte atrophy and necrosis. Unexplained panlobular or zonal steatosis or nodular regenerative hyperplasia may occur, and secondary infections may also be seen.

The differential diagnosis includes hepatic vein outflow obstruction, which can also cause hepatocyte necrosis. However, the zonal distribution is different in hepatic vein complications , mainly in the centrilobular and perivenular regions, with characteristic sinusoidal dilatation, red blood cells within the space of Disse, and perivenular fibrosis. Severe cases can lead to Budd-Chiari syndrome with hepatomegaly and ascites.

Biliary Complications

Biliary complications continue to be a major cause of morbidity in liver transplant patients, with a reported incidence of 10–30 % and a mortality rate of up to 10 % (Wojcicki et al. 2008). In a recent meta-analysis following OLT recipients from 2002 to 2012, the mean incidence of the most common biliary complications, namely biliary leak and stricture, was 7.9 % and 12.5 %, respectively (McElroy et al. 2014). Other common biliary complications include sphincter of Oddi dysfunction, hemobilia, biliary obstruction from cystic duct mucocele, stones, sludge, and casts. The majority of biliary complications occur within 6 months after transplantation, one-third occurring within 1 month and two-thirds within 3 months of surgery (Wojcicki et al. 2008). Biliary complications are one of the leading causes of allograft dysfunction within the first 3 months of liver transplantation.

Patients with biliary strictures present with cholestasis and associated abnormal liver function tests (selective elevation of alkaline phosphatase [ALP] and γ-glutamyltransferase [GGT] levels), pyrexia, or septicemia with coexisting cholangitis. Symptoms may be non-specific and are often masked by corticosteroid and immunosuppressive therapy. Biliary tract problems are often first suspected on routine liver biopsies, and cholangiography (magnetic resonance cholangiopancreatography [MRCP], endoscopic retrograde cholangiopancreatography [ERCP], or percutaneous transhepatic cholangiography [PTC]) is needed to confirm the diagnosis.

Pathologically, biliary strictures in liver allograft are identical to those seen in native liver. They show a biliary outflow obstruction pattern of injury: prominent ductular reaction, pericholangitis with neutrophilic infiltration within the bile duct epithelium, or ascending cholangitis with neutrophils within the bile duct lumen (Fig. 3). Hepatocellular and canalicular cholestasis may be seen, both of which are more prominent in the centrilobular region. Portal and periportal edema are seen in the early stages, whereas mixed portal inflammation, bile duct epithelial senescence-type damage, and fibrosis may develop when the condition becomes chronic.

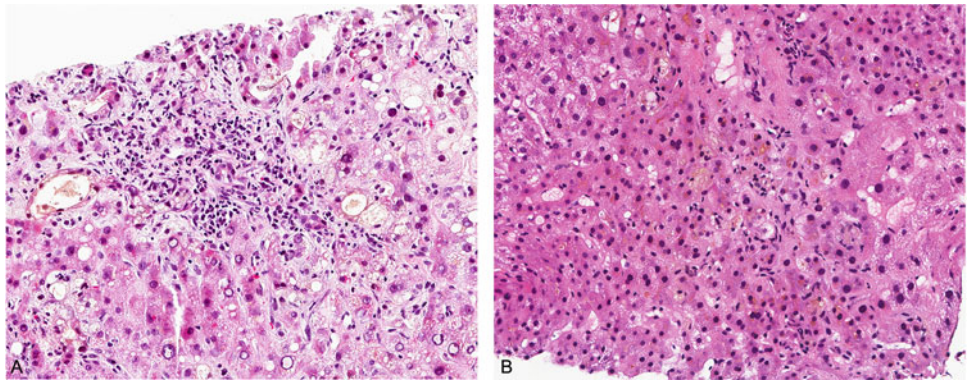

Fig. 3 Biliary outflow impairment. (**a**) Portal tract with prominent ductular reaction, mixed inflammation with lymphocytes and neutrophils, pericholangitis with associated bile duct/ductular epithelial damage, and cholestasis. Edematous stromal change is seen in the early stage. (**b**) Lobular inflammation and cholestasis

Rejection

Rejection is a host immune response against foreign donor antigens in the allograft. It has the potential to cause graft damage and graft failure in severe cases. The target cells involved in rejection include the bile duct epithelium and endothelial cells; hepatocytes are usually spared. Rejection is broadly divided into three main categories: humeral (or antibody-mediated) rejection, acute cellular (cell-mediated) rejection, and chronic rejection (Am J Gastroenterol 1994). In most cases, these processes reproducibly follow the time course post-transplantation: hyperacute antibody-mediated rejection occurs in the immediate post-operative period; acute cellular rejection (ACR) occurs within the first several months; and chronic rejection is a much later event. Nevertheless, there are reports that document chronic rejection within the first 3 months and ACR occurring years after transplant.

Humoral (Antibody-Mediated) Rejection

Primary humoral rejection is caused by pre-formed anti-donor antibodies in the recipient and occurs mainly in ABO-incompatible grafts. It may present as a hyperacute form within a few hours of transplantation, or as an acute form within a few days. The liver seems to have relatively high resistance to antibody-mediated injury. Thus, hyperacute rejection is rarely seen in clinical practice and when it does occur, effective therapy regimens usually transform it into a milder and delayed form that has later complications, such as increased acute rejection and late biliary strictures (Wu et al. 2011). Treatment options include plasmapheresis, splenectomy, and more aggressive immunotherapy. The employment of rituximab and mycophenolate therapies have also significantly improved the outcomes of ABO-incompatible grafts (Haberal and Dalgic 2004).

The earliest biopsy changes occur within a few hours and may show only fibrin deposition and neutrophils accumulating within sinusoids and small vessels. If left untreated, the graft may rapidly fail, and the pathologist will encounter a grossly enlarged explant with a hemorrhagic and mottled appearance. Sectioning shows extensive, geographic hemorrhagic necrosis. Microscopically, the liver parenchyma is diffusely congested and hemorrhagic with hepatocellular necrosis. Vascular thrombi and fibrinoid necrosis of blood vessels are also seen. Reperfusion injury and bile duct necrosis can also be present. A characteristic feature in this form of rejection is the lack of significant lymphocytic inflammation. Mild acute humoral rejection presents with portal edema, bile ductular reaction, and neutrophilic infiltration, reminiscent of bile duct obstruction. Deposition of C4d has been shown in sinusoids and portal vessels (Sakashita et al. 2007);

however, the significance and the utility of C4d deposition in diagnosis is uncertain. A definitive diagnosis of humoral rejection requires the presence of ABO incompatibility and anti-donor antibodies.

Acute Cellular Rejection

ACR is the most common form of liver allograft rejection. It usually occurs within the first month of transplantation, but is not uncommon in the first 3–6 months. ACR is associated with many risk factors, such as pre-existing autoimmune hepatitis or hepatitis C (Carbone and Neuberger 2014). Acute rejection can also occur months and even years post-transplantation, when it is mainly associated with inadequate immunosuppression. This form of rejection is mediated by inflammatory cells, mainly activated (blastic) lymphocytes, and the target tissue includes portal areas, bile ducts, and vascular structures.

Histologically, a characteristic triad is present during ACR: mixed portal-based inflammation, lymphocytic cholangitis, and endotheliitis (Fig. 4). The portal areas contain mixed inflammatory infiltrates, which include lymphocytes, macrophages, eosinophils, and neutrophils. Rarely, plasma cells may be seen. The lymphocytes are the predominant component of the portal areas; they are composed of activated or blastic lymphocytes as well as small T cells. The activated (blastic) lymphocytes are characterized by a larger cell size and vesicular chromatin with prominent nucleoli. Variable numbers of eosinophils are almost always present, and neutrophils may also be present. The bile duct shows lymphocyte-mediated injury that is manifested by lymphocytic infiltration within the ductal epithelium and associated ductal epithelial changes, including disarray, cytoplasmic vacuolation and eosinophilia, nuclear irregularity, overlapping, pyknosis, and apoptosis. Occasionally, mild ductular reaction and periductal neutrophilic infiltration may be seen and intraluminal neutrophils mimicking ascending cholangitis are observed rarely. Endotheliitis is the third feature of ACR and involves portal and central veins. Morphologically, it is characterized by subendothelial lymphocyte infiltrates lifting up and causing detachment of the endothelial cells.

Two of these three features (portal inflammation, bile duct injury, and endotheliitis) are required to establish a pathologic diagnosis of ACR. A Banff grading scheme is widely used in the transplant

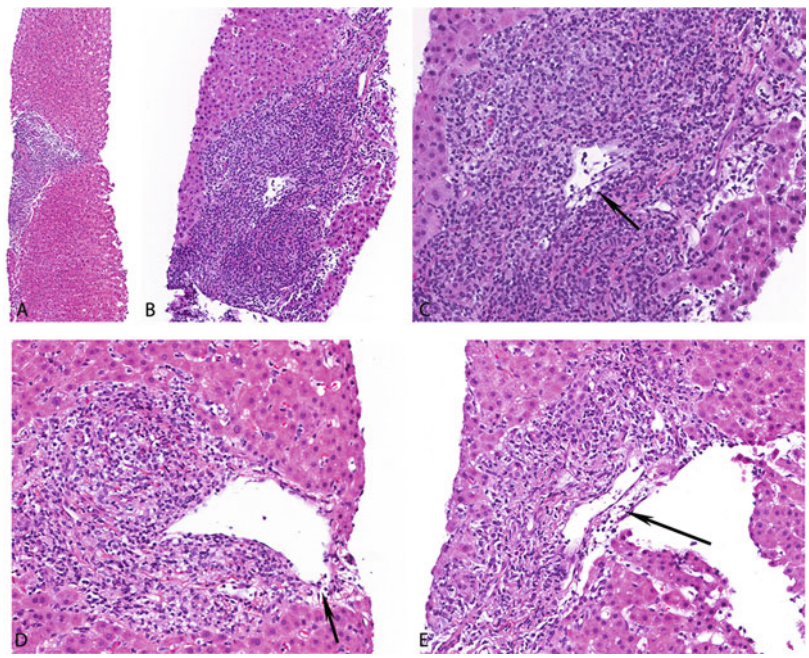

Fig. 4 Acute cellular rejection: (**a**) portal-based inflammation without lobular activity; (**b**) dense inflammation centered in the portal tract without interface activity; and (**c**, **d**, **e**) mixed inflammatory infiltrates are composed of lymphocytes (large, 'blastic'), eosinophils, neutrophils, and macrophages. Bile duct injury by lymphocytes and endotheliitis (*arrows*) are also prominent

Table 2 Banff working group criteria for acute liver allograft rejection (Adapted from Demetris et al. (1997))

Grade[a]	Criteria
Indeterminate	Portal inflammatory infiltrates that fail to meet the criteria for the diagnosis of acute rejection
Mild	Rejection infiltrate in a minority of the triads, which is generally mild and confined within the portal spaces
Moderate	Rejection infiltrate, expanding most or all of the triads
Severe	As above for mild, with spillover into periportal areas and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and its associated perivenular hepatocyte necrosis

[a]Grading is based on a global assessment of the liver biopsy and is carried out after a diagnosis of rejection has been established

community to grade ACR, in the form of either a descriptive grading scheme (Table 2) or a semi-quantitative Rejection Activity Index (RAI) (Table 3). A direct correlation exists between the total RAI score (rejection grade) and the risk of persistent/recurrent rejection, chronic rejection, and graft failure (Demetris et al. 2002). The total RAI scores range from indeterminate (score of 1–2), mild (score of 3–4), and moderate (score of 5–6) to severe (score >6). Most ACRs have a score <6 and respond well to increased immunosuppression. Severe ACR may cause inflammatory, necrotizing arteritis, but because it is usually located within the hilar region, it is generally not sampled on biopsy specimens.

Late ACRs (usually after 100 days, most often after 1 year) show similar histologic features to the early ACRs. However, they do have slightly different findings, such as fewer activated (blastic) lymphocytes, slightly greater interface activity, less endotheliitis, and slightly more lobular activity, which may mimic recurrent hepatidities (Banff Working Group et al. 2006). Late ACR can also manifest as isolated central perivenulitis (perivenular inflammation and hepatocyte dropout) and may develop into chronic rejection with ductopenia.

Classic ACR cases are usually diagnostically straightforward; it is the indeterminate cases that pose significant diagnostic challenges. The main differential diagnosis is recurrent hepatitis, especially in the setting of recurrent hepatitis C, with the two entities having overlapping histologic features, including portal-based mononuclear inflammation, endotheliitis, and bile duct injury. However,

Table 3 Rejection Activity Index (Adapted from Demetris et al. 1997)

Category	Criteria	Score[a]
Portal	Mostly lymphocytic inflammation involving, but not noticeably expanding, a minority of the triads	1
	Expansion of most or all of the triads by a mixed infiltrate containing lymphocytes with occasional blasts, neutrophils, and eosinophils	2
	Marked expansion of most or all of the triads by a mixed infiltrate containing numerous blasts and eosinophils with inflammatory spillover into the periportal parenchyma	3
Bile duct	A minority of the ducts are cuffed and infiltrated by inflammatory cells and show only mild reactive changes such as increased nuclear cytoplasmic ratio of the epithelial cells	1
	Most or all of the ducts infiltrated by inflammatory cells. More than an occasional duct shows degenerative changes such as nuclear pleomorphism, disordered polarity, and cytoplasmic vacuolization of the epithelium	2
	As above, with most or all of the ducts showing degenerative changes or focal luminal disruption	3
Venous	Subendothelial lymphocytic infiltration involving some, but not most, of the portal and/or hepatic venules	1
	Subendothelial infiltration involving most or all of the portal and/or hepatic venules	2
	As above, with moderate or severe perivenular inflammation that extends into the perivenular parenchyma and is associated with perivenular hepatocyte necrosis	3

[a]Total score equals the sum of all categories

early recurrent hepatitis C shows more prominent interface and lobular necroinflammatory activity, only mild endotheliitis and bile duct injury, and less blastic lymphocytes.

Chronic Rejection

Chronic rejection is an immune-mediated, potentially irreversible damage to the liver allograft, especially the bile ducts, arteries, and veins. It occurs in approximately 3–5 % of patients by 5 years post-transplant (Demetris et al. 2000; Banff Working Group et al. 2006). Histologically, chronic rejection has two main features: progressive bile duct injury with subsequent ductopenia and obliterative vasculopathy involving large- and medium-sized arteries. The latter is not usually seen in biopsy material, and the former is the most commonly identified finding in chronic rejection. Therefore, chronic rejection is also referred to as chronic ductopenic rejection or vanishing bile duct syndrome (Table 4).

In a biopsy specimen, the minimum diagnostic criteria for chronic rejection are (1) biliary epithelial senescence or degenerative changes affecting a majority of the bile ducts with or without bile duct loss; or (2) foam cell obliterative arteriopathy; or (3) bile duct loss affecting >50 % of the portal tracts (Banff Working Group et al. 2006). Bile duct epithelial senescence or degenerative-type changes include an eosinophilic cytoplasm with irregular, enlarged, and overlapping nuclei that mimicks a dysplasia-type appearance. Some small bile ducts may be only partially lined by biliary epithelial cells, a finding that is thought to precede frank duct loss. Perivenular hepatocyte dropout and central perivenulitis are typical of early chronic rejection (Fig. 5). When ductopenia (defined as loss of interlobular bile ducts in more than 50 % of the portal tracts) is present, there is usually a lack of inflammation as well as a bile ductular reaction (Fig. 5). In difficult cases, a CK7 immunostain may help delineate the bile ducts and secure the diagnosis. As stated earlier, the obliterative arteriopathy involves medium- to large-sized arteries; however, inflammatory or foam cell lesions may be seen in portal or hepatic venules, causing luminal fibrous obliteration.

Table 4 Early and late features of chronic rejection (Data from Demetris et al. 2000)

Structure	Early chronic rejection	Late chronic rejection
Small bile ducts	Bile duct loss in <50 % of portal tracts Degenerative and atrophic changes in the majority of the ducts (cytoplasmic eosinophilic change, nuclear overlapping, hyperchromasia, uneven nuclear spacing, nuclear loss, with epithelial attenuation)	Bile duct loss in at least 50 % of portal tracts Degenerative changes in remaining ducts
Central veins and zone 3 hepatocytes	Intimal/luminal inflammation, zone 3 necrosis and dropout, mild perivenular fibrosis	Focal obliteration with variable inflammation, severe fibrosis including bridging fibrosis
Hepatic arterioles	Loss of hepatic arterioles in <25 % of the portal tracts	Loss of hepatic arterioles in >25 % of the portal tracts
Large perihilar hepatic artery branches	Intimal inflammation, focal foam cell deposition without luminal compromise	Luminal narrowing by suboptimal foam cells, fibrointimal proliferation
Large perihilar bile ducts	Periductal inflammation, injury and focal foam cell deposition	Mural fibrosis
Lobules	Spotty hepatocyte necrosis ('transitional hepatitis')	Marked cholestasis, clusters of foamy macrophages

Recurrent Diseases

Almost all primary liver diseases recur after transplantation, although the incidence and time course varies according to each disease entity. Recurrence may pose a significant risk for long-term graft dysfunction, even graft loss. Liver biopsy is an important diagnostic tool in the

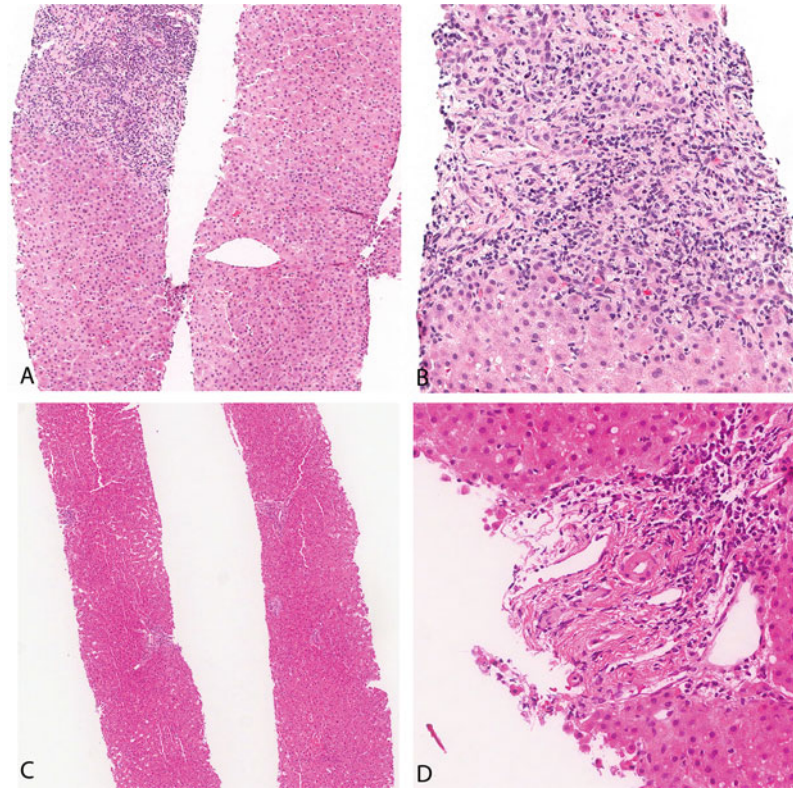

Fig. 5 Chronic rejection: (**a**, **b**) early chronic rejection with portal inflammation and bile duct injury, without endotheliitis; and (**c**, **d**) late chronic rejection with ductopenia (absence of bile duct in a portal tract in **d**)

evaluation of disease recurrence and activity (Table 5).

Hepatitis C Virus Infection

HCV infection recurs universally in liver transplant recipients (deLemos et al. 2014; Dumortier et al. 2014). Although the natural history is variable, 80 % of HCV patients develop recurrence on histologic evaluation within 5 years after liver transplant (Dumortier et al. 2014). In recurrent HCV infection, patients develop cirrhosis more rapidly (20–30 % by 5 years post-transplant), with an accelerated rate of decompensation (>40 % at 1 year and >70 % at 3 years post-transplant vs. <5 % and <10 %, respectively, in immunocompetent patients). There is also an accelerated rate from decompensation to death (3-year survival of <10 % following the first decompression vs. >60 % in immunocompetent patients) (Dumortier et al. 2014). Early (1 year) post-transplant biopsy has been shown to have prognostic value for graft cirrhosis (Gane et al. 1996; Prieto et al. 1999; Firpi et al. 2004) and survival (Neumann et al. 2004). Therefore, a 1-year post-transplant protocol biopsy is essential for every liver transplant recipient.

Risk factors for poor prognosis in the recurrent HCV graft include donor age (over 40–50 years), viral factors (HCV genotype 1, high level of pre-transplant HCV RNA, HCV RNA 4 months post-transplant $\geq 1 \times 10^9$ mEq/mL), concurrent CMV or HIV infections, recipient characteristics (female, African American, metabolic syndrome, *IL28B* non-CC genotype), and immunosuppression (use of corticosteroids, sirolimus, and OKT3) (Dumortier et al. 2014).

Recurrent hepatitis C can be classified into three categories: early acute hepatitis; late chronic hepatitis; and unusual variants, including fibrosing cholestatic hepatitis (FCH) and the plasma cell-rich variants.

Table 5 Recurrent diseases

Disease	Incidence (%)	Diagnostic tests	Timing[a]	Histologic similarity to native liver disease
HCV	60–100	Biopsy HCV RNA does not correlate accurately with histology	6–8 weeks, can be as early as 10 days	Similar to native liver; acute hepatitis more often identified due to careful monitoring
HBV	<10	Viral DNA, serology; serum DNA used to monitor recurrence and therapy	6–8 weeks, can be as early as 10 days	Similar to native liver
AIH	30	Autoantibodies	>6 months	Similar to native liver
PBC	20–30	Biopsy	>1 year	Similar to native liver
PSC	30	Cholangiogram	Usually >1 year	Similar to native liver
NASH	20–40	Biopsy		Similar to native liver
ALD	5–30	Biopsy, serum carbohydrate deficient transferrin		Similar to native liver

AIH autoimmune hepatitis, *ALD* alcoholic liver disease, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NASH* non-alcoholic staetohepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis
[a]Usual timing of first onset

Acute Recurrent Hepatitis C

The onset of acute recurrent hepatitis C is generally within 4–12 weeks after transplant, with the earliest recurrence being detectable between days 9 and 14 post-transplantation (Saraf et al. 2007; Demetris 2009). Acute recurrent hepatitis C shares similar histopathologic findings as those of native livers, including prominent lobular hepatitis with little or no portal tract involvement. Lobular hepatitis features hepatocyte disarray, apoptosis (Councilman bodies or acidophil bodies), Kupffer cell hypertrophy, and mild sinusoidal lymphocytosis. A greater number of the apoptotic bodies are more indicative of recurrent hepatitis C than of ACR (Saxena et al. 2002).

Chronic Hepatitis C

Chronic hepatitis C is usually evident in the 6–12 months post-transplantation and has similar histologic findings as in the native liver, with portal-based lymphocytic inflammation, lymphoid aggregates, interface activity, and lobular necroinflammatory activity. Lymphocyte-mediated bile duct injury, ductular reaction, as well as perivenulitis and endotheliitis may be seen, but are usually mild and affect only a few portal tracts (Fig. 6). Since these features are also present in ACR, the extent and severity are key to making the correct diagnosis. Similar to the native liver, grading for activity and staging for fibrosis is required for recurrent disease, and the Batts and Ludwig grading system is widely used (Batts and Ludwig 1995).

Unusual Variants

Fibrosing Cholestatic Hepatitis

First recognized in post-transplant recurrent HBV patients in the 1990s (Davies et al. 1991; O'Grady et al. 1992), FCH is a rapidly progressive and severe form of recurrent hepatitis C. It was later reported in HCV patients who are immunosuppressed following cytotoxic therapy, HIV infection, or another solid organ transplant. The incidence of FCH is estimated to be between 2 % and 14 % (Satapathy et al. 2011) and it carries a high risk of liver failure and mortality (Satapathy et al. 2011; Verna et al. 2013). In 2003, a consensus conference attempted to define this entity with the following criteria (Wiesner et al. 2003): (1) >1 month and usually <6 months post-transplant; (2) serum bilirubin level >6 mg/dL; (3) serum ALP and GGT levels >5 times the upper limit of normal; (4) characteristic histology with hepatocyte ballooning, a paucity of inflammation, and cholestasis; (5) very high HCV RNA levels; and (6) absence of biliary or hepatic artery complications. More recent advances in treating FCH with sofosbuvir and ribavirin has been shown to have promising results. In one study by

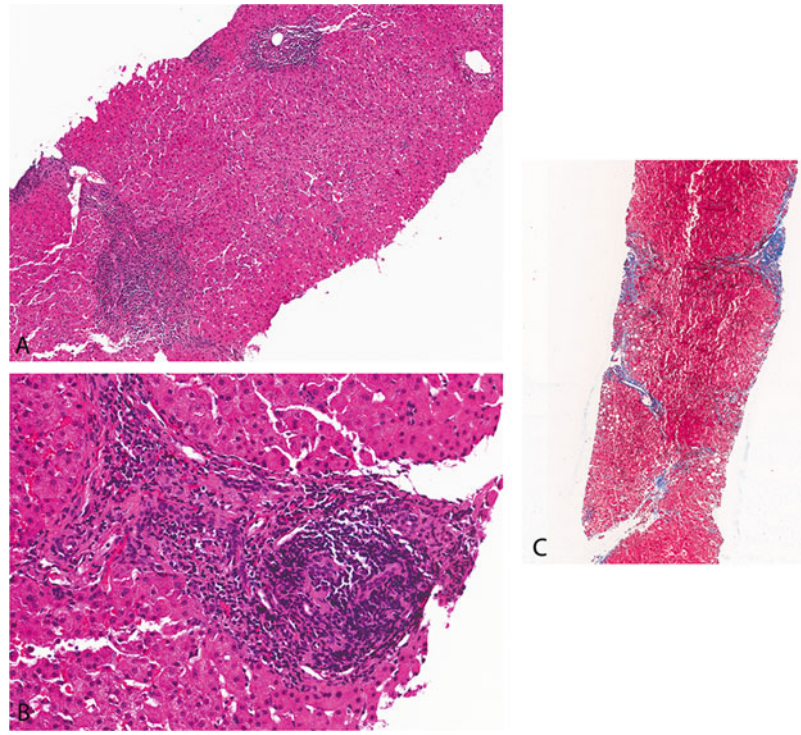

Fig. 6 Recurrent chronic hepatitis C: the usual variant. (**a**) Portal inflammation with interface activity and mild lobular activity. (**b**) Portal inflammation composed of predominantly small mature lymphocytes, with no bile duct injury or endotheliitis. (**c**) Trichrome stain shows bridging fibrosis

Saab et al. (2015), the 1-year patient and graft survival rates were 90 % and 80 %, respectively, in ten FCH patients treated with the above regimen. Another study of FCH patients treated with either sofosbuvir and daclatasvir, or sofosbuvir with ribavirin achieved a complete clinical response at week 36 (patient survival without retransplantation) (Leroy et al. 2015).

Histologically, FCH has a distinct set of morphologic features, including (1) prominent ductular reaction in the majority of portal tracts; (2) cholestasis (defined as canalicular bile plugs and/or intracellular bile pigment); (3) prominent hepatocyte swelling with lobular disarray; and (4) any degree of sinusoidal/pericellular fibrosis (Verna et al. 2013) (Fig. 7). The key differential diagnosis is biliary outflow obstruction. Salomao et al. (2013) compared the different histologic features between 13 FCH patients and 38 biliary obstruction (cholangiography-proven, HCV-negative cases). In their study, the portal tract features favoring biliary obstruction include bile duct dilatation, portal edema, acute cholangitis, and periductal fibrosis. Portal inflammation and periportal sinusoidal fibrosis (on Masson Trichrome stain) favor FCH. Ductular reaction is equally prominent in both groups (Table 6). Bile infarcts are only present in biliary obstruction cases, whereas hepatocellular swelling with lobular disarray was significantly more common in FCH. Also, a greater degree of lobular inflammation is seen in FCH. Salomao et al. (2013) also looked at copper/copper-binding proteins and CK7 immunostains and concluded that biliary obstruction cases have more abundant copper/copper-binding proteins. These same cases also showed a greater number of CK7+ periportal intermediary hepatocellular cells, displaying weak to moderate cytoplasmic staining, which is different to the strong membranous staining pattern of bile duct/ductules.

Recurrent Hepatitis C with Autoimmune Features

Recurrent hepatitis C with 'autoimmune features' (plasma cell-rich hepatitis) is a variant that is characterized by a plasma cell-rich interface and perivenular necroinflammatory activity in

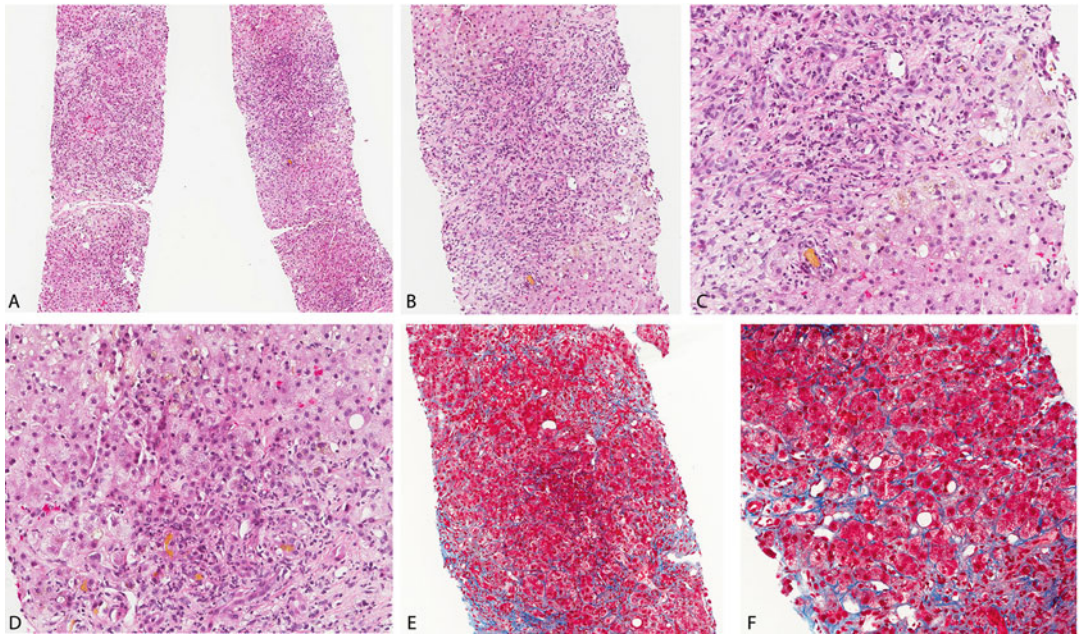

Fig. 7 Fibrosing cholestatic hepatitis. (**a**, **b**, **c**, **d**) Portal tracts show marked ductular proliferation, with pericholangitis, and cholestasis is seen. Lobular activity, hepatocyte ballooning and disarray, apoptosis are prominent. (**e**, **f**) The characteristic pericellular and perisinusoidal 'chicken wire-type' fibrosis on trichrome stain

Table 6 Histologic features to distinguish fibrosing cholestatic hepatitis from biliary obstruction (Adapted from Salomao et al. 2013)

	Histologic features
Favoring fibrosing cholestatic hepatitis	Portal inflammation Periportal sinusoidal fibrosis
	Hepatocyte swelling with lobular disarray
	Degree of lobular inflammation
Favoring biliary obstruction	Bile duct dilatation Portal edema Acute cholangitis Periductal fibrosis Bile infarcts Copper/copper-binding proteins present Abundant CK7+ periportal intermediate hepatobiliary cells
Equally present	Ductular reaction Ductular cholestasis

allografts of patients who underwent transplantation for reasons other than autoimmune hepatitis. It has been reported in patients transplanted for HCV (Ward et al. 2009). However, its pathogenesis is controversial. Current hypotheses include an autoimmune variant of HCV infection, acute rejection, de novo AIH, or a combination of these (Guido and Burra 2011). In some studies, this type of injury was associated with antiviral therapy, especially in the form of pegylated interferon and ribavirin, suggestive of an alloimmune response induced by interferon (Berardi et al. 2007; Feil et al. 2008; Merli et al. 2009; Levitsky et al. 2012). Other studies found no such association. Plasma cell-rich hepatitis has been shown to occur within 2 years of transplantation. In one study, 60 % of patients had a poor outcome (onset of cirrhosis, graft failure, and death) (Feil et al. 2008), which is worse than outcomes in those with classic recurrent HCV (Ward et al. 2009).

Histologically, plasma cell-rich hepatitis resembles classic AIH in native livers. It is characterized by prominent plasma cell-rich infiltrates within portal, periportal, and lobules (Fig. 8). Most of these patients also have increased serum immunoglobulins and autoantibodies, such as

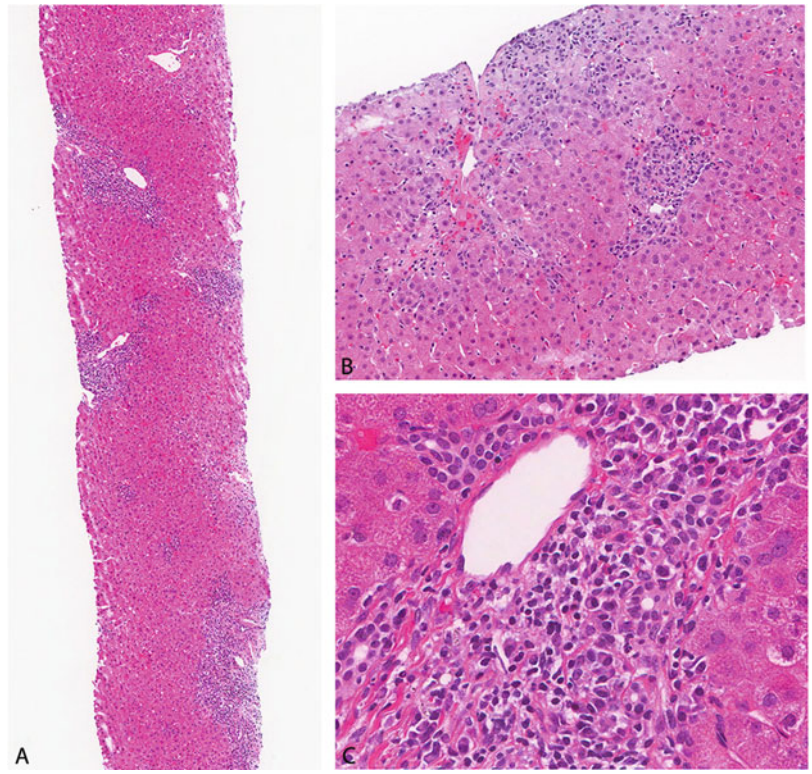

Fig. 8 Plasma cell-rich hepatitis: (**a**) portal inflammation with interface activity and lobular inflammation; and (**b**, **c**) plasma cell-rich inflammatory infiltrates within the portal tract and lobules

antinuclear antibodies (ANAs), anti-smooth muscle antibodies (ASMAs), etc. These patients are usually treated with corticosteroids and by optimizing calcineurin inhibitor levels. If the response is incomplete, other immunosuppressive agents, such as azathioprine or mycophenolate mofetil, are added. In the worst case scenario, retransplantation is considered.

Hepatitis B Infection (HBV)

HBV cirrhosis as an indication for liver transplantation has decreased dramatically in western countries as a result of the implementation of effective HBV vaccination. However, HBV cirrhosis remains a leading cause of liver transplantation in other countries, such as China. Before implementation of the prophylactic antiviral treatment, the rate of HBV recurrence ranged from 70 % to 90 % and was usually the rapid progressive FCH. Thus, liver transplantation was considered to be contraindicated in these patients (Katz et al. 2010; Ghaziani et al. 2014). This changed dramatically after prophylactic antiviral therapy, including nucleoside/nucleotide analogs such as lamivudine, adeforvir, tenofovir, entecavir, etc., along with hepatitis B immune globulin (HBIG). Since the introduction of lamivudine monotherapy following OLT in the late 1990s and early 2000s, the HBV recurrence rate has ranged from 3.8 % to 40.4 % (Mutimer et al. 2000; Lo et al. 2001; Perrillo et al. 2001). Combination therapy with lamivudine and HBIG has achieved encouraging outcomes, with 1- to 10-year studies demonstrating HBV recurrence rates shortly after OLT of less than 10 % (Katz et al. 2010).

Acute hepatitis B predominantly develops in patients with no treatment, and is mostly of historic interest. It develops immediately after transplantation, and becomes clinically evident 6–8 weeks later. Histopathology shows hepatocyte spotty necrosis, lobular activity and disarray, and Kupffer cell hyperplasia. A more severe form, FCH, can occur in this setting, although it

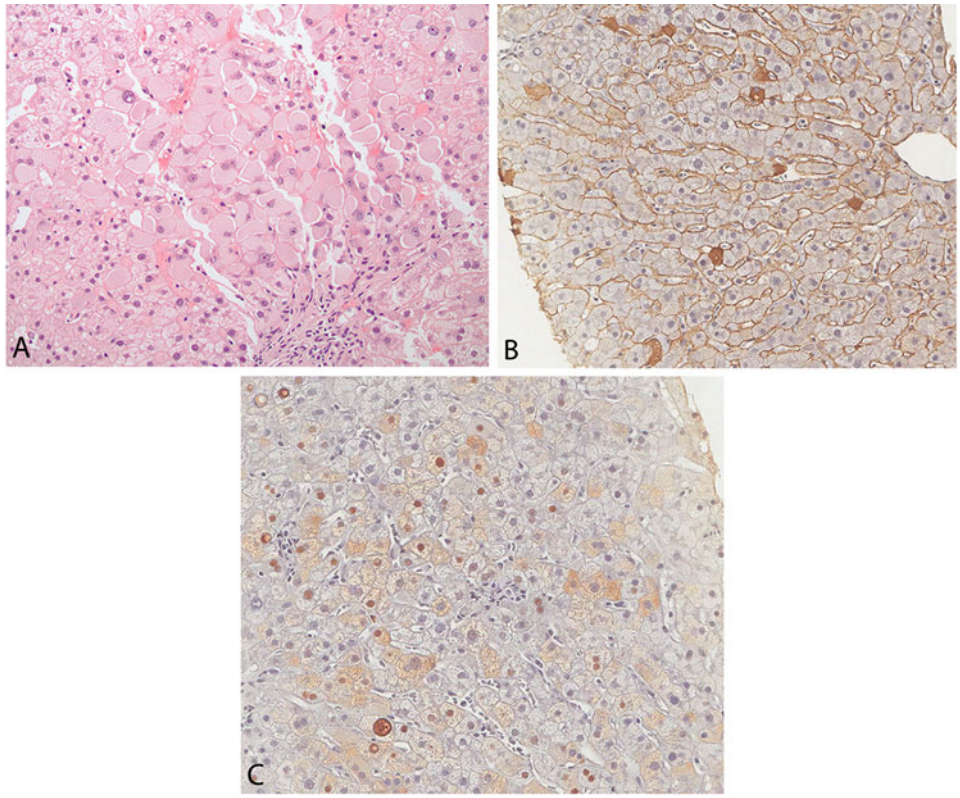

Fig. 9 Recurrent chronic hepatitis B: (**a**) ground glass hepatocytes; and (**b**) positive hepatitis B surface antigen (HBsAg) and (**c**) hepatitis B envelope antigen (HBeAg) on immunostains

occurred mostly in the era prior to the implementation of prophylactic antiviral treatment. It manifests as extensive hepatocyte damage with little inflammation but extensive bile ductular reaction, cholestasis, lobular disarray with hepatocyte swelling, and sinusoidal/pericellular fibrosis. Many ground glass cells are seen, which harbor hepatitis B surface antigen (HBsAg) and hepatitis B core antigen (HBcAg). This was thought to be the result of uncontrolled viral replication in immunocompromised patients, with a direct cytopathic effect induced by the large amount of viral DNA and protein (Lau et al. 1992; Mason et al. 1993).

In the majority of cases, acute hepatitis evolves into chronic hepatitis with a histopathology similar to that in the native setting and which spans the full spectrum of the disease, from a carrier state lacking inflammation to chronic hepatitis with degrees of severity (Fig. 9). Typical features include portal chronic inflammation, interface hepatitis, lobular necroinflammatory activity, and any degree of fibrosis. In a recent study of 184 patients who underwent OLT for HBV-related ESLD between 1999 and 2010, 156 received lamivudine plus HBIG and 28 were treated with lamivudine (Zhang et al. 2014). Of these patients, 97 % were alive at their last follow-up, and only 6 % had developed HBV recurrence at a median of 22 (range 6–46) months post-OLT. Four recipients who died of irreversible graft dysfunction secondary to HBV recurrence developed FCH because of no effective antiviral agents being available in the early stages of HBV recurrence after OLT. Six recipients who received adefovir and entecavir in the early stages of HBV recurrence following OLT achieved improvement in hepatic histology.

Autoimmune Hepatitis

Liver transplantation is indicated in patients with AIH for either end-stage cirrhosis or severe acute flairs. Due to the low incidence rate and highly effective medical therapy (corticosteroids and other immunosuppressive regimens), transplantation can be avoided in almost 90 % of AIH patients, and AIH accounts for only 2–3 % of pediatric liver transplants and 4–6 % of adult liver transplants in the USA (Kerkar and Yanni 2015). For end-stage AIH, liver transplant has achieved excellent outcomes with 1- and 5-year survival rates of 90 % and 80 %, respectively (Faisal and Renner 2015; Kerkar and Yanni 2015).

The recurrence rate of AIH in the allograft ranges between 15 % and 43 % (Faisal and Renner 2015; Kerkar and Yanni 2015), and has been reported in both pediatric and adult populations. The mean time to recurrence after transplantation is 4.6 years, but recurrence may occur as early as 35 days post-transplant (Liberal et al. 2012). Risk factors for AIH recurrence include an association with *HLA-DR3* and *HLA-DR4* mismatch, severe necroinflammatory activity in the native liver at the time of transplantation, early withdrawal of corticosteroids, inadequate immunosuppression due to non-adherence, co-existing autoimmune disorders, high titers of autoantibodies at the time of transplantation, prolonged disease course, and prolonged immunosuppression pre-transplantation (Kerkar and Yanni 2015).

Diagnosis of recurrent AIH is based on the proposed criteria listed in Table 7 (Tripathi and Neuberger 2009; Faisal and Renner 2015). Histologically, recurrent disease is similar to the native AIH (Fig. 10). There is often a significant portal inflammation with a mononuclear infiltrate, predominantly composed of plasma cells. Eosinophils can also be seen. Interface and lobular hepatitis are present with necroinflammatory activity characterized by apoptosis, with a varying degree of necrosis, including bridging necrosis in severe acute hepatitis. Central perivenulitis may be an early finding for recurrent AIH before the subsequent portal changes and focal bile duct injury may be seen.

Table 7 Diagnostic criteria for recurrent autoimmune hepatitis

Liver transplantation for confirmed diagnosis of autoimmune hepatitis
Elevated serum transaminases
Hypergammaglobulinemia (elevation of IgG)
Presence of autoantibodies (antinuclear antibodies, smooth muscle antibodies, and/or anti-liver kidney microsome type 1(LKM1) with titers >1:40
Compatible histopathology (interface hepatitis with portal inflammation and/or lymphoplasmacytic inflammatory infiltrates)
Response to corticosteroids
Exclusion of differential diagnostic considerations (including late/atypical, acute cellular rejection)

The key differential diagnosis for recurrent AIH is ACR, which can show overlapping histologic features. Marked lobular activity and bridging necrosis favor AIH, and widespread bile duct injury and endotheliitis favor rejection. In cases with subtle and early changes, the distinction may be very difficult to make, and correlation with clinical and serologic data, such as the antibody titers, may be helpful.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic disease that affects the extrahepatic and/or intrahepatic bile ducts. It often progresses with biliary stricture and fibrosis to cirrhosis and recurrent cholangitis, and carries an increased risk for cholangiocarcinoma. PSC has a strong association with idiopathic inflammatory bowel disease (IBD), with PSC developing in 5 % of IBD patients and up to 85 % of patients with PSC ultimately developing IBD. PSC is the fourth leading indication for liver transplantation in the USA (Faisal and Renner 2015) and the most common indication in Scandinavian countries (Fosby et al. 2012). It accounts for 4–5 % of adult liver transplantations in western countries (Faisal and Renner 2015). The long-term survival after transplantation for PSC is excellent, with a survival rate of more than 80 % and 70 % at 5 and 10 years, respectively (Tischendorf et al. 2007).

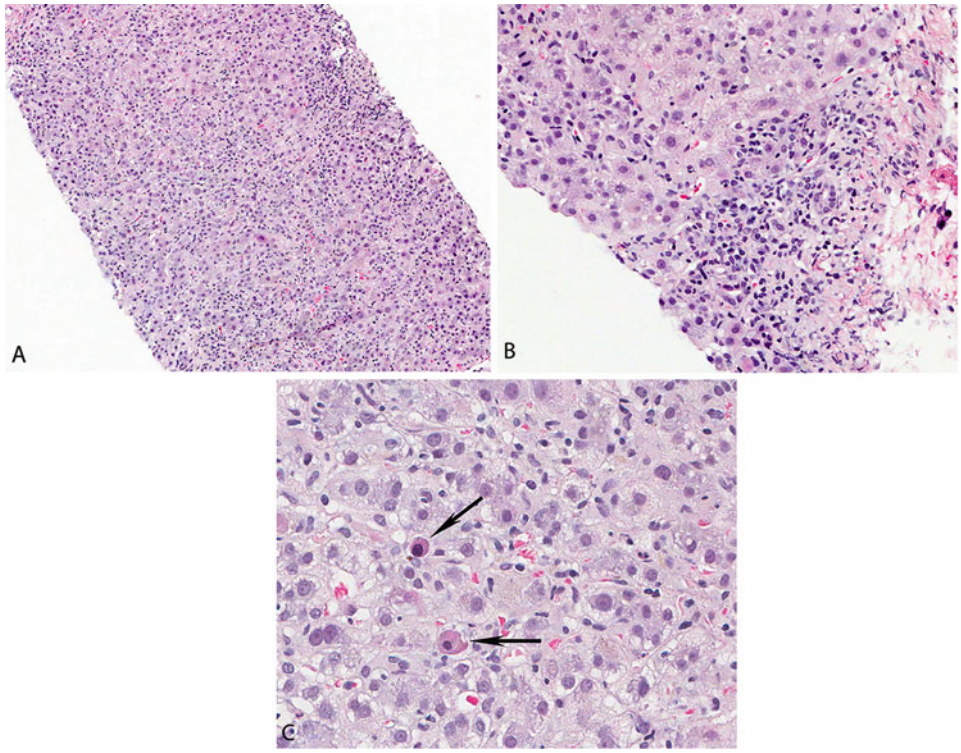

Fig. 10 Recurrent autoimmune hepatitis: (**a**) marked lobular inflammation; (**b**) portal and lobular inflammation with plasma cell-rich infiltrate; and (**c**) apoptotic bodies (*arrows*)

The recurrence rate of PSC is between 20 % and 30 % 5 years post-transplant, with the median time to recurrence ranging from 3 to 5 years (Campsen et al. 2008; Charatcharoenwitthaya and Lindor 2008; Alabraba et al. 2009). Risk factors associated with PSC recurrence include recipient or donor *HLA-DRB1**08, absence of donor *HLA-DR52*, male recipient, gender mismatch, an intact colon in the recipient prior to transplantation, the presence of ulcerative colitis after transplant, use of extended criteria donor grafts, ACR, corticosteroid-resistant ACR or use of OKT3, maintenance of corticosteroid therapy for ulcerative colitis for more than 3 months, presence of cholangiocarcinoma prior to transplant, and CMV infection in the recipient (Faisal and Renner 2015).

Early recurrence of PSC is very difficult to diagnose clinically due to the fact that various conditions, such as ischemic injury from prolonged preservation injury or DCDs, imperfect biliary anastomoses, inadequate arterial flow, and antibody-mediated rejection, can all cause intrahepatic biliary strictures mimicking recurrent PSC. Early recurrence manifests clinically after 6–9 months post-transplantation. Biliary strictures occurring before 90 days post-transplant are not usually attributed to recurrence. In later stages (>90 days), cholangiography findings help to distinguish recurrent PSC from other causes, including mural irregularity, diverticulum-like outpouchings, and features resembling PSC in native settings.

Diagnostic criteria for recurrent PSC are listed in Table 8 (Cholongitas and Burroughs 2012; Faisal and Renner 2015). Morphologically, biopsy findings of recurrent PSC are identical to those of the native liver. The characteristic onion skin-type concentric periductal fibrosis is usually present only within larger-sized ducts. Therefore, the biopsy is often non-diagnostic. The most common findings present on biopsies are those

Table 8 Diagnostic criteria for recurrent primary sclerosing cholangitis

Liver transplantation for primary sclerosing cholangitis
Cholangiography showing non-anastomotic biliary strictures of the intrahepatic and/or extrahepatic biliary system, with irregularities >90 days after liver transplant
Liver biopsy specimens showing fibrous cholangitis and/or fibroobliterative lesions with or without ductopenia
Absence of other pathology/disorders, including: Recurrent biliary infection Hepatic artery stenosis or thrombosis Chronic rejection Donor/recipient ABO incompatibility Non-anastomotic stricture developed during the first 90 days after liver transplant

secondary to biliary outflow obstruction, characterized by mild acute and chronic pericholangitis, ductular reaction, portal and periductal edema, cholestasis, and bile infarcts. Copper deposition and Mallory hyaline may be seen in periportal hepatocytes and bile duct loss may be seen. Rarely, periductal fibrosis and bile duct scars can be identified (Fig. 11).

As stated earlier, the main clinical differential diagnosis is biliary stricture due to other causes and requires radiographic and clinical correlation. The main histologic differential diagnosis is chronic rejection. Both PSC and rejection may show duct injury and duct loss. Recurrent PSC features ductular reaction, pericholangitis with neutrophils, and periductal concentric fibrosis; bile duct scars essentially rule out rejection.

Primary Biliary Cirrhosis

PBC is an immune-mediated chronic cholestatic liver disease that predominantly affects middle-aged women. It is characterized by positive anti-mitochondrial antibodies (AMAs) and progressive immune-mediated destruction of mid-sized intrahepatic bile ducts which ultimately leads to cirrhosis. Histologically, PBC manifests as destructive lymphogranulomatous cholangitis. PBC is the third most common indication for liver transplantation (9 %) in the European Liver Transplant Registry, after viral causes (hepatitis C and B) and alcohol-related cirrhosis (European Liver Transplant Registry) and is one of the top six for liver transplantation indications in the USA (Neuberger 2003). However, increased use of ursodeoxycholic acid (UDCA) has been associated with decreased mortality and, thus, the need for transplantation has decreased in recent years (Faisal and Renner 2015). In Europe, the post-transplant survival rates for PBC at 1, 5, and 10 years are 86 %, 80 %, and 72 % (Faisal and Renner 2015). The recurrence rate ranges between 10 % and 50 %, with a median time to recurrence ranging from 3.5 to 5 years post-transplantation (Sanchez et al. 2003; Sylvestre et al. 2003; Faisal and Renner 2015).

The diagnostic criteria for PBC are listed in Table 9. Histologically, the definitive feature of recurrent PBC is the presence of a florid duct lesion that is defined as a non-necrotizing granulomatous bile duct injury (Fig. 11), excluding infectious etiology. It is usually associated with lymphocytic cholangitis resulting in the damage to the bile duct epithelium. However, florid duct lesions are not always found in biopsies. Other less specific features seen in recurrent PBC include portal dense mononuclear infiltrates, focal lymphocytic cholangitis, and lymphoid aggregates (Fig. 11). Findings suggestive of a biliary cause of the injury also include a prominent ductular reaction, portal edema, cholate stasis, copper and copper-associated pigment deposition within the periportal hepatocytes, and patchy loss of small bile ducts. Lobular changes in recurrent PBC are usually mild and non-specific. If there is significant lobular activity, a concurrent disorder should be considered. Fibrosis is assessed using Masson trichrome stain and is staged the same as the native PBC: stage 0 (no fibrosis), stage 1 (portal fibrosis), stage 2 (periportal fibrosis), stage 3 (bridging fibrosis), and stage 4 (cirrhosis).

The differential diagnosis for recurrent PBC depends on the histologic pattern of injury. For granulomas, other causes, including infection (fungal, mycobacterial), sarcoidosis, and medication effects, need to be ruled out with special stains and a clinical history. If there is lymphocytic cholangitis, ACR needs to be considered;

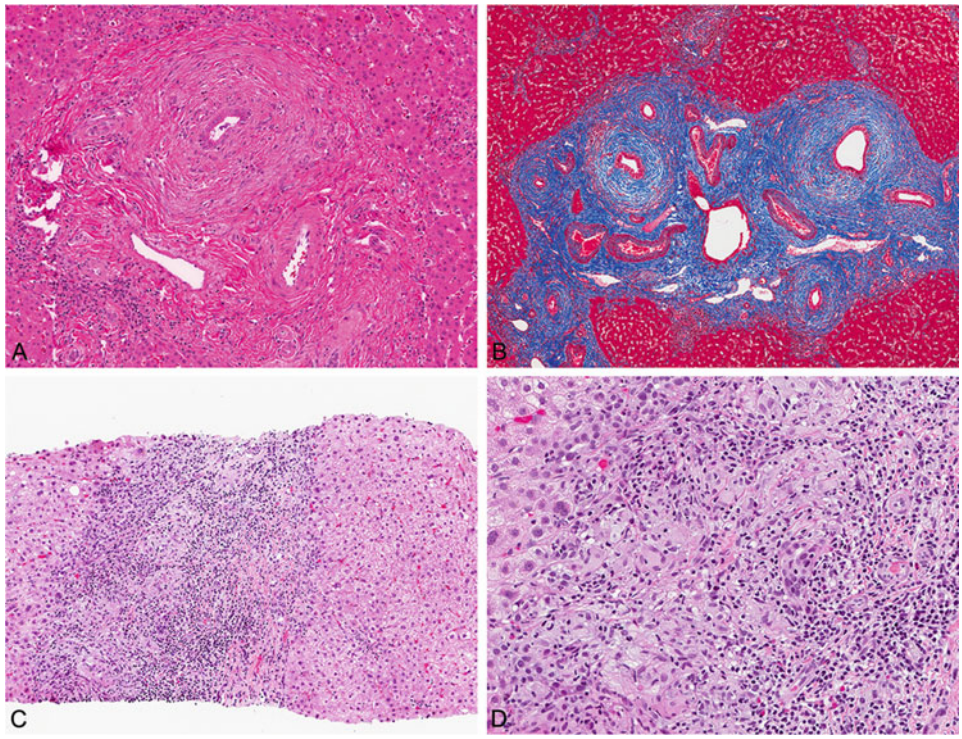

Fig. 11 Recurrent biliary disease: recurrent primary sclerosing cholangitis (a, b) with periductal 'onion skin'-type fibrosis on hematoxylin and eosin (H&E) (a) and trichrome (b) stains; and recurrent primary biliary cirrhosis (c, d), with a florid duct lesion (d)

ACR will usually have concurrent endotheliitis and lacks the prominent ductular reaction. De novo AIH or overlap syndrome may develop in patients with PBC after transplant, and the diagnostic criteria for native overlap syndrome also apply in the post-transplant setting. Overlap in serology (positive ANAs/ASMAs with positive AMAs), biochemistry (ALP $>3 \times$ upper limit of normal with aspartate aminotransaminase [AST]/alanine aminotransferase [ALT] $>5 \times$ upper limit of normal), and histology (lymphoplasmacytic infiltrate with interface activity and lobular inflammation, with concurrent bile duct lesions) are usually present in overlap syndrome (Trivedi and Hirschfield 2012). The bile duct injury pattern, especially with a prominent bile ductular reaction, should be differentiated from bile duct obstruction, the latter having portal edema, neutrophilic pericholangitis, and there should be radiographic evidence of biliary tract stricture.

Non-Alcoholic Fatty Liver Disease and Steatohepatitis

Non-alcoholic fatty liver disease (NAFLD) is a very common etiology of chronic liver disease in the USA. However, while highly effective antiviral treatments promise to reduce chronic HCV-related ESLD, increasing obesity, insulin-resistance, and metabolic syndrome in the population makes ESLD caused by NAFLD likely to become a leading indication for liver transplantation in the USA (Patel et al. 2016). Despite its co-morbidities (obesity, diabetes mellitus, cardiovascular disease, etc.) and the older age it is associated with, the post-transplant survival of NAFLD patients is at least comparable with that of other etiologies of ESLD. Risk factors for poor survival include increased age ($\geq$60 years), obesity (body mass index [BMI] $\geq$30 kg/m^2), pre-transplant diabetes mellitus, and hypertension (Malik et al. 2009; Agopian et al. 2012).

Table 9 Diagnostic criteria for recurrent primary biliary cirrhosis

Confirmed diagnosis of PBC in the explant histology
Characteristic histologic features[a]
Lymphoplasmacytic portal infiltrate
Lymphoid aggregates
Epithelioid granulomas
Evidence of bile duct injury
Persistence of AMA or AMA-M2
Exclusion of other causes of graft dysfunction
Acute and chronic rejection
Graft-versus-host disease
Bile flow impairment or cholangitis
Vascular complications
Viral hepatitis
Drug-induced hepatitis

AMA anti-mitochondrial antibodies, *PBC* primary biliary cirrhosis

[a]Definite recurrent PBC: three of four portal tract lesions are observed; probable recurrent PBC: two of four portal tract lesions are observed

The incidence of recurrent steatosis and recurrent non-alcoholic steatohepatitis (NASH) both range widely from 8 % to 100 % after 4 months to 10 years' follow-up (recurrent steatosis) and after 6 months to 20 years' follow-up (NASH) (Malik et al. 2009; Dureja et al. 2011; Agopian et al. 2012; Patil and Yerian 2012; Patel et al. 2016). Although recurrent NAFLD is very common, the need for retransplant is as low as 7 % which is similar to other causes of ESLD (Agopian et al. 2012).

NAFLD also develops in patients who undergo liver transplant for cryptogenic cirrhosis. However, several studies have shown a significantly lower occurrence of steatosis, NASH, and advanced fibrosis in patients with cryptogenic cirrhosis than in those with NASH cirrhosis pre-transplantation, with most studies showing a two- to three-fold reduction (Contos et al. 2001; Seo et al. 2007; Klintmalm et al. 2010; Vallin et al. 2014). Therefore, although some of the cases of cryptogenic cirrhosis may have been caused by unrecognizable NASH at the time of transplant, the exact pathogenesis is unknown in this group of patients. The risk factors for de novo allograft NAFLD include increased BMI, diabetes mellitus, hypertension, and donor liver graft steatosis (Contos et al. 2001; Seo et al. 2007; Klintmalm et al. 2010; Patil and Yerian 2012; Vallin et al. 2014; Patel et al. 2016).

Histologically, the minimal amount of steatosis required for a diagnosis of NAFLD is 5 %. NASH is assessed in a similar fashion as in the native liver (Fig. 12) and the diagnosis is based on the findings of steatosis, lobular inflammation, and hepatocyte ballooning. Fibrosis is evaluated using a trichrome stain, which typically begins in a pericellular/perisinusoidal pattern. A Brunt scoring system for NASH in the native liver can also be applied in the post-transplant setting (Table 10).

Alcohol-Induced Liver Disease

ALD is the second most common indication for liver transplantation in the USA (20 % of transplants) and Western Europe (40 % of transplants) (Iruzubieta et al. 2013; Berlakovich 2014). Although allocation of livers to patients with alcoholic disease remains controversial, the 5- and 10-year survival rates post-transplant for alcoholic cirrhosis in Europe are 73 % and 58 %, respectively, which are the same as those in recipients with other etiologies and are better than those for patients with HCV (Iruzubieta et al. 2013; Berlakovich 2014). The incidence of relapsed alcoholism is difficult to determine with certainty, and the reported rate of relapse ranges from 15 % to 50 % at 5 years post-transplantation (Iruzubieta et al. 2013). A recent large-scale study in France reported recurrent alcoholic cirrhosis in 6 % of patients transplanted for ALD, with younger age and a short period of pre-transplant abstinence identified as risk factors (Dumortier et al. 2015).

Clinically, recurrent alcohol abuse is usually detected via abnormal liver function tests, including a high GGT/ALP ratio and high blood alcohol level, as well as inappropriate social behavior and non-compliance with therapy.

Histologically, the recurrence of ALD shows identical features to those in native livers. Steatosis (small and large droplet) involving the centrilobular area is common. Steatohepatitis manifests as lobular inflammation, hepatocyte

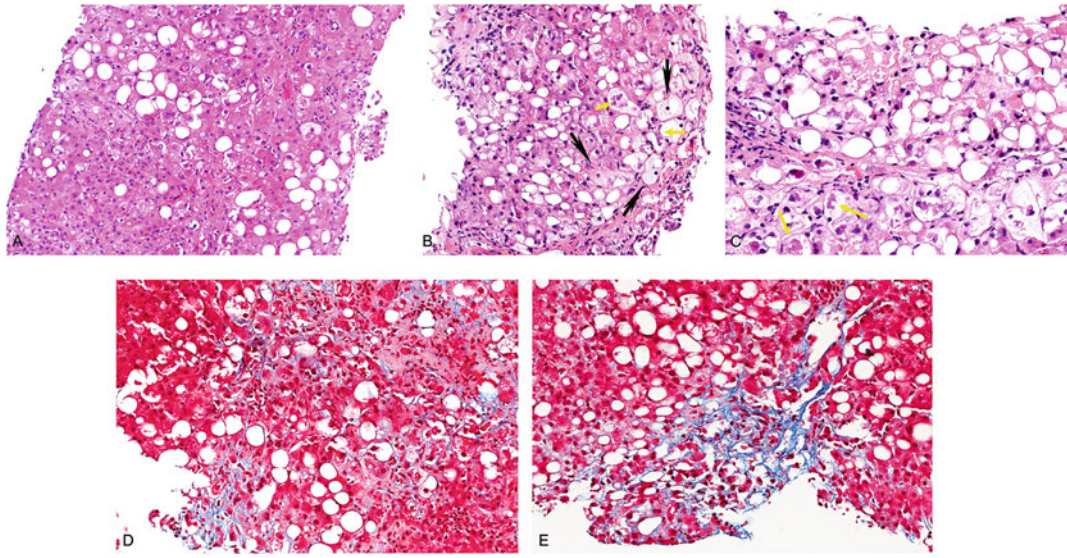

Fig. 12 Recurrent steatohepatitis: (**a**) macrovesicular steatosis, lobular inflammation, and hepatocyte ballooning; and (**b**, **c**) steatosis, lobular inflammation, ballooning (*black arrows*), and Mallory hyaline (*yellow arrows*)

Table 10 The Brunt scoring system for NAFLD

NAFLD Activity Score (NAS)
Steatosis:
0 (<5 %)
1 (5–33 %)
2 (34–66 %)
3 (>66 %)
Lobular inflammation (foci per 20× field):
0 (0)
1 (<2)
2 (2–4)
3 (>4)
Hepatocyte ballooning:
0 (none)
1 (few)
2 (many)
Total Score: ___/8
Stage:
0 (none)
1a (zone 3, perisinusoidal, need trichrome to identify)
1b (zone 3 perisinusoidal but easily seen on H&E)
1c (portal/periportal only)
2 (zone 3 and periportal, any combination)
3 (bridging)
4 (cirrhosis)

Reference: Kleiner et al. (2005)

ballooning, Mallory hyaline, and acidophil bodies. If alcohol abuse persists, fibrosis will develop, starting within the perivenular/perisinusoidal areas. Advanced alcoholic cirrhosis occurs in a minority of patients, and concurrent insults such as HCV will accelerate the process.

Differential diagnoses for both recurrent NAFLD and ALD are extensive, including all of the conditions that will cause steatosis and steatohepatitis. The most common causes include medications (amiodarone, synthetic estrogens, calcium channel blockers, tamoxifen, methotrexate, etc.), metabolic disorders, IBD, toxin exposure, etc. Impaired hepatic blood flow after transplantation is also an important etiology.

Metabolic Diseases

Jaffe (1998) classifies metabolic diseases into three categories, based on their effect on the transplanted liver. In Group 1, the liver is the primary site of the defect and is associated with ESLD. Examples include α_1-antitrypsin

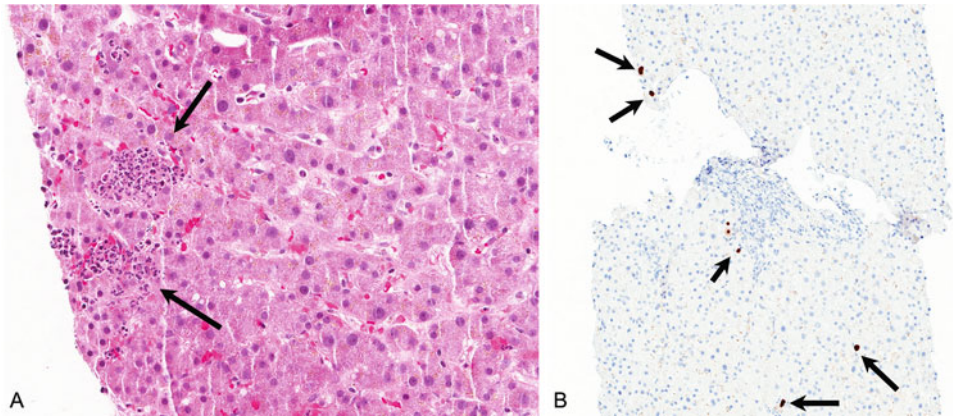

Fig. 13 Cytomegalovirus (CMV) hepatitis: (**a**) microabscesses (*arrows*); and (**b**) immunostain for CMV showing positive viral inclusions (*arrows*)

deficiency, familial intrahepatic cholestasis syndromes, some glycogen storage diseases, and Wilson's disease. Liver transplantation is curative in these patients, but certain types of disease may recur. In Group 2, the native liver is normal or near normal, and transplantation is required to relieve the symptoms caused by abnormal liver physiology. The resected native liver from these patients may be transplanted into patients with other chronic diseases in a process called 'domino transplantation.' Branched chain amino acid deficiencies, Crigler-Najjar syndrome, and hemophilia A and B are some examples in this group. In Group 3, the primary site of the metabolic defect is extrahepatic, and liver transplantation decreases liver disease-related morbidity and mortality, although metabolic disease persists after transplantation. Cystic fibrosis, porphyria, and Niemann-Pick disease belong to this group.

Infections

Post-transplantation infections are rare, with CMV and Epstein-Barr wire virus (EBV) among the most common agents in this setting. Other viruses, such as herpes simplex virus, varicella-zoster virus, and adenovirus, are occasionally seen. If necrosis or granulomas are identified in the biopsy specimen, special stains for fungal elements and mycobacterial organisms should be performed.

CMV hepatitis occurs as a result of the reactivation of latent viral infection from either donor or recipient origin and usually occurs in the early post-transplantation period. Histologically, it is characterized by microabscesses consisting of small clusters of neutrophils surrounding a necrotic cell. Patchy lobular inflammation, apoptosis, disarray, and Kupffer cell hyperplasia are seen. Viral inclusions may be identified on H&E stained slides, and the diagnosis is confirmed by a positive immunostain for CMV (Fig. 13).

EBV hepatitis in the allograft manifests as sinusoidal lymphocytosis as well as portal lymphocytic infiltration. The lymphocytes are predominantly large and atypical-appearing B cells. A positive in situ hybridization study for EBV-encoded small RNA within the lymphocytes confirms the diagnosis.

Medication/Toxin Effect

Drugs/toxins can cause liver injury, and many different patterns may be seen and are often non-specific. It is beyond the scope of this chapter to provide a detailed review. However, from a histology point of view, if a mixed pattern of injury is shown on a biopsy, then it is prudent to

seek a history regarding medications and toxins in addition to other relevant information.

Conclusion

The clinical management of liver transplant patients depends heavily on the use of a liver biopsy, which provides a diagnosis and assesses disease activity and chronicity, thereby serving to guide further therapeutic decisions. This chapter has reviewed the major concerns of liver transplant pathology, giving attention to pre-transplant donor biopsies, ischemia/preservation injury, early and late surgical complications following transplantation, acute and chronic rejection, and the problem of recurrent disease. It is crucial that pathologists who deal with liver transplant biopsies recognize the nature of the particular histopathological injury present in the biopsy and, in turn, communicate the specific nature of the alterations present to the clinical team so that informed therapeutic decisions can be made and implemented.

Cross-References

- ▶ Infections and Sepsis after Liver Transplantation
- ▶ Interventional Radiology for the Pre-Transplant Patient
- ▶ Orthotopic Liver Transplantation: Complications
- ▶ Orthotopic Liver Transplantation: Surgical Techniques

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Part VI

Radiology and Liver Transplantation

Radiology in Liver Transplantation

22

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Contents

Abstract

Radiology plays a major role in the care throughout the life cycle of the liver transplant candidate and recipient. Key diagnostic imaging modalities include ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) used for surveillance for the liver transplant candidate and for identifying and managing procedural complications related to tumor ablative techniques and transplantation. US generally serves as a screening modality and provides anatomic, or gray-scale, images to assess anatomic structures and Doppler images to evaluate blood flow in structures such as the hepatic artery and portal vein. CT and MRI provide an anatomic overview and are optimally performed with dynamic contrast-enhanced technique to evaluate the liver. While US is the usual screening modality in the pretransplant setting, CT and MRI are favored at some centers and fulfill problem-solving roles. Additionally, US and CT provide guidance for targeted procedures, including biopsy, ablation, and drainage. Catheter-directed therapy is also an important component of the pretransplant care program and includes the targeted delivery of therapeutic agents, such as chemotherapeutic agents and radiopharmaceuticals. Imaging plays a pivotal role in detecting posttransplant complications and determining the cause of graft failure, and understanding the modality-specific limitations and capabilities is critical to optimizing outcomes.

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Introduction

Radiology plays an important role in pre- and post-liver transplantation (LT). Periodic imaging surveillance is recommended to exclude hepatocellular carcinoma (HCC) prior to LT and to monitor for the development of complications after LT. Selecting the appropriate imaging modality depends on the clinical scenario and institutional preference, as outlined in the American Association for the Study of Liver Disease (AASLD) guidelines (Lucey et al. 2012; Martin et al. 2013). The primary imaging modalities used to evaluate the liver include ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). PET/CT serves an ancillary role in evaluating malignancy and potential metastatic disease. Interventional radiologic (IR) procedures are generally reserved for potential interventions to treat pretransplant HCC and posttransplant complications (see Table 1).

Imaging Modalities

Ultrasound

US generates diagnostic images by sending sound waves from a probe placed on the region of interest (ROI) (using acoustic gel to enhance sound wave transmission) and receiving the reverberated sound waves using the same probe device. The US images are updated in real time for review by the operator who chooses selected images for capture and documentation of key structures. Sound waves pass through fluid and solid organs, yielding diagnostic images of these structures, but fail to transmit through gas and skeletal structures and fail to render these structures sonographically. Because sound waves emanate only centimeters into the body from an operator-directed probe, US is a focused exam where the US technologist targets the ROI according to the provided history. The procedure is relatively labor and time intensive and operator dependent compared with other imaging modalities, and procedures are generally best tailored to the clinical question. For example, in the setting of right upper quadrant pain, a "right upper quadrant" US is typically ordered, which directs the technologist/operator to focus on the liver, biliary system, and gallbladder. In the setting of pre- and post-LT patients, imaging the

Table 1 Imaging modalities in the context of liver transplantation

Modality	Cost	Radiation	Nephrotoxicity	Other side effects	Imaging medium
US	+	–	None	None	Sound waves
CT	++	+++ (generally performed as a three-phase study)	+ (eGFR >/= 40–45 poses minimal risk)	None	Ionizing radiation
MRI	+++	–	None	Interaction with implanted devices and ferromagnetic objects, NSF in ESRD	Radiofrequency waves in a strong magnetic field
PET/CT	+++ +	++	None	None	Ionizing radiation (CT) and gamma rays emitted from radiotracer
IR	+++ +	+++	+	Bleeding, organ injury, infection (depending on the procedure)	Ionizing radiation and/or sound waves

hepatic vasculature is also important and this requires ordering "Doppler ultrasound" (DUS).

DUS capitalizes on the Doppler effect, which represents the change in frequency of a (sound) wave for an observer (a vessel) moving relative to its source (the transducer). Color Doppler US uses this principle to depict blood flow in color-encoding terms with increasingly intense red and blue colors reflecting flow toward and away from the transducer, respectively and conventionally. Additionally, spectral Doppler generates a velocity-versus-time graph depicting blood flow at a point defined by the operator. As such, DUS offers the ability to evaluate the hepatic vasculature in the pre- and post-LT settings to evaluate (1) the evidence of portal hypertension; (2) portal, superior mesenteric, splenic, and hepatic venous patency; (3) hepatic arterial stenosis or thrombosis; and (4) flow derangements in the setting of transplant rejection and other post-LT complications.

Computed Tomography (CT)

CT generates images by jointly rotating an X-ray tube and X-ray detector around a circular gantry. The table moves the patient through the gantry while the tube and detector spin and the CT computer system deconvolutes the accumulated data into diagnostic images through an image reconstruction process. Filtered back projection (FBP) was the original image reconstruction methodology, while most modern scanners rely on iterative reconstruction to convert source data into diagnostic CT images incurring a fraction of the radiation dose required by FBP. In addition to the reconstruction algorithm, the CT radiation dose depends on the number of series obtained. For example, liver imaging for HCC or transplant surveillance generally requires "triphasic technique," which means obtaining precontrast, arterial phase, and portal phase sets of images, as well as delayed postcontrast images. The risk-to-benefit ratio in the LT setting generally argues in favor of proceeding with CT scanning, given the very small risk of ionizing radiation complications and the great diagnostic yield.

Nephrotoxicity from iodinated contrast is another consideration, which is generally considered in the context of the estimated glomerular filtration rate (eGFR), which is calculated from serum creatinine and several other patient parameters. Contrast-induced nephrotoxicity (CIN) has experienced a long history of controversy, and current work has significantly curtailed the risk. With a stable GFR of at least 45 mL/min/1.73 m^2, the CIN risk is essentially nonexistent; with GFR between 30 and 44 mL/min/1.73 m^2, the CIN risk is minimal (odds ratio = 1.40); and when the GFR is below 30, the CIN risk is substantial (odds ratio = 2.96) (Davenport et al. 2015). Clearly, patients already committed to a long-term dialysis have nothing to risk from iodinated contrast (as long as they are not allergic). The only other contraindication to iodinated contrast is acute renal failure, although the nephrotoxicity risk is low (ACR 2013).

Magnetic Resonance Imaging (MRI)

MRI generates diagnostic images by exploiting the behavior of protons subjected to radiofrequency energy in a strong magnetic field. Hydrogen protons in the body are magnetized by the strong magnetic field of the MR system and shift between high- and low-energy states as radiofrequency energy is applied to the system. These energy shifts release energy that ultimately provides the information used to generate MR images. The basic components include the MRI system, which is usually a superconducting magnet in a solenoid configuration housed in a cylindrical gantry; the gradient system, which modifies the magnetic field to provide spatial localizing information; and the radiofrequency coils, which send and receive the radiofrequency energy to interact with the protons and receive their emitted energy, respectively.

While MRI is generally considered a safe imaging modality and avoids the potentially harmful effects of ionizing radiation, a few risks need to be heeded. The strong static magnetic field interacts with ferromagnetic objects, potentially accelerating them toward the center of the

magnetic field. Safety provisions – in the form of access restriction, education, metal detectors, etc. – are undertaken to avoid the projectile effect, whereby an extrinsic ferromagnetic object (i.e., oxygen tank) experiences the projectile effect. Careful patient screening protects patients from dislodgement of implanted devices (i.e., cochlear implant, aneurysm clip, etc.) and device malfunction (i.e., cardiac pacing device). Weaker time-varying magnetic fields, used to encode spatial information, can induce electrical currents in conducting devices and may cause neuromuscular stimulation. The thermogenic effect of the radiofrequency energy converts some of the applied energy to heat, and heating sensations are occasionally experienced. Radiofrequency energy also induces electrical current in wires and leads, potentially triggering arrhythmias (Dill 2008). Practically speaking, the vast majority of implanted devices are MRI compatible but require confirmation of the manufacturing information. Foreign bodies almost never contraindicate MRI, except when lodged in or in close proximity to either the central nervous system or the orbit.

Positron Emission Tomography (PET/CT)

PET/CT houses both a positron emission tomography and a computed tomography scanner with a single-gantry system. Consequently, images from both systems are sequentially obtained, correcting for gamma-ray attenuation differences throughout the body and facilitating fusion and cross-correlation of functional information (from PET) and anatomic information (from CT). PET scanning involves localizing the gamma rays produced when an injected radionuclide – usually fluorodeoxyglucose (FDG) – emits a positron colliding with and annihilating an electron-positron pair. The FDG serves as a glucose analog, localizing in highest concentrations in areas of the greatest metabolism – generally tumors and inflammation. Normoglycemia is important to preempt competitive uptake between FDG and endogenous glucose and maximize FDG metabolism. Ionizing radiation constitutes the chief risk associated with PET/CT. While the radiation dose contribution from the CT component of the examination is generally relatively low, the additive radiation dose from CT and PET is not insignificant. PET/CT is not included in the routine evaluation of hepatobiliary malignancies, as outlined in the National Comprehensive Cancer Network Guidelines Version 2.2015. However, PET/CT potentially plays a role in assessing metastatic disease.

Interventional Radiology (IR)

Interventional radiology (IR) procedures are generally undertaken to address a complication and occasionally for diagnostic purposes. IR procedures encompass a wide spectrum from image-guided biopsy and drainage to percutaneous biliary procedures to vascular interventions, such as catheter-directed angiography and chemoembolization and transjugular intrahepatic portosystemic shunt (TIPS) placement. Image-guided biopsy and drainage procedures are usually performed with either CT or US guidance, depending on lesion and surrounding structure visibility or conspicuity. Biliary and vascular interventional procedures are generally performed in an interventional suite guided primarily with fluoroscopic visualization supplemented by ultrasound. In addition to the risks of ionizing radiation – which can be substantial, depending on the duration of the procedure – risks related to procedural invasiveness and the structures involved must be considered. Potential procedural complications include bleeding, organ injury, infection, biliary leak, bowel perforation, and pneumothorax.

Pretransplantation Imaging

Chronic Liver Disease and Malignancy

Candidates for LT with chronic liver disease require periodic imaging surveillance for HCC, which is typically performed with US, although

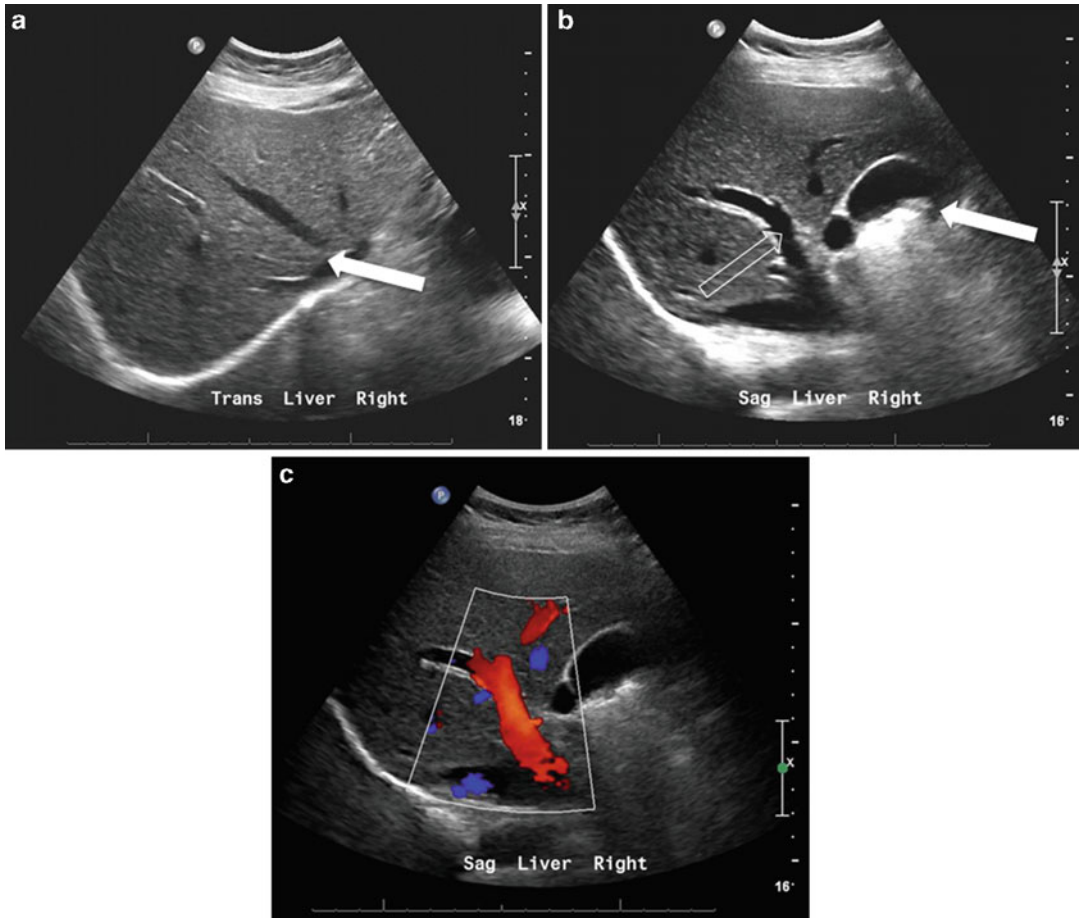

Fig. 1 Representative US images. (**a**) Transverse gray-scale US image near the level of the hepatic vein confluence (*arrow*) shows the normal homogeneous appearance of the liver. (**b**) Longitudinal gray-scale image through the right hepatic lobe and gallbladder (*arrow*) shows the normal appearance of a portal vein branch with echogenic walls (*open arrow*). (**c**) Corresponding longitudinal color DUS image through the same portal venous branch demonstrates hepatopetal flow with red signaling flow toward the US probe

CT or MRI are used in some North American transplant centers routinely or when US images are prohibitively limited (i.e., body habitus, limited positioning and breath holding, etc.). For definitive diagnosis or in problem-solving situations, MRI is usually the favored imaging study, although multiphasic CT is a reasonable alternative. With MRI contraindications, CT (with and without intravenous contrast) serves as a reasonable alternative. US images are obtained systematically with representative transverse and longitudinal images recording anatomic landmarks to ensure that all relevant anatomy is covered (see Fig. 1).

The normal liver appears homogeneously hypoechoic (or dark) traversed by anechoic (even darker) tubular biliary and vascular structures. Portal venous branches discriminate themselves from other fluid-filled structures by their echogenic (bright) walls. With the progression of chronic liver disease and inflammation, a number of sonographic changes occur. Heterogeneity and coarsening of the hepatic echotexture with increasing echogenicity and potentially hepatomegaly (over 15.5 cm in the midclavicular line) develop early but are generally insensitive and not reliable (Tchelepi et al. 2002). With ensuing parenchymal destruction, fibrosis, and

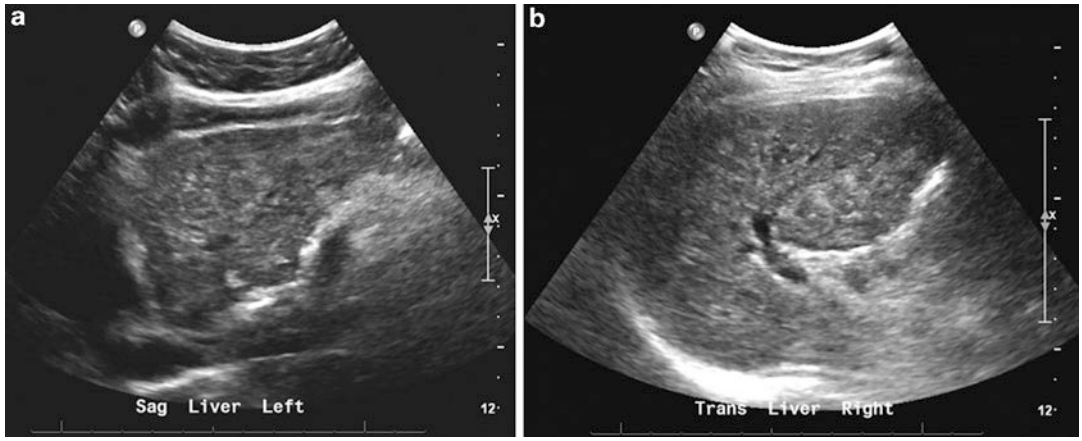

Fig. 2 Sonographic features of chronic liver disease and cirrhosis. (**a**) Longitudinal gray-scale US image through the left hepatic lobe shows coarsening and heterogeneity of the liver parenchyma in a patient with chronic viral hepatitis. (**b**) Transverse gray-scale US image reveals the same findings

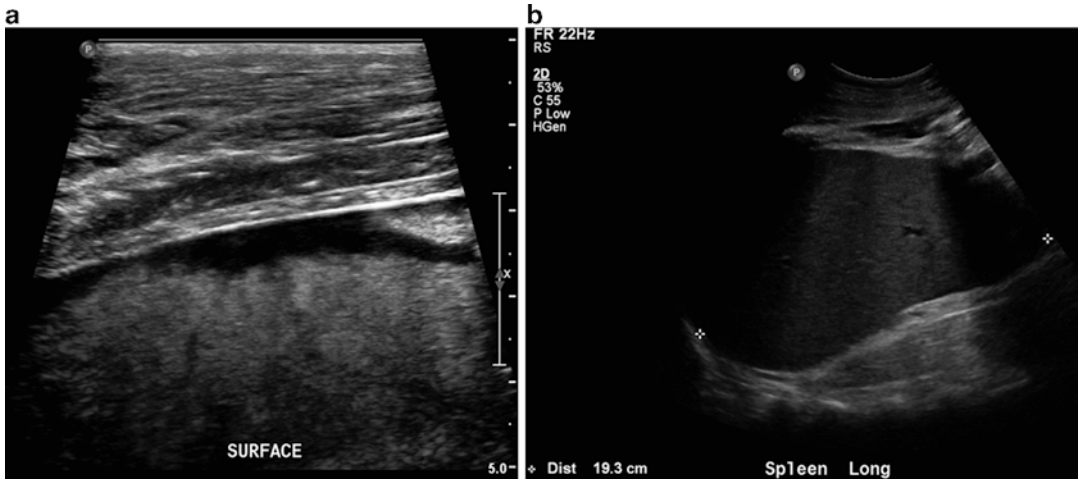

Fig. 3 Sonographic features of portal hypertension. (**a**) Gray-scale US image shows nodularity of the liver surface indicating cirrhosis, which is outlined by anechoic ascites. (**b**) Longitudinal gray-scale image through the spleen with calipers placed yielding a measurement of 19.3 cm in a patient with portal hypertension

regeneration, surface nodularity becomes apparent and signals underlying cirrhosis (see Fig. 2).

Supporting findings of portal hypertension include ascites, which appears as anechoic fluid pockets, splenomegaly, portosystemic collateral vessels, and enlargement of the main portal vein (over 13 mm) (see Fig. 3) (McGahan and Goldberg 2008).

DUS adds additional diagnostic information in the setting of cirrhosis and portal hypertension. Diminished and ultimately reversed portal venous flow is reflected using color DUS and spectral DUS images (see Fig. 4).

Associated hepatic arterial hemodynamic derangements are also characterized sonographically using DUS. Hepatic venous waveforms gradually transform from a triphasic pattern in the normal liver to a monophasic waveform with the progression of cirrhosis.

US is highly specific (over 90 %) but less sensitive (approximately 60 %) for HCC and is the usual primary imaging screening modality

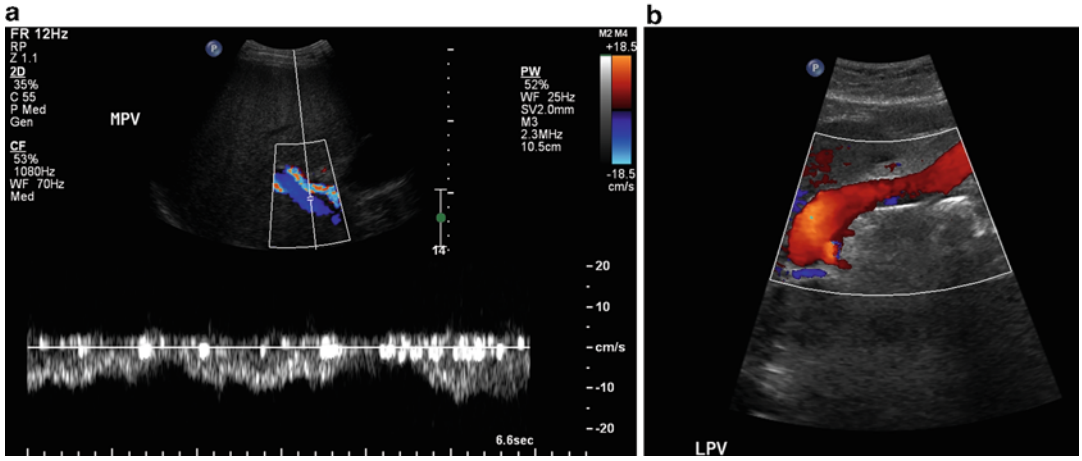

Fig. 4 DUS of portal hypertension. (**a**) Color DUS image through the porta hepatis reveals hepatofugal portal venous flow reflected by the blue color with the spectral tracing (*arrow*) recording the flow velocity. (**b**) Longitudinal color DUS image through the left hepatic lobe showing a large paraumbilical collateral vessel directing flow toward the US probe and away from the liver

(Bennett et al. 2002; Colli et al. 2006; Singal et al. 2009). The AASLD recommends US surveillance every 6 months in patients with cirrhosis. HCC is discriminated from the background liver by its heterogeneity and difference in echogenicity compared with the background liver parenchyma (see Fig. 5).

With the liver disease progression, however, HCC conspicuity generally fades as the background liver often becomes increasingly heterogeneous and echogenic. This is exacerbated by the variable sonographic appearance of HCC, ranging from hypo- to hyperechoic (McEvoy et al. 2013). Size criteria provide some guidance with new nodular lesions exceeding 1 cm more likely corresponding to HCC. Nodular lesions below 1 cm undergo surveillance with 3-month-follow-up US for 2 years, while those exceeding 1 cm should undergo contrast-enhanced MRI or CT for definitive diagnosis (Bruix and Sherman 2005; Bruix and Sherman 2011). Associated portal and/or hepatic venous invasion is demonstrated by replacement of the anechoic lumen by relatively echogenic material with tumor thrombus exhibiting DUS evidence of vascularity.

MRI covers the entire abdomen and portions of the lower chest and upper pelvis, depending on patient size and technical parameters. Various pulse sequences are obtained exploiting the rich tissue contrast capabilities of MRI and include T1-weighted images (T1WIs) with sensitivity to microscopic fat and T1WIs with sensitivity to iron; T2-weighted images (T2WIs) with sensitivity to water bound to macromolecules (high content in solid neoplasms); T2WIs with sensitivity to free water (i.e., ascites, bile, etc.); diffusion-weighted images (DWIs) with sensitivity to hypercellular lesions; and pre- and postcontrast dynamic images with sensitivity to paramagnetic substances (i.e., hemorrhage and gadolinium), vascular structures, and solid lesions/neoplasms (see Fig. 6).

Most of these pulse sequences are performed with breath-hold technique within 20 sec or so, although some employ respiratory gating to trigger image acquisition only during the quiescent phase of respiration to eliminate breathing motion artifact.

The normal liver appears homogeneously T1-hyper- and T2-hypointense and exhibits a characteristic enhancement pattern. During the arterial phase, the liver enhances modestly in proportion to the relatively small contribution of the hepatic artery. In the subsequent portal venous phase, the liver enhances maximally. The delayed postcontrast appearance of the liver depends on the contrast agent used. Extracellular agents are cleared by the kidneys fairly rapidly and hepatic

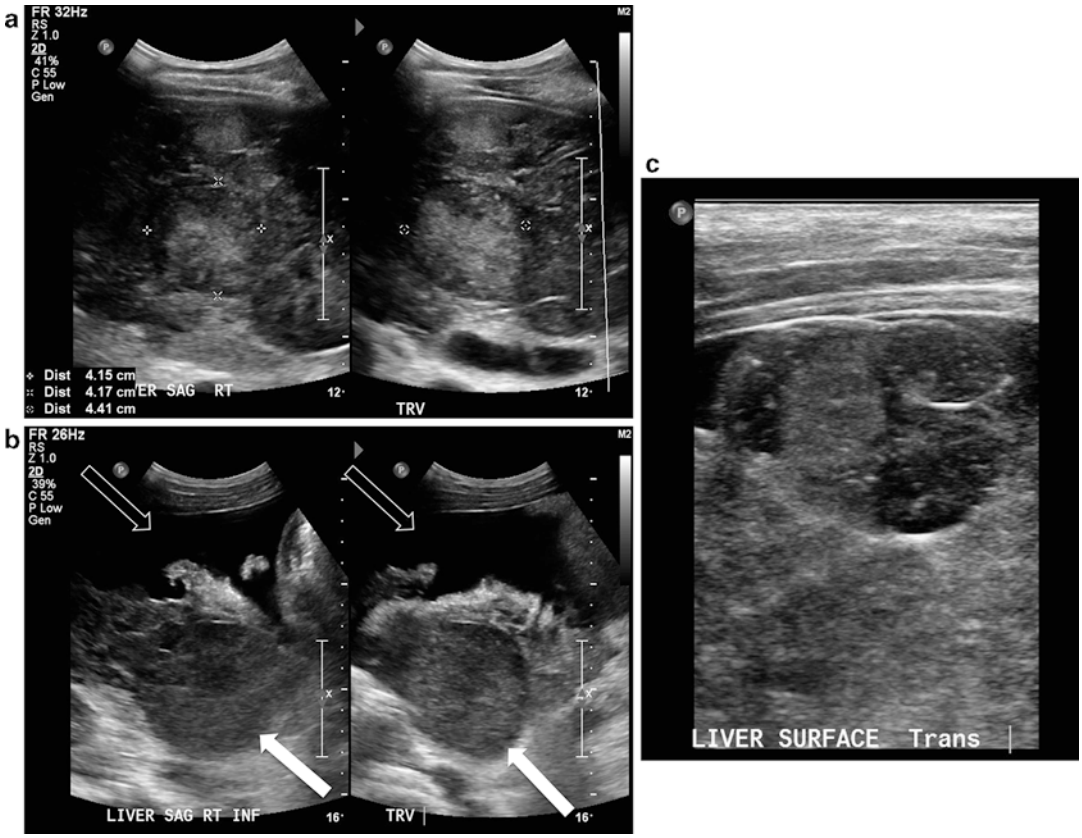

Fig. 5 US of HCC. (**a**) Longitudinal and transverse gray-scale images through a heterogeneous, cirrhotic liver demonstrate a heterogeneously hyperechoic solid mass indicated by the calipers. (**b**) Longitudinal and transverse gray-scale images in the same patient obtained more caudally reveal a large, exophytic isoechoic mass (*arrows*) with overlying ascites (*open arrow*). (**c**) Transverse gray-scale image shows a heterogeneous hyper- and hypoechoic mass deforming the capsular surface in the same patient with multifocal HCC

enhancement fades. However, combination agents are also metabolized by the liver, which induces progressive hyperintensity over 20 min or so. Consequently, non-hepatocellular lesions, including HCC (except for 10–20 % of well-differentiated HCCs) (Kim et al. 2009; Frericks et al. 2009), fail to take up the contrast agent and appear hypointense against the hyperintense background of the normal liver parenchyma (see Fig. 7).

This phenomenon is a function of the transporter molecule organic anion-transporting peptides (OATP) located on the normal hepatocyte basolateral membrane. While agents with hepatic metabolism provide this diagnostic benefit, cirrhosis limits its utility because of the limited contrast agent uptake and variable OATP expression (Chanyaputhipong et al. 2011), so extracellular agents are preferred at most centers for evaluating cirrhotic livers.

MRI clearly depicts hepatic morphologic changes in chronic liver disease. Trophic changes generally constitute the earliest imaging signs of underlying liver disease and include caudate lobe and lateral segmental hypertrophy and right lobe and medial segment atrophy. These changes are reflected by enlargement of the periportal space, gallbladder fossa, and major interlobar fissure and an increased ratio of the length of the caudate lobe to the right lobe. With progressing inflammation and evolving cirrhosis, nodularity and fibrosis develop leading to a cobblestone appearance.

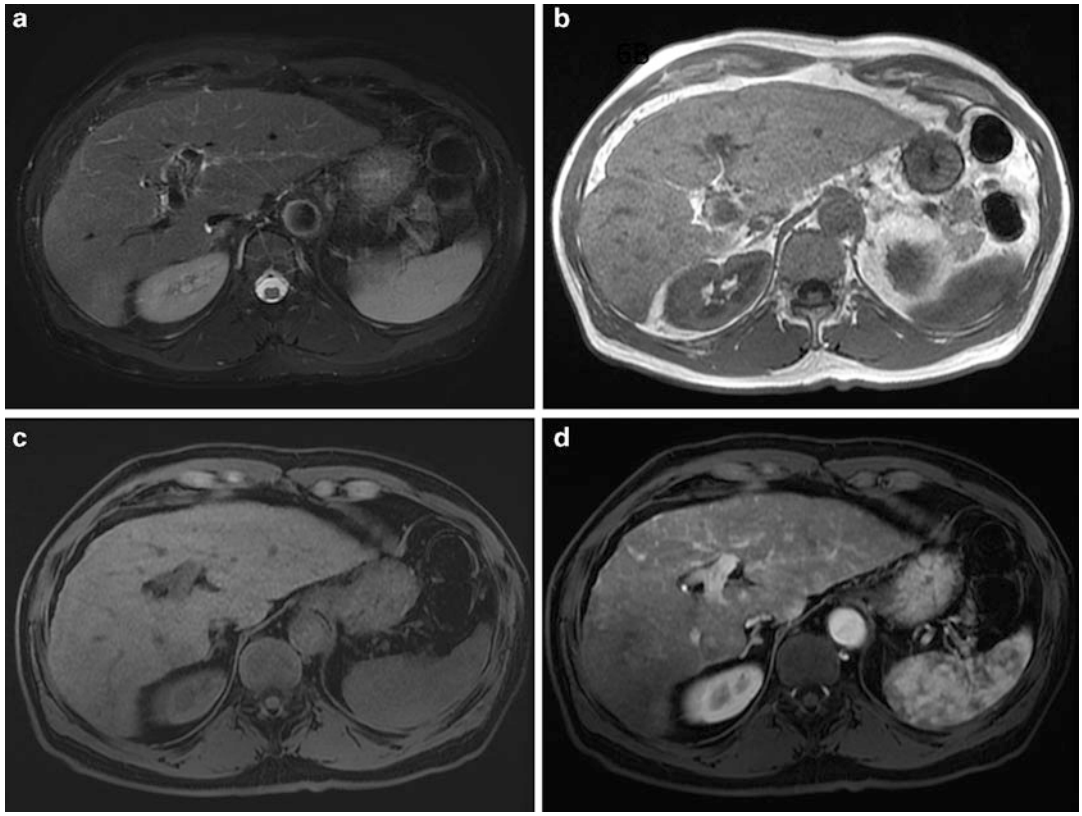

Fig. 6 Representative MRI images. (**a**) Axial T2WI with fat suppression renders tissues with higher contents of bound water (i.e., the spleen, kidneys, and malignant lesions) relatively hyperintense. (**b**) Axial T1W inphase image – the liver appears relatively hyperintense under normal circumstances. (**c**) The axial T1W fat-suppressed image is the precontrast component of the dynamic contrast-enhanced portion of the study, and only paramagnetic substances are hyperintense (i.e., gadolinium, hemorrhage, melanin, etc.). (**d**) The axial T1W fat-suppressed arterial phase image is designed to render hypervascular lesions (i.e., HCC, focal nodular hyperplasia, etc.) hyperintense

Nodular regenerative and dysplastic tissue generally exhibits signal characteristics similar to normal liver, although some nodular lesions appear T1-hyper- and T2-hypointense. Reticulated fibrosis surrounding the nodular lesions is characteristically T2-hyperintense with progressively delayed enhancement (see Fig. 8) (Ito et al. 2002; Gupta et al. 2004).

MRI performance in detecting HCC has varied in the literature as a function of technological innovation and lesion size considerations. With technical improvements in MR systems over the years, the MRI accuracy has clearly improved, yet research substantiates limitations in evaluating small lesions. Forner et al. (2008) reported high specificity (93.1 %) but relative insensitivity (61.7 %) for HCC lesions smaller than 2 cm. Marin et al. (2009) observed similar performance with MRI sensitivity and specificity depending on lesion size: 42.8 and 100 % when <1 cm, 83.3 and 80 % when 1–2 cm, and 100 and 91 % when >2 cm. MRI features are well established, and arterial hyperenhancement is a virtual sine qua non of HCC diagnosis and figures prominently into the Liver Imaging Reporting and Data System (LI-RADS) developed and promoted by the American College of Radiology (ACR) to "standardize the reporting and data collection of CT and MR imaging for hepatocellular carcinoma" (ACR 2014) (see Table 2).

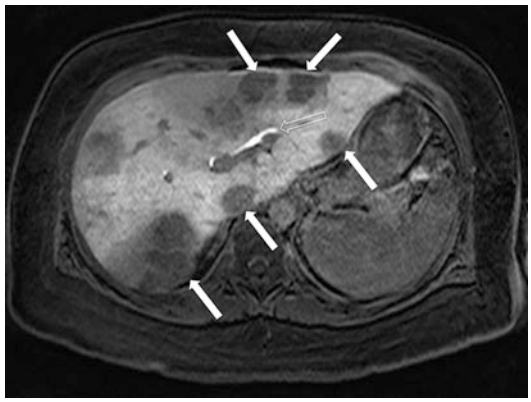

Fig. 7 Appearance of non-hepatocellular lesions on hepatobiliary phase images. An axial T1W fat-suppressed image obtained 20 min after the administration of combination contrast agent isolates non-hepatocellular lesions – breast cancer metastases, in this case (*arrows*) – as hypointense against the normal hyperintense parenchymal background. Hyperintense contrast is excreted into the biliary system (*open arrow*) on delayed images

Additional major features include washout (the lesion becomes hypointense compared with the liver on portal phase and delayed images), delayed-enhancing capsule, and growth. A number of ancillary features are observed – T2-hyperintensity, diffusion restriction, mosaic architecture, intralesional fat, etc. – in addition to the propensity of HCC to invade venous structures (see Fig. 9).

While smaller lesions typically adhere to the nodular morphologic pattern, larger, more progressed lesions typically fall into three main morphologic categories: (1) solitary, (2) multifocal, and (3) infiltrative (see Fig. 10).

Many of the MR features of HCC apply to CT, including arterial hyperenhancement, washout, delayed-enhancing capsule, mosaic architecture, corona enhancement, and intralesional fat (see Fig. 11).

CT lacks the capability of assessing diffusion restriction and availability of contrast agents with hepatobiliary activity. CT performs nearly as well as MRI in HCC detection, but implicates ionizing radiation and its risks along with at least the specter of nephrotoxicity from iodinated contrast agents. Therefore, MRI is generally favored over CT for liver evaluation and lesion detection.

Although cholangiocarcinoma shares some of the same risk factors as HCC, its prevalence on imaging studies in the setting of chronic liver disease is far less frequent. While its imaging appearance depends on its location and growth pattern, in the setting of chronic liver disease, cholangiocarcinoma is typically intrahepatic (as opposed to the Klatskin and extrahepatic varieties) exhibiting either mass forming or infiltrative growth patterns. The sonographic appearance of the mass varies from hypo- to hyperechoic or mixed echogenicity, and upstream biliary dilatation with abrupt ductal obliteration is occasionally associated (Sainani et al. 2008). CT reveals a hypodense mass on unenhanced images that demonstrates a peripheral hypovascular and progressively centripetal enhancement pattern, reiterating its peripherally cellular and centrally desmoplastic histology (Han et al. 2002). On MR images, this often conforms to peripheral hyperintensity and central hypointensity on T2WIs with the same centripetal enhancement pattern. Because of the desmoplastic content, capsular retraction is occasionally observed. Diffusion restriction and hepatobiliary phase hypointensity are additional MRI features (see Fig. 12) (Chung et al. 2009; El Fattach et al. 2015).

Elastography

For patients with chronic liver disease such as hepatitis B or C or fatty liver disease, standard imaging techniques are useful for identifying advanced liver disease and portal hypertension, although with low sensitivity for identifying underlying fibrosis. Diagnosing fibrosis is clinically important since hepatic fibrosis is a dynamic process potentially stopped or reversed with medical treatment. Liver biopsy, the current gold standard for diagnosing fibrosis, has many drawbacks including patient reluctance, biopsy complications, sampling error, and interobserver variability in reporting pathology results. Liver elastography, an imaging technique performed using MRI or ultrasound, quantifies fibrosis and in many cases eliminates the need for liver biopsy.

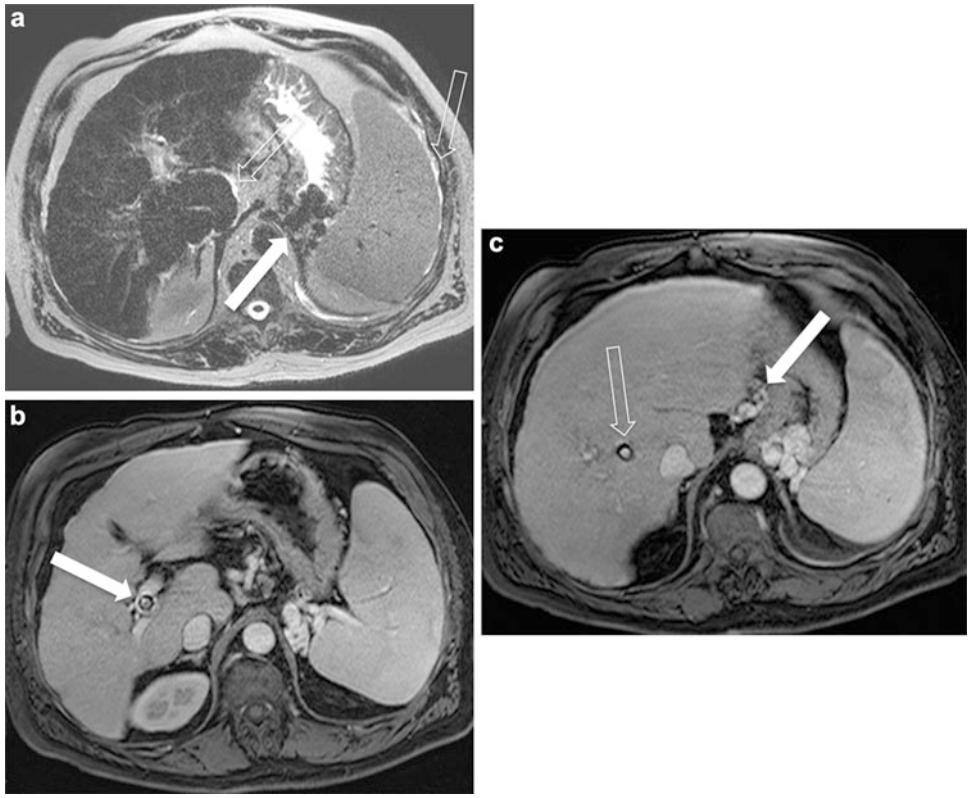

Fig. 8 MRI appearance of chronic liver disease and cirrhosis. (**a**) Axial T2W MRI image shows the nodular liver contour indicating cirrhosis with trophic changes characteristic of chronic liver disease – caudate and lateral segmental hypertrophy and medial segment and right lobe atrophy. Splenomegaly and gastric varices corresponding to signal voids (*arrow*) and trace ascites (*open arrows*) indicate portal hypertension. (**b**) Postcontrast fat-suppressed T1W MR image shows the hepatic morphologic derangements, splenomegaly, and varices, along with a TIPS (*arrow*). (**c**) More cephalad postcontrast fat-suppressed T1W MR image at the same level as (**a**) shows the same gastric varices after enhancement, along with gastrohepatic varices (*arrow*) and the mid-segment of the TIPS (*open arrow*)

Elastography interrogates the mechanical properties of tissues based on the speed of shear wave propagation. Using MRI or ultrasound, a mechanical device deforms tissues to generate shear waves. The shear wave velocity is then measured yielding quantitative results measured in kilopascal (kPa). In general, the propagation of shear waves is faster in stiff or hard tissues. Studies have shown that an increase in liver stiffness is correlated with increasing stages of hepatic fibrosis (Yin et al. 2007; Bonekamp et al. 2009).

Various ultrasound elastography methods exist. Fibroscan®, the first ultrasound machine to perform elastography, uses mechanical push pulses to generate shear waves. While well established in the literature, Fibroscan® has drawbacks including a small tissue sample size, isolated peripheral right lobe sampling, and a high diagnostic failure rate due to patient obesity or ascites. Also, Fibroscan® is an exclusively elastography system without the capabilities of performing the standard diagnostic ultrasound study to identify liver lesions and characterize other findings.

However, many of the ultrasound vendors have added elastography to standard ultrasound machines. Rather than mechanical pulses, elastography is commonly performed using acoustic radiation force imaging to generate shear waves. The major benefit of the combined

Table 2 LI-RADS (ACR 2014)

Categorization	LR-1	Definitely benign
	LR-2	Probably benign
	LR-3	Intermediate probability
	LR-4	Probably HCC
	LR-5	Definitely HCC
	LR-5 V	Tumor in the vein
	LR-M	Probably malignant, not specific for HCC
	LR treated	Treated observation
Applicable imaging modalities	CT with extracellular agent	
	MRI with extracellular agent	
	MRI with combination agent	
Imaging features assessed	Arterial phase hyperenhancement	
	Washout	
	Diameter	
	Diameter increase (growth)	
	Capsule appearance	
	Visibility at surveillance US	
	Ancillary features	Hepatobiliary phase hypointensity
		Mild to moderate T2-hyperintensity
		Restricted diffusion
		Distinctive rim
		Corona enhancement
		Mosaic architecture
		Nodule-in-nodule appearance
		Intralesional fat
		Lesional fat sparing
		Blood products
		Diameter increase less than threshold

ultrasound/elastography units is the ability to combine the elastography and diagnostic ultrasound components of the study into one exam. Another advantage of this technique over Fibroscan® is a lower technical failure rate since a diagnostic ultrasound machine directs where the elastography measurement is taken optimizing measurement accuracy. Finally, ascites is generally not a limitation compared with Fibroscan®. The disadvantages include a small liver sample size, similar to Fibroscan®, and less available literature to establish fibrosis thresholds.

With MR elastography, a passive driver placed on the abdomen over the liver generates mechanical vibration to create shear waves propagating through the liver. The shear waves are measured by the equipment and generate a wave image (see Fig. 13a), which is then used to create an elastogram (see Fig. 13b, c).

Liver stiffness is measured both quantitatively in kPa and qualitatively using a color map. Four images of the liver are obtained which include a large portion of the liver to sample. The benefits of MR over ultrasound elastography include sampling much larger segments of the liver and a higher technical success rate. Ascites, obesity, and overlying bowel gas usually do not preclude performing MR elastography. Similar to the combined ultrasound/elastography units, a standard MRI exam can be performed at the same time to evaluate for liver morphology/masses and for portal hypertension. Another advantage is that liver fat and iron quantification can be performed at the same time yielding the most comprehensive non-invasive liver imaging exam available. The addition of elastography and liver fat and iron quantification to a standard MRI exam only adds about 5 min of imaging time. The disadvantages of MR elastography include possible non-diagnostic studies due to liver iron overload or motion artifact and the higher cost of MRI compared to ultrasound.

Interventional Radiology Procedures

Patients often require interventional procedures to ablate lesions threatening to exclude their suitability for LT. These procedures fall into two main categories: (1) image-guided tumor ablation and (2) image-guided transcatheter tumor therapy. The former is generally performed under either US or CT guidance utilizing radiofrequency (usually), chemical, thermal, or cryoablative techniques. The latter involves the delivery of chemotherapeutic agents, embolic particles, or radioactive materials selectively into the arterial territory supplying the tumor using fluoroscopic guidance. The technical details of these procedures are beyond the scope of this text, but the appearance of procedural

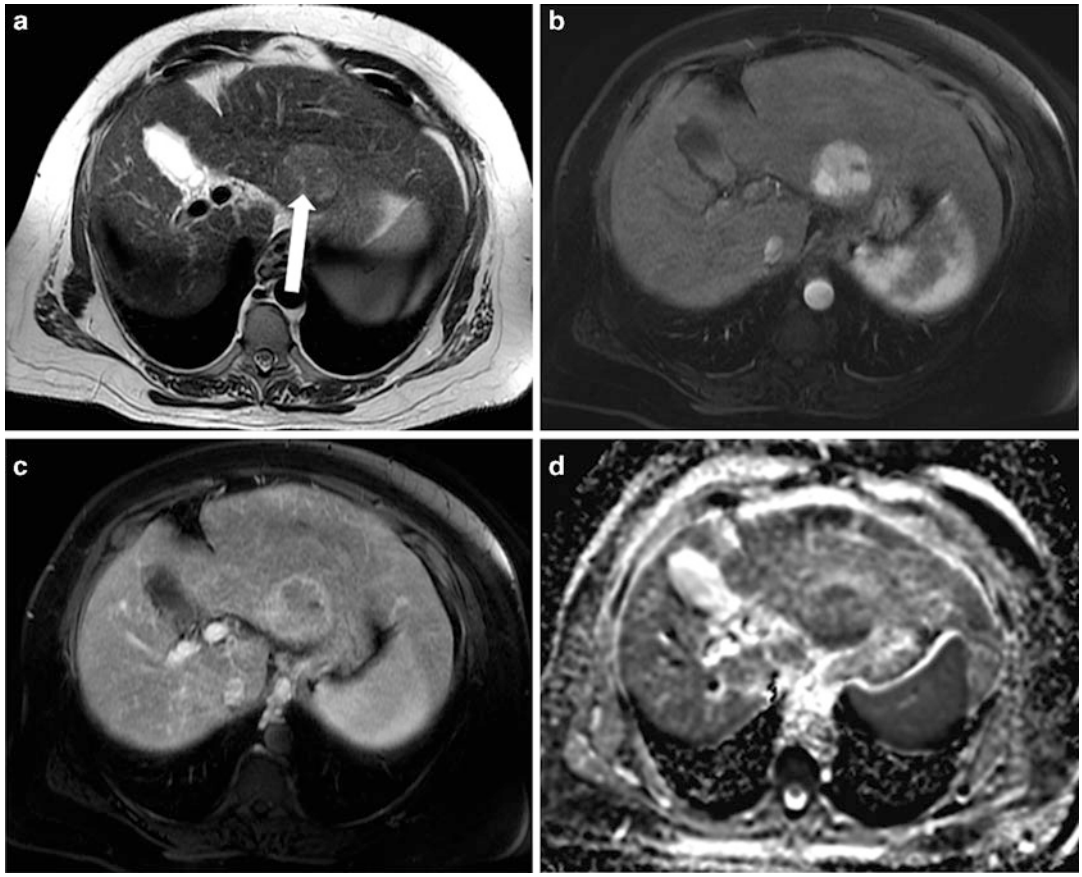

Fig. 9 MRI features of HCC. (**a**) Axial T2W MR image in a cirrhotic liver with trophic changes (lateral segmental hypertrophy and medial segmental and right lobar atrophy) reveals a mildly hyperintense lesion reflecting an increased bound water content (*arrow*). (**b**) The lesion exhibits avid heterogeneous enhancement on the arterial-phase postcontrast T1W fat-suppressed MR image. (**c**) The delayed postcontrast T1W fat-suppressed MR image demonstrates the typical washout pattern with the late-enhancing capsule. (**d**) The ADC map MR image shows lesional hypointensity reflecting decreased diffusivity due to the relative hypercellularity

complications and the post-procedural appearance of lesions deserve attention.

Image-guided tumor ablation procedures incur a number of potential complications (see Table 3).

Major complications occur with an approximate frequency of 1–2 % (Livraghi et al. 2002; Giorgio et al. 2005). Some complications demonstrate revealing imaging findings, such as bowel injury, biliary injury, bilomas and hematomas, infection, and vascular thrombosis and infarction. Bowel injury most commonly involves the colon and manifests with focal, often eccentric wall thickening with or without adjacent infiltration of the mesenteric fat, pericolonic fluid collections, and/or perforation, depending on whether perforation has ensued. Injury to the biliary tract potentially induces structuring or biloma formation. Proximal biliary dilatation is the most conspicuous sign of an underlying biliary stricture, and the underlying stricture appears as a short segment of luminal narrowing and wall thickening. US is a useful screening study, which readily identifies biliary dilatation with near 100 % sensitivity but lacks utility in stricture and mass detection (Singh et al. 2014). As such, biliary dilatation in this setting generally prompts CT and/or MRI, which has the advantage of volumetric imaging covering the entirety of the biliary tract for a panoramic overview. The CT findings are more clearly defined following intravenous

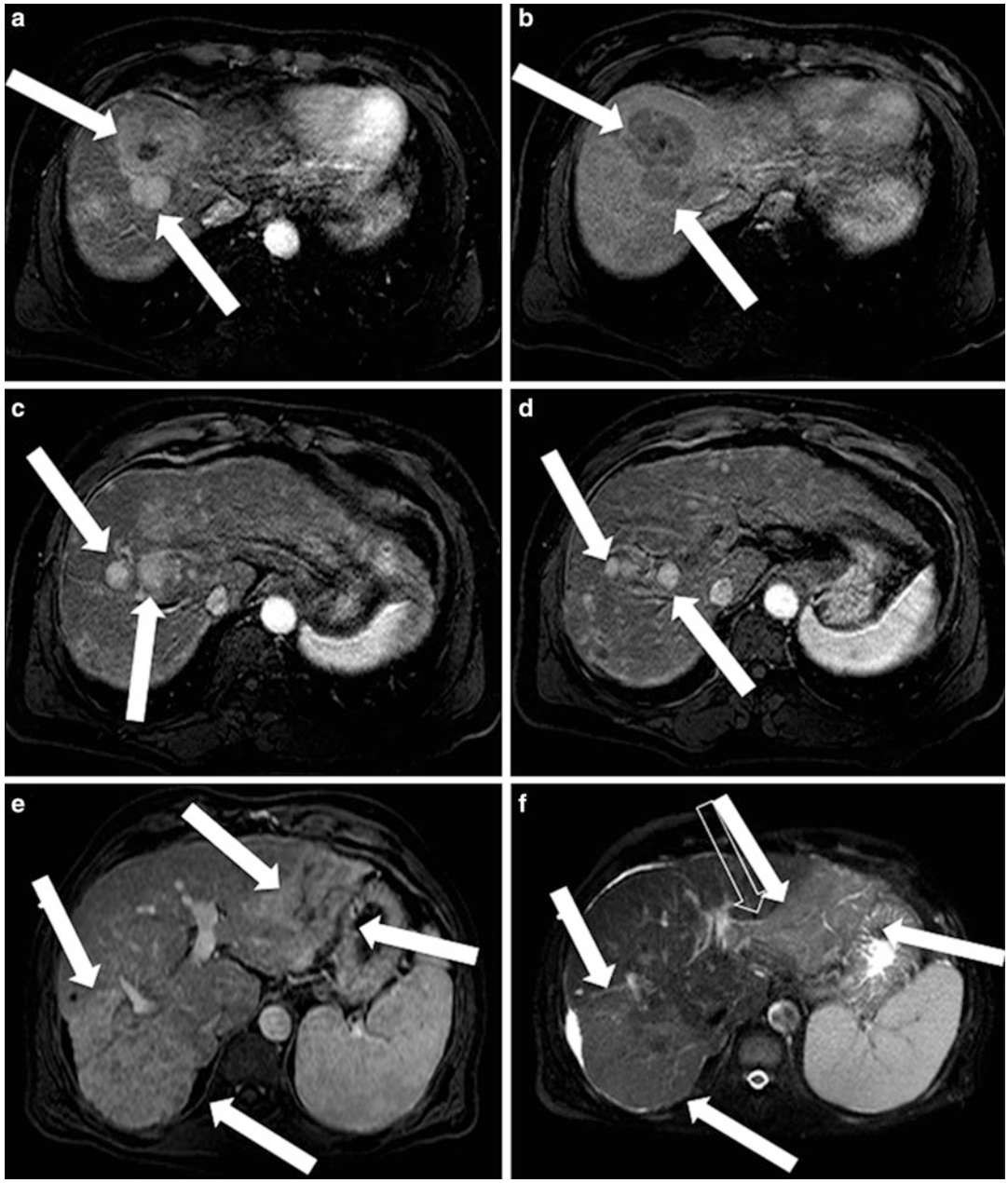

Fig. 10 MRI of HCC growth patterns. (**a**) T1W postcontrast arterial-phase image with fat suppression demonstrates two hypervascular lesions (*arrows*) corresponding to HCC lesions in a patient with multifocal HCC. (**b**) The lesions (*arrows*) washout on the T1W delayed postcontrast image. (**c**) A more caudal T1W postcontrast arterial-phase image with fat suppression reveals additional hypervascular HCCs (*arrows*). (**d**) Another T1W postcontrast arterial-phase image slightly more caudally shows additional HCCs (*arrows*). (**e**) The T1W postcontrast arterial-phase image in a different patient reveals two discrete geographic heterogeneously hypervascular regions indicting infiltrative HCC (*arrows*). (**f**) The fat-suppressed T2WI demonstrates the hyperintensity of the increased bound water content (*arrows*) and focal invasion of the left portal vein (*open arrow*)

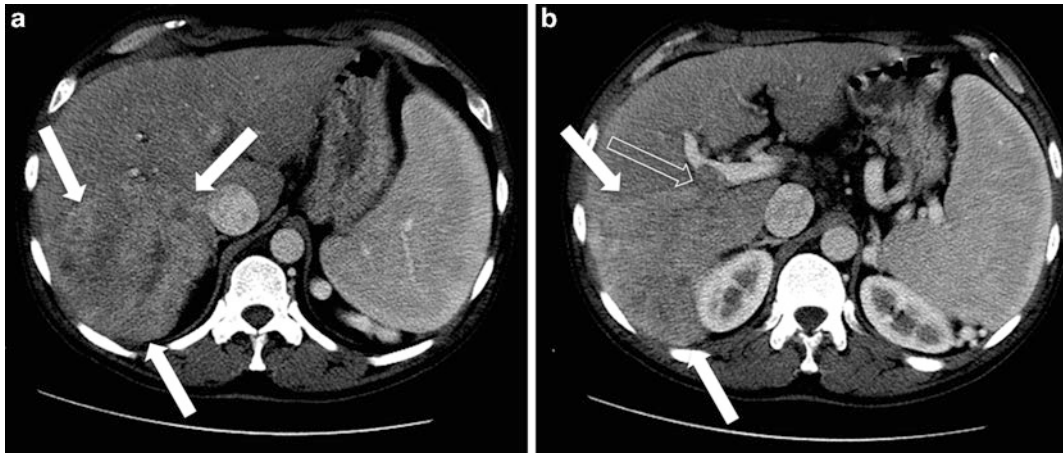

Fig. 11 CT of HCC. (**a**) Axial postcontrast arterial-phase CT image reveals a large heterogeneously hypervascular lesion in hepatic segment 7(*arrows*). (**b**) A slightly more caudal postcontrast arterial-phase CT image through the lesion (*arrows*) shows portal venous invasion with tumor thrombus (*arrowhead*)

contrast administration with relatively hypodense, branching tubular structures converging and tapering at the site of the stricture against the hyperdense backdrop of enhancing liver parenchyma. The strictures typically extend over a short segment (a cm or less) and feature concentric relatively mild and smooth wall thickening (as opposed to malignant strictures with longer segmental involvement and a greater wall thickness and degree of heterogeneity) (Park et al. 2004; Choi et al. 2005; Shanbhogue et al. 2011). MRI demonstrates these findings with greater tissue contrast in a number of ways and adds additional diagnostic information. In a similar fashion, dilated bile ducts appear hypointense adjacent to hyperintense, enhancing liver on postcontrast T1WIs. Additionally, T2WIs portray the biliary system as hyperintense against background tissue in a scalable fashion ranging from standard T2WIs where adjacent structure visibility provides anatomic reference points to magnetic resonance cholangiopancreatography (MRCP) where only fluid-filled structures, such as the biliary tree, are visible. Consequently, the margins and configuration of the biliary stricture are demonstrated – additional features discriminating benign from malignant strictures. Benign strictures tend to feature smooth symmetric borders with tapered margins, whereas malignant strictures typically exhibit irregular, asymmetric involvement with shouldered margins (see Fig. 14) (Soto et al. 2000).

The biliary excretion of a combination contrast agent affords the opportunity to positively enhance the biliary tree, providing yet another means to evaluate underlying strictures and bilomas and biliary leaks. In fact, hepatobiliary phase imaging complements the other MRI techniques in identifying and localizing bile duct injury by demonstrating abnormal contrast accumulation outside the biliary system into the hepatic parenchyma (biloma) or leaking into the peritoneal cavity (see Fig. 15) (Kentarci et al. 2013).

Post-procedural fluid collections include bilomas, hematomas, and abscesses. Fortunately, these collections each frequently exhibit characteristic differentiating MRI features. In addition to the features described above, bilomas are typically intermediately intense on T1WIs and hyperintense on T2WIs. Also T2-hyperintense hematomas demonstrate T1-hyperintensity reflecting their methemoglobin content (Shigemura et al. 1995). Pyogenic abscesses typically demonstrate a complicated cystic imaging appearance with heterogeneously T2-hyperintense and T1-hypointense contents, complicated morphology with a multicystic or clustered cystic appearance, and

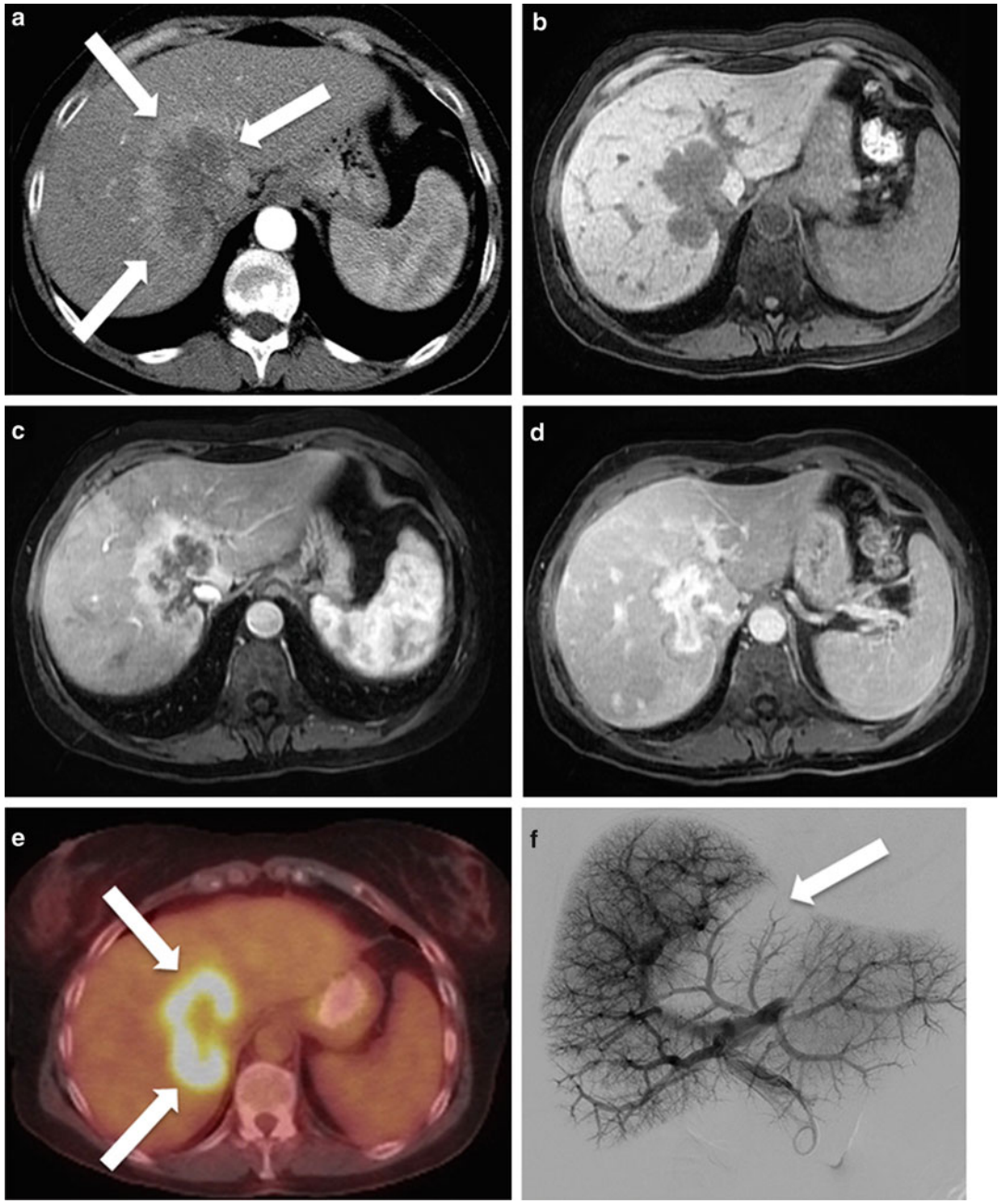

Fig. 12 Imaging of cholangiocarcinoma. (**a**) Axial postcontrast arterial-phase CT image shows an irregularly marginated lesion (*arrows*) with peripheral enhancement corresponding to viable tumor cells and central hypovascularity indicating necrosis and desmoplasia. (**b**) T1W fat-suppressed MR image demonstrates lesional hypointensity. (**c**) The T1W fat-suppressed postcontrast arterial-phase MR image demonstrates the same enhancement pattern. (**d**) The delayed T1W fat-suppressed postcontrast MR image typifies the characteristic progressive enhancement pattern. (**e**) Fused PET/CT image shows marked hypermetabolism in the peripheral cellular portion of the tumor (*arrows*). (**f**) An image from a portal venogram prior to embolization isolates the lesion (*arrow*) due to its exclusive arterial blood supply in contradistinction to the normal liver receiving 75–80 % of its blood supply from the portal venous system

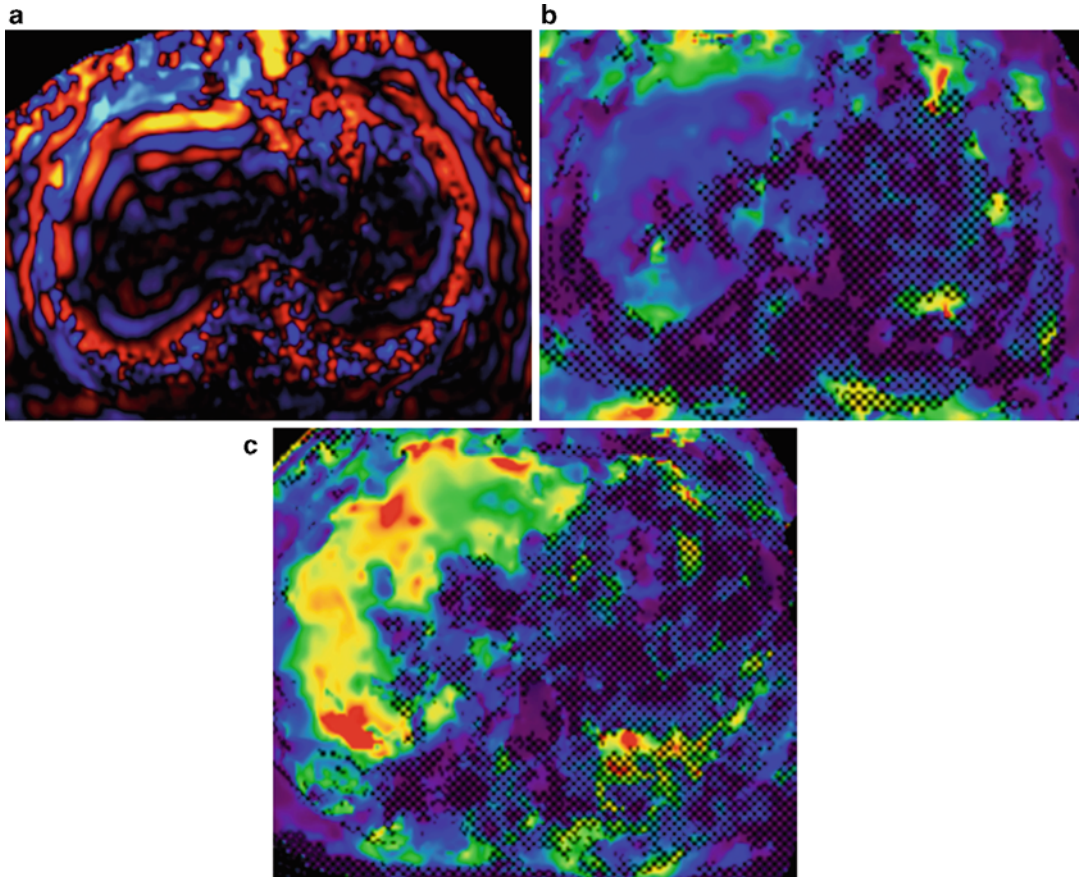

Fig. 13 MR elastography. (**a**) Wave image that is used to generate an elastogram. A passive driver placed on the right anterior abdominal wall generates the mechanical vibration that is used to create this image. (**b**) Elastogram which was generated from the wave image in Fig. 1 in a patient with a normal liver stiffness of 2.2 kPa. The color map ranges from lower kPa values (*blue*) to higher values (*red*). (**c**) Elastogram in a patient with fatty liver with cirrhosis and stage four fibrosis. The liver stiffness values were elevated at 5.1 kPa, and the color scale demonstrates areas, which are *red* indicating higher liver stiffness values

reactive changes in the surrounding hepatic parenchyma. Reactive changes include edematous, T2-hyperintense signal and increased arterial enhancement (see Fig. 16) (Roth 2012).

US is a good screening tool to identify potential post-procedural fluid collections and presents some specific imaging features, but often prompts MRI or CT for further characterization. Pyogenic abscesses assume a wide range of appearances from hypoechoic to hyperechoic with heterogeneity and occasional acoustic shadowing (blockage to the passage of sound waves) from intralesional gas (Power et al. 2007). Hematomas often exhibit a very characteristic lacy internal septation pattern or heterogeneous echogenicity sonographically, and bilomas tend to appear as simple unilocular, anechoic cystic lesions. Similarly, bilomas demonstrate fairly nonspecific findings on CT images and appear as well defined to slightly irregular hypodense collections. The appearance of hematomas depends on chronicity because acute hemorrhage is hyperdense – with a layering fluid-fluid hematocrit level developing over time – with density gradually diminishing with the evolution of blood products (see Fig. 17).

The CT appearance of abscesses mirrors the MRI appearance, although the multicystic/

clustered cystic appearance and reactive changes may be less apparent. However, CT is much more sensitive to the presence of intralesional gas, which seals the diagnosis in the absence of instrumentation (Mortelé and Ros 2001).

Table 3 Complications of hepatic radiofrequency ablation procedures (Nemcek 2009)

Complications related to Rf energy and heat	Thermal effects	GI tract (potentially fatal)
		Diaphragm
		Biliary system (strictures and bilomas)
		Gallbladder (cholecystitis > perforation)
	Rf device and pacemaker dysfunction	
	Postablation syndrome	
Complications related to electrode insertion and removal	Hemorrhage	
	Infection	
	Tumor seeding	
Other complications	Vascular thrombosis and hepatic infarction	
	Pleural complications	
	Arteriovenous fistula	
	Skin burns	

When considering the possibility of a post-procedural biloma, cholescintigraphy is an alternative diagnostic strategy. Prior to hepatobiliary phase imaging in MRI with combination contrast agents, cholescintigraphy was essentially the only specific noninvasive test. Cholescintigraphy involves the intravenous injection of a radiolabeled compound, such as iminodiacetic acid in the case of the HIDA scan, which is metabolized by the liver and excreted into bile. Planar images are obtained over time by gamma cameras that capture the radiation emitted by the radiopharmaceutical. Where the radiopharmaceutical appears outside the normal metabolic pathway identifies the site of the bile leak and biloma. Exposure to ionizing radiation is the only practical risk; the procedure ranges in duration from 1 to 2 h, and its major limitation is the lack of supplemental information provided. Cholescintigraphy only provides information regarding hepatic metabolism and bile flow; fluid collections not arising from bile leaks and other complications and findings are not evaluated.

Vascular complications of percutaneous procedures include portal and hepatic venous thrombosis, hepatic infarction, arteriovenous fistula, and hepatic pseudoaneurysm (Howenstein and Sato 2010). Portal venous thrombosis occurs most

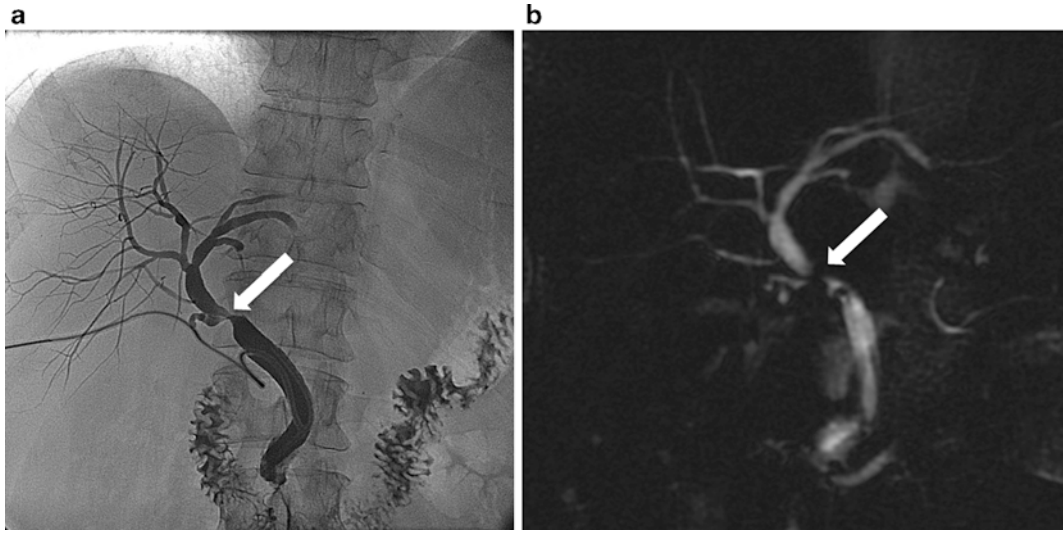

Fig. 14 Imaging features of post-procedural biliary stricture. (**a**) The T-tube cholangiogram image week after liver transplantation shows focal anastomotic narrowing (*arrow*). (**b**) The MRCP image exaggerates the degree of stenosis (*arrow*) without the benefit of active luminal distention

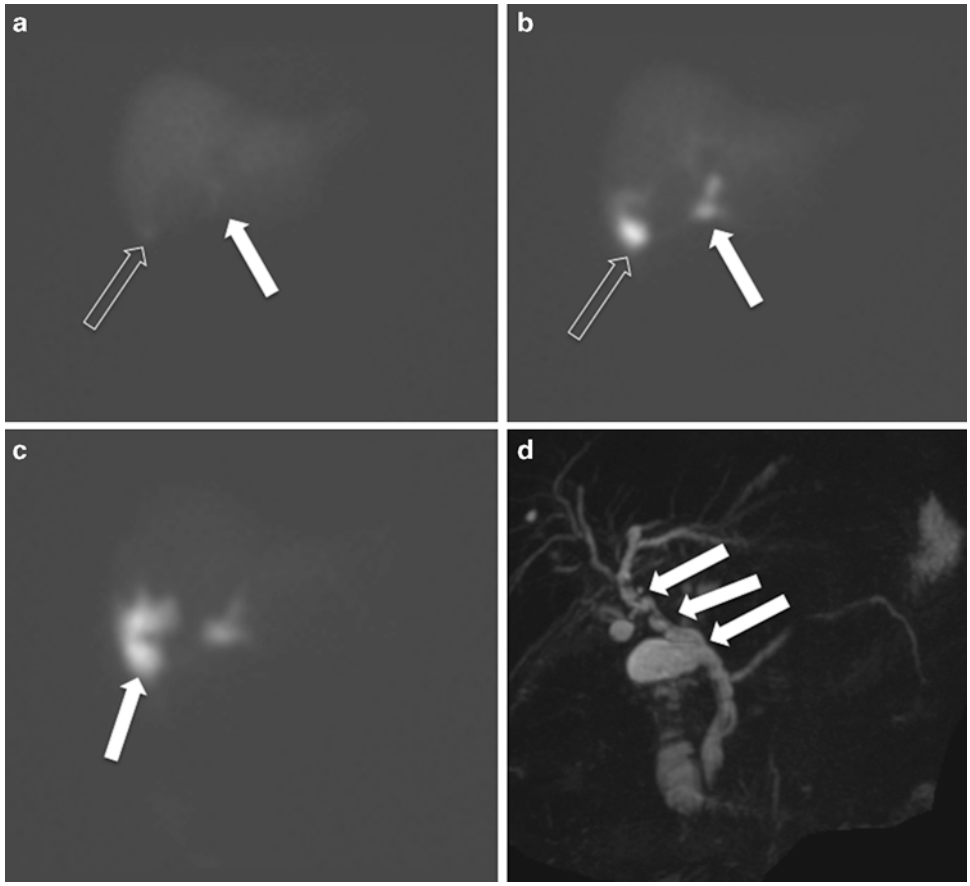

Fig. 15 MR imaging of biliary leak. (**a**) An early image from a cholescintigram shows hepatic uptake of the radiopharmaceutical and faint biliary excretion into the common bile duct (*arrow*) and a minimal focus of radiotracer activity in the subhepatic space (*open arrow*). (**b**) A subsequent image better demonstrates biliary excretion into the common bile duct (*arrow*) and increased subhepatic radionuclide accumulation (*open arrow*). (**c**) The final cholescintigraphic image shows near-complete washout from the liver with progressive radionuclide spillage into the subhepatic space (*arrow*) from an anastomotic leak. (**d**) The MRCP image shows diffuse contour irregularity throughout the peri-anastomotic bile duct (*arrows*) reflecting the underlying injury

frequently with a rate approaching 2 % with hepatic venous infarction rates closer to 1 % (de Baère et al. 2003). US demonstrates thrombus as an echogenic filling defect replacing the normal anechoic venous lumen on gray-scale images and the normal color-encoded appearance on color Doppler images. CT and MR images reveal filling defects within the venous lumen corresponding to thrombi. The CT diagnosis requires intravenous contrast administration and appropriate image acquisition timing to guarantee enhancement of the vascular structure in question. Conversely, contrast enhancement is not a mandatory component in the MRI evaluation of the hepatic and portal veins for thrombus, although contrast adds the capability of distinguishing between bland and tumor thrombus. Bright-blood imaging (a technique used in cardiac MR imaging) renders all fluid – flowing or not – hyperintense and all non-fluid structures, such as thrombi, as relatively hypointense (Boll and Merckle 2009). Additionally, time-of-flight imaging selectively captures signal from flowing blood, and all static tissues, including thrombi, appear relatively hypointense. Nonetheless, postcontrast MR images demonstrate portal and hepatic venous thrombus very effectively and should be obtained when possible (see Fig. 18).

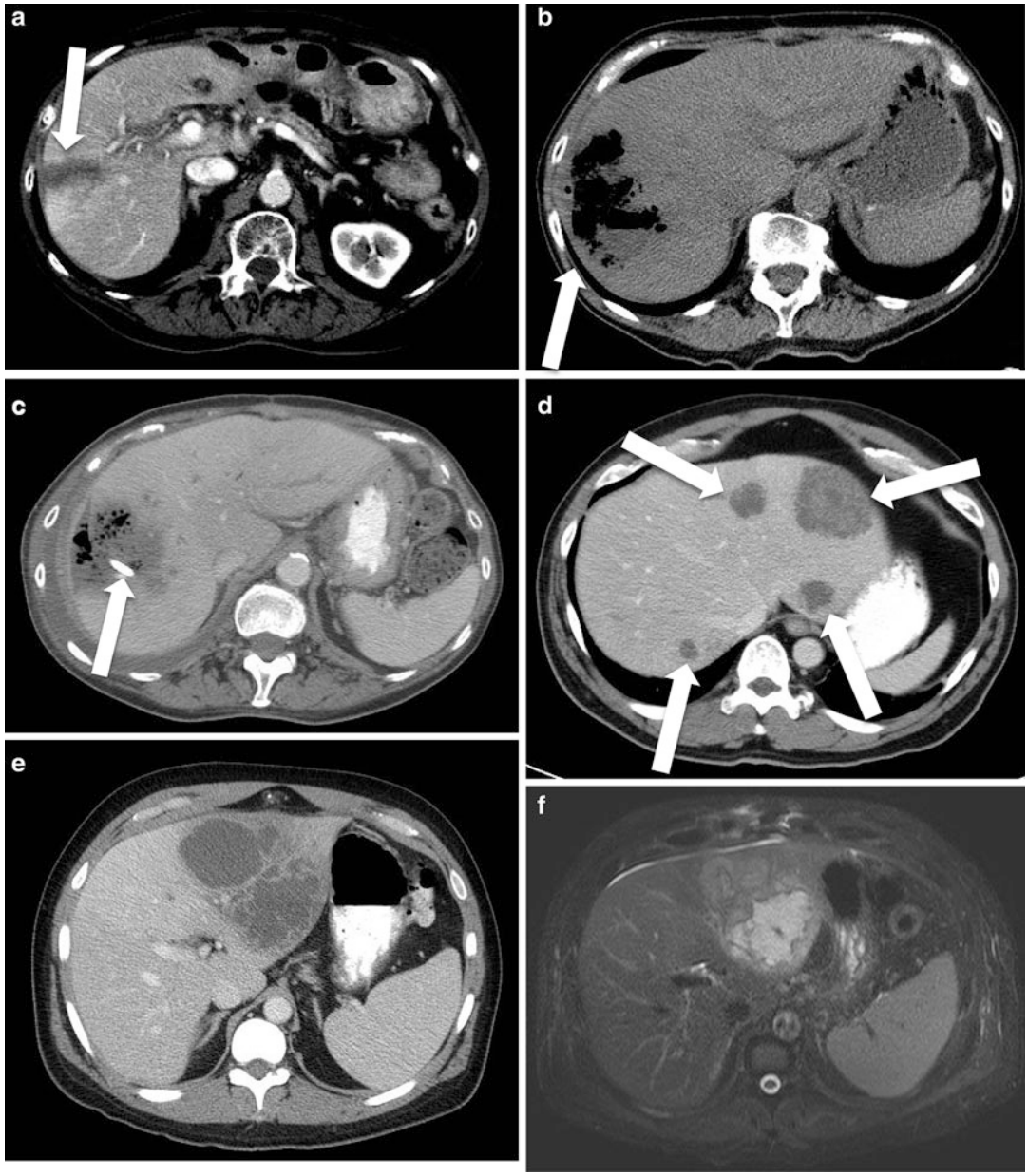

Fig. 16 Imaging of pyogenic abscess. (**a**) The axial postcontrast CT image shows a wedge-shaped subcapsular hypovascular lesion (*arrow*) with perilesional arterial hyperenhancement. (**b**) Axial image from an unenhanced CT image obtained approximately 2 weeks later demonstrates interval development and superimposition of a large gas-filled collection (*arrow*) indicating superinfection and pyogenic abscess formation. (**c**) Axial image from a subsequent contrast-enhanced CT obtained a few days later after percutaneous drain placement (*arrow*) with decreased size of the abscess. (**d**) Axial contrast-enhanced CT image in a different patient shows multifocal collections (*arrows*) characterized by the "clustered cyst" appearance. (**e**) More caudal postcontrast CT image in the same patient shows a large abscess in the lateral segment. (**f**) Axial fat-suppressed T2WI illustrates the complexity of the abscess with heterogeneous signal intensity of the collection with debris and variable stages of tissue liquefaction

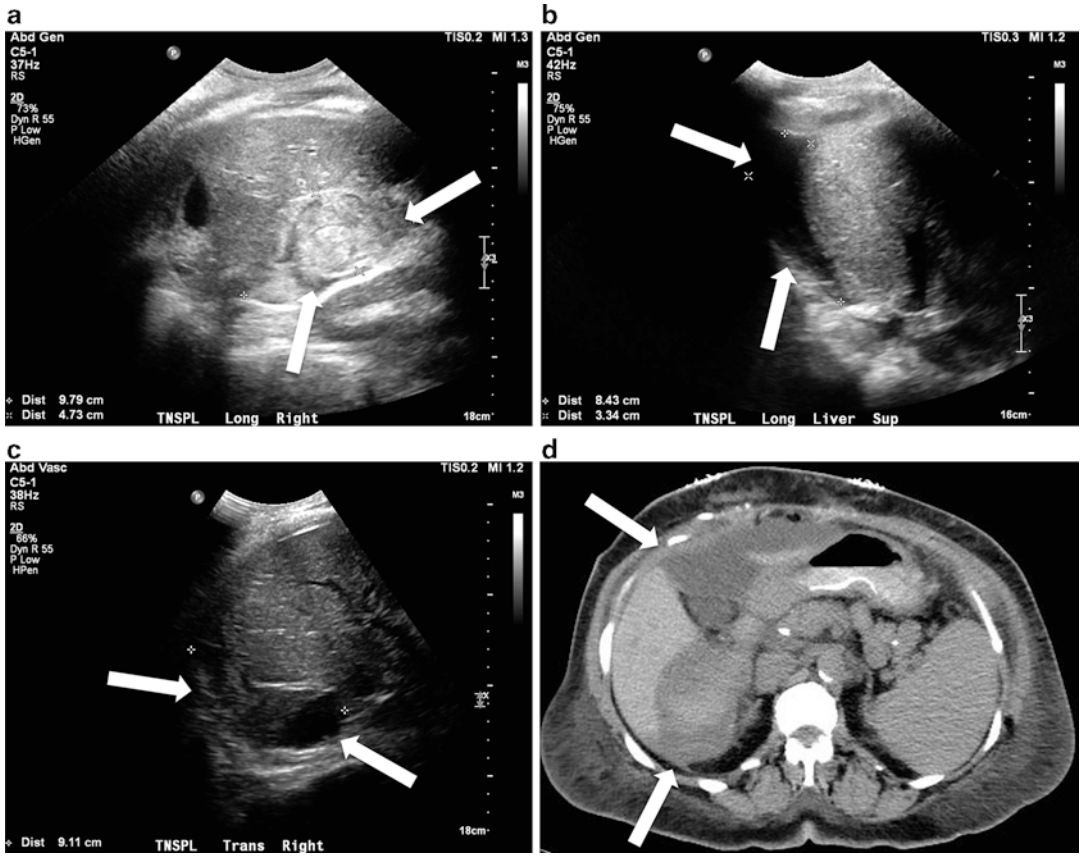

Fig. 17 Imaging of post-procedural hematoma. (**a**) Longitudinal US image shows a subhepatic heterogeneously hyperechoic collection (*arrows*) in the immediate posttransplant setting. (**b**) More caudally positioned longitudinal US image reveals another anechoic fluid collection along the superior margin of the liver (*arrows*). (**c**) A transverse US image demonstrates a mildly complicated collection (*arrows*) along the posterior liver margin with internal hypoechoic material. (**d**) The fluid collections appear variably dense depending on their chronicity (*arrows*) on the unenhanced CT image

Hepatic infarction rarely occurs as a consequence of the dual hepatic blood supply. Infarcts are not reliably detected sonographically, and potential findings include an ill-defined hypoechoic area with an indistinct border rarely complicated by echogenic gas with "dirty shadowing" (even in sterile infarction) (Lev-Toaff et al. 1987). Unenhanced CT demonstrates wedge-shaped, rounded, or irregularly shaped low-density areas usually adjacent to the ablated lesion. Postcontrast images increase tissue contrast as the normal liver enhances while the infarct remains unenhanced and hypodense, and any associated portal venous thrombus manifests as an intraluminal filling defect (Masaaki et al. 2005; Torabi et al. 2008). The same morphology is observed on MR images with T1-hypointensity and T2-hyperintensity, lack of enhancement, and diffusion restriction (see Fig. 19).

Other vascular complications – arteriovenous fistula (AVF) and pseudoaneurysm – are less commonly observed. US manifestations include hepatic arterial enlargement and focal portal venous dilatation at the AFV site. DUS shows pulsatile hepatofugal flow and color speckling in the surrounding hepatic parenchyma reflecting

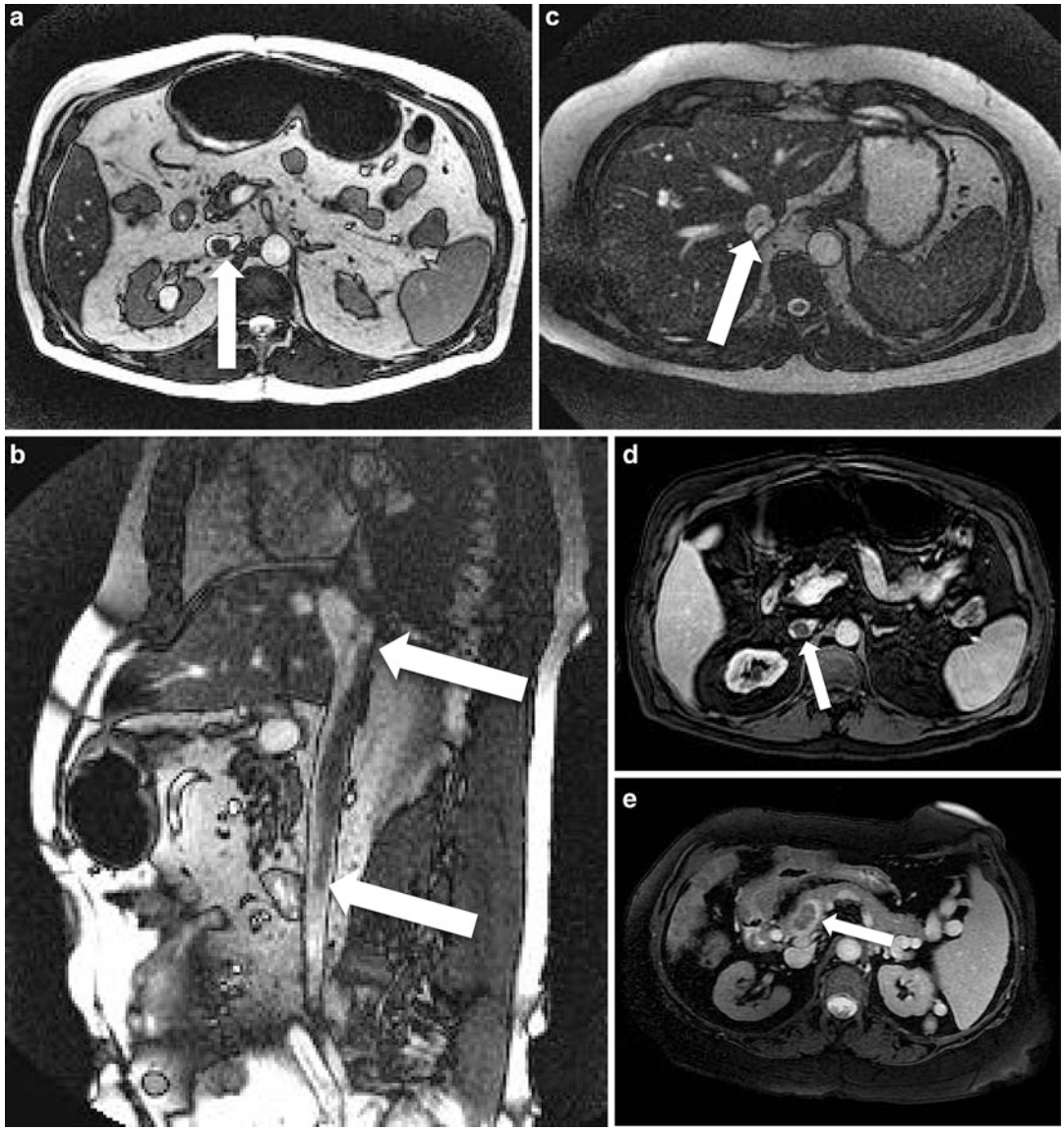

Fig. 18 Imaging of portal and hepatic venous thrombosis. (**a**) Axial bright-blood MR image shows a nonocclusive filling defect in the infrahepatic IVC (*arrow*). (**b**) Sagittal bright-blood MR image shows the longitudinal extent of the clot (*arrows*). (**c**) Axial bright-blood MR image near the hepatic vein confluence shows linear hypointensity corresponding to the anastomosis (*arrow*). (**d**) Fat-suppressed postcontrast T1WI shows the enhancing IVC lumen surrounding the nonocclusive thrombus (*arrow*). (**e**) Axial fat-suppressed bright-blood MR image in another patient reveals near-occlusive thrombus within the main portal vein (*arrow*)

vibration artifact. On CT and MR imaging, AVF manifests with early opacification of the portal or hepatic vein during the arterial phase after contrast administration, and venous enhancement approaches the CT density or MR intensity of arterial structures. Regionally increased arterial enhancement develops with portal AVFs in response to inverted portal flow or increased portal inflow from the shunt.

Pseudoaneurysms develop as saccular outpouchings from the hepatic artery or its branches. Gray-scale US reveals an anechoic

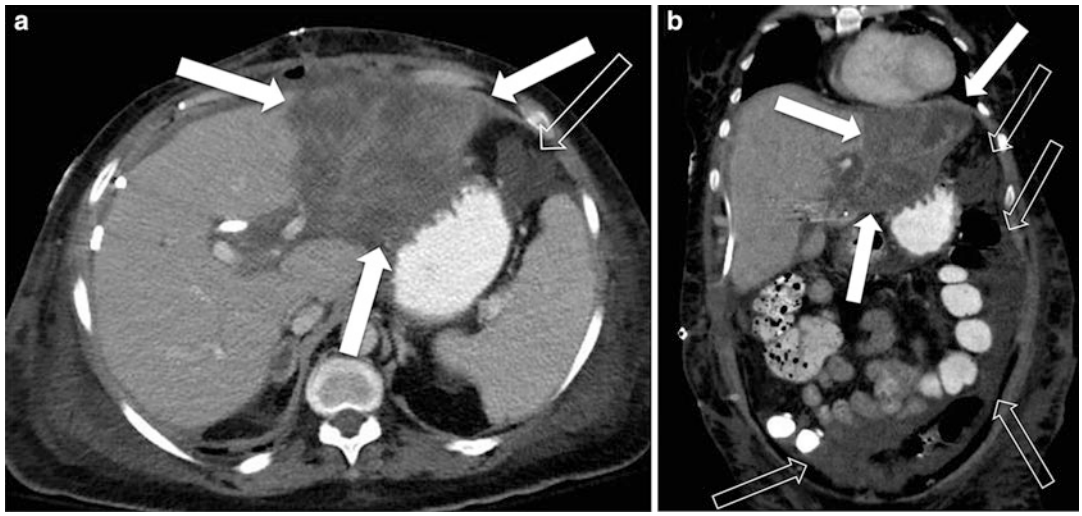

Fig. 19 Imaging of hepatic infarct. (**a**) Axial postcontrast CT image shows a large, wedge-shaped, subcapsular lateral segmental lesion (*arrows*) without enhancement in the early posttransplant setting. Ascites is present (*open arrow*). (**b**) The corresponding coronally reformatted CT image demonstrates the extensive lateral segmental involvement (*arrows*) and scattered pockets of ascites (*open arrows*)

outpouching along the margin of an artery and the characteristic "yin-yang sign" or "to and fro flow" referring to the swirling blood flow pattern (see Fig. 20) (Saad et al. 2005).

The saccular outpouching is generally readily appreciated on postcontrast CT and MR images, although vessel tortuosity potentially complicates or limits detection. Postprocessing with multiplanar reformatting into orthogonal planes and volume-rendered images helps untangle tortuosity and isolate the pseudoaneurysm (Sainani et al. 2013).

Image-guided transcatheter tumor therapy poses potential complications related to access site injury, arterial injury, nontarget embolization, infection, systemic side effects, and postembolization syndrome. Access site injuries include hematomas, AVFs, and pseudoaneurysms. Watchful waiting generally suffices for managing groin hematomas, unless associated with one of the other complications. AVFs exhibit the same features as discussed previously in the context of hepatic AVFs and occur in nearly 1 % of cases with nearly 40 % closing spontaneously (Kelm et al. 2002). US-guided compression is the first-line treatment and surgical primary or patch closure repair is the definitive treatment. Femoral pseudoaneurysms feature the same imaging findings as their hepatic counterparts – saccular outpouching with the "yin-yang sign" – and treatment options include US-guided compression, US-guided thrombin injection, and surgery (see Fig. 21).

Time and pain are the limiting factors regarding US-guided compression, requiring up to 120 min and averaging 33 min (Cox et al. 1994). While US-guided compression success rates have been reported in the 80 % range, US-guided thrombin injection has become the treatment of choice for post-catheterization pseudoaneurysms with reported success rates in the 91–100 % range (La Perna et al. 2000; Weinmann et al. 2002; Krueger et al. 2005; Webber et al. 2007). US-guided treatment failures, mycotic pseudoaneurysms, peri-anastomotic pseudoaneurysms, and large pseudoaneurysms exerting mass effect on adjacent structures with neuropathy or limb ischemia require surgical repair.

Hepatic arterial tortuosity and anatomic variations complicate transcatheter interventions and incur extensive catheter manipulation, increasing the risk of direct arterial injury. Additionally, embolization agents potentially induce contact

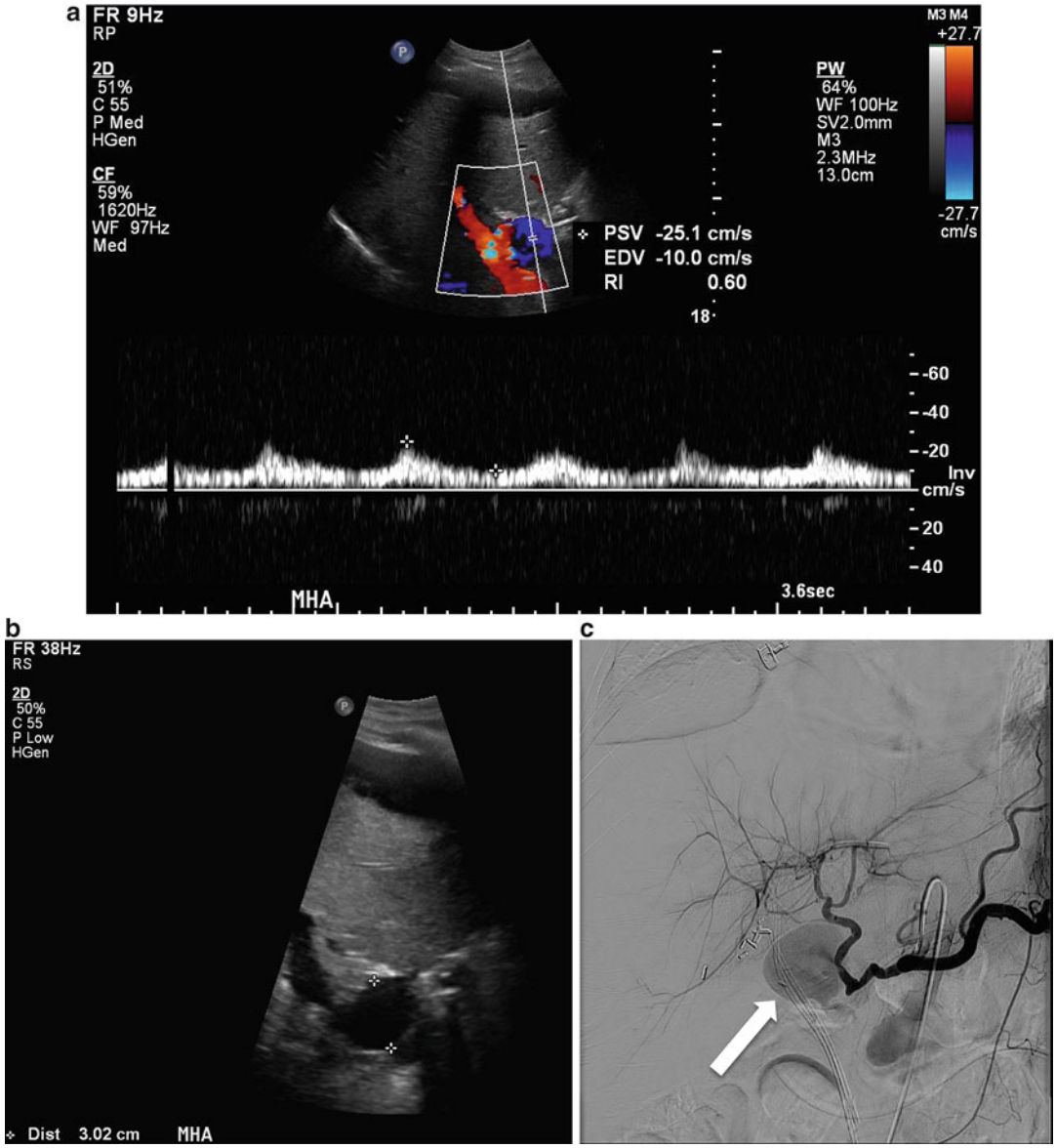

Fig. 20 Imaging of hepatic artery pseudoaneurysm. (**a**) DUS image of the main hepatic artery shows a round structure with swirling flow reflected by the *red* and *blue* color (yin-yang sign). (**b**) Gray-scale US image obtained to measure the pseudoaneurysm (calipers) records a measurement of "3.02 cm." (**c**) Angiographic image from a common hepatic artery injection reveals contrast filling the peri-anastomotic pseudoaneurysm (*arrow*) with a jet of contrast at the site of the leak

damage to the arterial wall, and arterial injuries sustained include spasm, dissection, and thrombosis. Spasm responds to vasodilator therapy without further imaging or intervention. However, hepatic artery dissection and thrombosis generally invoke imaging procedures for diagnosis to guide treatment. Intimal damage from transcatheter procedures constitutes a potential issue complicating the surgical approach to LT. In a series by Lin et al. (2009), 58 % of LT candidates undergoing transcatheter interventions experienced intimal damage. US is generally the first-line diagnostic

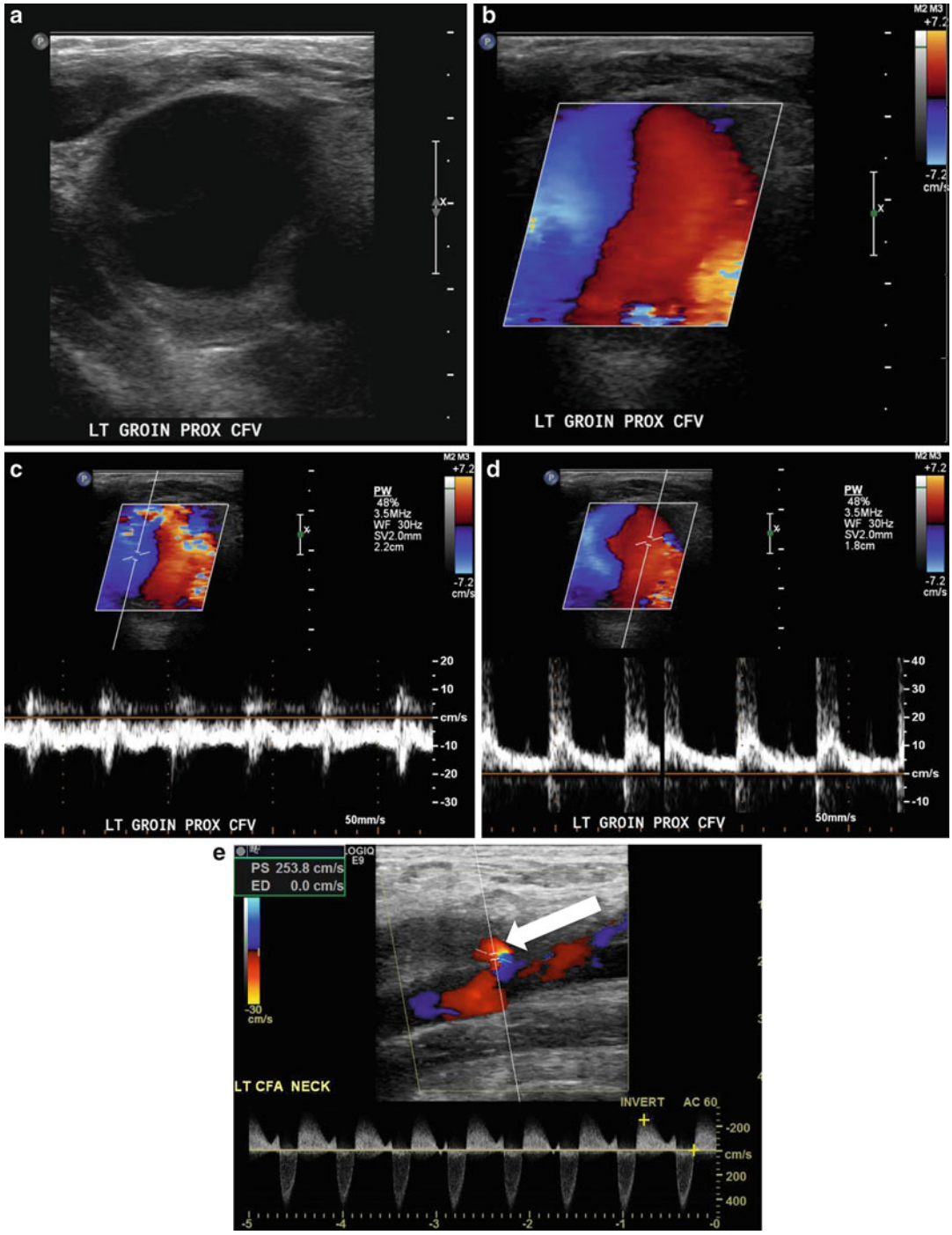

Fig. 21 Ultrasound imaging of femoral pseudoaneurysm. (**a**) Gray-scale US image shows a round anechoic structure in the region of the common femoral vessels. (**b**) The corresponding color DUS image demonstrates the classic "yin-yang" sign reflecting the swirling nature of the blood flow. (**c**, **d**) The pulsed DUS images show spectral tracings with the characteristic "to and fro" flow pattern. (**e**) Longitudinal pulsed DUS image through the common femoral artery shows the neck of the pseudoaneurysm (*arrow*) also exhibiting "to and fro" flow (the remainder of the pseudoaneurysm is out of plane on this image)

test to evaluate potential hepatic arterial complications because of its wide availability, portability, noninvasiveness, and relatively high success rate. Gray-scale US shows the echogenic linear intimal flap deflected inwardly separating adjacent anechoic true and false lumens. CT and MRI provide a more comprehensive overview of the arterial anatomy and extent of the dissection. The CT diagnosis requires intravenous contrast to highlight the hypodense linear intimal flap surrounded by hyperdense contrast in the true and false lumens. MRI is optimally performed with and without contrast-enhanced pulse sequences, and MR imaging findings are similar to CT findings – a hypointense intimal flap with adjacent true and false lumen hyperintensity on both postcontrast and bright-blood unenhanced images (see Fig. 22).

Sonographically, hepatic artery thrombosis exhibits relatively echogenic replacement of the normal anechoic vessel lumen with lack of DUS evidence of flow. DUS changes in the hepatic artery inflow suggest the diagnosis, such as an elevated resistive index (RI = systolic velocity – diastolic velocity/systolic velocity) and absent diastolic flow. As with dissection, contrast is required to diagnose hepatic artery thrombosis with CT, and absent vessel enhancement confirms the diagnosis. Lack of enhancement or hyperintensity on unenhanced bright-blood images confirms the diagnosis on MR images (see Fig. 23).

Nontarget embolization during transcatheter interventions occurs from either failure to recognize arterial supply to non-hepatic structures or refluxed chemoembolic agents retrograde along the course of the catheter during delivery. Hepatic arterial variant anatomy is common, observed in nearly half the population (Covey et al. 2002). Consequently, that standard of care recommends characterizing the arterial anatomy on multiphasic CT or MRI prior to planned transcatheter intervention to minimize the potential risk of nontarget embolization (Ingraham et al. 2011). Nontarget embolization (of the left gastric or gastroduodenal arteries) into gastrointestinal vascular territory threatens stomach or duodenal mucosal ulceration and perforation. Refluxed chemoembolic material into the dorsal pancreatic or gastroduodenal artery risks pancreatitis, and inadvertent cystic artery embolization may induce chemical cholecystitis (Clark 2006).

Postembolization syndrome occurs in the majority of patients undergoing transcatheter chemoembolization, presenting with fever, malaise, right upper quadrant pain, nausea, and vomiting. Other complications related to the chemotherapeutic agent include alopecia, myelosuppression, leukopenia, and anemia. Infection develops (1) from biloma superinfection in patients with biliary tree colonization with enteric flora, (2) from abscess development within a devascularized tumor, and (3) as bacteremia or sepsis as a known complication of transcatheter procedures (minimized with the use of prophylactic antibiotics) (Reed et al. 1994).

The effects of image-guided ablative and transcatheter procedures are evident in the ablated lesion and surrounding tissue, and imaging follow-up is performed with either CT or MRI usually immediately post-procedurally (within 1 week) and then every 3 months for 1 year followed by biannually thereafter (Limanond et al. 2003; Braga et al. 2005; Smith and Gillams 2008). Optimally, the treated lesion fails to enhance, indicating the success of the procedure. However, peripheral rim enhancement reflecting a vascularized inflammatory reaction, hemorrhage, and granulation tissue is typical and indicates reactive change in the adjacent normal parenchyma, which fades over months (up to 6–12 months) (Limanond et al. 2003; Braga et al. 2005; Thabet et al. 2008; Özkavukcu et al. 2009). Internal enhancement is nonspecific and more likely to represent residual tumor when hypervascular, as opposed to progressive enhancement – more typical of posttreatment changes. An early incremental size increase is nonspecific and either reflects the effects of posttreatment change or tumor growth. In fact, in the case of image-guided ablation, the total volume of the ablated tumor and ablative margin must exceed that of the index lesion – the ablative margin threshold is 5 mm (Choi et al. 2001; Goldberg et al. 2005; Goldberg et al. 2000; Kim et al. 2003; Lim et al. 2001). DWI has been studied as a potential marker of tumor cell death and response to treatment with variable

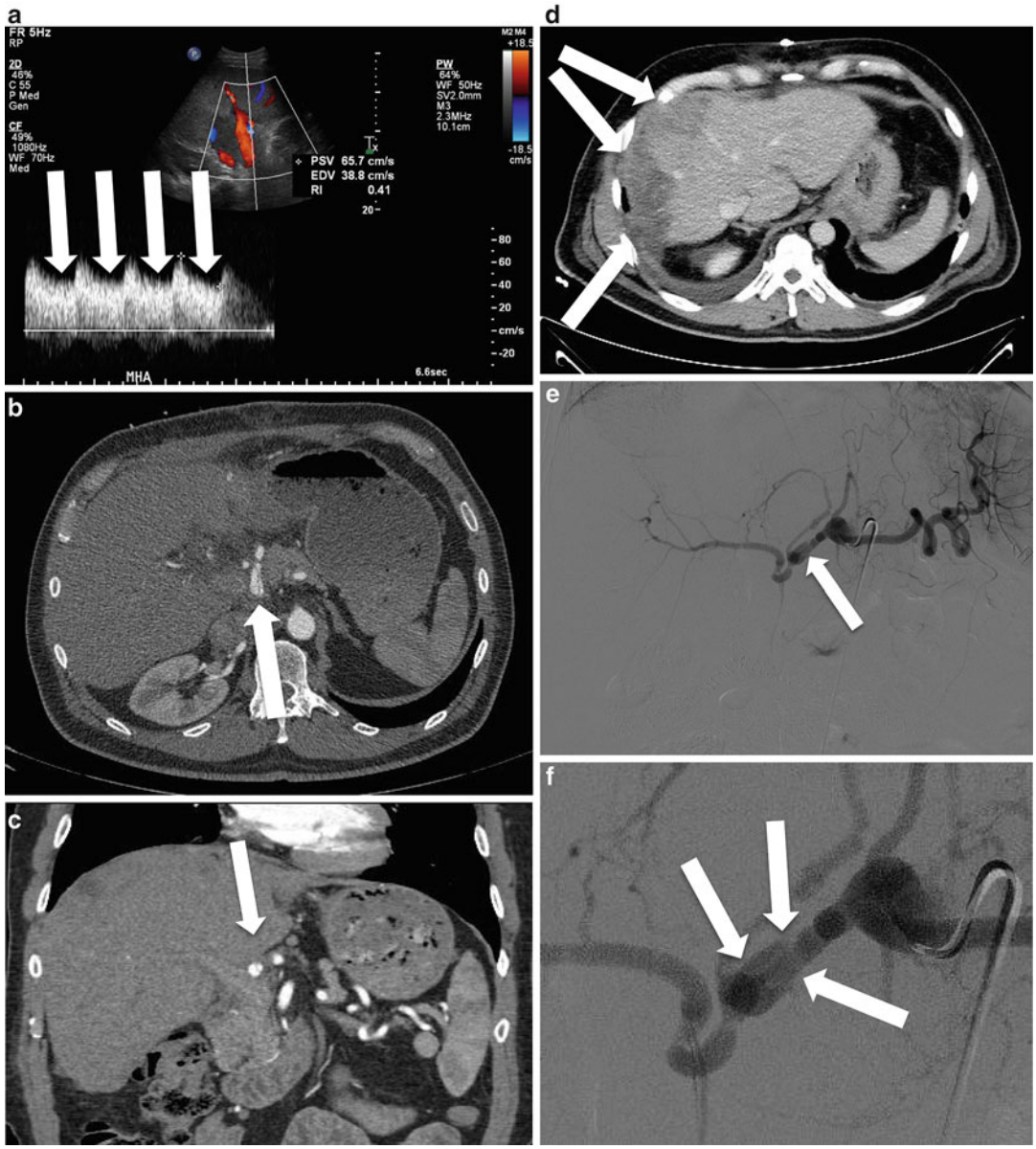

Fig. 22 Imaging of hepatic artery dissection. (**a**) DUS image interrogating the main hepatic artery reveals a reduced resistive index (0.41) as a consequence of markedly increased diastolic flow, reflected by the relatively high diastolic flow velocity on the spectral tracing (*arrows*). (**b**) The axial contrast-enhanced CTA image shows a linear, hypodense filling defect in the common hepatic artery (*arrow*). (**c**) The coronally reformatted image from the same CTA study shows the hypodense intimal flap separating the false from the true lumen (*arrow*). (**d**) Axial postcontrast CT image a few days later reveals multiple subcapsular, hypodense, wedge-shaped lesions corresponding to hepatic infarcts (*arrows*). (**e**) Angiographic image from a celiac axis injection demonstrates an abnormally dilated segment of the peri-anastomotic common hepatic artery (*arrow*). (**f**) Magnified view of the same angiographic image shows the dilated, peri-anastomotic segment and the double-barreled appearance of the dissected segment (*arrows*)

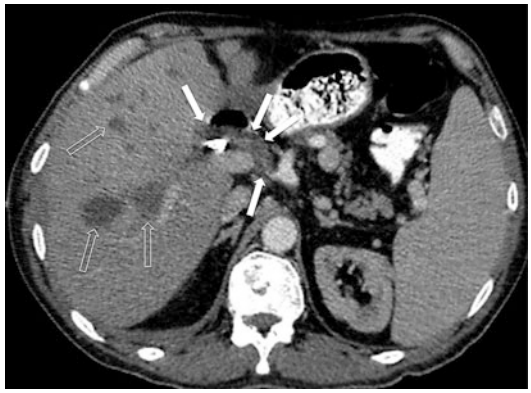

Fig. 23 Imaging of hepatic artery thrombosis. Contrast-enhanced CT image shows hypodense enlargement of the common hepatic artery (*arrows*) indicating thrombosis and occlusion. The amorphous parenchymal hypodensities (*open arrows*) correspond to hepatic infarcts

results. Studies have shown the utility of DWI in discriminating viable from nonviable tumor following ablation to a greater degree than following chemoembolization (Morani et al. 2013; Kele and van der Jagt 2010; Schraml et al. 2009; Goshima et al. 2008; Yu et al. 2009). Signal changes often ensue, but provide no definitive evidence of residual or recurrent tumor. Coagulative necrosis and hemorrhage frequently develop post-ablation reflected by T1-hyperintensity and T2-hypointensity. The surrounding parenchyma often exhibits post-procedural changes ranging from hyperemia with increased arterial enhancement and edematous increased T2 signal to infarcted foci as previously discussed (see Fig. 24).

While residual and recurrent lesion imaging features generally reiterate pretreatment features, dynamic contrast-enhanced images have achieved the greatest correlation. Recurrent and residual tumor usually arises at the periphery and thickening; irregularity or nodularity of the commonly present thin peripheral rim of enhancement is suggestive (Dromain et al. 2002; Thabet et al. 2008). Additionally, MRI surpasses CT in identifying recurrent and residual tumor with increased conspicuity of enhancement and tissue contrast and the benefit of myriad pulse sequences (Dromain et al. 2002; Kloeckner et al. 2010; Granata et al. 2013).

CT Volumetry

In addition to lesion surveillance and characterizing the vascular and biliary features of the liver, transplant planning also implicates volumetry. Since the late 1980s, the use of split cadaveric and living donor right hepatic lobe transplantation has increased to overcome organ availability (Fan et al. 2000a, b). Preoperative multidetector CT evaluation has played an increasing role over the last 10 years in identifying vascular anatomy and variants, assessing hepatic parenchyma, as well as the calculation of graft and remnant volumes to identify suitable donors and minimize donor risk. Reduced remnant volume places the donor at risk for acute liver failure. Decreased graft size places the recipient at risk for small for size syndrome (SFSS) (Alonso-Torres et al. 2005). SFSS is multifactorial and may be related to insufficient size of the graft or vascular compromise of the graft, whether it be related to arterial or portal hypoperfusion or venous congestion. Graft weight to receipt body weight (GWRW) and graft volume compared to standard liver volume have been used as predictors of SFSS (Gonzalez et al. 2010). For this reason, over the past 10 years, CT liver volumetry has played an increasingly important role in preoperative planning for living donor liver transplantation. Measured CT graft volume correlates well with actual graft volume, ensuring that there is sufficient graft and remnant volume for adequate function during the immediate postoperative period, as well as liver regeneration (Williams et al. 2003; Pomfret et al. 2001; Ishfuro et al. 2002). Liver grafts are deemed acceptable when the GWRW is 0.8 or the graft volume is 40 % of the standard liver volume (Alonso-Torres et al. 2005; Gonzalez et al. 2010).

Posttransplantation Imaging

Normal Appearance

The transplanted liver has a morphologic appearance that depends on the surgical approach and harvested graft. Living-donor liver transplants (LDLT) most commonly involve recipient

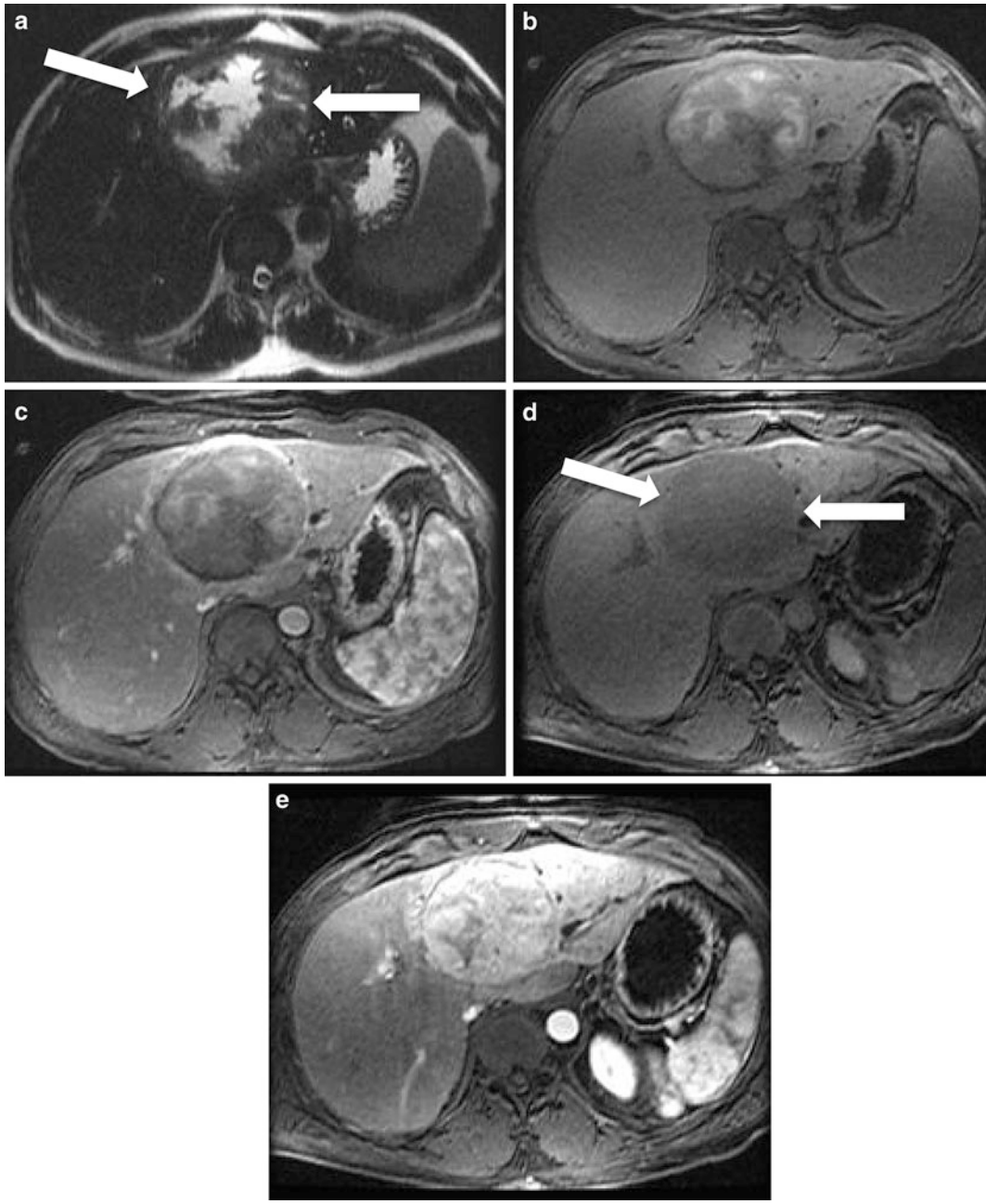

Fig. 24 Imaging of ablated lesions. (**a**) Axial T2W MR image following left hepatic artery chemoembolization reveals a large partially cystic lesion (*arrows*). (**b**) Axial precontrast, fat-suppressed T1W MR image shows heterogeneously increased signal indicated hemorrhagic necrosis. (**c**) Axial postcontrast, fat-suppressed T1W MR image shows the lack of lesional enhancement reflecting loss of viable tissue. (**d**) Axial precontrast, fat-suppressed T1W MR image obtained prior to chemoembolization shows the typical T1-hypointensity of an HCC (*arrow*). (**e**) Axial arterial-phase postcontrast fat-suppressed T1W MR image shows avid arterial enhancement in the viable tumor

transplantation of either segments 2 through 4 or 4 through 8, while cadaveric LTs include the entire liver. As such, the respective hepatic morphology, anastomotic connections, and vascular anatomy differ. Regardless, lymphedema is a common denominator as a consequence of the loss of lymphatic drainage posttransplant. This manifests with small periportal lymph nodes and periportal edema. Periportal edema appears as concentric CT hypodensity and MR T2-hyperintensity surrounding portal tracts with delayed enhancement (Ito et al. 2000; Lang et al. 1995). Periportal edema persists on imaging studies for up to 1 year posttransplantation.

Posttransplantation Complications

The spectrum of posttransplant complications is broad and many are amenable to imaging diagnosis (see Fig. 25).

Perihepatic fluid collections are a common incidental finding discovered in nearly half of patients post-LT and often portend little to no significance (Halliday et al. 1997; Crossin et al. 2003; Akin et al. 2006). Post-LT fluid collections are typically small, composed of either simple fluid (seroma) or blood (hematoma) and often inhabit characteristic locations, such as the right subhepatic space and interlobar fissure. Simple fluid contents appear uniformly anechoic, hypodense, and T1-hypointense and T2-hyperintense on US, CT, and MR images, respectively, and demonstrate no enhancement. Hematomas demonstrate the lacy septations sonographically, CT hyperdensity acutely fading with chronicity, and MRI T1-hyperintensity and T2-hyperintensity without enhancement, as previously discussed (see Fig. 26).

Hematomas are clinically significant when superinfected or indicating loss of anastomotic integrity and leaking. Therefore, signs of infection – wall thickening and enhancement and edematous and hypervascular surrounding reactive parenchymal changes – and integrity of the vascular anastomoses should be assessed. A biloma implies loss of integrity of the biliary anastomosis, bile duct injury, or arterial insufficiency (Akin et al. 2006; Kaplan et al. 1990; Hoffer et al. 1988). Because the biliary system is solely dependent on hepatic arterial supply, arterial compromise leads to bile ductal epithelial necrosis, leading to extravasation and biloma formation. Imaging plays a vital role in elucidating the underlying etiology – often either the arterial or biliary anastomoses – which implicates drastically different treatment implications. The imaging appearance has been previously discussed and the etiologic anastomotic complications will be discussed. Pyogenic abscesses develop as a consequence of (1) bacteremia; (2) superinfection of a seroma, hematoma, or biloma; or (3) superinfection of an infarcted area (Girometti et al. 2014), and the imaging appearance has been previously discussed.

Anastomotic complications must be distinguished from their normal respective postoperative appearances. Posttransplant anastomotic structures tend to differ from their native appearances. In the case of arterial anastomoses, the donor celiac axis is anastomosed to either (1) the recipient hepatic artery at the right/left bifurcation, (2) origin of the gastroduodenal artery, or (3) directly to the recipient aorta. Depending on the approach and anatomic factors, the reconstructed artery tends to appear redundant and relatively tortuous compared with the native appearance. Also, the resistive index obtained at DUS is often elevated in the immediate postoperative period (>0.80) and normalize rapidly (Itri et al. 2013; Garcia-Críado et al. 2003). Hepatic arterial anastomotic complications include thrombosis, stenosis, pseudoaneurysm, and arterioportal fistula. The most common and serious vascular complication is hepatic artery thrombosis, occurring in up to 3–10 % of cases (Singh et al. 2010; Caiado et al. 2007; Bismpa et al. 2012). DUS is usually the first-line diagnostic modality with reported accuracy of 92 % (Flint et al. 1988). Lack of flow establishes the diagnosis, although false-positive results are associated with low cardiac output, arterial spasm, or severe parenchymal edema and false-negative results are related to flow from collateral arteries developing in the subacute phase (Girometti et al. 2014; Itri et al. 2013; García-Criado et al. 2002). However,

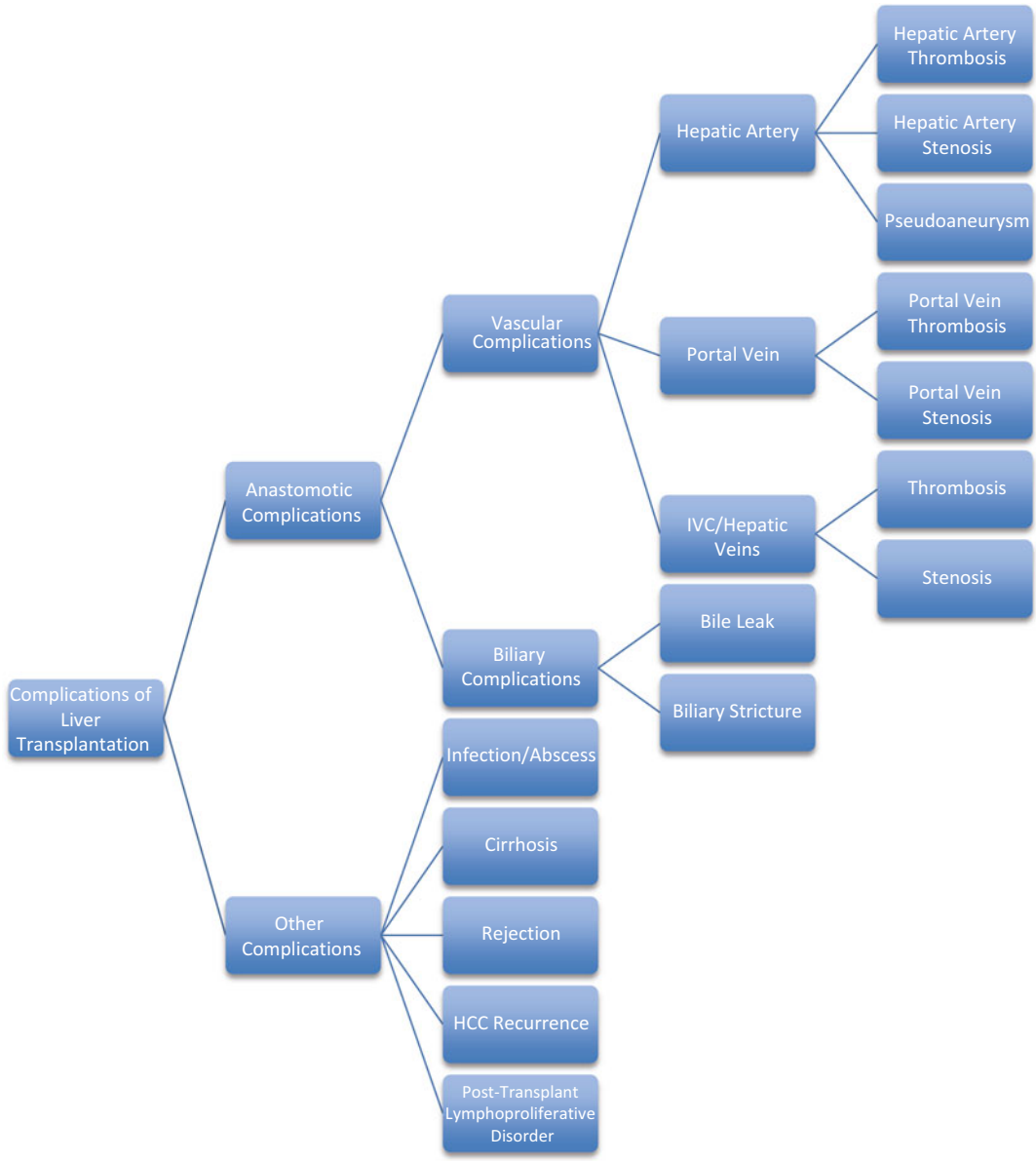

Fig. 25 Posttransplant complications

collateralization exhibits intra- or extrahepatic parvus-tardus waveforms (dampened arterial waveform with prolonged systolic upstroke) with a prolonged acceleration time (>0.08 s) and low resistive index (<0.5) (Dodd et al. 1994; Vit et al. 2003). CT or MR angiography solves problematic US cases, and hepatic artery thrombus primary findings include either an intraluminal filling defect or vessel amputation with secondary findings including hepatic infarcts and evidence of biliary ischemia – bilomas, biliary structuring, and upstream biliary dilatation (see Fig. 27).

Hepatic artery stenosis is the next most common vascular complication of LT and usually occurs at the anastomotic site within 3 months of transplantation (Bhargava et al. 2011). Ultimately, hepatic artery stenosis risks thrombosis and the attendant complications and potential need for

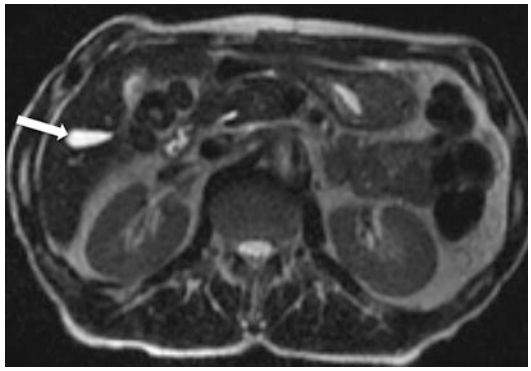

Fig. 26 Imaging of posttransplant fluid collections. Axial T2W image in the early posttransplant period demonstrates a small lenticular fluid collection in hepatic segment 5 (*arrow*)

re-transplantation. A peak systolic arterial velocity of greater than 200 cm/s with turbulent flow detected on DUS indicates stenosis (Dodd et al. 1994; Crossin et al. 2003). Intrahepatic parvus-tardus waveforms corroborate the diagnosis. CTA or MRA confirms the diagnosis with equivocal or technically limited US findings by demonstrating segmental narrowing at the anastomotic site, and image postprocessing helps to illustrate and quantify the degree of stenosis (see Fig. 28).

Hepatic artery pseudoaneurysms rarely complicate LT and are frequently mycotic involving the anastomotic site. Rarely, intrahepatic pseudoaneurysms develop at the site of percutaneous interventions. Aside from anastomotic involvement, the appearance of hepatic artery pseudoaneurysm is the same as previously discussed.

Portal vein complications – thrombosis and stenosis – affect 1–2 % of patients (Wozney et al. 1986; Lerut et al. 1988; Langnas et al. 1991). The reconstructed portal vein often features a waist, or mild anastomotic narrowing, corresponding to discrepant recipient-donor vessel size (Ito et al. 2000; Girometti et al. 2014). Sonographically, "an echogenic shelf-like ring often can be seen at the anastomotic site," not to be confused with a stenosis, which typically occurs at the anastomosis (Chong 2004; Bhargava et al. 2011). Using a threshold flow velocity in the portal vein of 125 cm/s on DUS yields a sensitivity of 73 % and specificity of 95 % for stenosis, and an anastomotic-to-preanastomotic velocity ratio of 3:1 is 73 % and 100 % specific (Chong 2004). Supporting sonographic findings include persistence of the transient normal early posttransplant helical flow pattern, post-stenosis dilatation, and signs of portal hypertension. CTA or MRA confirms the sonographic diagnosis (see Fig. 29), when necessary and percutaneous transhepatic direct portography showing a minimum of a 5 mmHg gradient is the definitive diagnostic criterion (Glockner and Forauer 1999).

Percutaneous transhepatic venoplasty is the first-line nonsurgical therapeutic approach, and transjugular venoplasty offers an alternative approach; Shibata et al. (2005) reported a 74 % success rate with a 28 % recurrence rate (O'Neill et al. 2013). Portal vein thrombosis also usually involves the extrahepatic segment and demonstrates absent portal venous flow on DUS with or without replacement of the normally anechoic lumen with echogenic thrombus on gray-scale images. Partial, nonocclusive thrombus fills a portion of the lumen with preserved flow detectable on DUS and a residual enhancing lumen on enhanced CT and MR images (see Fig. 30).

The IVC anastomosis also potentially experiences stenosis or thrombosis with a combined incidence of 1–2 % of transplantations (Uzochukwu et al. 2005). IVC stenosis separates into primary and secondary types, and primary stenosis results from recipient-donor size discrepancy, suprahepatic caval kinking from organ rotation, or delayed fibrosis or neointimal hyperplasia (Crossin et al. 2003). DUS provides strong negative predictive value in the form of a normal triphasic or a biphasic waveform. While a monophasic waveform is relatively nonspecific, the sensitivity is higher and magnified when combined with a pulsatility index ([systolic velocity – diastolic velocity]/average velocity) of less than 0.45, which is 95.7 %, specific for stenosis (Caiado et al. 2007; Chong 2004). Ancillary findings include hepatic venous flow reversal or loss of phasicity (Nghiem et al. 1996). In the setting of thrombosis, US reveals either vessel narrowing or echogenic intraluminal thrombus with absent

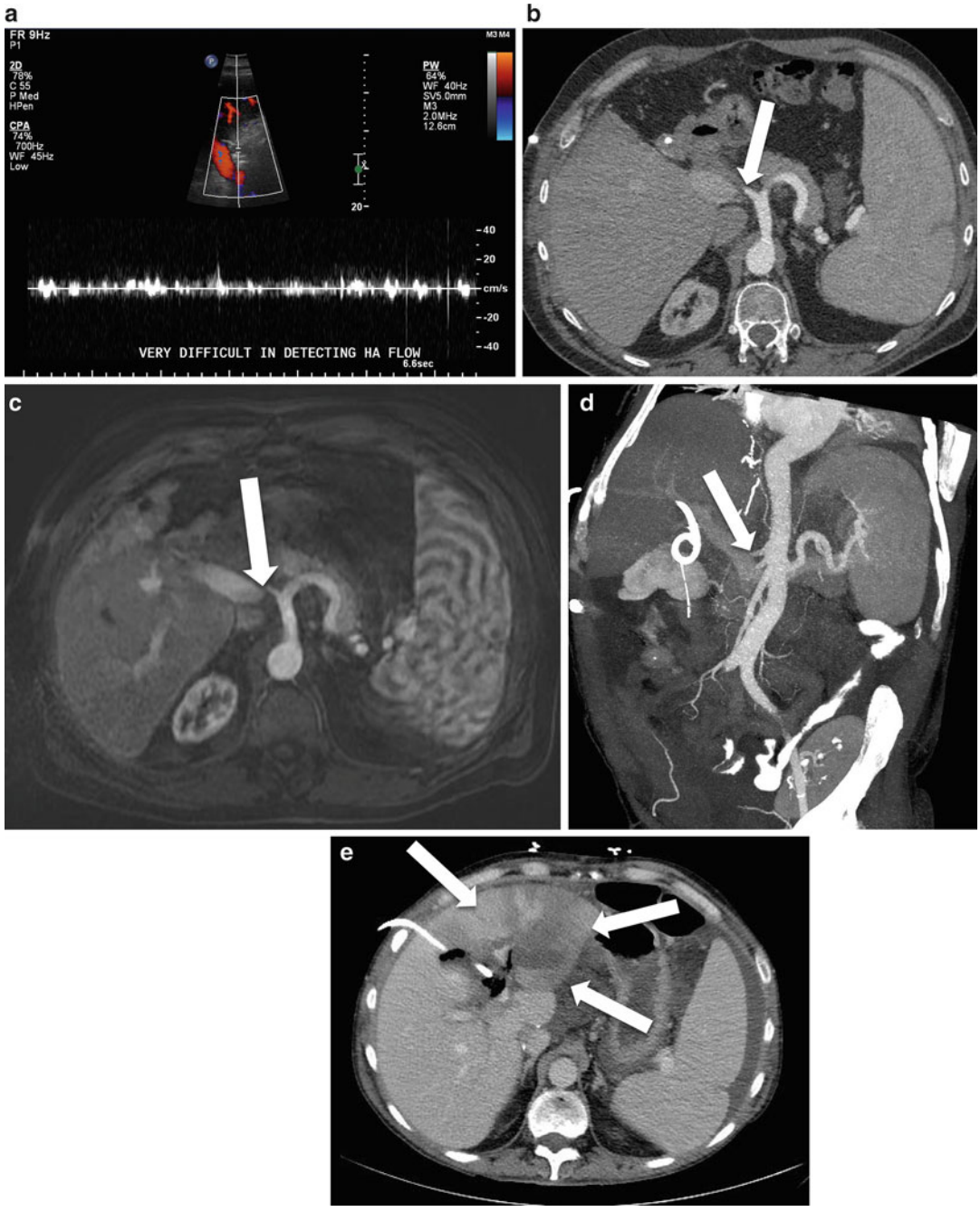

Fig. 27 Imaging of hepatic artery thrombosis. (**a**) DUS image shows no discernible flow in the main hepatic artery – the portal vein appears normal with hepatopetal flow encoded in *red* (*arrow*). (**b**) Axial CTA image demonstrates abrupt termination of the proximal common hepatic artery (*arrow*). (**c**) The arterial-phase postcontrast T1W fat-suppressed MR image also shows hepatic arterial occlusion (*arrow*). (**d**) Maximal intensity projectional image reformatted from the CTA demonstrates the abrupt hepatic arterial termination and lack of peripheral enhancement (*arrow*). (**e**) Postcontrast CT image a few days later shows infarcts throughout the lateral segment (*arrows*)

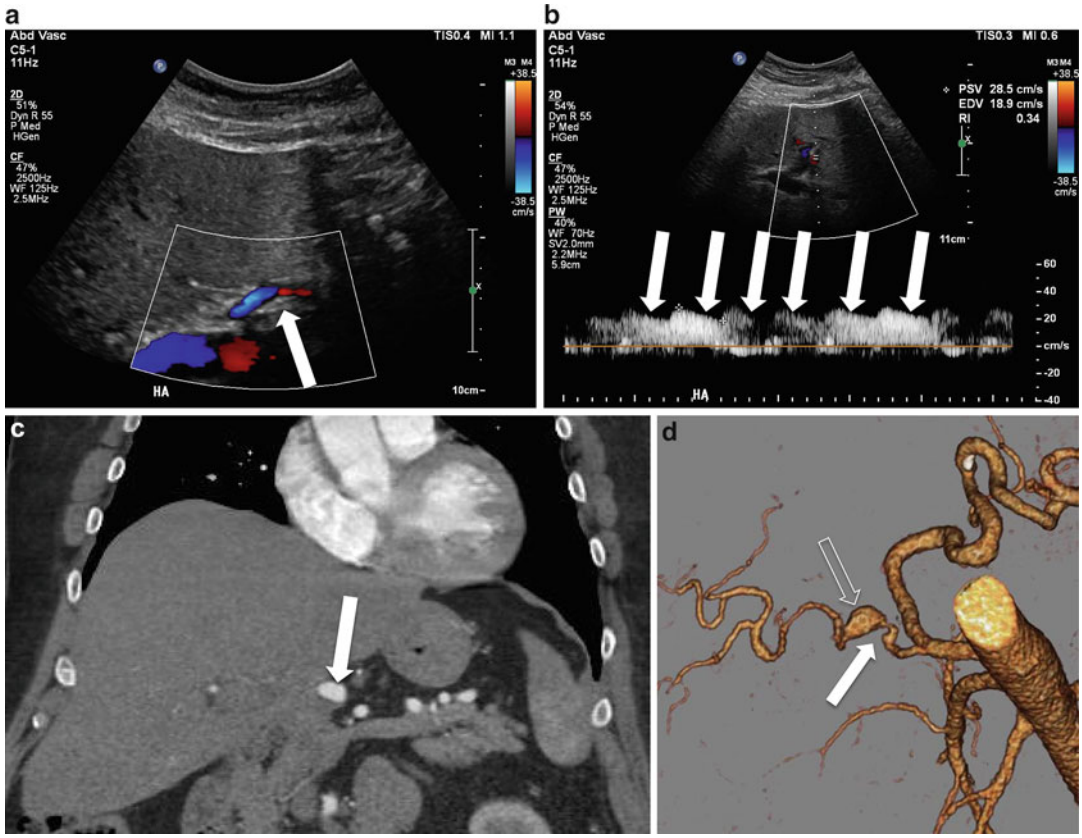

Fig. 28 Imaging of hepatic artery stenosis. (**a**) Color DUS image shows the common hepatic artery with appropriate flow direction toward the liver (*arrow*). (**b**) DUS image of a peripheral, intrahepatic arterial branch reveals a spectral tracing with high diastolic flow (*arrows*) and a low resistive index (0.34). (**c**) A coronally reformatted image from a CTA reveals a dilated hepatic arterial segment (*arrow*). (**d**) A volume-rendered post-processed image from the CTA shows the peri-anastomotic stenosis (*arrow*) proximal to the dilated common hepatic arterial segment (*open arrow*)

Doppler signal (Crossin et al. 2003). CT or MRI confirms the IVC stenosis or thrombosis by demonstrating absent enhancement, vessel narrowing and upstream hepatic venous distention, intraluminal filling defects or thrombus, and secondary findings such as hepatomegaly, ascites, and signs of portal hypertension and Budd-Chiari syndrome (Quiroga et al. 2001).

Biliary complications usually occur within 3 months of transplantation with a wide range of reported frequency – from 5 % to 34 % of cases (Greif et al. 1994; Nghiem et al. 1996; Fulcher and Turner 1999; Haberal 2006; Friedewald et al. 2003). Potential biliary complications include bile duct obstruction, anastomotic stenosis, bile duct stricture, stone formation, bile leak/biloma, biliary necrosis, and cholangitis. Evaluating the biliary tree post-LT is optimally performed with T-tube cholangiography, performed with active contrast-induced bile duct distention for better stricture delineation and functional assessment (Singh et al. 2010). MRI is the next best noninvasive alternative (obviating potential complications from percutaneous transhepatic cholangiography and endoscopic retrograde cholangiography) and also provides additional information beyond the biliary system. CT preempts some of the logistical difficulties of MRI, but performs less accurately in assessing the postoperative biliary tree than MRI (Zoepf et al. 2005). While US generally serves the role as a primary screening tool for post-LT complications, its

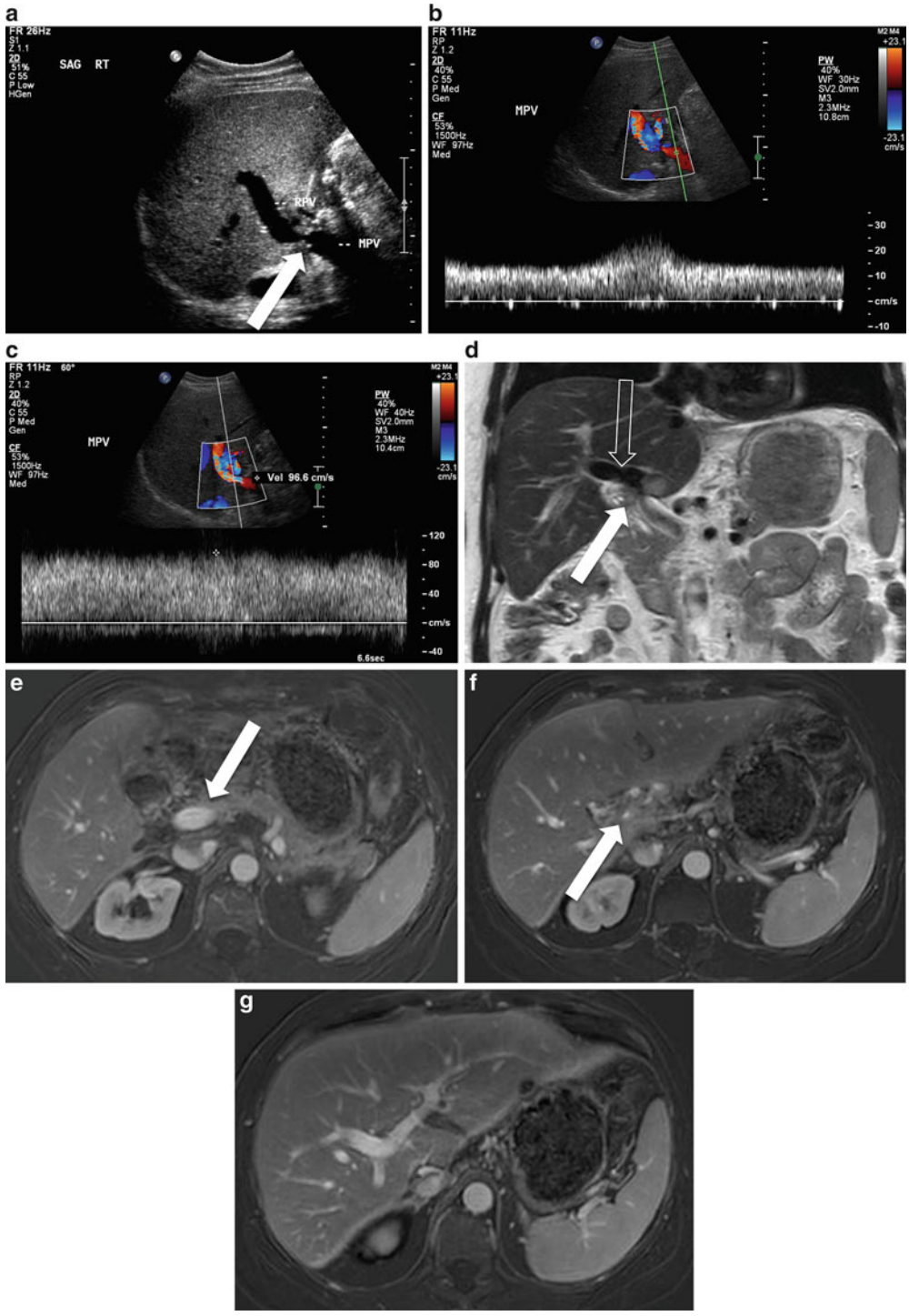

Fig. 29 Imaging of portal vein stenosis. (**a**) Oblique gray-scale US image through the portal vein shows an anastomotic stenosis (*arrow*). (**b**) The DUS image shows normal flow direction and velocity in the pre-anastomotic portal vein. (**c**) DUS image distal to the stenosis reveals an abnormal spectral tracing with elevated portal venous flow velocity with a turbulent flow pattern. (**d**) Coronal T2W MR image shows the stenosis (*arrow*) with a distal flow

sensitivity for biliary complications is relatively low – 54 %, as reported by Zemel et al. 1988.

Obstruction is the most common biliary complication post-LT, usually due to anastomotic fibrosis obliterating the lumen. Ischemia induced by hepatic artery stenosis or thrombosis is a less common cause of anastomotic stricture (Fulcher and Turner 1999). Underlying diseases, such as primary sclerosing cholangitis, biliary ischemia, and infection, in addition to sludge and stones account for non-anastomotic strictures. Although bile duct dilatation may signal obstruction or downstream stricture, interpreting this finding requires understanding the clinical context. Mild post-LT biliary dilatation is observed on imaging studies in the absence of mechanical obstruction (Fulcher and Turner 1999; Caiado et al. 2007). Conversely, occasionally strong clinical and laboratory evidence of biliary obstruction coexists without biliary dilatation on imaging studies (Quiroga et al. 2001). Finally, donor-recipient duct caliber discrepancy simulates dilatation in the form of a transition point.

Because of its availability and screening utility, US is often the initial imaging study, and the most obvious finding is biliary dilatation subtended by the point of obstruction. While the normal common bile and common hepatic ducts measure 7 or 8 mm or less, following cholecystectomy, the upper limit is redefined at 10 mm (Park et al. 2012; Yeh et al. 2009). Normal intrahepatic bile ducts are generally below the detection threshold of US and CT and faintly visualized on MR/MRCP images. The sonographic appearance of biliary dilatation conforms to anechoic branching tubular structures without discernible flow on DUS. While an offending stricture often eludes US, stones appear very echogenic with acoustic shadowing, while sludge is morphologically amorphous with variable echogenicity. However, while US constitutes the gold standard for detecting gallstones with a sensitivity of at least 95 % (Shea et al. 1994), the sonographic sensitivity of intrabiliary stones ranges from 21 % to 63 % due to the limited acoustic window, lack of surrounding fluid, and anatomic considerations (compared with gallstones confined to the gallbladder by definition, intrabiliary stones potentially arise anywhere in the biliary tree) (Stott et al. 1991; Sugiyama and Atomi 1997; Majeed et al. 1999). CT intrabiliary stone visibility is also limited, although visible when calcified and hyperdense, although a minority of stones contains hypodense gas rendering even non-calcified stones visible. CT identifies biliary dilatation reliably, especially with intravenous contrast increasing the tissue contrast between relatively hypodense biliary fluid and the adjacent liver. MRI achieves the highest accuracy in detecting biliary dilatation with a sensitivity and specificity of 98 % and 100 %, respectively (Nandalur et al. 2008). This superior performance derives from the multiplicity of pulse sequences with rich tissue contrast – specifically, the T2WIs, MRCP images, and postcontrast images (especially delayed postcontrast images). Even without intravenous contrast, the unenhanced sequences – T2WIs and MRCP – demonstrate the biliary tree and biliary dilatation very reliably. Following the tortuous, dilated intrahepatic ducts centrally converging to the transition point reveal the obstructing lesion. MRI exceeds the performance of both CT and US in detecting intrabiliary stones with proven sensitivity and specificity ranging from 81–100 % to 85–100 %, respectively (Guibaud et al. 1995; Regan et al. 1996; Fulcher et al. 1999; Halefoglu 2007). Stones constitute signal voids on T2WIs and MRCP images with variable T1 signal intensity, depending upon stone content with pigment conferring

Fig. 29 (continued) void (*open arrow*) due to the elevated velocities. (**e**) Postcontrast T1W fat-suppressed MR image reveals a normal-caliber pre-anastomotic portal vein (*arrow*). (**f**) Slightly more cephalad postcontrast T1W fat-suppressed MR image shows the markedly small caliber at the level of the anastomosis (*arrow*). (**g**) More cephalad postcontrast T1W fat-suppressed MR image shows normal-caliber distal portal venous branches

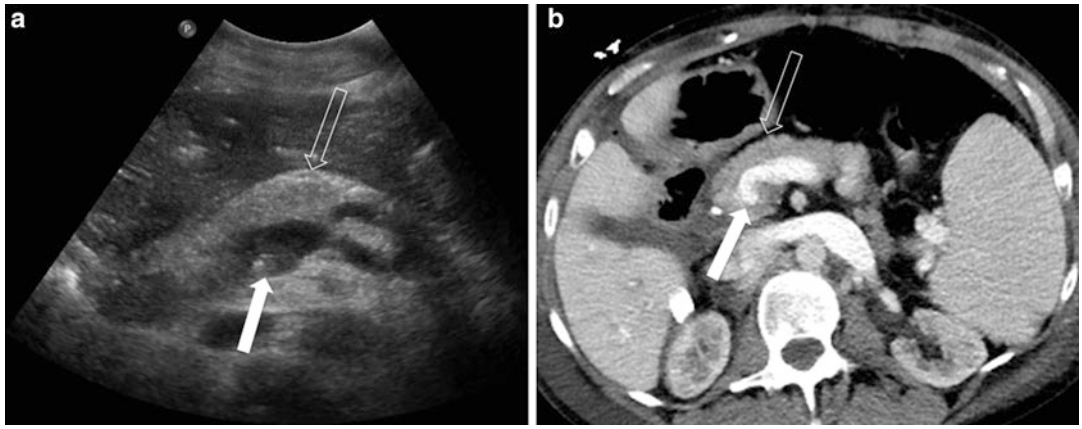

Fig. 30 Imaging of portal vein thrombosis (see Fig. 22e). (**a**) Gray-scale US image through the pancreatic head (*open arrow*) reveals partially occlusive thrombus within the portal vein just distal to the confluence (*arrow*). (**b**) Postcontrast CT image at the same level – note the pancreas (*open arrow*) – shows the hypodense filling defect in the portal vein (*arrow*)

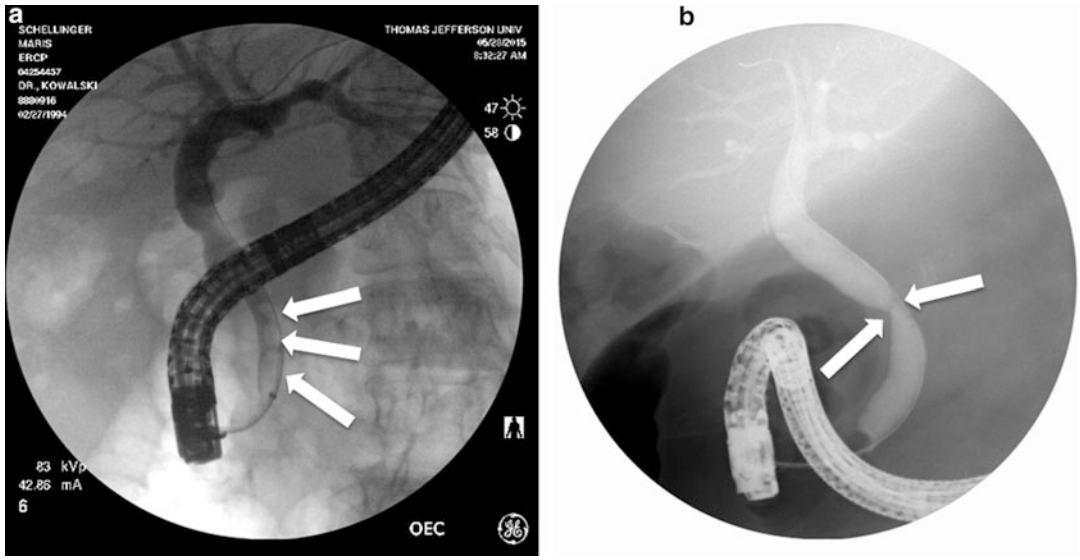

Fig. 31 Imaging of stones complicating liver transplantation. (**a**) ERCP image following contrast opacification of the bile duct reveals multiple lucent filling defects (*arrows*) corresponding to stones. (**b**) A subsequent image following stone removal shows the mild anastomotic narrowing (*arrows*) to better advantage

T1-hyperintensity (Tsai et al. 2004; Baron et al. 1989). While T2WIs vividly depict stones, secondary signs highlight the presence of the underlying stone – a dependent, posterior location, a crescent of bile or gas (with pneumobilia) outlining the anterior margin of the stone, and bile duct mural thickening and enhancement (see Fig. 31).

Strictures are best visualized with MRI using a combination of T2WIs and MRCP images and contrast-enhanced images. MRCP and T2W images demonstrate an abrupt, smoothly

marginated tapering from upstream dilated hyperintense, branching ducts to downstream normal-caliber ducts. T1W postcontrast images render the bile ducts hypointense and the underlying stricture as a short segment of mural thickening with progressive enhancement. CT demonstrates similar features, but lacks the extreme tissue contrast and panoramic portrayal of the biliary system in a single image (with MRCP) (see Fig. 32).

When ischemic, US, CT, and MRI show the associated findings of hepatic artery disease, as previously discussed. Ischemic strictures typically progress centrifugally from the hilum (Ito et al. 2000; Shanbhogue et al. 2011), and strictures related to primary sclerosing cholangitis are distinguished by their multifocality and irregular, beaded appearance of the biliary tree. Biliary leakage usually occurs at the biliary anastomosis or the T-tube defect and contrast extravasates into the peritoneal cavity at direct cholangiography. As previously discussed, the only imaging modalities that replicate the extravasation phenomenon and diagnose and identify the leak are cholescintigraphy and hepatobiliary phase MRI. While cholescintigraphy poses less logistical difficulties than MRI, a small biloma is potentially obscured by the physiologic accumulation of radiotracer in the bowel, especially in patients with a Roux-en-Y limb where the blind end of the limb simulates a biloma (Young et al. 2003). While hepatobiliary phase MRI eliminates this problem, it requires adequate hepatic function to metabolize the contrast agent and a much longer delay to increase the sensitivity for identifying a leak – up to 2 h instead of the standard 20-min delay.

Infection often develops on top of liver infarction in the setting of LT, (Ito et al. 2000) although hematoma, seroma, or biloma superinfection and bacteremia constitute additional infection pathways. Pyogenic abscesses have been previously discussed and these imaging features generally apply in the post-LT setting. However, superinfecting of a preexisting fluid collection simulates its native appearance variably complicated by a few characteristic features: gas or a gas-fluid fluid with gas most conspicuous from the susceptibility artifact induced (blooming signal void on gradient-echo images), reactive edematous and hyperemic changes in the surrounding liver parenchyma, and an enhancing wall. Ultimately, fluid collection imaging features are often nonspecific and with a high clinical index of suspicion; imaging serves to guide percutaneous drainage for diagnosis and treatment.

While rejection is the most common cause of graft failure, imaging plays little to no role in its diagnosis and biopsy establishes the diagnosis (Nghiem 1998; Bhargava et al. 2011). In fact, a host of "primary hepatic complications" manifest with graft dysfunction and share the distinction of demonstrating nonspecific imaging features, such as immunologic disorders (rejection or recurrent or de novo autoimmune disease), viral infection (recurrent hepatitis B or C virus, de novo cytomegalovirus, and others), toxic effects (drug induced), and ischemic disease (effects of ischemic and reperfusion injury days after LT) (Neuberger 2005; Desai and Neuberger 2009; Girometti et al. 2014). The common denominator is the lack of diagnostic imaging findings, and the chief role of imaging is to exclude alternative etiologies of graft dysfunction. Heterogeneity is often the only US finding and DUS serves to exclude hepatic artery compromise, but discloses no diagnostic findings. Sandrasegaran et al. (2011) showed correlation between DWI and the presence of underlying inflammation (acute rejection or recurrent hepatitis) with greater diffusion restriction compared with the normal transplanted liver, and these promising results have not been adequately consolidated and adopted into routine practice.

Persistent viremia (usually hepatitis B or C) threatens the recurrence of chronic liver disease and cirrhosis with portal hypertension, and the imaging features have been previously reviewed. Of course, this engages the carcinogenesis pathway and the increased risk of HCC as in the pretransplant setting. However, other malignancies arise in the posttransplant setting because of immunosuppressive therapy, and the most common are skin cancers and posttransplant lymphoproliferative disease (PTLD). Post-LT PTLD features intrahepatic and extrahepatic forms; the more common extrahepatic type

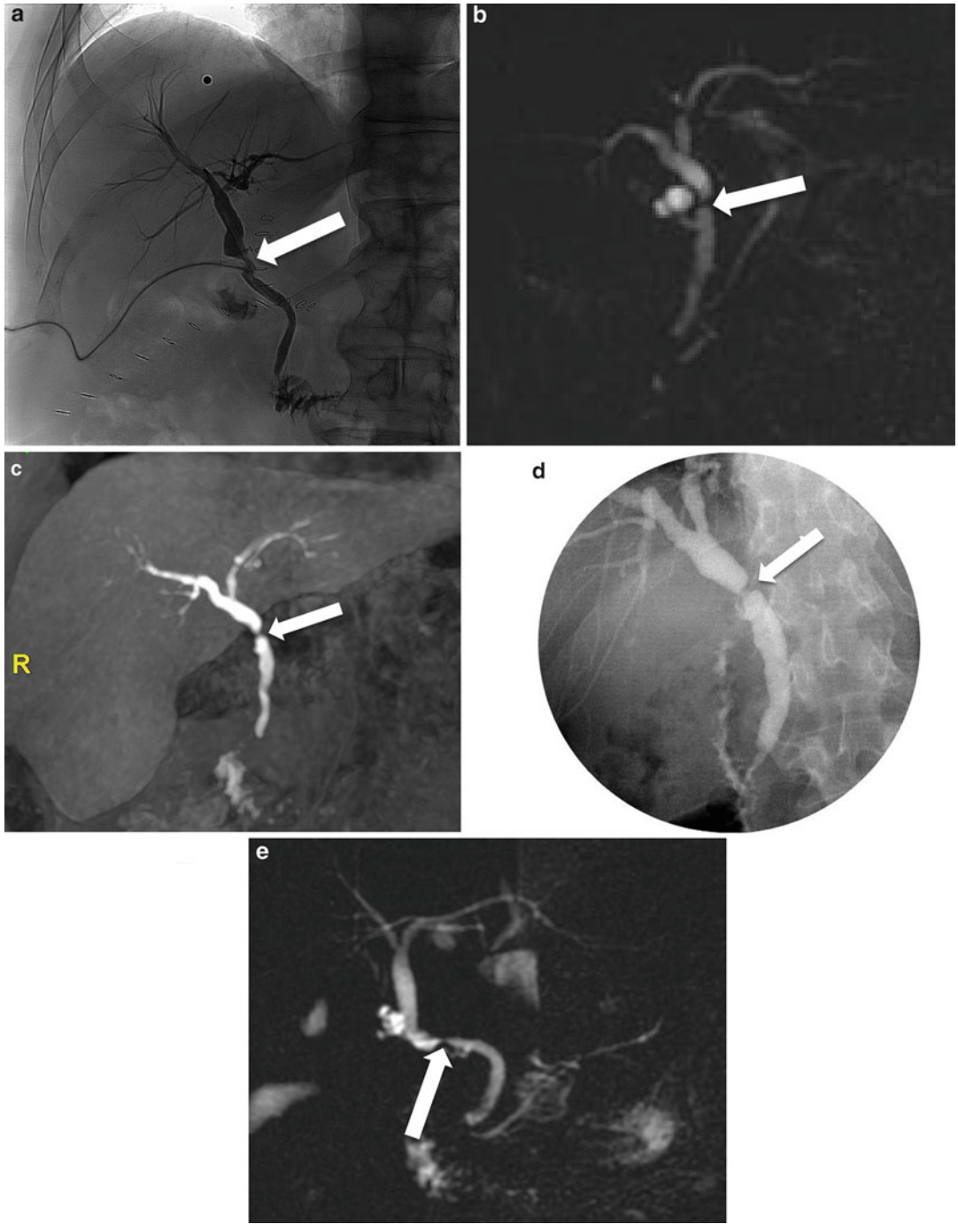

Fig. 32 Imaging of biliary stricture. (**a**) T-tube cholangiogram shows a moderate-grade anastomotic stricture (*arrow*). (**b**) MRCP image overestimates the degree of stenosis (*arrow*). (**c**) Maximal intensity projectional reformatted image from a hepatobiliary phase postcontrast MR image relies on the biliary excretion of contrast to enhance the bile ducts and show underlying pathology, such as the anastomotic stricture (*arrow*). (**d**) Contrast opacification of the biliary tree after T-tube removal demonstrates a persistent anastomotic stricture (*arrow*). (**e**) MRCP image in a different patient reveals a high-grade anastomotic biliary stricture (*arrow*)

typically presents as an ill-defined mass at the hepatic hilum with encasement or narrowing of the hepatic artery, portal vein, and common bile duct. Imaging features include hypoechogenicity sonographically, uniform CT hypodensity, and mild T1-hypo- and T2-hyperintensity on MR images (Borhani et al. 2009). Heterogeneous and peripheral enhancement patterns have been described by Beaty et al. (2008). Intrahepatic involvement presents with either the more common well-defined focal mass pattern or the infiltrative pattern, and imaging features are otherwise similar to the extrahepatic form.

Conclusion

Imaging plays a major role in the pretransplant surveillance and planning and posttransplant treatment guidance and surveillance functions. US is an operator-directed modality generally serving as the first-line screening tool in both the pretransplant surveillance and posttransplant complication settings. DUS offers the unique capability of interrogating flow characteristics of the hepatic vasculature to identify signs of portal hypertension and vascular complications of LT. CT and MRI provide a general anatomic overview with sensitivity and specificity for liver lesions and HCC and many post-LT complications. MRI generally exceeds other noninvasive imaging modalities in identifying and characterizing findings as a consequence of the multiplicity of unique tissue-specific pulse sequences. Additionally, the use of MRI contrast agents metabolized by the liver adds the capability of highlighting non-hepatocellular lesions with exquisite sensitivity, another means of evaluating the biliary tree and an alternative to cholescintigraphy and direct cholangiography. US and MR elastography have emerged as viable alternatives to liver biopsy to accurately grade liver fibrosis and plan treatment accordingly. CT volumetry accurately estimates potential graft viability based on measurements obtained from CT images. Catheter-directed and image-guided percutaneous interventional techniques target HCCs threatening transplant candidacy. While successful in this capacity, complications occasionally ensue and noninvasive imaging modalities generally detect them. Radiology is a vital component of the liver transplantation life cycle, and understanding the respective indications, utility, complications, and limitations of each modality is essential to maximizing its value.

Cross-References

- ▶ Infections and Sepsis After Liver Transplantation
- ▶ Interventional Radiology for the Pre-transplant Patient
- ▶ Orthotopic Liver Transplantation: Complications
- ▶ Orthotopic Liver Transplantation: Surgical Techniques

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Interventional Radiology for the Pre-transplant Patient

23

Susan Shamimi-Noori

Contents

Abstract

Interventional radiology is essential to the multidisciplinary liver transplant program. The goal of the interventional radiologist is to decrease the dropout rate from the transplant waiting list. Decreasing the dropout rate is accomplished twofold: (1) treating sequelae of portal hypertension and (2) treating hepatocellular carcinoma. The interventional radiologist has the knowledge base and skill set to treat sequelae of severe portal hypertension by creating transjugular intrahepatic portosystemic shunts (TIPS), thereby treating life-threatening hemorrhage and/or improving the patients' quality of life. In patients with hepatocellular carcinoma, the interventional radiologist performs palliative therapies in order to maintain the disease within size and number criteria required for transplantation. In patients with hepatocellular carcinoma beyond transplant criteria, the same palliative therapies are performed to potentially downstage cancer so that patients become eligible for transplant candidacy. Numerous prospective and retrospective clinical trials, which will be discussed in this chapter, have shown the efficacy of procedures performed by interventional radiologists. Through a discussion of these procedures, an understanding of the critical role of interventional radiology for the pretransplant patient can be made.

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Introduction

The knowledge base and skill set of an interventional radiologist can be invaluable for patients awaiting liver transplantation. Numerous prospective and retrospective clinical trials have shown that procedures performed by interventional radiologists have a beneficial role in the treatment of symptomatic portal hypertension as well as hepatocellular carcinoma. Treatment of these disease processes is invaluable for decreasing dropout rates for patients on the transplant list in an era of potential long wait times.

Transjugular Portosystemic Shunts

While awaiting transplantation, patients may develop decompensated cirrhosis and complications of portal hypertension resulting in a decreased quality of life and increased mortality. The goal of transjugular portosystemic shunt (TIPS) creation in the pretransplant patient is to create a low resistance pathway between the portal and systemic vasculature, thereby decreasing portal pressures and associated complications of portal hypertension. The shunt is created while maintaining the extrahepatic venous vasculature needed for transplantation (Amesur and Zajko 2006). Interventional radiologists or specialty-trained physicians create TIPS. Using internal jugular access, a hepatic vein is catheterized and, most often under fluoroscopic guidance, a needle is advanced from the hepatic vein into an intrahepatic portal vein branch. Using this access, a stent is placed across the hepatic parenchyma from the portal vein to the hepatic vein-inferior vena cava confluence. The detailed technique of TIPS creation and variations on these technique have been previously published (Bilbao et al. 2002; Ferral and Bilbao 2005; Kalva et al. 2009; Rösch and Keller 2014)

Technical and clinical success rates for TIPS creation are high. The Society of Interventional Radiology quality improvement guidelines recommend technical and hemodynamic success rates of 95 % and a clinical success rate > 90 % (Rossle et al. 1994; Haskal et al. 2003). Technical success is defined as patent TIPS creation. Hemodynamic success is defined as reduction of the portosystemic gradient to a targeted level. For example, the gold standard portosystemic gradient reduction for patients with variceal bleeding is a reduction of 25–50 % or a gradient < 12 mmHg. Achieving these levels has been shown to decrease the risk of rebleeding (Casado et al. 1998; Rossle et al. 2001). The necessary portosystemic gradient reduction for other indications of TIPS is less defined. A portosystemic gradient reduction to < 8 mmHg has been suggested for patients with refractory cirrhotic ascites; however, data is limited and development of ascites may be multifactorial reflecting both hepatic and renal function (Rector 1986; Sanyal et al. 2003; Boyer et al. 2010).

Patient Selection

Patient selection is paramount for TIPS creation. Predictors of poor outcome after TIPS include various scoring systems, emergent versus elective procedures, and comorbidities. The Child-Pugh score was originally used to predict mortality after TIPS and is still often used. Multiple studies have shown small differences in the ability of the Child-Pugh score and the model for end-stage liver disease (MELD) score to predict mortality post-TIPS (Salerno et al. 2002; Schepke et al. 2003; Ferral et al. 2004a, b). Due to the "ceiling effect" of the Child-Pugh score, the MELD score may be more easily applied (Schepke et al. 2003; Ferral 2005). The MELD score is specifically designed to predict mortality

after elective TIPS and has been validated as a predictor of mortality (Malinchoc et al. 2000; Kamath et al. 2001; Angermayr et al. 2003; Montgomery et al. 2005; Pan et al. 2008). Studies have shown that patients undergoing elective TIPS with a MELD score < 18 have significantly lower mortality rates compared to patients with MELD scores ≥ 18 (Angermayr et al. 2003; Ferral et al. 2004a,b). In the emergent setting or with high risk patients, a multidisciplinary approach in evaluation of risks and benefits of TIPS creation is recommended (Lopera 2005; Boyer et al. 2010).

Indications and Contraindications of TIPS

Controlled trials have established the efficacy of TIPS for secondary prevention of variceal bleeding and refractory cirrhotic ascites (Rössle et al. 2000; Salerno et al. 2007; Zheng et al. 2008; Boyer et al. 2010; García-Pagán et al. 2010, 2013; Bai 2014). Additional indications for TIPS are based on uncontrolled series. These indications include refractory acutely bleeding varices, portal hypertensive gastropathy, gastric antral vascular ectasia, refractory hepatic hydrothorax, hepatorenal syndrome type 1 and 2, Budd-Chiari syndrome, veno-occlusive disease, and hepatopulmonary syndrome. Note that primary prevention of variceal bleeding is currently not an indication for TIPS (Boyer et al. 2010; Gaba et al. 2012; Copelan et al. 2014).

Due to increased cardiac preload after TIPS creation, absolute contraindications to the procedure include severe congestive heart failure, tricuspid regurgitation, and severe pulmonary hypertension. Systemic infection and sepsis are also absolute contraindications. Relative contraindications related to anatomic conditions increasing the technical difficulty of TIPS creation include presence of multiple hepatic cysts, primary or metastatic hepatic malignancy, and unrelieved biliary obstruction. Due to shunting of portal blood flow away from the liver, severe uncontrolled hepatic encephalopathy and rapidly progressive liver failure are also relative contraindications to TIPS creation. Other relative contraindications include uncorrectable severe coagulopathy and severe thrombocytopenia (Haskal et al. 2003; Boyer et al. 2010; Copelan et al. 2014). Portal vein thrombosis has historically been a relative contraindication to TIPS creation and liver transplantation; however, techniques for TIPS creation in patients with portal vein thrombosis are described and can potentially allow patients to achieve transplant candidacy (Blum et al. 1995; Bilbao et al. 2004; Habib et al. 2015; Salem et al. 2015).

Preprocedure Evaluation

The purpose of the preprocedure evaluation is to determine presence of an appropriate indication, to exclude contraindications, and to assess the risks and benefits of TIPS creation. Preprocedure evaluation includes obtaining a complete clinical history, physical examination including evaluation for hepatic encephalopathy, and obtaining pertinent laboratory data. Specifically, a complete blood count, liver function, renal function, and coagulation status are assessed. Based on the clinical and laboratory data, prognostic scores such as the MELD and Child-Pugh scores are applied to assess risk (Ferral 2005; Copelan et al. 2014).

Contraindications should be excluded. Doppler ultrasound, contrast-enhanced computed tomography, and contrast-enhanced magnetic resonance imaging are helpful tools for determining patency of the portal and hepatic vasculature and for assessing presence of hepatic cysts or other hepatic lesions. Echocardiography and cardiac consultation are not necessities but are recommended in patients with known history of cardiac disease or pulmonary hypertension (Ferral 2005). If there is an emergent life-threatening indication for TIPS, time for imaging and cardiac evaluation may not be available.

After careful patient evaluation, the risks of the procedure are assessed against the severity of patient's portal hypertension complication and the likelihood of survival until transplantation. The risks and benefits of TIPS creation should then be discussed with the multidisciplinary

team, the patient, and the patient's family (Boyer et al. 2010).

Complications

Acute complications related to the technical aspects of the procedure include biliary fistula formation, arterial injury, nontarget organ injury, hemoperitoneum, shunt malposition, infection, contrast-induced nephropathy, radiation dermatitis, and shunt dysfunction. Biliary fistula formation has an incidence < 5 % and can result in hemobilia, cholangitis, sepsis, stent infection, or stent occlusion. Biliary fistula can be treated with biliary diversion, arterial embolization, and/or realignment of the hepatic track with a covered stent. Arterial puncture during TIPS creation is rare with a risk of symptomatic arterial injury of < 2 %. Arterial puncture can result in hemorrhage, pseudoaneurysm formation, vascular occlusion, or arterial portal shunt creation. The risk of hemoperitoneum and the risk of injury to the gallbladder, right kidney, duodenum, and colonic hepatic flexure can be reduced by preprocedure planning and analysis of cross-sectional imaging. Careful technique during and after stent deployment decreases the risk of shunt malposition and migration. Periprocedural infection or sepsis is uncommon, but reported, therefore preprocedure antibiotic prophylaxis is recommended (Gaba et al. 2011).

TIPS creation may require long procedure and fluoroscopy times, therefore careful monitoring and documentation of patient dose should be made. The risk of major radiation injury related to fluoroscopic procedures is low and estimated to be between 1:10,000 and 1:100,000 procedures (Padovani et al. 2005). Sequelae of radiation skin injury can be seen with skin doses > 2 Gy. The Society of Interventional Radiology recommends patient follow-up if peak skin dose is $>$ 3,000 mGy, reference point air kerma is $>$ 5,000 mGy, Kerma-area product is $>$ 500 $Gycm^2$, and fluoroscopy time is > 60 min. Dermatologic consultation is recommended if skin changes are noted on follow-up (Stecker et al. 2009; Gaba et al. 2011).

Early shunt dysfunction or thrombosis is often technical related to stent shortening or migration. In the earlier experience of TIPS placement when bare metal stents were utilized, biliary-TIPS fistulae were a common cause of shunt dysfunction. Currently, the use of expanded polytetrafluoroethylene (ePTFE)-covered stent grafts has decreased shunt dysfunction with a multicenter trial showing a 1-year stent patency rate of 84 % (Charon et al. 2004; Cura et al. 2008). Other causes of shunt dysfunction include pseudointimal hyperplasia at the hepatic venous end of the shunt, hypercoagulopathy, and poor inflow related to portal vein dissection or shunting of flow through varices and mesocaval shunts (Cura et al. 2008).

Subacute and chronic complications of TIPS are related to physiologic changes and include hepatic encephalopathy, liver ischemia, progressive liver failure, pulmonary hypertension, and congestive heart failure. Shunt dysfunction can also be a subacute or delayed complication. The reported rate of hepatic encephalopathy after TIPS creation is between 14 % and 25 %, with a 5–10 % incidence of refractory encephalopathy (Haskal et al. 2003; Charon et al. 2004; Pomier-Layrargues et al. 2012). Due to shunting of portal flow to the systemic system, hepatic perfusion after portosystemic shunt creation depends on arterial reserve. If the arterial reserve is low or there is arterial injury, hepatic infarction or progressive liver failure may ensue. A negative correlation has been postulated between hepatic arterial reserve and the Child-Pugh score (Gaba et al. 2011). Transplantation can be used as salvage therapy for liver failure after TIPS creation.

Hyperdynamic circulatory states are reported after portosystemic shunt creation; however, the rate of clinically significant pulmonary hypertension or worsening cardiac function is likely low and not readily reported in the literature (Azoulay et al. 1994; Van der Linden et al. 1996; Sawhney and Wall 1998). Nevertheless, careful patient selection is important to avoid cardiopulmonary complications. A variety of percutaneous shunt reduction and occlusion techniques have been described to treat these physiologic complications

when they are refractory to medical therapy (Madoff and Wallace 2005).

Periprocedural mortality has been reported at < 2 % with 30-day mortality reported between 7 % and 45 %. Mortality is correlated with severity of underlying liver disease and comorbidities. This correlation emphasizes the importance of preprocedure patient assessment (Sawhney and Wall 1998).

Postprocedure Management

Postprocedure care entails observing for and treating acute and subacute complications of TIPS creation including bleeding and encephalopathy. Hepatic function and renal function are also monitored. Transient hemolysis, hyperbilirubinemia, and transaminitis can be seen post-TIPS creation (Sanyal et al. 1996; Pomier-Layrargues et al. 2012). In order to decrease the risk of cardiopulmonary complications and aide the decompressive effect of the TIPS on the portal system, some experts advocate overnight diuresis of > 1 l if the postshunt mean right atrial pressure has increased to > 10 mmHg (Valji 2006; Kandarpa and Machan 2011).

Ultrasound surveillance protocols for evaluation of TIPS dysfunction were originally created in the era of bare metal stent placement. Typically sonography was performed at 24–72 h after TIPS creation then at 1 month, 3 months, and 6 months postplacement and every 6 months thereafter. Frequent surveillance and subsequent portal venography and intervention resulted in a primary assisted patency rate for bare metal stent TIPS of approximately 85 %. With the development and current use of ePTFE-covered stent grafts for TIPS, the primary patency rate is reported between 81 % and 84 %. Due to the superior patency rate of the ePTFE stent grafts, frequent ultrasound surveillance is no longer necessary. Carr et al. showed that in the ePTFE-covered stent graft era, only 4 % of ultrasound examinations effected clinical management, and 83 % of these examinations were the baseline evaluation. Due to air bubbles in the ePTFE material after deployment, baseline ultrasound is recommended after postprocedure day 5 rather than within the immediate 24–72 h period (Carr et al. 2006).

Long-term clinical evaluation of patients is recommended. If there are clinical signs of shunt malfunction, the patient should be referred to the interventional radiologist for portography, direct pressure measurements, and possible intervention. Depending on the findings of portography, balloon dilation, stent placement, varix and mesocaval shunt embolization as well as pharmacomechanical thrombolysis can be performed to improve TIPS patency.

Bridging and Downstaging Treatments for Liver Tumors

Hepatocellular carcinoma is the fifth most common cancer in men and the seventh most common cancer in women (Mittal and El-Serag 2013). In noncirrhotic patients, surgical resection is the treatment of choice. In patients with cirrhosis and poor hepatic reserve, liver transplantation is the preferred treatment due to the potential of cure from both the cancer and the underlying liver disease. An international consensus conference in 2010 recommended that liver transplantation be reserved for hepatocellular carcinoma patients with predicted 5-year posttransplant survival similar to nonhepatocellular carcinoma patients and that the Milan criteria be used as the benchmark for selection of hepatocellular carcinoma candidates for liver transplantation (Clavien et al. 2012). This recommendation is supported by a systematic review including 90 studies showing that Milan criteria is an independent prognostic factor for outcome after liver transplant with a 5-year posttransplant survival of 65–78 % for patients with hepatocellular carcinoma meeting Milan criteria compared to a 5-year posttransplant survival of 68–87 % for patients with nontumor transplant indications (Mazzaferro et al. 2011).

The waiting time for liver transplant is unpredictable, and long waiting times are associated with a risk of disease progression beyond accepted size-number criteria for liver transplantation. The goal of the interventional radiologist is

to provide neoadjuvant therapies for hepatocellular carcinoma in order to keep disease within accepted criteria. These neoadjuvant therapies, known as bridging therapies, have three purposes including (1) controlling cancer progression thereby decreasing wait list dropout rates, (2) identifying patients with more biological aggressive tumors and less favorable posttransplant outcomes, and (3) helping balance prioritization of liver transplant candidates with and without hepatocellular carcinoma (Majno et al. 2011; Cescon et al. 2013). The interventional radiologist also performs locoregional therapies as potential downstaging procedures with the goals of (1) reducing tumor burden from beyond accepted size-number criteria for transplantation to within the criteria and (2) identifying patients with potentially low rates of tumor recurrence after liver transplantation among those initially excluded according to accepted criteria (Pompili et al. 2013). In a systematic review which included 13 studies and 950 patients, the success of downstaging to within Milan criteria was found to be 48 % (Parikh et al. 2015). Posttransplant survival and low rates of tumor recurrence have been shown to be comparable in patients who underwent downstaging compared to patients presenting within tumor size-number criteria. Inclusion criteria for downstaging and a mandatory wait time prior to transplantation have been proposed by several institutions in order to improve posttransplantation recurrence rates and survival in patients undergoing downstaging (Yao et al. 2015; Parikh et al. 2015).

The locoregional treatment options for bridging and downstaging are historically based off of the Barcelona-Clínic Liver Cancer (BCLC) staging system and associated treatment recommendations which include surgical resection, ablation techniques, and transarterial chemoembolization (Llovet et al. 2012). Other transarterial therapies including transarterial hepatic radioembolization and transarterial bland embolization have also gained favor as effective locoregional therapies. Due to lack of strong comparative evidence between the treatment modalities, the 2010 international consensus conference made no recommendation for a preferred type of therapy to be used for bridging or downstaging (Clavien et al. 2012).

Surgical Resection

Surgical resection is the ideal first line therapy for hepatocellular carcinoma. Surgical resection provides the best potential for tumor control. Other locoregional therapies do not remove the cancer and may not yield complete necrosis. Resection also allows pathological evaluation of the specimen to understand the biological aggressiveness of the tumor. Conversely, surgical resection is potentially more costly and may have increased periprocedural risks. The technical difficulty and potential postoperative complications of liver transplantation after surgical resection are also increased. Liver resection is limited to patients with well-compensated liver disease, minimal to no portal hypertension and tumor location amenable to resection (Pompili et al. 2013).

Percutaneous Tumor Ablation

Using minimally invasive techniques, nonthermal technologies, such as percutaneous ethanol injection (PEI) and irreversible electroporation (IRE), as well as thermal technologies, such as radiofrequency ablation (RFA) and microwave ablation (MWA), are used to achieve targeted tumor cell death. Typically under ultrasound or computed tomography guidance, one or more applicators (needles, electrodes, or antennae) are advanced from the skin into or adjacent to the targeted hepatic tumor. Percutaneous ablation allows for targeted tumor cell death with intended margin necrosis and with relative sparing of the remainder of the nontumor liver parenchyma. Historically, percutaneous ablation techniques were used for the treatment of liver tumors $\leq$ 3 cm; however, new technologies and techniques have enabled the use of percutaneous ablation for larger tumors. According to the BCLC classification, radiofrequency ablation is recommended for patients with very early (BCLC stage A) or early (BCLC stage B) stage hepatocellular carcinoma.

In practice, this recommendation is often expanded to also include other percutaneous ablation modalities and to include the treatment of liver-dominant metastatic disease in nonsurgical candidates meeting tumor size and number criteria. In some transplant centers, needle track seeding after percutaneous ablation is a concern. In 2001, Llovet et al. showed a needle track seeding incidence of 12.5 % in a group of 32 patients. Subsequent studies have shown much lower needle track seeding rates with an estimated incidence of 0–2.8 %. In a study of 1314 patients, Livaraghi et al. showed RFA of hepatocellular carcinoma resulted in a track seeding rate of 0.9 %. Increased risk of tumor seeding has been associated with subcapsular tumor location, poorly differentiated tumors, elevated serum alpha-fetoprotein levels, and prior biopsy (Llovet et al. 2001; Jaskolka et al. 2005; Livraghi et al. 2005).

Contraindications of percutaneous ablation of hepatic malignancy include tumor location near the main biliary ducts, intrahepatic biliary dilation, and uncorrectable coagulopathy. Due to increased risk of complications, care must be taken in the treatment of patients with bilioenteric anastomosis and treatment of lesions near vital structures such as the bowel, stomach, or gallbladder. Hydrodissection or gas dissection can be used to decrease deleterious effects to adjacent organs.

Thermal Ablation: Radiofrequency Ablation (RFA) and Microwave Ablation (MWA)

RFA uses an electric current to heat tissue. Current propagation is limited by tissue impedance. Tissue impedance increases with increasing water vapor, tissue desiccation, and charring. Therefore, tissue impedance limits the size of the ablation zone as well as achievable temperatures. Temperatures generated by radiofrequency technology are also limited by blood flow-related heat sinks of nearby large vessels. Microwave technology has advantages over radiofrequency technology. During MWA, an oscillating microwave field causes water and other polar molecules to continuously realign resulting in increased kinetic energy and tissue temperatures. Microwaves can radiate through high impedance tissues and are less affected by heat sinks. Therefore, theoretically MWA is faster, creates higher temperatures, and can achieve larger ablation zones than RFA (Hinshaw et al. 2014). Comparative studies of RFA versus MWA have shown equivalent therapeutic effects and complication rates for the treatment of hepatocellular carcinoma (Shibata et al. 2002; Xu et al. 2004; Vogl et al. 2015).

Nonthermal Ablation: Percutaneous Ethanol Injection (PEI) and Irreversible Electroporation (IRE)

PEI results in tumor cell dehydration, protein denaturation, and coagulative necrosis. The alcohol also permeates into surrounding vasculature resulting in endothelial damage, vascular thrombosis, and resultant ischemic tissue necrosis (Ahmed et al. 2011). PEI is limited by alcohol penetration into the tissue and often requires multiple sessions. PEI is less frequently used for locoregional liver tumor treatment due to multiple randomized controlled studies showing better local disease control with RFA compared to PEI and meta-analyses showing a survival benefit of RFA compared to PEI (Lencioni and Crocetti 2012).

During IRE, a strong electrical field is created between multiple electrodes placed in and around the tumor. The electrical field increases cell membrane permeability resulting in apoptosis. Extracellular matrix is preserved; therefore adjacent vascular and ductal structural integrity is preserved. IRE is also fast and avoids the heat-sink effect. Due to the strong electrical field generated, there is risk for cardiac arrhythmias and muscle contractions during the procedure. IRE technology is relatively new and actively being developed (Zivin and Gaba 2014).

Transarterial Therapies

The goal of catheter-directed transarterial therapy is to deliver concentrated antitumor therapy to a hepatic tumor with relative sparing of liver parenchyma and low systemic toxicity. Due to the dual blood supply of the liver, patients can undergo

selective transarterial treatments with low complication rates. More recently, selective transarterial treatments are also performed in patients with portal vein thrombosis. Transarterial hepatic therapies include bland embolization, chemoembolization, and radioembolization.

In transarterial bland embolization, infused particles (gelfoam, polyvinyl alcohol, acrylic copolymer gelatin particles) cause end arteriole blockade and resultant hypoxic cell death. In transarterial chemoembolization, a high-dose cytotoxic agent is delivered to and retained within a tumor via drug-eluting beads or in an emulsion with iodized oil. After the local delivery of chemotherapy, further particle embolization is often performed for the added effect of hypoxia. There is no standard technique or chemotherapy cocktail for chemoembolization. In the United States a combination of doxyrubicin, mitomycin C, and cisplatin (if available) is commonly used. Single-agent doxyrubicin is generally used elsewhere in the world.

During radioembolization, Yttrium-90-labeled glass or resin microspheres are infused into a selective artery and preferentially flow toward and become embedded within hypervascular tumors. There is some embolic effect of the Yttrium-90-labeled microspheres; however, the main therapeutic mechanism is through radiation-induced cell death. The use of resin versus glass microspheres depends on the institution. Resin microspheres have been granted full premarketing Food and Drug Administration approval for the treatment of colorectal metastases in conjunction with intrahepatic chemotherapy and have been used off-label for hepatocellular carcinoma and other malignancies within the liver. Glass microspheres are approved by the Food and Drug Administration under a humanitarian device exemption for the treatment of unresectable hepatocellular carcinoma with and without portal vein occlusion in patients who can have appropriately positioned hepatic arterial catheters, and therefore the use of glass microspheres currently requires institutional review board oversight (Lewandowski et al. 2011).

Selection and exclusion criteria are similar between the transarterial therapies and help decrease the risk of liver decompensation after treatment. Patients undergoing transarterial therapy should have a good performance status (Eastern Cooperative Oncology Group $\leq$ 2) and adequate liver function reserve. Selective (sublobar or subsegemental) arterial delivery of therapy is needed for patients with portal vein thrombosis and/or serum total bilirubin levels between 2 and 3. A serum total bilirubin level $>$ 3 is a contraindication to transarterial hepatic therapy. Caution is also advised in treatment of patients with a Child-Pugh B score greater than 8 and patients with tumor occupying $>$ 50–70 % of the total liver volume. Technical considerations such as the presence of large arterioportal or arteriovenous shunting, renal insufficiency, and other confounding comorbidities should also be taken into account. Transarterial radioembolization can be limited by the radiation dose to the lungs and prior radiation therapies. Planning hepatic arteriography, arterial infusion of technicium-99m microaggregated albumin, and subsequent lung and liver scintigraphy are performed as a separate procedure prior to radioembolization to evaluate for any dosimetry or anatomical contraindications and to calculate the appropriate treatment dose.

Transarterial Therapy Comparison

Transarterial conventional chemoembolization has been the accepted standard transarterial therapy for hepatocellular carcinoma since the early 2000s due to two randomized controlled studies showing survival benefit of conventional chemoembolization compared to best supportive care (Lo et al. 2002; Llovet et al. 2002). Subsequent studies comparing conventional chemoembolization to bland embolization and conventional chemoembolization to radioembolization have shown no difference in survival rates between the treatment modalities (Marelli et al. 2007; Salem et al. 2011; Kluger et al. 2014). In a retrospective study of patients with hepatocellular carcinoma comparing treatment with conventional chemoembolization versus bland embolization, there was no difference in wait list dropout, overall survival, or recurrence-

free survival rates (Kluger et al. 2014). When comparing conventional chemoembolization to chemoembolization with drug-eluting beads, small retrospective studies showed that chemoembolization with drug-eluting beads had a higher complete necrosis rate and a higher 3-year recurrence-free survival rate for transplant patients. Further studies are needed to validate these results (Nicolini et al. 2010, 2013).

Radioembolization has been shown to be promising for downstaging to within transplant criteria. In a retrospective study, Lewandowski et al. showed the rate of downstaging from UNOS T3 to UNOS T2 was significantly higher with radioembolization compared to conventional chemoembolization (Lewandowski et al. 2009). Furthermore, radiologic-pathologic studies show a higher complete pathologic necrosis rate of hepatocellular carcinoma after radioembolization compared to conventional chemoembolization for lesions < 5 cm (Riaz et al. 2009, 2010). In a retrospective study of 245 patients, radioembolization was shown to have a longer time to progression compared to conventional chemoembolization (Salem et al. 2011). Quality of life and toxicity profiles also tend to favor radioembolization over chemoembolization. In the same retrospective study, Salem et al. showed that patients treated with chemoembolization had significantly higher rates of postprocedure abdominal pain and elevated transaminases compared to patients treated with radioembolization (Salem et al. 2011). A smaller prospective study evaluating quality of life after transarterial treatment showed that radioembolization had a significantly better quality of life based on social well-being and functional well-being scores; there was no difference in overall quality of life, possibly related to the limited sample size (Salem et al. 2013).

Conclusion

Interventional radiology has a critical role in the multidisciplinary liver tumor team. Over the past three decades, advances in technology and technique have allowed the interventional radiology to perform lifesaving procedures in the pretransplant patient with portal hypertension and effective neoadjuvant therapies in the pretransplant patient with hepatocellular carcinoma. Not discussed in this chapter, the interventional radiologist also has a role in the treatment of posttransplant patients with arterial, venous, portal, and biliary anastomotic complications as well as a role in the monitoring of rejection and recurrent cirrhosis with transjugular and percutaneous liver biopsies.

Cross-References

- ▶ Downstaging Hepatocellular Carcinoma for Liver Transplantation
- ▶ HCC: The San Francisco Criteria
- ▶ Hepatopulmonary Syndrome and Portopulmonary Hypertension
- ▶ Liver Transplantation for HCC: The Milan Criteria
- ▶ Radiology in Liver Transplantation

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Part VII

Basic Science in Liver Transplantation

Xenotransplantation

24

Zhengyu Wei

Contents

Abstract

Transplantation is a major clinical means to replace damaged or failed human organs to improve or save a patient's life. The demand for organ transplantation has increased dramatically worldwide. However, the current dilemma is that the more that human organ transplants are performed, the less transplantable organs are available; the shortage of human organs is the major limiting factor for benefiting patients with organ dysfunction. Each year, thousands of patients are either removed from the waiting list due to death or become too sick for treatment. To solve the problem of organ shortages, several possible approaches have been considered and are under intensive investigations. These include artificial organs, tissue-engineered organs, and xenotransplantation (cross-species transplantation). While the former two hold hopes for the future, but with much higher social costs, xenotransplantation appears to have the potential to meet the current need of transplantation by providing adequate transplantable organs. However, several important issues, including immunological rejections, physiological incompatibilities, and safety, must be addressed before this approach can be a clinical reality. This review summarizes recent progress made in this field, the hurdles to be overcome, and the possible solutions for them.

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Introduction

Allotransplantation (organs being transplanted from one person to another person) is currently the most effective surgical procedure for curing human end-stage organ failure, but a dramatically large number of patients who need a functioning organ to save their life do not have a chance to receive this therapy due to the shortage of human organs. The imbalance between organ demand and supply is a global problem despite the fact that significant efforts have been made to increase the donor pool. This discrepancy is becoming even larger as organ donations have actually gone down in recent years, while the number of patients being added to the waiting lists has increased dramatically. According to the United Network for Organ Sharing (UNOS), there are more than 110,000 people on the waiting list for an organ transplant in the USA alone, and at least 17,000 patients among them are waiting for liver donors (Ekser et al. 2011; Tisato and Cozzi 2012). In 2010, approximately 4,000 patients were removed from the waiting list due to death, organ deterioration preventing a surgical procedure, or some other unknown reasons (Ekser et al. 2011).

The fact that the demand for organs has far outpaced the supply opens a new multidisciplinary research field aimed at providing alternative solutions to fill this gap, with the aim of finding a practical solution to the shortage of human organs. Currently, there are three strategies available: the use of artificial organs, the development of tissue-engineered organs through regenerative medicine, and xenotransplantation, a process where animal organs are transplanted into humans for replacement of dysfunctional human organs.

The use of artificial organs seems to be a promising alternative to transplantation with regard to the shortage of human organs. However, this strategy is mainly applied to heart and kidney diseases. An artificial heart is a man-made device that is used to replace the heart or bridge the time until heart transplantation is possible. However, the cost is very high and the effects are limited due to biological incompatibilities. Hemodialysis is usually referred to as an artificial kidney that removes wastes from blood when the kidney is dysfunctional. Again, this treatment cannot permanently relieve the pain relating to the patient's renal failure, and the medical cost for this treatment is huge with a long-term burden on society. Thus, artificial organs deserve more investigation to improve the quality of patients' lives and to reduce costs.

Another alternative to transplantation is tissue-engineered organs. Regenerative medicine has opened a new and promising option by providing needed organs for transplantation. One example is the use of cardiac patches seeded with cardiac cells to make the artificial heart more biocompatible (Ott et al. 2008). The same method of repopulating the decellularized organ matrix with appropriate cell lines has been used to generate transplantable liver and lung in order to reconstitute the original structure and features of these organs (Uygun et al. 2010; Petersen et al. 2010). However, although these experimental results are encouraging, the clinical use of such bioartificial organs becoming a reality in today's hospitals remains a difficult challenge as many important issues such as organ quality and function are yet to be addressed.

To meet the current and future needs of organ transplantation, the most important issue is to find a supply of donor organs with sufficient quantity and transplantable quality. Xenotransplantation, as compared with artificial organs and tissue-engineered organs, has the potential to meet these requirements. Xenotransplantation utilizes nonhuman animals as donor organ sources, which makes this approach more practical as a stable supply of organs. Of course, there are still several barriers to be overcome before this therapeutic approach can be a reality. These barriers

and possible solutions are reviewed and discussed below.

Brief History of Xenotransplantation

Although the use of organ transplantation between humans (allotransplantation) was reported more than 2,000 years ago, real xenotransplantation as we know it began in the seventeenth century, first with cells and tissues and later organs.

The first documented description of xenotransplantation is a transfusion of blood cells from a lamb to a 15-year-old boy to cure his severe fever by French doctors Jean-Baptiste Denis and Paul Emmerez on 15 June 1667 (Farr 1980). In the same year, several other xenotransfusions were also performed, with disappointing outcomes. The failure of xenotransfusion was later found to be due to incompatibility with heterologous blood. Inter-human transfusion was recommended, although at that time the need for blood type matching was not known.

Early xenotransplantation of tissues was attempted using animal bone, skin, tooth, and pancreas to humans. The first bone xenotransplantation was made by a Russian using a portion of a dog skull to repair a nobleman's skull. The surgery was claimed a success; unfortunately, under threat of being excommunicated by the Russian Church, the nobleman was forced to have the graft removed (Rodriguez Umana 1995). A relatively successful tissue xenotransplantation was achieved through the transplantation of testicles from animals to humans in order to rejuvenate men. Early attempts were made by using an extract of crushed testicles from dogs or guinea pigs. Serge Voronoff, a French Russian whose interest was in reversing aging, carried out a significant number of chimpanzee or baboon testicular transplants in human male recipients. Slices of testicles from chimpanzees or baboons were inserted into elderly men's testicles (Schultheiss et al. 1997). Several hundreds of these operations were performed without significant inflammatory or infectious complications. This can be explained by the fact that testicles are isolated glands that are relatively more resistant to human immune responses.

With the development of techniques to control bleeding after resection of a sick organ and to restore circulation after transplantation, solid-organ xenotransplantation became accessible in the twentieth century for repairing failed human organs. Two Frenchmen, Alexis Carrel and Mathieu Jaboulay, pioneered a key technique called anastomosis that can restore the vascularization of a transplanted organ, which enabled the first solid-organ transplantation to be carried out successfully. Alexis Carrel was thus awarded the Nobel Prize in Physiology or Medicine in 1912 "in recognition of his work on vascular suture and the transplantation of blood vessels and organs." Mathieu Jaboulay used this technique to carry out two kidney xenotransplantations from a pig and a goat to humans on 24 January 1906 and 9 April 1906, respectively. Although these transplanted kidneys had to be removed after 3 days due to thrombosis, the transplantation itself is reported as being the first true transplantation and, of course, the first true xenotransplantation.

The disappointing outcomes of early transplantation experiments were found to be caused by human immune responses to xenografts. With the availability of immunosuppressive drugs, modern xenotransplantation experiments started in the 1960s. Keith Reemtsma, an American surgeon, suggested that organs from nonhuman primates, due to their close evolutionary relationship to humans, may function in humans. On 13 January 1964, he carried out a kidney xenotransplantation from a chimpanzee to a 23-year-old schoolteacher (Reemtsma et al. 1964). Although the recipient died 9 months later, it marked the longest survival record ever for the xenotransplantation of an organ. Surprisingly, an autopsy was conducted, and the cause of death was found to be acute electrolyte imbalance. The 9-month survival without rejection of the chimpanzee kidney provided evidence of the feasibility of xenotransplantation. Thomas Starzl, one of the greatest pioneers in the field of kidney and liver transplantation, carried out three liver xenotransplantations between chimpanzees and children in Colorado in the 1960s without lasting success. In

the 1990s, with the addition of the immunosuppressive drug tacrolimus, he and his team in Pittsburgh achieved 26 and 70 days of survival using baboon livers in two adult patients with chronic liver failure (Starzl et al. 1993). One of the advantages of using baboon over human liver was found to be its resistance to infection by the hepatitis B virus. Thomas Starzl also participated in xenotransplantation of kidney from baboons to humans in the early 1960s.

The first heart xenotransplantation was carried out by James Hardy in 1964. He used a chimpanzee heart to replace a patient's dying heart. Unfortunately, the patient died a couple of hours after the transplantation. It was found that the baboon heart was not large enough to support the circulation of a human. However, this experiment helped a later attempt to save a 12-day-old infant girl named Baby Fae in 1984. Leonard Bailey carried out this cardiac xenotransplantation as Hardy did by using a baboon heart, which should be comparable to a human baby heart. Although the surgery itself was claimed a success, the baboon heart in Baby Fae underwent acute rejection, most likely due to blood incompatibility. Baby Fae died 20 days after the surgery (Bailey et al. 1985). This attempt became well known and drew both public and medical specialist attention to the necessity of organ donation.

The first islet xenotransplantation was conducted from pigs to human patients with diabetes mellitus by Carl Groth in 1993. Pig insulin has only one amino acid different from its human counterpart and was used for the treatment of diabetic patients for decades before recombinant human insulin was available. The patient did not obtain any clinical benefit from this xenotransplantation, but one encouraging point was that the pig islet was found to survive in some patients (Groth et al. 1994).

In summary, most of the early xenotransplantation attempts used nonhuman primate species as sources of the organ; a few attempts used other non-primate mammals such as dogs and goats, but the outcomes showed no significant success. Thus, the choice of suitable animals for xenotransplantation remains a challenge.

Suitable Animals for Xenotransplantation

Since humans are primates, the obvious choice of donor animal for xenotransplantation would be another member of the primate family such as chimpanzees and baboons, because these animals have a close evolutionary relationship and physiological similarity to humans. However, nonhuman primates have been ruled out as human organ donors for practical and ethical reasons.

Primates, our closest cousins in the animal kingdom, are more likely than other animals to carry viruses capable of infecting humans. One example is HIV, which originates in chimpanzees. In addition, it is hard to breed enough primates to provide a sufficient number of organs to meet the increasing demand for donor organs. Furthermore, the close evolutionary relationship between primates and humans also poses ethical problems, as people are more reluctant to exploit animals that share many features with humans.

Pigs, on the other hand, seem to meet most of the requirements as a suitable animal for the donor source of organs (Fig. 1). First, pigs can be raised in a clean environment to reduce the risk of infection. The pig herd for transplantation can be housed under ideal conditions and be monitored at regular intervals for infectious agents, which almost guarantees that the donor animal would be free of all known pathogenic organisms that the average deceased human donor may have. Second, pigs are easy to breed and are already widely used in the food industry, so it is not hard to imagine that there would be an unlimited supply of donor organs, resolving the supply issue and ethical dilemma. Third, organs could be excised from a healthy pig under anesthesia, which avoids the problem of organ injury or no function that may be the case with a deceased human. Moreover, organs from a pig could be obtained whenever a patient needed it, helping improve survival. Fourth, pig organs have a similar size to human organs, so the transplants have the potential to match the human organs and function. Fifth, evidence obtained from animal models suggests that

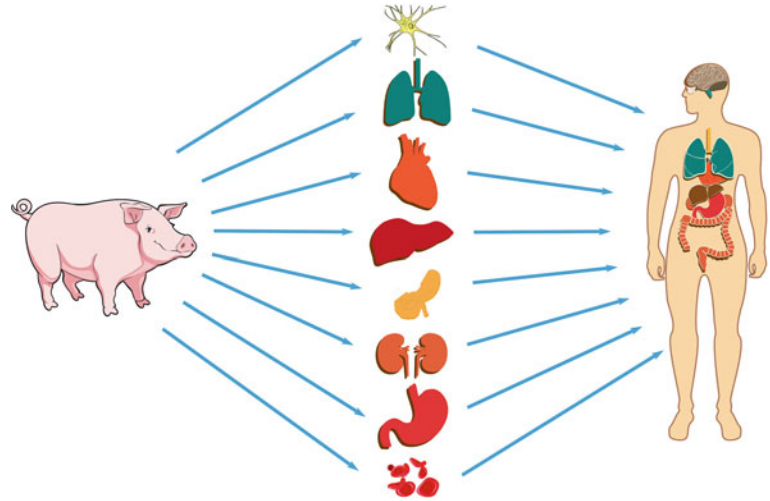

Fig. 1 Pig-to-human xenotransplantation as a potential solution to the organ shortage for human end-stage organ diseases

most pig organs would work properly in human recipients. In fact, material from pigs has been routinely and safely used for medical purposes for decades, with the best known example being heart valves.

Despite the above advantages of using pigs as a donor organ source, there are also disadvantages. Pigs have a shorter life span than humans, so the organ transplant will have to be performed more than once since the pig organs have the potential to deteriorate at a much faster pace than an actual human organ. In addition, as pigs have a distant evolutionary relationship with humans, the human immune system would mount a very strong response to pig organs, leading to the organ transplants being rejected quickly, even when the immunosuppressive drugs that are supposed to prevent rejection of human transplants are used. It seems that drugs are simply not powerful enough to prevent rejection when pig organs are transplanted to humans.

To make pigs more suitable as the organ source for xenotransplantation, the problem of xenograft-induced immunological rejection needs to be solved. One solution for this is to take advantage of genetic engineering methods to modify pigs so that their organs will appear to be a part of the human body and will not be recognized as "non-self" when transplanted into humans. Genetically modified (GM) pigs have thus been produced for xenotransplantation research around the world. Although these GM pigs are still in the laboratory, progress made in the last decade suggests that the move to the clinic is not too far away, with cell xenotransplantation probably more feasible in the near future.

In order for GM pigs to serve well as an organ source for xenotransplantation, we need to know what the immunological challenges are and how to prevent them.

Immunological Challenges

The most profound obstacle to a successful pig-to-primate xenotransplantation is the rejection of the organ transplant by a cascade of immune responses commonly known as hyperacute rejection, acute humoral xenograft rejection, cell-mediated immune rejection, and chronic rejection.

Hyperacute rejection is a rapid process of powerful immune responses that lead to the rejection of xenografts within a few minutes or hours after the surgery of xenotransplantation. It mainly destroys the vasculature of the xenografts, with subsequent interstitial hemorrhage, edema, and thrombosis of the small vessels. The process is initiated by binding of the host antibodies to the xenograft antigens that trigger the complement activation, resulting in endothelial damage,

inflammation, and necrosis of the xenografts and leading to transplant failure. It is widely accepted that the host xenograft antigen's active IgM or IgG initiates the hyperacute rejection process. Thus, hyperacute rejection represents the first barrier to clinical solid-organ xenotransplantation.

The main target antigen of the pig organs recognized by the primate immune system is α-1,3-galactose (α1,3Gal), an oligosaccharide that is produced by an enzyme called α-1,3-galactosyl transferase (α1,3GalT) (Galili et al. 1988). As most non-primate animals, including pigs, have this enzyme, the α1,3Gal is naturally expressed in endothelial cells and becomes the target of the host immune system. However, primates, including humans, actually lack α1,3GalT, so no α1,3Gal is expressed in the primates; however, primates have been exposed to α1,3Gal-similar epitopes derived from gut bacteria and have a high titer of anti-α1,3Gal antibodies in the body (spleen, lymph nodes, and bone marrow) already, which is why primates can mount an immune response to this antigen so quickly.

To reduce the frequency of hyperacute rejection, many approaches have been pursued to either remove the preexisting anti-α1,3Gal antibodies or control their effectors' functions by inhibiting complement cascade. Among them, the most well-known approach is to generate GM pigs by knocking out the gene that is responsible for α1,3GalT, so no α1,3Gal will be produced (Phelps et al. 2003).

Acute humoral xenograft rejection is a later immune response reaction that follows the hyperacute rejection. This delayed process is much more complex than hyperacute rejection and is mainly driven by interactions between the xenograft endothelial cells and host antibodies, leading to loss of the xenograft within days or weeks of transplantation (Crikis et al. 2006). An inflammatory infiltrate of mostly macrophages and natural killer (NK) cells, intravascular thrombosis, and fibrin deposition are involved in the rejection. The detailed mechanism of acute humoral xenograft rejection is currently not completely understood. Recent evidence demonstrates that anti-non-α1,3Gal antibodies directed against both carbohydrates and proteins play a critical role in the acute humoral xenograft rejection (Breimer 2011). Due to its multifactorial features, strategies to overcome acute humoral xenograft rejection require the combination of different approaches to generate synergistic effects. Thus, the use of immunosuppressive drugs along with GM pigs as organ donor should result in improved survival.

Cell-mediated immune rejection, which is different from hyperacute rejection and acute humoral xenograft rejection which are both xenograft antigen dependent, is mainly mediated by T cells. T cells play a role in the induction of anti-xenograft antibodies, but their role in direct involvement of rejection has not completely been clarified. However, it is clear that T cells can recognize xenograft antigens presented by major histocompatibility complex (MHC) molecules in direct and indirect pathways. Direct xenorecognition is via CD4 T cells, in which xenograft antigens are presented directly by MHC class II molecules on antigen-presenting cells from the xenograft; indirect xenorecognition is via CD8 T cells, in which xenograft antigens are first phagocytosed by the host antigen-presenting cells and then presented by MHC class I molecules on the host antigen-presenting cells. The indirect xenorecognition is thus expected to be stronger than its allogeneic counterpart, since the large number of antigens from xenografts is more readily recognized as foreign and elicits stronger immune responses.

Evidence obtained from pig-to-primate xenotransplantation experiments has demonstrated that CD8 T cells, monocytes/macrophages, B cells, and some NK cells are the predominant cells detected in the xenograft; CD4 T cells are only described in a limited number of cases (Ashton-Chess et al. 2003; Hisashi et al. 2008). It is generally believed that the cell-mediated immune rejection can be controlled by using the current immunosuppressive regimens.

Chronic rejection usually occurs in the xenografts after the initial acute antibody-based and cellular rejections. It is relatively slow and progressive. Knowledge in this area is poor as most xenografts rarely survive long enough for it to be studied. However, it is known that fibrosis of the xenograft vessel wall is the major cause of chronic

rejection. Arteriosclerosis occurs as a result of the combinatorial effects of T cells, macrophages, cytokines, and healing, leading to the hardening and narrowing of the vessels within the xenograft. Chronic rejection is believed to be more aggressive in xenografts than in allografts. As chronic rejection causes pathological changes in the organ, the xenograft will have to be replaced after several years.

In addition to immunological challenges, dysregulated coagulation remains another barrier to successful xenotransplantation, particularly pig-to-primate xenotransplantation. There is a difference in the coagulation dysfunction in different organ xenotransplants. Lung xenotransplant is the most rapidly damaged organ xenograft by coagulation dysfunction and rarely lasts more than a day in nonhuman primates. Kidney xenotransplants have a higher degree of coagulation dysfunction than that of the heart, while liver xenografts are more easily affected by thrombocytopenia. Coagulation dysfunction is one of the molecular incompatibilities in pig-to-primate xenotransplantation and represents the most problematic issue. Strategies to overcome coagulation dysfunction in xenotransplantation will include the combination of GM pigs to reduce the effects of clotting cascade in the xenograft donor and the systemic treatment of the recipient to aid ready acceptance of the xenograft.

Among these immunological rejections, hyperacute rejection, acute humoral xenograft rejection, and acute cellular rejection are generally controllable when an adequate immunosuppressive regimen is given, but chronic rejection in the form of xenograft vasculopathy has been documented in cardiac transplants that survive for several months. Xenograft vasculopathy could be increasingly delayed as the immunological challenges of xenotransplantation are overcome. One of the practical approaches is to use GM pigs.

Genetically Modified Pigs

The ultimate goal of generating GM pigs is to reduce or eliminate immunological responses of the donor organs and make the xenografts more acceptable by the recipient.

As described above, the pig is the preferred species as an organ donor for xenotransplantation due to its comparable organ size, rapid growth rate, large litters, and a more manageable ethical profile in comparison with other species. However, it is well documented that the existence of xenoreactive natural antibodies (XNA) in the recipient can recognize the α1,3Gal epitope and triggers a hyperacute rejection, a very rapid immune response that results in irreversible xenograft damage and loss within minutes to hours after the transplantation. Nevertheless, selection of donor organs that do not express α1,3Gal would be a better strategy for xenotransplantation. Thanks to the development of modern molecular biology, this can be achieved by generating GM pigs that lack the expression of α1,3Gal through genetic engineering.

The production of α1,3Gal is catalyzed by an enzyme α1,3GalT, which is encoded by the gene *GGTA1*. This gene is expressed in fetal fibroblasts and the α1,3Gal is readily detectable on the cell surface. To make the cell lack α1,3Gal expression and, hence, the epitopes to XNA, inactivation of the *GGTA1* gene is needed. α1,3GalT, a 371 amino acid protein, is encoded by 4–9 exons of *GGTA1*. The gene's endogenous translation start codon ATG is in exon 4, while the major portion of the protein including the catalytic domain is in exon 9. Thus, both exons have become the targets for the functional inactivation of *GGTA1* in transgenic pigs. The first transgenic pig ($\alpha1,3GalT^{-/-}$) lacking the α1,3GalT was generated using a somatic cell nuclear transfer (SCNT) method in 2002 (Lai et al. 2002). Grafts from $\alpha1,3GalT^{-/-}$ pigs can generally achieve an extended graft survival time and allow the use of reduced levels of the immunosuppressive therapy. The associated rejection is not caused by the classical acute humoral xenograft rejection, but predominantly by the development of a thrombotic microangiopathy that can ultimately result in coagulopathy. Moreover, the level of antibodies against non-α1,3Gal epitopes has been found to be elevated at the time of rejection, indicating the importance of antibodies against non-α1,3Gal antigens in xenotransplantation. It appears that the anti-non-α1,3Gal antibodies represent a

major critical barrier for the successful clinical application of xenografts. Apparently, transgenic pigs will be used with a combination of not only the functional inactivation of *GGTA1* but also other genetic factors for the further reduction of the rejection process in xenotransplantation.

Another xenoantigen, *N*-glycolylneuraminic acid (Neu5Gc), has been identified recently (Song et al. 2010). Humans do not produce Neu5Gc as humans have a DNA mutation that can cause the functional inactivation of cytidine monophosphate-*N*-acetylneuraminic acid hydroxylase (CMAH), the enzyme responsible for Neu5Gc production, but CMAH is synthesized in pigs and other mammals, including nonhuman primates. It is therefore expected that deleting both the *GGTA1* and *CMAH* genes to create double-knockout (KO) pigs may further reduce the xenoantigenicity of pig organs in humans and thus further reduce the severity of humoral rejection as seen in the *GGTA1* single KO mentioned above.

To generate double-KO pigs, a zinc-finger nuclease (ZFN) technology has been used with sequential disruption of the *GGTA1* and *CMAH* genes in cultured cells followed by SCNT to yield viable GM pigs. Compared with the standard technique based on homologous recombination, ZFN technology is more efficient and is able to knock out more than one gene at a time, which should accelerate the development of GM donor pigs to evaluate for clinical xenotransplantation.

Transgenic pigs expressing human complement regulatory proteins have shown great promise in reducing the rejection of pig organs following transplantation into nonhuman primates. Various transgenic pigs expressing a single gene product of CD46, CD55, and CD59 have been produced. Double- and triple-transgenic pigs are also established. The gene expression levels vary in different transgenic pigs. In order to control the expression of transgenic genes, the tetracycline-regulated Tet-On and Tet-Off system is used. This system allows the transgene expression in a controllable way by exogenous stimuli.

Transgenic pigs expressing the enzyme α-1,2-FT can reduce expression of the major pig xenoantigen α-1,3-Gal by enzymatic competition between α-1,3-GalT and other terminal glycosyltransferases for the common acceptor substrate, resulting in a reduction in xenoreactive human natural antibody binding and complement activation. Therefore, pigs transgenic for the human *α-1,2-FT* gene can be comparable with their α-1,3-Gal-deficient counterparts.

It is expected that donor organs from GM pigs with a combination of some specific gene KOs and transgenes might even further reduce the immunological rejection rates for clinical xenotransplantation. Indeed, such multi-transgenic pigs with α-1,3-Gal KO and other transgenes such as CD55 or/and α-1,2-FT have been produced.

With regard to cell-mediated immune rejection, expression of human tumor necrosis factor (TNF)-α-related apoptosis-inducing ligand (TRAIL) in transgenic pigs has been used as a strategy to control post-hyperacute rejection mechanisms mediated by cellular components of the immune system. Another strategy is to inhibit the activity of NK cells by expressing HLA transgenes, mainly HLA-E. In addition to T cells and NK cells, macrophages play an essential role in both innate and adaptive immune responses. Signaling regulatory protein (SIRP)-α is expressed on macrophages that can recognize CD47, a cell surface protein expressed ubiquitously on most cells as a marker of "self." "Self" cells thus use this SIRP-α–CD47 interaction to avoid being phagocytosed by macrophages (Ide et al. 2007). Hence, transgenic pigs expressing human CD47 are likely to contribute to the xenotransplantation by inducing immune tolerance in xenografts.

With the availability of a plethora of GM pigs, it is expected that various immunological rejections can be reduced and xenotransplantation will likely become a clinical reality in the not-too-far future, at least as a bridge to allotransplantation.

Cellular Xenotransplantation

The xenotransplantation of non-vascularized tissue, such as pancreatic islets, is not believed to be subject to classical hyperacute rejection. In

general, cellular xenotransplantation made in pig-to-nonhuman primate experiments has achieved much more encouraging results than in solid organs, and it appears much closer to clinical application than solid-organ xenotransplantation.

Currently, there are more than one million people in the USA with type 1 diabetes. Although islet allotransplantation has improved significantly in recent years, the need for islets from two deceased human donor pancreases for a single allotransplantation has greatly limited this procedure due to the very small number of suitable donors. In the past decade, it is estimated that fewer than 1,000 such procedures were carried out in the Western countries. It is therefore reasonable to consider islet xenotransplantation in order to meet the growing demand.

The first islet xenotransplantation was carried out in 1994 (Groth et al. 1994). In this attempt, pig islets were transplanted into ten type 1 diabetic patients who received kidney and islet double transplantation; four patients excreted detectable pig C-peptide in urine for 200–400 days, and there was insulin-positive staining in one patient. In several independent pig-to-nonhuman primate experiments that followed, a period of more than 6 months of normoglycemia and graft survival could be achieved. It has been found that an immunosuppressive regimen is needed to prevent immunological rejection when free pig islets are transplanted, while encapsulated islets can be transplanted in the absence of such immunosuppressive treatment. The latest approach is being tested in New Zealand with encapsulated pig islets transplanted into the peritoneal cavity to avoid the use of immunosuppressive treatment.

Despite the encouraging progress made in the field, successful clinical application of islet xenotransplantation is currently hampered by a number of barriers. These include the immediate loss of islets in an instant blood-mediated inflammatory reaction (IBMIR), T cell-mediated rejection, and the use of excessive immunosuppression.

IBMIR occurs with kinetics similar to hyperacute rejection in solid-organ xenotransplantation but with no antibody deposition on the graft, and the mechanisms behind it are poorly understood. Nevertheless, xenotransplantation of pig islets into the portal vein, the same site as used in allotransplantation, is associated with early graft loss, and IBMIR may account for the early loss of grafted islets and the consequent large tissue volume required to achieve a functional islet mass following transplantation via this route.

Xenotransplanted pig islets that survive IBMIR may subsequently encounter strong cell-mediated rejection phenomena. Studies have demonstrated that pig islets, following transplantation to nonhuman primates in the absence of immunosuppression, are predominantly destroyed via the infiltration of immune cells, largely T cells, at the graft site, leading to localized graft destruction. However, with an immunosuppressive regimen containing various antibodies and drugs, pig islets xenotransplanted into nonhuman primates can achieve a survival of more than 180 days (Hering et al. 2006). Apparently, the use of novel immunosuppressive strategies designed to abrogate cell-mediated rejection, such as using T cell co-stimulatory pathway blocker cytotoxic T lymphocyte antigen 4 (CTLA4)-Ig, is likely to produce extended islet survival and a better outcome of the cellular xenotransplantation.

Encapsulation of pig islets as mentioned above is another approach to prevent cell-mediated rejection and has been demonstrated to be effective in nonhuman primates. Of course, transgenic pigs represent the most promising solution to the immune responses, with an aim of providing resistance to the effects elicited by IBMIR and cell-mediated rejection. Various transgenic pigs expressing CTLA4-Ig, hCD46, and TRAIL have been produced. Islets from these pigs are thus expected to have reduced immunological rejections. Overall, the combined use of the above immunosuppression strategies forms the basis for future clinical application of pig islet xenotransplantation.

Other cellular xenotransplantations have been attempted using pig red blood cells, pig neuronal cells, pig corneas, pig mesenchymal stem cells, and pig hepatocytes. Again, the progress made in cellular xenotransplantation is much more encouraging than that in solid-organ transplantation and holds the promise of not-too-far away future

clinical application to meet the ever-growing demand and benefit the patients.

Pig Liver Xenotransplantation

Transplantation is currently the most efficient way to treat liver failure, but the wailing list is extremely long as the availability of transplantable donor livers is very limited worldwide. One of the potential solutions to the liver shortage is to take advantage of xenografts from pigs for liver xenotransplantation or at least as a bridge to allotransplantation.

The first pig liver xenotransplantation was carried out in 1968 by Calne's team. They performed seven pig-to-baboon liver transplantations: four died within a day from hemorrhage, and the other three lived no more than 4 days, even with the addition of human fibrinogen which stops xenograft bleeding (Calne et al. 1968). After this attempt, several other groups tried pig liver xenotransplantation in other nonhuman primates such as rhesus monkeys and chimpanzees. Different immunosuppressive regimens were attempted with an aim of reducing the host immunological rejection and prolonging the survival of the transplanted pig liver. Unfortunately, these efforts did not significantly help extend the pig liver survival.

The emergence of GM pigs makes it possible to genetically modify immune responses of the pig and enable its organs to be more compatible with that of human or nonhuman primates. Pigs transgenic for the human complement regulatory protein CD55 were first used in liver xenotransplantation. This experiment achieved 4 and 8 days survival in two baboons. It seems progress has been made by using GM pigs. However, a later attempt using CD55, CD59, and H-transferase triple-transgenic pigs did not obtain a better result. In addition, the use of α1,3GalT$^{-/-}$ pigs as the liver donor in baboon xenotransplantation by the Pittsburgh group did not improve survival (Ekser et al. 2010). It was found that thrombocytopenia, which developed within 1 h after reperfusion of the xenograft, caused complications in the recipients, preventing prolonged survival.

The mechanisms underlying the rapid thrombocytopenia are still not clear, but evidence has shown that the main reason is that pig liver induced recipient platelet phagocytosis which leads to reduced platelet production. Several factors have been identified as causing this phenomenon to occur. These include the interaction between von Willebrand factor and endothelial cells, the interaction between von Willebrand factor and glycoprotein (GP) Ib, and the interaction between CD47 and SIRP-α (Burlak et al. 2010). Further investigations into the factors associated with the development of the rapid thrombocytopenia after pig liver xenotransplantation are still under way.

Nevertheless, the only clinical pig liver xenotransplantation was performed in an attempt to bridge a 26-year-old patient with fulminant hepatic failure to allotransplantation (Makowka et al. 1995). In this case, even though the majority of the circulating natural anti-pig antibodies were removed from the patient before the pig liver was transplanted, the xenograft failed to survive as it was damaged by a rapid return of the antibodies and the associated immunological rejection, suggesting that GM pigs with reduced immunological rejection may provide some benefits.

Taken together, it is now clear that the rapid development of thrombocytopenia remains the major obstacle in pig liver xenotransplantation. Strategies of preventing the development of thrombocytopenia are thus absolutely necessary before a clinical transplantation using a pig liver could be successful.

Physiology and Safety

Although pigs are considered to be the most appropriate organ source for xenotransplantation due to their comparable organ size, rapid growth rate, a more manageable ethical profile, and the chance for genetic modification, physiological incompatibilities, mainly the molecular difference in the complement and coagulation system, have been detected between pigs and primates.

With regard to coagulation, it has been found that the pig von Willebrand factor is able to bind to

human platelet GPIb receptors with high affinity, leading to increased procoagulant activity. In addition, despite the fact that pig thrombomodulin has been shown to bind to human thrombin, the resulting hybrid complex is a weak activator of human protein C. Therefore, there is not sufficient production of activated protein C, causing an increased level of thrombin and eventually leading to the initiation of clotting. Moreover, as the pig tissue factor pathway inhibitor (TFPI) is unable to neutralize human factor Xa, pig TFPI could not inhibit the activation process of human prothrombin to thrombin, resulting in the accumulation of thrombin and thus clotting.

Approaches to reducing the physiological incompatibilities and prolonging the survival of xenografted organs have been proposed. These include the use of platelet fibrinogen receptor antagonist (GPIIb/IIIa), P-selectin inhibitor, soluble adenosine triphosphate (ATP) diphosphohydrolase, and, of course, GM pigs with several specific gene targets for either KO (e.g., procoagulant proteins) or transgenic overexpression (TFPI, thrombomodulin, CD39, etc.). Overall, thrombocytopenia appears to be a crucial barrier in xenotransplantation regarding physiological incompatibilities. The survival of xenografts can be extended if this problem can be overcome.

Besides physiological incompatibilities and thus the long-term xenograft survival, another important consideration in xenotransplantation with regard to a possible clinical application is safety. Viruses, such as cytomegalovirus and Epstein–Barr virus, are frequently transferred from an allograft to the recipient, and the same is true for other donor-derived microorganisms that can cause infectious complications in recipients. Pig organs or cells would not carry such microorganisms as the organ-source herd would be monitored at regular intervals to ensure that organs and cells are free of such infectious agents. However, endogenous retrovirus, which is integrated in the genome of pig cells, will be inevitably carried with the pig xenografts, even if the pigs are housed in a "clean" environment (Patience et al. 1997). Fortunately, humans who are exposed to pig tissues and cells have never been identified as having active replication of the pig endogenous retrovirus, and transfer of this virus is thus not currently considered a serious risk.

It has been pointed out that strategies aimed at reducing xenograft immunological rejections may have the potential to increase the risk of microorganism infections. These include the use of immunosuppressive regimens that decrease the antivirus immune responses, the application of an α1,3GalT$^{-/-}$ pig which lacks α1,3Gal expression and thus is less sensitive to complement-mediated inactivation, and the transgenic pig-expressing human complement regulators. Nevertheless, several approaches have been taken to relieve the above concerns. These include the use of currently available virus-sensitive antivirus agents, generation of GM pigs that inactivate the endogenous retrovirus replication, and the application of small interfering RNA (siRNA) to block the endogenous retrovirus transcription. Furthermore, novel techniques such as microarray-based technology and whole-genome DNA sequencing allow rapid identification of potential infectious agents and help ensure that infectious agent-free organs are used in xenotransplantation (Wang et al. 2002).

It is therefore anticipated that a high-safety profile of xenotransplantation will be ultimately achieved with the combined use of the above strategies.

Conclusion

Xenotransplantation is a multidisciplinary science involving cell biology, immunology, developmental biology, regenerative medicine, and genetic engineering. Although remarkable progress has been made in the past decade, the clinical application of xenotransplantation to replace human organs is still not a reality in today's hospitals as several major obstacles remain. These are immunological rejections, the development of rapid thrombocytopenia, molecular incompatibilities, physiological discrepancies, microbiological safety issues, and ethical issues. However, results obtained from preclinical transplantation of pig cells – such as islets, neuronal cells,

hepatocytes, or corneas – are much more encouraging than those from solid-organ transplantation, with a general survival longer than 1 year in all cases. In addition, the risk of transferring an infectious microorganism to the recipient is much smaller in cellular xenotransplantation.

The development of genetic engineering technology has provided a powerful tool for genetic modifications of organ donor pigs, with the aim of overcoming the hurdles that are associated with pig-to-primate xenotransplantation. Thus, various GM pigs have been produced to try and achieve elimination of immunological rejections. Such GM pigs, when used in combination with other novel immunosuppressive drugs, provide hope for enabling safe and long-term xenograft survival. Because of the much easier protection from the recipient's immune system for cells than organs, it is expected that clinical xenotransplantation of pig cells will be a reality in the not-too-distant future.

Cross-References

- ▶ Cell Therapy for Liver Failure: A New Horizon
- ▶ Downstaging Hepatocellular Carcinoma for Liver Transplantation
- ▶ History of Liver and Other Splanchnic Organ Transplantation
- ▶ Immunology of Liver Transplantation
- ▶ Systemic Chemotherapy in Orthotopic Liver Transplantation

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Cell Therapy for Liver Failure: A New Horizon

25

Neil H. Riordan

Contents

Abstract

Liver failure is the seventh largest cause of death in industrialized countries. The only available cure, liver transplantation, is severely limited by a lack of donors and further complicated by the adverse effects of chronic immune suppression. Molecular mechanisms associated with the process of liver regeneration and the role of various progenitor cells in healing injury will be discussed in this chapter. Preclinical and clinical data will be reviewed from studies involving bone marrow mesenchymal stem cells (BM-MSC), adipose tissue MSC (AT-MSC), and bone marrow mononuclear cells (BMMC) including their purified subsets. From analyzing published clinical trials, it appears that there is some efficacy utilizing autologous cells, but these seem to be limited to a timeframe of less than a year. Promising sources of MSC such as the umbilical cord and fetal liver cells which have been used in allogeneic settings will also be described.

Keywords

Liver failure • Liver regeneration • Stem cell • Mesenchymal stem cells • Cell therapy • Fetal liver cells • Progenitor cells

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Introduction

Liver failure is a serious and, if untreated, fatal medical condition that occurs as a result of a number of acute and chronic clinical inciting factors, including drug-/alcohol-induced hepatotoxicity, viral infections, vascular injury, autoimmune disease, or genetic predisposition (Kelso 2008). Manifestations of liver failure include fulminant acute hepatitis, chronic hepatitis, or cirrhosis. Subsequent to various acute insults to the liver, the organ regenerates due to its unique ability to self-renew. If the insult is continuously occurring, the liver's capacity to regenerate new cells is overwhelmed, and fibrotic nonfunctional tissue is deposited, diminishing the functional capacity of the hepatic parenchyma. The subsequent reduction of hepatocyte function can give rise to metabolic instability combined with disruption of essential bodily functions (i.e., energy supply, acid–base balance, and coagulation) (Bernuau et al. 1986; Farci et al. 1996; Navarro and Senior 2006). If not rapidly addressed, complications of hepatic dysfunction such as uncontrolled bleeding and sepsis occur, and dependent organs such as the brain and kidneys cease to function because of accumulation of toxic metabolites (Sargent 2006). In critical cases, such as when patients progress to acute-on-chronic liver failure (ACLF), liver transplant is considered to be the standard treatment. However, it is often extremely difficult to obtain a suitable donor, and many complications can arise after transplantation, including rejection and long-term adherence to immunosuppressant regimes (Kisseleva et al. 2010; Wu et al. 2008).

Liver Regeneration

Interest in regenerative approaches toward liver failure is not only due to the unmet medical need for novel interventions but is also based on the inherent ability of the liver to self-regenerate. It has been demonstrated that up to 70 % resection of the liver results in complete regeneration (Fausto et al. 2006; Michalopoulos 2011). Clinically, the potent regenerative ability of the liver allows for procedures such as living donor transplantation, two-stage hepatectomies, and split liver transplantation, which would be impossible with other organs that do not possess the potent inherent regenerative properties of the liver (Adam et al. 2000; Brown 2008; Clavien et al. 2007). However, liver regeneration is a tightly regulated process which adapts to the size of each specific body. In a partial hepatectomy, the liver will only regenerate to the original size, without hypertrophy. Transplantation medicine provides further insight into the tight regulation of liver regeneration. For example, smaller livers transplanted in proportionally larger recipients take on a larger size and vice versa (Michalopoulos 2013; Van Thiel et al. 1987).

Mechanistically, the process of liver regeneration occurs in three broad phases: (a) priming, (b) proliferation, and (c) termination (Fausto et al. 2006). It is important to note that hepatocytes are not terminally differentiated cells but cells that reside in a state of proliferative quiescence. Specifically, they share features with other regenerative cells such hematopoietic stem cells, in that they are normally in the G0 phase of cell cycle. This is altered during liver regeneration, which is described below.

During the priming phase, numerous injury signals are generated as a result of the underlying injury; these include activators of Toll-like receptors, complement degradation products, and damage-associated molecular patterns (DAMPs). These signals stimulate various cells, primarily Kupffer cells, to produce cytokines and growth factors such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and hepatocyte growth factor (HGF), which induce entry of hepatocytes into cell cycle. The importance of these molecular signals in the initiation of liver regeneration is highlighted by knockout studies. Cressman et al. (1996) demonstrated blockade of liver regeneration in a partial hepatectomy IL-6 knockout model that was associated with blunted exit from the G0 phase of cell cycle in hepatocytes of these mice but not in non-parenchymal liver cells. Furthermore, they conclusively showed the importance of IL-6 in that a single preoperative dose of recombinant IL-6 restored post-injury hepatocyte entry into G1/2 to levels observed in

wild-type mice and restored biochemical function (Cressman et al. 1996). Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappa B) is a major downstream effector of various inflammatory cytokines including TNF-alpha and IL-6. Malato et al. (2008) generated hepatic-specific knockout mice in which the inhibitor of NF-kappa B, inhibitor of nuclear factor kappa B kinase subunit beta (IKK2), was ablated, thus giving rise to a higher level of background NF-kappa B activation. In these mice, partial hepatectomy resulted in accelerated entry of hepatocytes into cell cycle (Malato et al. 2008). The role of a variety of inflammatory or "danger"-associated pathways in the initial priming of hepatocyte proliferation after injury has been confirmed using DNA microarray analysis of genes associated with these signaling pathways such as STAT, p38MAPK, and Ras/ERK (Li et al. 2014).

The proliferation phase of hepatic regeneration is associated with "primed" hepatocytes leaving the G_1 stage of cell cycle and entering the S phase, which is accompanied by phosphorylation of the retinoblastoma protein (pRb) and by upregulated expression of a number of proliferation-associated genes including cyclin E, cyclin A, and DNA polymerase (Fan et al. 1995; Spiewak Rinaudo and Thorgeirsson 1997). Key cytokines involved in stimulation of proliferation of the hepatocytes include HGF and epidermal growth factor (EGF). HGF is produced by mesenchymal cells, hepatic stellate cells, and liver sinusoidal endothelial cells as a proprotein, which acts both systemically and locally (DeLeve 2013; Maher 1993). Systemic elevations in HGF are observed after partial hepatectomy (Matsumoto et al. 2013), whereas local HGF is released from its latent form which is often bound to extracellular matrix proteins (Nakamura et al. 2011). Activation of HGF occurs typically via enzymatic cleavage mediated by urokinase-type plasminogen activator (uPA) (Mars et al. 1995; Shanmukhappa et al. 2006). The importance of HGF in the proliferation phase of liver regeneration is observed in animals where the HGF receptor c-MET is conditionally inactivated, displaying a reduction in hepatocyte entry into the S phase of cell cycle post-injury (Borowiak et al. 2004). EGF signaling has also been demonstrated to be involved in entry into the proliferative phase post-injury. Natarajan et al. (2007) performed perinatal deletion of epithelial growth factor receptor (EGFR) in hepatocytes prior to partial hepatectomy. They showed that, after hepatic injury, mice lacking EGFR in the liver had an increased mortality accompanied by increased levels of serum transaminases indicating liver damage. Liver regeneration was delayed in the mutants because of reduced hepatocyte proliferation. Analysis of cell cycle progression in EGFR-deficient livers indicated a defective G (1)-S phase entry with delayed transcriptional activation and reduced protein expression of cyclin D1, followed by reduced cyclin-dependent kinase 2 and cyclin-dependent kinase 1 (Natarajan et al. 2007).

The termination phase of liver regeneration occurs when the normal liver mass/body weight ratio of 2.5 % has been restored (Nygard et al. 2012). While in the priming phase of liver regeneration, several inflammatory cytokines are critical, in the termination phase, anti-inflammatory cytokines such as IL-10 (Mosser and Zhang 2008) are upregulated, which dampen proliferative stimuli (Yin et al. 2011). Additionally, cytokines with direct antiproliferative activity such as TGF-beta are generated, which results in cell cycle arrest of proliferating hepatocytes.

While classical liver regeneration is mediated by hepatocytes (Fausto et al. 2006; Miyaoka and Miyajima 2013) in certain situations, such as in liver failure, the ability of the hepatocytes to mediate regeneration is limited, and liver progenitor cells (LPCs) must carry out the process. The concept of a LPC taking over regenerative function when hepatocyte multiplication is stunted was first demonstrated in 1956 when Farber treated rats with various liver carcinogens that blocked division of hepatocytes (Farber 1956). He discovered the existence of "oval cells" which were subsequently demonstrated to act as LPCs having the ability to differentiate into both hepatocytes and biliary cells (Evarts et al. 1987). LPCs are found in the canals of Hering and bile ductules in human liver and found increased in patients with chronic liver disease (Libbrecht and Roskams 2002). It is unclear what the origin of

LPCs is, whether they derive from local cells or directly from MSC (Banas et al. 2007), particularly bone marrow-derived MSC (Petersen et al. 1999), but the cellular mechanisms are poorly understood (Margini et al. 2014). In 2000, Theise et al. (2000b) found hepatocytes and cholangiocytes derived from extrahepatic circulating stem cells in the livers of female patients who had undergone therapeutic bone marrow transplantations. In the two female recipients from male donors and four male recipients from female donors, hepatocyte and cholangiocyte engraftment ranged from 4 % to 43 % and from 4 % to 38 %, respectively (Theise et al. 2000b).

Given the potent regenerative nature of the liver, combined with the possibility that extrahepatic cellular sources may contribute to regeneration, numerous attempts have been made to utilize cellular therapy for treatment of liver failure. The original hepatic cellular therapies involved the administration of allogeneic hepatocytes, which was initially attempted in animal models more than 30 years ago and is experimentally used clinically. Unfortunately, major hurdles exist that block this procedures from routine use, specifically (a) low number of suitable donors; (b) extremely poor hepatocyte viability after transplantation, with some groups as low as 30 %; and (c) need for continuous immune suppression which possesses inherent adverse effects (Filippi and Dhawan 2014).

Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) are adult stem cells with self-renewing abilities (Jackson et al. 2007) and have been shown to differentiate into a wide range of tissues including mesoderm and nonmesoderm (Jackson et al. 2007; Pittenger et al. 1999), including hepatocytes (Banas et al. 2009; Cho et al. 2009; Hong et al. 2005; Ishikawa et al. 2010; Lee et al. 2004; Seo et al. 2005). MSC are capable of entering and maintaining satellite cell niches, particularly in hematopoiesis (Crisan et al. 2008; Tavian and Peault 2005), and are key in tissue repair and regeneration, aging, and regulating homeostasis (Aggarwal and Pittenger 2005; Caplan 2007; Chamberlain et al. 2007a; Peault et al. 2007). In the case of liver failure, MSCs can aid in regeneration of hepatic tissue (Banas et al. 2008; Chang et al. 2009; Kharaziha et al. 2009; Kuo et al. 2008; Lu et al. 2006; Mohamadnejad et al. 2007; Terai et al. 2006), and their interactions with the immune system (Chang et al. 2006; Iyer and Rojas 2008; Nauta and Fibbe 2007; Shi et al. 2011; Uccelli et al. 2007; Wolbank et al. 2007; Wolf and Wolf 2008) have potential as adjuvants during organ transplants (Sordi and Piemonti 2011), including liver transplantation (Popp et al. 2009).

MSC were discovered in 1970 by Friedenstein et al., who demonstrated that bone marrow (BM) contained both hematopoietic stem cells (HSCs), which are nonplastic adherent, and a population of a more rare adherent cell. The adherent cells were able to form single-cell colonies and were referred to as stromal cells. Those stromal cells, which are capable of self-renewal and expansion in culture, are now referred to as mesenchymal stem cells (MSC). Friedenstein was the first to show that MSC could differentiate into mesoderm and to demonstrate their importance in controlling the hematopoietic niche (Friedenstein et al. 1974).

In the 1980s, more research on MSC found that they could differentiate into muscle-, cartilage-, bone-, and adipose-derived cells (Caplan 1986). Caplan (1991) showed that MSC are responsible for bone and cartilage regeneration induced by local cuing and genetic potential.

In the 1990s, Pittenger et al. isolated MSC from bone marrow and found that they retained their multilineage potential after expanding into selectively differentiated adipocytic, chondrocytic, or osteocytic lineages (Pittenger et al. 1999). Likewise, Kopen et al. showed that bone marrow MSC differentiated into neural cells when exposed to the brain microenvironment (Kopen et al. 1999). In 1999, Petersen et al. found that bone marrow-derived stem cells could be a source of hepatic oval cells in a rat model (Petersen et al. 1999). Specifically, they used male-to-female bone marrow transplant and subsequently induced blockade of hepatocyte proliferation by administration of a hepatotoxin followed by partial hepatectomy. As previously described, this procedure stimulates

proliferation of LPC or "reserve cells" which generate new hepatocytes, such cells having been previously identified as oval cells. Subsequent to the hepatectomy, Y chromosome, dipeptidyl peptidase IV enzyme, and L21-6 antigen were used to identify the newly generated oval cells and their hepatocytic progeny to be of bone marrow origin.

The first decade of the twenty-first century saw a surge of research on MSC, leading to a greater understanding of their nature and of the cellular process behind regeneration (Caplan 2007; Chamberlain et al. 2007a; Jackson et al. 2007). In 2005, Teratani et al. identified growth factors allowing hepatic fate specification in mice and showed that embryonic stem cells could differentiate into functional hepatocytes (Teratani et al. 2005). In 2007, Chamberlain et al. generated human hepatocytes from clonal MSC in fetal sheep hepatic tissue, differentiating into hepatocytes both throughout the liver parenchyma and the periportal space (Chamberlain et al. 2007b). The lack of need for donor matching compounded by their ease of expansion and the standardized protocols for manufacturing and administration make MSCs attractive for clinical development. Of particular interest for liver conditions is the observation that intravenous administration of MSC results in a primary homing of cells to the lung, followed by homing and retention to the liver (Gao et al. 2001). A unique property of MSC is their apparent hypoimmunogenicity and immune modulatory activity (Le Blanc and Ringden 2007), which is present in MSC derived from various sources (Keyser et al. 2007). This is believed to account for the ability to achieve therapeutic effects in an allogeneic manner. Allogeneic bone marrow-derived MSC have been used by academic investigators with clinical benefit in the treatment of diseases such as graft-versus-host disease (GVHD) (Ball et al. 2008; Le Blanc et al. 2004, 2008; Muller et al. 2008; Ning et al. 2008; Ringden et al. 2006), osteogenesis imperfecta (Horwitz et al. 2002), Hurler syndrome, metachromatic leukodystrophy (Koc et al. 2002), and acceleration of hematopoietic stem cell engraftment (Ball et al. 2007; Lazarus et al. 2005; Le Blanc et al. 2007). The company Athersys has successfully completed Phase I safety studies using allogeneic bone marrow MSC and is now in efficacy seeking clinical trials (Phase II and Phase III) for multiple sclerosis, Crohn's disease, and graft-versus-host disease using allogeneic bone marrow-derived MSC. Intravenous administration of allogeneic MSC by Osiris was also reported to induce a statistically significant improvement in cardiac function in a double-blind study (Osiris Therapeutics 2007).

Currently, there are several MSC-based therapies that have received governmental approvals including Prochymal™, registered in Canada and New Zealand for treatment of graft-versus-host disease (Kellathur and Lou 2012; Kurtzberg et al. 2014). Although in terms of clinical translation bone marrow MSC are the most advanced, several other sources of MSC are known which possess various properties that may be useful for specific conditions. Bone marrow is also a source for hematopoietic stem cells (HSCs), which have also been used for liver regeneration. Likewise, human placenta is an easily accessible source of abundant MSC, which can be differentiated in vitro. Finally, MSC with tissue regenerative abilities can also be isolated from adipose tissue and induced to hepatocytes in large numbers.

Bone Marrow MSC for Treatment of Liver Failure

Early studies have suggested that out of the hepatic regenerative cells found in bone marrow, the MSC component is the most regenerative cell type as compared to other cell types such as hematopoietic stem cells (Cho et al. 2009). Given that BM-MSC are capable of differentiating into various tissues in vitro, combined with the putative bone marrow origin of the hepatic-repairing oval cell (Petersen et al. 1999), investigators sought to determine whether BM-MSC could be induced to differentiate into hepatocyte cells in vitro through culture in conditions that would imitate hepatic regeneration. Lee et al. (2004) developed a 2-step protocol for hepatocyte differentiation using culture in hepatocyte growth factor, followed by oncostatin M. After 4 weeks of induction, the investigators reported the

spindle-like BM-MSC taking a cuboidal morphology, which is characteristic of hepatocytes. Furthermore, the differentiating cells were seen to initiate expression of hepatic-specific genes in a time-dependent manner correlating with morphological changes. From a functional perspective, the generated hepatocytes exhibited features of liver cells, specifically albumin production, glycogen storage, urea secretion, uptake of low-density lipoprotein, and phenobarbital-inducible cytochrome P450 activity (Lee et al. 2004). To improve yield and potency of BM-MSC-generated hepatocytes, Chen et al. utilized conditioned media from cultured hepatocytes as part of the differentiation culture conditions. They reported that BM-MSC cultures in the differentiation conditions started taking an epithelioid, binucleated morphology at days 10 and 20. Gene assessment revealed increase in AFP, HNF-3beta, CK19, CK18, ALB, TAT, and G-6-Pase mRNA, which was confirmed at the protein levels. Additionally, the cells started taking a functional phenotype similar to hepatocytes. The hepatocyte-like cells by culture in conditioned medium further demonstrated in vitro functions characteristic of liver cells, including glycogen storage and urea secretion activities. Upon transplantation to immune-deficient animals exposed to chemically induced liver injury (Chen et al. 2007), restoration of albumin activity and suppression of liver enzymes were seen, demonstrating in vivo relevance of these artificially generated hepatic-like cells. In accordance with the concept that injured tissue mediates MSC activation and subsequent repair, Mohsin et al. (2011) demonstrated that coculture of BM-MSC with chemically injured hepatocytes augments hepatic differentiation as compared to coculture with naïve hepatocytes.

Based on in vitro differentiation, as well as the possibility of MSC producing cytokines such as HGF (Lange et al. 2005; Li et al. 2012; Soleymaninejadian et al. 2012), which are known to stimulate hepatic regeneration and/or decrease hepatocyte apoptosis (Enriquez-Cortina et al. 2013; Francois et al. 2013; Hua et al. 2012; Kaldenbach et al. 2012; Kroy et al. 2014; Lee et al. 2010b, 2012; Li et al. 2013), several animal studies were conducted using BM-MSC in models of liver injury. Fang et al. (2004) utilized a carbon tetrachloride-induced hepatic injury model to assess the effects of systemically administered BM-MSC on fibrosis and hepatocyte demise. It was found that MSC infusion after exposure to the hepatotoxin significantly reduced liver damage and collagen deposition. Levels of hepatic hydroxyproline and serum fibrosis markers in mice receiving cells were significantly lower compared with those of control mice, supporting the possibility of a concurrent protective and regenerative effect. Histologic examination suggested that hepatic damage recovery was accelerated in the treated mice. Donor cell engraftment and possible in vivo hepatic differentiation were supported by immunofluorescence, polymerase chain reaction, and fluorescence in situ hybridization analysis, which demonstrated donor-derived cells possessing epithelium-like morphology and expressed albumin (Fang et al. 2004). Interestingly, the amount of engrafted cells was minute and could not explain the functional recovery of serum albumin, suggesting the possibility of paracrine effects. A subsequent study using the same carbon tetrachloride model demonstrated that BM-MSC administration resulted in reactive oxygen species ex vivo, reduced oxidative stress in recipient mice, and accelerated repopulation of hepatocytes after liver damage (Kuo et al. 2008). To optimize the route of administration, Zhao et al. (2012) assessed intravenous, intrahepatic, and intraperitoneal administration of BM-MSC in rats treated with carbon tetrachloride. Functional recovery was most profound in the intravenous administration group, which was correlated with increased IL-10 and decreased IL-1, TNF-alpha, and TGF-beta. Furthermore, in vivo differentiation of the BM-MSC was observed based on expression of α-fetoprotein, albumin, and cytokeratin 18 in cells derived from donor origin (Zhao et al. 2012).

In order to assess whether the therapeutic effects of BM-MSC are specific to the carbon tetrachloride model or whether they may be extrapolated to other models of hepatic injury, investigators assessed the usefulness of BM-MSC in hepatectomy recovery models. While recovery is generally observed after

two-thirds or 70 % hepatectomy, 90 % hepatectomy is lethal in rats. In one study, BM-MSC were differentiated in vitro by culture on Matrigel with hepatocyte growth factor and fibroblast growth factor-4 into cells expressing hepatocyte-like properties. Specifically, the cells expressed a hepatic-like cuboidal morphology and were positive for albumin, cytochrome P450 (CYP)1A1, CYP1A2, glucose 6-phosphatase, tryptophane-2,3-dioxygenase, tyrosine aminotransferase, hepatocyte nuclear factor (HNF) 1 alpha, and HNF4alpha. Intrasplenic administration of differentiated cells subsequent to the 90 % hepatectomy resulted in the prevention of lethality (Miyazaki et al. 2007). Another study confirmed the efficacy of BM-MSC at accelerating post-hepatectomy liver regeneration subsequent to intraportal administration. Regenerative effects were associated with upregulation of HGF expression in the newly synthesized tissue (Kaibori et al. 2014). It is interesting that the regenerative effects of BM-MSC are observed not only in acute settings but also in chronic conditions leading to liver failure. Nonalcoholic steatohepatitis (NASH) is a precursor to cirrhosis and is characterized by lipid accumulation, hepatocyte damage, leukocyte infiltration, and fibrosis. It was demonstrated that in C57BL/6 mice chronically fed with high-fat diet, the intravenous administration of BM-MSC resulted in reduction of plasma levels of hepatic enzyme, hepatomegaly, liver fibrosis, inflammatory cell infiltration, and inflammatory cytokine gene expression, as compared to control mice (Ezquer et al. 2011). Overall, these data suggest that BM-MSC have some reparative and/or regenerative activity on livers that are damaged in either chronic or acute settings.

Additional animal studies have been conducted in both chronic and acute liver toxicity settings. For example, Hwang et al. (2012) treated Sprague–Dawley rats with 0.04 % thioacetamide (TAA)-containing water for 8 weeks, and BM-MSC were injected into the spleen with the intent of transsplenic migration into the liver. Ingestion of TAA for 8 weeks induced micronodular liver cirrhosis in 93 % of rats. Examination of MSC microscopically revealed that the injected cells were diffusely engrafted in the liver parenchyma, differentiated into CK19 (cytokeratin 19)- and Thy1-positive oval cells and later into albumin-producing hepatocyte-like cells. MSC engraftment rate per slice was measured as 1.0–1.6 %. MSC injection resulted in apoptosis of hepatic stellate cells and resultant resolution of fibrosis but did not cause apoptosis of hepatocytes. Given that stellate cells are responsible for matrix deposition and fibrosis (Novo et al. 2014; Xu et al. 2014), this is an interesting observation. Injection of MSC treated with HGF in vitro for 2 weeks, which became CD90 negative and CK18 positive, resulted in chronological advancement of hepatogenic cellular differentiation by 2 weeks and decrease in antifibrotic activity. Mechanistically, it appeared that the BM-MSC directly differentiated to oval cells and hepatocytes, which was associated with repair of damaged hepatocytes, intracellular glycogen restoration, and resolution of fibrosis.

An acute model of liver failure is produced by administration to animals of D-galactosamine, a TNF-alpha-stimulating hepatotoxin (Wu et al. 2014), and lipopolysaccharide (LPS), a potent inflammatory stimulus that replicates translocation of gut bacteria often seen in liver failure (Lindros and Jarvelainen 2005; Sandler et al. 2011). In this model, it was demonstrated that administration of BM-MSC in pretreated rats resulted in reduction of ALT, AST, caspase-1 and IL-18 proteins, and mRNA as compared to the control group (Yuan et al. 2013). Mechanistic elucidation at a cellular level demonstrated that the injected BM-MSC were inhibiting hepatocyte apoptosis. Interestingly, the authors also found that recovering animals possessed higher levels of VEGF protein as compared to non-treated animals. This is intuitively logical given that VEGF is a key cytokine in the angiogenesis cascade, and angiogenesis seems to be required in the regression of liver failure (Kajdaniuk et al. 2011; Sturm et al. 2004; Tekkesin et al. 2011; Ueno et al. 2006). Using the same D-galactosamine/LPS model, Sun et al. (2014) sought to identify optimal route of delivery for BM-MSC. They divided the rats into the following groups: (a) hepatic artery injection group, (b) portal vein injection group, (c) tail vein injection group, and

(d) intraperitoneal injection group. They found that compared with the control group, ALT, AST, and damage to the liver tissue improved in vivo in the hepatic artery group, the portal vein group, and the tail vein group. The expression of PCNA and HGF in the liver was higher, and caspase-3 expression was lower in the hepatic artery injection group, the portal vein injection group, and the tail vein injection group than in the intraperitoneal injection and control groups. The BrdU-labeled BM-MSC were only observed homing to the liver tissue in these three groups. However, no significant differences were observed between these three groups. Liver function was improved following BM-MSC transplantation via three endovascular implantation methods (through the hepatic artery, portal vein, and vena caudalis). These data suggest that intrahepatic artery injection was most effective and that intraperitoneal administration is ineffective. A large animal study using similar hepatotoxins was performed in the pig. Li et al. (2014) administered 3 × 10(7) human BM-MSC via the intraportal route or peripheral vein immediately after D-galactosamine injection, and a sham group underwent intraportal transplantation (IPT) without cells (IPT, peripheral vein transplantation [PVT], and control groups, respectively, n = 15 per group). All of the animals in the PVT and control groups died of FHF within 96 h. In contrast, 13 of 15 animals in the IPT group achieved long-term survival (>6 months). Immunohistochemistry demonstrated that transplanted human BM-MSC-derived hepatocytes in surviving animals were widely distributed in the hepatic lobules and the liver parenchyma from weeks 2–10. Thirty percent of the hepatocytes were BM-MSC derived. However, the number of transplanted cells decreased significantly at week 15. Only a few single cells were scattered in the regenerated liver lobules at week 20, and the liver tissues exhibited a nearly normal structure. These data suggest that intraportal delivery may be ideal and also reinforce the notion that MSC may be transplanted across allo- and xeno-barriers without need for immune suppression.

Clinical trials utilizing BM-MSC have shown an excellent safety profile, with various levels of efficacy in liver failure. Mohamadnejad et al. (2007) conducted a 4-patient study with decompensated liver cirrhosis. Patient bone marrow was aspirated, mesenchymal stem cells were cultured, and a mean 31.73 × 10(6) mesenchymal stem cells were infused through a peripheral vein. There were no side effects in the patients during follow-up. The model for end-stage liver disease (MELD) scores of patients 1 and 4 improved by four and three points, respectively, by the end of follow-up. Furthermore, the quality of life of all four patients improved by the end of follow-up. Using the SF-36 questionnaire, the mean physical component scale increased from 31.44 to 65.19, and the mean mental component scale increased from 36.32 to 65.55. Another study treated 8 patients (four hepatitis B, one hepatitis C, one alcoholic, and two cryptogenic) with end-stage liver disease having MELD score greater than or equal to 10 were included. Autologous bone marrow was taken from the iliac crest. Approximately 30–50 million ex vivo expanded BM-MSC were injected into the peripheral or the portal vein. Subsequent to experiment, the MELD score was decreased from 17.9+/−5.6 to 10.7+/−6.3 ($P < 0.05$) and prothrombin complex from international normalized ratio 1.9+/−0.4 to 1.4+/−0.5 ($P < 0.05$). Serum creatinine decreased from 114+/−35 to 80+/−18 μmol/l ($P < 0.05$). This trial supports the safety with signal of efficacy of the BM-MSC activity in liver failure clinically.

A larger trial of autologous BM-MSC focused on patients with liver failure associated with hepatitis B infection (Peng et al. 2011). Part of the rationale was previous studies showing that BM-MSC-derived hepatocytes are resistant to hepatitis B infection (Xie et al. 2009). Peng et al. (2011) treated 53 patients and as controls used 105 patients matched for age, sex, and biochemical indexes, including alanine aminotransferase (ALT), albumin, total bilirubin (TBIL), prothrombin time (PT), and MELD score. In the 2–3-week period after cell administration, efficacy was observed based on the levels of ALB, TBIL, and PT and MELD score, compared with those in the control group. Safety of the procedure was demonstrated in that there were no differences in incidence of hepatocellular carcinoma

(HCC) or mortality between the treated and control groups at 192 weeks. Unfortunately, liver function between the two groups was also similar at 192 weeks, suggesting the beneficial effects of BM-MSC were transient in nature. Supporting the possibility of transient effects of BM-MSC was a 27-patient study in patients with decompensated cirrhosis in which 15 patients received BM-MSC and 12 patients received placebo. The absolute changes in Child scores, MELD scores, serum albumin, INR, serum transaminases, and liver volumes did not differ significantly between the MSC and placebo groups at 12 months of follow-up. Unfortunately, the publication did not provide 3- or 6-month values (Mohamadnejad et al. 2013). In contrast, a more recent study administered BM-MSC into 12 patients (11 males, 1 female) with baseline biopsy-proven alcoholic cirrhosis who had been alcohol free for at least 6 months (Jang et al. 2014). A 3-month assessment of histological improvement and reduction of fibrosis was quantified according to the Laennec fibrosis scoring scale in 6 of 11 patients. Additionally, at 3 months post-cell administration, the Child–Pugh score improved significantly in ten patients, and the levels of transforming growth factor-β1, type 1 collagen, and α-smooth muscle actin significantly decreased (as assessed by real-time reverse transcriptase polymerase chain reaction) after BM-MSC therapy. Overall, the different underlying conditions, route of administration, and time points of assessments between studies make it difficult to draw solid conclusions; it appears that some therapeutic effect exists, although longevity of effect is not known.

One possibility for the lack of long term efficacy in the previous study may be inappropriate level of hepatocyte differentiation in vivo, Amer et al. (2011) conducted a clinical trial where BM-MSC were pre-differentiated toward the hepatocyte lineage by a culture cocktail containing HGF. They conducted a 40-patient trial in hepatitis C patients in which 20 patients were treated with partially differentiated cells either intrasplenically or intrahepatically and 20 patients received placebo control. At the 3- and 6-month time points, a significant improvement in ascites, lower limb edema, and serum albumin, over the control group, was observed. Additionally, significant benefit was quantified in the Child–Pugh and MELD scores. No difference was observed between intrahepatic and intrasplenic administration. This study demonstrates the potential of semi-differentiated hepatocytes from BM-MSC to yield therapeutic benefit without reported adverse effects.

Out of the BM-MSC studies described, one potential reason for relatively mediocre results could be the fact that autologous cells were utilized in all of the studies. While autologous MSC possess the benefit of lack of immunogenicity, a drawback may be a relative dysfunction of these cells given the poor health condition of the patients. Several studies have demonstrated that MSC from patients suffering from chronic conditions possess inhibited regenerative activity when compared with MSC from healthy donors (Bozdag-Turan et al. 2012; Cipriani et al. 2007; Rodriguez-Menocal et al. 2012; Sugihara et al. 2007; Teraa et al. 2013; Walter et al. 2005; Zhuo et al. 2010).

Adipose-Derived MSC for Treatment of Liver Failure

Adipose tissue is an attractive alternative to bone marrow as a source of stem cells for treatment of degenerative conditions in general and liver failure specifically (Ishikawa et al. 2010; Puglisi et al. 2011) for the following reasons: (a) extraction of adipose-derived cells is a simpler procedure that is much less invasive than bone marrow extraction; (b) adipose tissue contains a higher content of mesenchymal stem cells (MSC) as compared to bone marrow; therefore, shorter in vitro expansion times are needed; and (c) MSC from adipose tissue do not decrease in number with aging (Mosna et al. 2010; Strioga et al. 2012; Yi and Song 2012). Adipose derived MSC were originally described by Zuk et al. who demonstrated that the stromal vascular fraction (SVF) of adipose tissue contains large numbers of cells that could be induced to differentiate into adipogenic, chondrogenic, myogenic, and osteogenic lineages and morphologically resembled

MSC (Zuk et al. 2001). Subsequent to the initial description, the same group reported that in vitro expanded SVF-derived cells had surface marker expression similar to bone marrow-derived MSC, displaying expression of CD29, CD44, CD71, CD90, CD105/SH2, and SH3 and lacking CD31, CD34, and CD45 expression (Zuk et al. 2002). This suggested that SVF-expanded adherent cells were indeed members of the MSC family, a notion that has subsequently gained acceptance (Bassi et al. 2012; Ong and Sugii 2013; Tallone et al. 2011). To date, clinical trials on adipose-derived cells have all utilized ex vivo expanded cells, which share properties with bone marrow-derived MSC (Fang et al. 2006, 2007a, b; Garcia-Olmo et al. 2005, 2008; Stillaert et al. 2008). Preparations of MSC expanded from adipose tissue are equivalent or superior to bone marrow in terms of differentiation ability (Hayashi et al. 2008; Noel et al. 2008), angiogenesis-stimulating potential (Kim et al. 2007), and immune modulatory effects (Keyser et al. 2007; Lin et al. 2012).

In the area of liver failure, Banas et al. (2009) created a 13-day in vitro differentiation protocol to generate hepatocyte-like cells from human adipose tissue MSC (AT-MSC). The differentiated cells possessed a hepatocyte-like morphology and phenotypically resembled primary hepatocytes. Administration of the cells in a carbon tetrachloride-induced liver failure model resulted in diminished liver injury, AST, ALT, as well as ammonia. Unfortunately, comparison with BM-MSC was not performed. A subsequent study utilized AT-MSC that were not differentiated and injected into the tail vein (Yukawa et al. 2009). Administration of cells led to death in 4 of 6 mice due to lung infarction, presumably as a result of cell accumulation in pulmonary microcapillaries. To overcome this, the investigators utilized a combination of AT-MSC and heparin. This resulted in a trend that did not reach significance for reduced ALT, AST, and LDH in the treated group. It was demonstrated in a subsequent tracking study by the same group that heparin decreased pulmonary retention and increased hepatic retention by 30 % (Yukawa et al. 2012). In order to elucidate whether alternative routes of AT-MSC administration may augment therapeutic activities, Kim et al. (2011) assessed intravenous, intrahepatic parenchyma, and intraportal vein delivery of cells in the same carbon tetrachloride model as utilized by the previous two experiments. They found that all three routes led to significant decrease in histological injury as well as AST, ALT, and ammonia. The most profound protective effects were observed in the intravenous group. One possible reason for statistical significant efficacy in this study and not in the previous study may be that in this study AT-MSC were injected at days 1 and 3 after carbon tetrachloride administration whereas the previous study involved only one injection. The previous AT-MSC experiments utilized human cells administered in animals; Deng et al. (2014) utilized syngeneic AT-MSC that were derived from mice transgenic with enhanced green fluorescent protein (eGFP) in mice treated with carbon tetrachloride. The survival rate of the cell-treated group significantly increased compared to the PBS group. Furthermore, the transplanted cells were well integrated into injured livers and produced albumin and cytokeratin-18. Overall, it appears that in the carbon tetrachloride model, both xenogeneic and syngeneic AT-MSC have therapeutic effects. However, standardization of protocols and models is needed to obtain a clearer picture of potency of effects.

Other models of hepatic injury have been utilized with AT-MSC. Salomone et al. (2013) assessed human AT-MSC transfected with eGFP in rats treated with a hepatotoxic dose of acetaminophen. It was found that AT-MSC infusion decreased AST, ALT, and prothrombin time to the levels observed in control rats. Furthermore, clinical signs of liver failure such as encephalopathy were not observed in treated animals. Histologically, control animals displayed lobular necrosis and diffuse vacuolar degeneration, which was not seen in the treated group. Mechanistically, transplanted AT-MSC induced an increase in antioxidant status and decrease in inflammatory cytokines in the recipients. Additionally, proliferation of endogenous hepatocytes was observed. These data suggest that AT-MSC effects on liver injury are not limited to carbon tetrachloride but may be more widespread. Indeed, another study utilized

two chemicals that block hepatocyte regeneration together with partial hepatectomy. Specifically, using a model of a toxic liver damage in Sprague–Dawley rats, generated by repetitive intraperitoneal application of retrorsine and allyl alcohol followed by two-thirds partial hepatectomy, investigators assessed the regenerative effects of human AT-MSC. Six and twelve weeks after hepatectomy, animals were sacrificed and histological sections were analyzed. AT-MSC-treated animals exhibited significantly raised albumin, total protein, glutamic oxaloacetic transaminase, and LDH. The infused cells were found in histological sections up to 12 weeks after surgery. Although clinical studies of AT-MSC in liver disease have not been reported at the time of writing, one clinical trial (NCT01062750) is reported to be enrolling. This trial, run by Shuichi Kaneko of Kanazawa University in Japan, comprises of intrahepatic administration of AT-MSC.

Bone Marrow Mononuclear Cells and Isolated Subsets

Although numerous studies have examined the ability of MSC to induce hepatic regeneration, the original studies that demonstrated BM liver regenerative effects suggested that other cells in the BM compartment besides MSC may have therapeutic activities (Avital et al. 2002). Given that bone marrow mononuclear cells (BMMC) have demonstrated therapeutic activities in numerous ischemic and chronic conditions (de Vasconcelos Dos Santos et al. 2010; Fernandez-Aviles et al. 2004; Iihoshi et al. 2004; Nizankowski et al. 2005; Strauer et al. 2002; Tateishi-Yuyama et al. 2002), investigators sought to assess whether this mixture of cells would possess activity in animal models of liver failure. Terai et al. (2003) administered BMMC isolated from mice transgenic for GFP to mice whose livers where injured by carbon tetrachloride. It was observed that the transplanted GFP-positive BMMC migrated into the periportal area of liver lobules after 1 day and repopulated as much as 25 % of the recipient liver by 4 weeks. Interestingly, when mice were administered with BMMC but not carbon tetrachloride, no donor cells could be detected at 4 weeks, indicating that injury must be present for long-term hepatic retention. It appeared that the transplanted BMMC differentiated into functional mature hepatocytes, which would overtake function of hepatocytes from carbon tetrachloride-injured mice (Terai et al. 2003). A subsequent study by the same group examined the mechanisms of the anti-fibrotic and/or regenerative effect of the BMMC and found matrix metalloproteinase (MMP) activation to be involved (Sakaida et al. 2004). MMPs are important in liver regeneration not only because of their ability to cleave through fibrotic tissue in order to alter the local environment but also because of their role in angiogenesis, which is important for liver regeneration (Bellayr et al. 2009; Kawai et al. 2012; Malemud 2006). Interestingly, regression of liver fibrosis by dendritic cells also is mediated through MMP activation (Jiao et al. 2012).

One of the first clinical uses of BMMC in the liver involved purification of CD133-positive cells prior to administration, with the notion that CD133 selects for cells with enhanced regenerative potential (Handgretinger and Kuci 2013). Additionally, the CD133 subset of bone marrow cells may represent a hepatogenic precursor cell since cells of this phenotype are mobilized from the bone marrow subsequent to partial hepatectomy (Gehling et al. 2005; Harb et al. 2009; Zocco et al. 2011). Another interesting point is that CD133 has been reported by some to be expressed on oval cells in the liver, although the bone marrow origin is controversial (Rountree et al. 2007, 2011; Yovchev et al. 2007). In 2005, Esch et al. described 3 patients subjected to intraportal administration of autologous CD133(+) BMMC subsequent to portal venous embolization of right liver segments, used to expand left lateral hepatic segments. Computerized tomography scan volumetry revealed 2.5-fold increased mean proliferation rates of left lateral segments compared with a group of three consecutive patients treated without application of BMMC (am Esch et al. 2005). In 2012, the same group reported on 11 patients treated with this procedure and 11 controls. They found that mean hepatic growth of

segments II/III 14 days after portal vein embolization in the group that received CD133 cells was significantly higher (138.66 mL ± 66.29) when compared with the control group (62.95 mL ± 40.03; $P = 0.004$) (am Esch et al. 2012). Post hoc analysis revealed a better survival for the group that received cells as compared to the control. A similar study by another group involved 6 patients receiving CD133 cells to accelerate left lateral segment regeneration, with 7 matched control patients. The increase of the mean absolute future liver remnant volume (FLRV) in the treated group (from 239.3 mL +/− 103.5 to 417.1 mL +/− 150.4) was significantly higher than that in the control group (from 286.3 mL +/− 77.1 to 395.9 mL +/− 94.1). The daily hepatic growth rate in the treated group (9.5 mL/d +/− 4.3) was significantly higher than in the control group (4.1 mL/d +/− 1.9) ($P = 03$). Furthermore, time to surgery was 27 days +/− 11 in the treated group and 45 days +/− 21 in the control group ($P = 057$) (Furst et al. 2007). These data suggest that in the clinical situation, CD133 cells isolated from BMMC appear to accelerate liver regeneration.

Another purified cell type from BMMC is CD34-expressing cells, which conventionally are known to possess the hematopoietic stem cell compartment (Sidney et al. 2014). Additionally, similar to CD133, CD34 is found on oval cells in the liver, suggesting the possibility that bone marrow-derived CD34 cells play a role in liver regeneration when hepatocyte proliferation is inhibited (Crosby et al. 2001; Theise et al. 2000a). Gordon et al. (2006) reported five patients with liver failure that were treated with isolated CD34-positive cells. Interestingly, instead of collecting the cells from bone marrow harvest, the investigators mobilized the bone marrow cells by treatment with G-CSF. The investigators first demonstrated that these CD34 cells were capable of differentiating in vitro into albumin-producing hepatocyte-like cells. A pilot clinical investigation was attempted in five patients with liver failure. The CD34 cells were injected into the portal vein (three patients) or hepatic artery (two patients). No complications or specific side effects related to the procedure were observed. Three of the five patients showed improvement in serum bilirubin and four of five in serum albumin. A subsequent publication by the same group reported that the improvement in bilirubin levels was maintained for 18 months (Levicar et al. 2008). A subsequent case report by Gasbarrini et al. (Levicar et al. 2008) described the use of autologous $CD34^+$ BMMC administered via the portal vein as a rescue treatment in an alcoholic patient with nimesulide-induced acute liver failure. A liver biopsy performed at 20 days following infusion showed augmentation of hepatocyte replication around necrotic foci; there was also improvement in synthetic liver function within the first 30 days.

Subsequent to the initial studies on CD133 and CD34 cells, investigators assessed the effects of unpurified BMMC on liver failure. Terai et al. (2006) treated 9 patients with liver cirrhosis from a variety of causes with autologous BMMC administered intravenously. Significant improvements in serum albumin levels and total protein were observed at 24 weeks after BMMC therapy. Significantly improved Child–Pugh scores were seen at 4 and 24 weeks. Alpha-fetoprotein and proliferating cell nuclear antigen (PCNA) expression in liver biopsy tissue was significantly elevated after BMMC infusion. No major adverse effects were noted. A subsequent study in alcohol-associated decompensated liver failure examined the effects of autologous BMMC administered intraportally in 28 patients compared to 30 patients receiving standard medical care. After 3 months, two and four patients died in the BMMC and control groups, respectively. Adverse events were equally distributed between groups. The MELD score improved in parallel in both groups during follow-up. Comparing liver biopsy at 4 weeks to baseline, steatosis improved, and proliferating HPC tended to decrease in both groups (Spahr et al. 2013). It is unclear why this larger study generated a negative outcome compared to the initial smaller study. Interestingly, significant improvements were observed in another study in which 32 patients with decompensating liver cirrhosis were treated with autologous BMMC and 15 patients received standard of care. Specifically, improvements in ALT, AST, albumin, bilirubin, and histological score

were observed. The efficacy of BMMC transplantation lasted 3–12 months as compared with the control group. Serious complications such as hepatic encephalopathy and spontaneous bacterial peritonitis were also significantly reduced in BMMC-transfused patients compared with the controls. However, these improvements disappeared in 24 months after transplantation (Bai et al. 2014). It is possible that effects of BMMC are transient in liver failure, lasting less than 12 months. For example, Lyra et al. (2007) reported on ten patients with Child–Pugh B and C liver failure who received autologous BMMC. Bilirubin levels were lower at 1 (2.19 +/− 0.9) and 4 months (2.10 +/− 1.0) after cell transplantation than baseline levels (2.78 +/− 1.2). Albumin levels 4 months after BMMC infusion (3.73 +/− 0.5) were higher than baseline levels (3.47 +/− 0.5). International normalized ratio (INR) decreased from 1.48 (SD = 0.23) to 1.43 (SD = 0.23) 1 month after cell transplantation. A larger study by the same group utilizing similar methodology reported similar transient benefit (Lyra et al. 2010). Specifically, a 30-patient study was conducted with hepatic cirrhosis patients on the transplant list who were randomized to receive BMMC or supportive care. Child–Pugh score improved in the first 90 days in the cell therapy group compared with controls. The MELD score remained stable in the treated group but increased during follow-up in the control group. Albumin levels improved in the treatment arm, whereas they remained stable among controls in the first 90 days. Bilirubin levels increased among controls, whereas they decreased in the therapy arm during the first 60 days; INR RC differences between groups reached up to 10 %. The changes observed did not persist beyond 90 days.

Other means of utilizing bone marrow stem cells for hepatic regeneration include stimulating mobilization of endogenous stem cells by providing agents such as G-CSF. Experimental studies to investigate the mobilization of HSCs for hepatocyte formation have yielded conflicting results (Cantz et al. 2004; Jang et al. 2004, Kanazawa and Verma 2003), but Shitzhu et al. (2012) showed beneficial effects in a murine model of acute liver failure.

Other Stem Cell Types

Several experimental studies have shown that MSC isolated from human placenta promote healing in diseased rat livers, with an anti-fibrotic effect in liver cirrhosis (Lee et al. 2010a) or reduction of fibrotic tissue (Mohsin et al. 2011). By transplanting placenta-derived MSC in the portal vein, Cao et al. observed promising results in pigs, not only by producing hepatocytes but also by prolonging survival time, reducing necrosis, and promoting regeneration (Cao et al. 2012).

Another fetal-associated tissue that has demonstrated to be a potent source of MSC is umbilical cord. Shi et al. (2012) utilized umbilical cord-derived MSC (UC-MSC) administration to treat acute-on-chronic liver failure (ACLF) patients that had HBV infection. Twenty-four patients were treated with UC-MSC, and 19 patients were treated with saline as controls. The UC-MSC transfusions significantly increased the survival rates of the patients; diminished the MELD score; increased the serum albumin, cholinesterase, and prothrombin activity; and increased the platelet counts. Serum total bilirubin and ALT levels were significantly decreased after the UC-MSC administration at 48 and 72 weeks.

Fetal liver cells have been utilized clinically for hematopoietic stem cell transplantation with positive safety data. Given the potent proliferative and regenerative activities of these cells in the hepatic setting, a case report was described of a patient who received intrahepatic administration of these cells. Subsequent to administration, decrease in MELD score, AST, and ALT was reported. At 18-month follow-up, MELD score reduced from 18 to 10 (Gridelli et al. 2012). Khan et al. (2012) showed clinical improvement in end-stage decompensated liver cirrhosis patients after injection of fetal liver cells into the hepatic artery without the use of immunosuppression. At 6-month follow-up, there was a significant decrease in the mean MELD score ($P < 0.01$). At 2-, 4-, and 6-month time points, there was significant improvement in SGOT, ALP, bilirubin, and albumin levels compared to baseline. No hepatic stem cell treatment-related complications were seen during or after the

transplantation. It is interesting to note that in spite of the fact that the number of transplanted cells represented a maximum of 0.2–0.5 % of a normal liver mass, the liver function was enhanced (Khan et al. 2010).

Conclusion

The potent inherent regenerative nature of the liver intuitively suggests applicability of stem cells to conditions associated with dysfunction of this organ. Unfortunately, the complexity of hepatic regeneration leaves more questions than answers. Specifically, there is still debate regarding the extent to which bone marrow contributes to hepatic regeneration and whether processes involved are trans-differentiation, cell fusion, or simply paracrine support. Regardless of mechanisms, clinical trials have demonstrated some signals of efficacy, leaving room for optimization of protocols. Autologous approaches may be limited by the amount of donor material available, as well as poor quality of cells from patients suffering from chronic conditions. The use of allogeneic and younger cells, such as found in umbilical cord MSC and fetal liver, provides possible solutions that need to be assessed in future clinical trials.

Cross-References

- ▶ Finance of Liver Transplantation
- ▶ Fulminant Hepatic Failure: Diagnosis and Management
- ▶ Immunology of Liver Transplantation
- ▶ Minimally Invasive Live Donor Liver Hepatectomy

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Part VIII

Special Topics

Pregnancy After Liver Transplantation 26

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Contents

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Abstract

Pregnancy after liver transplantation has been reported worldwide since the 1980s. This chapter includes a review of the relevant literature regarding pregnancy, maternal and newborn outcomes in this population, and clinical management guidelines for the care of liver transplant recipients before, during, and after pregnancy. After successful liver transplantation, fertility in female liver recipients often resumes quickly and prompt counselling and appropriate contraception should be key components of pre- and post-transplant care. Whenever possible, prepregnancy planning is recommended. If a mycophenolic acid (MPA) product is part of the liver transplant recipient's immunosuppressive regimen, there appears to be increased risks to the fetus and modifying the medication regimen prior to conception should be considered. Close observation of the recipient and monitoring of her medications should continue throughout the pregnancy and postpartum. Although many transplant recipients have reported successful pregnancies after their transplant, these are high-risk pregnancies warranting close collaboration among multiple disciplines to provide the best possible outcome for mother, her graft, and child.

Keywords

Liver transplantation • Pregnancy • Immunosuppression • High-risk • Fetus • Prenatal • Birth defects

Introduction

In the first reported successful pregnancy after liver transplantation in 1977, the recipient delivered a healthy baby at 40.5 weeks, weighing 2,400 g, and doing well at the time of publication (Walcott et al. 1978). There were significant concerns at that time including the effect of transplantation on the pregnancy, potential teratogenic effects of immunosuppressive drugs, and the effect of pregnancy on graft function and survival. Many case and series reports since then have discussed the outcomes of pregnancies in liver transplant recipients and other issues of special interest in this population (Jain et al. 2003; Christopher et al. 2006; Jabiry-Zieniewicz et al. 2011; Armenti et al. 2008; Alvaro et al. 2013; Ramirez et al. 2014). Some of these reports have originated from the National Transplantation Pregnancy Registry (NTPR), one of the largest repositories of data worldwide regarding pregnancy after transplantation, established in the United States to analyze pregnancy outcomes in solid organ transplant recipients and in pregnancies fathered by male transplant recipients (NTPR Annual Report 2014). The majority of publications support the view that pregnancy after liver transplantation is safe if prepregnancy transplant function is stable and MPA products are avoided. This chapter will review the literature on pregnancy after liver transplantation, assessing what is now known that allays some of the early concerns, discussing recommendations about how best to counsel the liver transplant recipient with childbearing potential and her partner, as well as guidelines for antenatal care.

Overview of Immunosuppressive Agents

The vast majority of liver transplant recipients will take immunosuppressive medications throughout their lives including during their pregnancy. Close monitoring of immunosuppressive drug levels during pregnancy is essential due to the physiologic changes of pregnancy, including an increase in plasma volume distribution and alterations in drug metabolism as a result of hormonal changes, adipose tissue deposition, and fetal drug metabolism.

Although the need for immunosuppressive medication(s) during pregnancy must be weighed against the potential effects the medication(s) may have on the developing fetus, the consequences of a liver recipient discontinuing immunosuppression can be dire. It is, however, possible that recipients may be able to switch to different medications that are safer for use in pregnancy. The categories established by the United States Food

and Drug Administration (FDA) to indicate the potential of a drug used during pregnancy to cause birth defects are described below.

Category A – if adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)

Category B – if animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women

Category C – if animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks

Category D – if there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks

Category X – if studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or post-marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit

A description of the most commonly used maintenance immunosuppressive agents with their potential for teratogenicity is as follows.

Prednisone (FDA Category C)

Prednisone in therapeutic dosages poses a minimal risk to the developing fetus. There was not a higher rate of major anomalies in a meta-analysis of women (not transplant recipients) taking oral corticosteroids during the first trimester; however there was a 3.4-fold increase of oral clefts. This is similar to animal reproductive studies (Park-Wyllie et al. 2000). However, later analyses did not show an increase in oral clefts (Oren et al. 2004; Hviid and Mølgaard-Nielson 2011; NTPR Annual Report 2014).

Azathioprine (FDA Category D)

Azathioprine has been used in combination with steroids for the prevention of rejection since the early days of transplantation. Its Category D assignment is based on the higher doses when used as a primary immunosuppressant (often >2 mg/kg/day), prior to the introduction of the calcineurin inhibitors (CNI). Azathioprine at adjunctive doses (i.e., when used with a CNI at doses $< =1$ mg/kg/day) is considered a safe option for maintenance immunosuppressive therapy during pregnancy with respect to teratogenic risk. Originally, in animal studies when administered at doses similar to the human primary immunosuppressant dose of >2 mg/kg/day, teratogenicity of azathioprine was associated with embryonic resorption and/or fetal anomalies and thus was initially and continues to be listed as a Category D agent. Results from the animal studies, however, have not been supported by clinical outcome data. Preterm delivery and fetal growth restriction (FGR) have been noted, but without any predominant structural malformation pattern (Cleary and Kallen 2009). Based on data from the NTPR and other large cohorts, there is neither an increase in the incidence of malformations nor any obvious pattern of malformations among the offspring exposed to azathioprine (Davison et al. 1985; Armenti et al. 1994; Davison 1994; Langagergaard et al. 2007).

Cyclosporine (FDA Category C)

Cyclosporine is a CNI introduced in the 1980s and became the primary immunosuppressant of choice due to lower rates of rejection and increased graft survival, supplanting azathioprine. Although there is a potential risk of FGR, the consensus is that the teratogenic risk of cyclosporine is minimal (Paziana et al. 2013). In animal studies, fetal abnormalities and toxicities were

noted at higher dosages than those in clinical use (Mason et al. 1985). Early reports raised concerns about the safety of cyclosporine use during pregnancy (Pickrell et al. 1989), but clinical data have not demonstrated an increased incidence or pattern of birth defects (Oz et al. 2001; NTPR Annual Report 2014).

Tacrolimus (FDA Category C)

Introduced in the 1990s, tacrolimus, the second CNI, has become the drug of choice for post–liver transplant immunosuppression. Analysis of NTPR data and other large cohorts have not revealed any increase in the incidence of malformations or any specific pattern of malformations among the offspring exposed to tacrolimus (NTPR Annual Report 2014; Kainz et al. 2000). In animal studies, fetal resorptions occurred at tacrolimus doses higher than those in clinical use. However, in a lower dosage group (0.17 mg/kg/day), surviving fetuses appeared no different than controls in mice (Farley et al. 1991).

In a report of nine pregnancies in nine liver recipients with exposure to tacrolimus (Jain et al. 1993), the majority (67 %) of the infants were preterm (<37 week gestation) and had transient hyperkalemia (5 of 9) which resolved without intervention in 24–48 h. Although postpartum maternal graft function was not reported, the authors did conclude that successful outcomes can be anticipated in the majority of pregnancies in liver transplant recipients on tacrolimus.

Two additional articles from the University of Pittsburgh group regarding pregnancy after liver transplantation with exposure to tacrolimus (Jain et al. 1997, 2003) reported a total of 37 recipients delivering 49 infants, whose mean gestational age was 36.4 ± 3.2 weeks and mean birthweight was 2,697 ± 775 g. There were three neonatal deaths: two due to extreme prematurity and one due to birth defects which included tracheoesophageal fistula and cardiac anomalies. Another child had a unilateral cystic kidney and a familial accessory nipple. Twelve recipients had increased liver enzymes (six during pregnancy and six postpartum) which were treated with an increase in maintenance immunosuppression and/or steroid bolus. There were no reports of biopsy proven acute rejection. One mother died 2 days after delivery as her infra-aortic arterial graft became compromised by the gravid uterus during labor and thrombosed. Additionally, three other mothers died 30, 40, and 67 months after delivery; two had a history of non-compliance and the other died from complications of re-transplantation. Of the remaining 33 recipients, one recipient required re-transplantation after two pregnancies for recurrent autoimmune hepatitis and chronic rejection. She received a liver-kidney transplant and subsequently had a third pregnancy. The authors concluded that pregnancy after liver transplantation with tacrolimus was safe and although there were high rates of prematurity and low birthweight infants, the rates of preeclampsia and hypertension during pregnancy appeared to be lower with tacrolimus than with other immunosuppressive medications.

Mycophenolic Acid Products (FDA Category D)

Two oral mycophenolic acid (MPA) products are available, the mofetil ester (MMF) and enteric coated mycophenolate sodium (EC-MPS). Usually MPA products are used in conjunction with a CNI, with or without prednisone. In animal studies, developmental toxicity, malformations, intrauterine death, and intrauterine growth retardation occurred at MPA doses which were within the recommended clinical doses based on body surface area (MMF package insert 2013; EC-MPS package insert 2013). Post-marketing surveillance (not always in transplant recipients) and NTPR data (mostly from kidney recipients) demonstrated that exposure to MPA during pregnancy is associated with an increased incidence of miscarriage and a specific pattern and increased incidence of malformations (18 % compared with 4.2 % of the non-MPA exposed NTPR liver recipient live born and 3–5 % of the general population) (Sifontis et al. 2006). It is recommended that females of childbearing potential use two forms of effective contraception while taking

MPA and that it should be discontinued 6 weeks prior to conceiving. These risks have not been noted in pregnancies fathered by transplant recipients taking MPA (Jones et al. 2013).

When a patient approaches her healthcare provider to plan a pregnancy, strategies such as temporary replacement of MPA with azathioprine along with adding or increasing prednisone should be considered in an attempt to balance the risks to the transplanted liver and the risks to the fetus.

Sirolimus (FDA Category C)

Sirolimus is usually used in conjunction with a CNI. In animal studies, decreased fetal weights and delayed ossification of skeletal structures were reported, but no teratogenicity was noted. When administered in combination with cyclosporine to pregnant animals, there was increased fetal mortality, increased numbers of resorptions, and decreased numbers of live fetuses, suggesting increased toxicity in conjunction with calcineurin inhibition (Sirolimus package insert 2012). A case report from Poland documented sirolimus exposure in a pregnant liver recipient who conceived 3 years post-transplant while taking both sirolimus and prednisone. The pregnancy was diagnosed at 6 weeks and sirolimus was switched to tacrolimus, with a healthy 2,950 g infant with no malformation delivered at 39 weeks. Transplant function remained stable (Jankowska et al. 2004). To date, NTPR data, admittedly limited, have not demonstrated a specific pattern of birth defects (NTPR Annual Report 2014).

Everolimus (Category C)

Everolimus is similar to sirolimus and used in combination with a CNI. Everolimus administration to pregnant rats at 0.1 mg/kg/day before mating through organogenesis resulted in increased preimplantation loss and early fetal resorptions. The area under the curve (AUC) in rats at this dose was approximately one-third that of humans administered the starting clinical dose (0.75 mg twice daily). Everolimus administered at 0.8 mg/kg/day to pregnant rabbits resulted in increased late fetal resorptions, with AUCs slightly lower than humans given the starting clinical dose (Everolimus package insert 2013). No malformations were noted in the two reports of pregnancy exposure to everolimus to date (Veroux et al. 2011; Carta et al. 2012).

Belatacept (FDA category C)

Belatacept was introduced in 2011 and is given via infusion monthly at 5 mg/kg as maintenance immunosuppression in combination with MPA and prednisone. Data regarding human pregnancy exposure are limited but in animal studies, when belatacept was administered to female rats during pregnancy (and throughout the lactation period), it was associated with maternal toxicity (infections) in a small percentage of rats at doses of $\geq$20 mg per kg resulting in increased pup mortality. In pups that survived, there were no abnormalities or malformations at doses up to 200 mg per kg, which is >20 times higher than the human dose (Belatacept package insert 2013). The NTPR reported one exposure to belatacept and MPA during a pregnancy which resulted in an 11-week miscarriage (NTPR Annual Report 2014).

Fertility and Contraception After Liver Transplantation

- Fertility is restored soon after successful transplant
- Appropriate birth control and pregnancy counselling should begin before and continue early after transplant

As nearly half of the women who suffer from chronic liver disease have menstrual abnormalities or amenorrhea with reduced fertility (Nagy et al. 2003), the return of fertility post transplantation is an important discussion point during transplant counselling. In a survey of 209 solid organ transplant recipients (including 59 liver recipients) regarding fertility and contraception,

44 % were not aware pre transplantation that they could become pregnant after their transplant (French et al. 2013). In an early study of 19 liver recipients, 13 (68 %) had return of regular menstrual cycles at a median of 8 weeks post-transplantation (DeKoning and Haagsma 1990). The return of menstrual function in 24 patients with end-stage liver disease who underwent liver transplantation was compared to a control group of 27 healthy women of reproductive age. Only 35 % of recipients reported regular menses 3 months post-transplant, but as liver function improved, this rose to 70 % at 1 year (Jabiry-Zieniewicz et al. 2009). Similarly, earlier studies of liver transplant recipients of child-bearing age noted that nearly 90 % resumed menstrual function ($n = 28$) within 7 months post-transplantation (Cundy et al. 1990), a figure akin to the 87 % eventually recovering menstrual function ($n = 22$) in another study (Parolin et al. 2004).

Thus, the likelihood of rapid return of fertility after liver transplantation makes it essential to have adequate contraception in place, especially in the first post-transplant year (Tepper et al. 2011; Ramirez et al. 2013). One survey found more post-transplant pregnancies were planned than in the general population, which was ascribed to the recipients' health concerns. However, only 50 % of the transplant recipients of child-bearing age who were surveyed were using contraception (French et al. 2013). Due to the increase in reproductive counselling related to the widespread dissemination of information regarding the risks of conceiving while on MPA products, pregnancy planning and contraceptive use among transplant recipients may be on the rise. The safety and efficacy of contraceptive methods for solid organ transplant recipients are rated in the 2010 Centers for Disease Control Prevention Report, based on published case and series reports in the transplant population and inferences from their use in the general population (Curtis 2010).

The most common methods of contraception reportedly used by kidney and liver transplant recipients are barrier methods and tubal ligation (Guazzelli et al. 2008; Xu et al. 2011; Kosola et al. 2012); however, long-acting contraceptives, such as IUDs and the progesterone implant, are effective, remain reversible, and may be the best choice for female transplant recipients. Progesterone-only hormonal contraceptives are considered safe for transplant recipients (Curtis 2010).

It is reasonable to consider estrogen-containing contraceptives for liver transplant recipients with stable graft function and well-controlled hypertension who do not have other contraindications to these formulations, such as thromboembolic risks (Constantinescu et al. 2014). When 15 liver recipients administered low-dose hormonal contraception (nine combined oral contraceptives; six transdermal contraceptive patch) as soon as their liver transplant function was stable (range 6 months to 7 years) were monitored, it was determined that low-dose hormonal contraception was well-tolerated and effective in all of the recipients with no significant changes in general health and graft function (Jabiry-Zieniewicz et al. 2007). The AST consensus conference found no evidence that combined oral contraceptives are associated with adverse consequences among hypertensive transplant patients when hypertension is well-controlled (McKay et al. 2005). Similarly, the theoretic risk that estrogen-containing contraceptives could affect immunosuppressant levels has not been shown to be clinically significant, thus it has been concluded that combined oral contraceptives are suitable for solid organ transplant recipients when they are closely monitored (Estes and Westhoff 2007). Combined oral contraceptives are contraindicated for recipients with a more complicated course (Curtis 2010). No restrictions have been placed on the use of emergency contraception for solid organ transplant recipients (Curtis 2010).

Much of the scanty published data regarding IUD use in solid organ transplant recipients is limited to experience in kidney recipients. In liver recipients with Wilson's disease, copper IUDs are not recommended as they can be associated with increased menstrual bleeding (Constantinescu et al. 2014). The theoretical risks to the use of IUDs in all transplant recipients are the potential for infection and the possible reduction in their efficacy due to interactions with immunosuppressive medications (Zerner et al. 1981;

McKay et al. 2005; Estes and Westhoff 2007). At least two studies have shown no reduction in the efficacy of IUDs due to immunosuppression (Xu et al. 2011; Bahamondes et al. 2011). To date, there are no reports of infection due to IUD usage by liver transplant recipients, with the published data all from kidney recipients. It has been proposed that IUDs can be cautiously recommended in transplant recipients with uncomplicated courses or for those who are maintaining IUDs that were inserted pre-transplantation, but the risks of initiating an IUD in those recipients with a complicated course are probably greater than the advantages, so another contraceptive method should be considered (Curtis 2010).

In transplant recipients desiring a pregnancy where fertility is compromised, there is guidance from limited reports on the use of assisted reproductive techniques (ART) in transplant recipients (Tamaki et al. 2003; Fichez et al. 2008; Nouri et al. 2011; Termini et al. 2011; Wyld et al. 2013; Kennedy et al. 2012). Two reports describe successful pregnancies in liver transplant recipients whose partners had fertility issues. In one case, where conception occurred after controlled ovarian stimulation and intracytoplasmic sperm injection (ICSI) due to oligoasthenoteratospermia in her partner, the recipient experienced preterm labor and delivered a healthy low birthweight baby at 31 weeks (Ulug et al. 2005). In the second case, a successful twin pregnancy in a liver recipient resulted from in vitro fertilization (IVF) with ICSI due to oligozoospermia in her partner, a former kidney recipient who resumed dialysis. Although the mother developed mild preeclampsia and discordant growth of the twins requiring hospitalization, healthy twins were delivered by cesarean section at 34 weeks (Case et al. 2000). This report concluded that ART may be safely considered in a liver transplant recipient provided she has been assessed as physically fit for pregnancy, her immunosuppression carefully reviewed, thrombotic risk screened and an inheritable diseases check undertaken. The couple should also be aware of potential risks associated with pregnancy and the use of ART and appreciate the need for careful evaluation and monitoring from a multidisciplinary team. An NTPR study (Termini et al. 2011) has assessed IVF in transplant recipients including data from three liver recipients who had three pregnancies after IVF, with six pregnancy outcomes (five live births, one miscarriage). The mean gestational age of the five infants was 34 weeks and the mean birthweight was 2,140 g and follow-up revealed all children were healthy and developing well and there were no graft losses in the mothers. Along with the encouraging outcomes in 11 kidney recipients in this NTPR study, these preliminary data support the use of ART following transplantation. Practitioners should be aware that healthy offspring conceived by ART in *any* woman might later display systemic and pulmonary vascular dysfunction (as evidenced by endothelial dysfunction) which does not appear to be related to parental factors but to the ART procedure itself (Scherrer et al. 2012; Rexhaj et al. 2014).

Transplant to Conception Interval (TCI)

- It is recommended that a liver recipient wait at least a year to two years after transplantation before conceiving.

Nagy et al. (2003) reported on 29 women with 38 pregnancies post-liver transplantation where ten of the pregnancies were terminated for worsening liver function and concluded from their analysis that good maternal and neonatal outcomes were much more likely when pregnancy is planned after at least 2 years of stable liver function. Christopher et al. (2006) recommended a TCI of at least 1 year based on their review of 45 recipients with 72 pregnancies, 60 % of whom were on tacrolimus, with a median TCI of 40 months. A comparison between pregnancies conceived less than 12 months with those conceived greater than 12 months after transplant revealed that the only significantly different outcome was rejection during pregnancy (33 % vs. 14 %), prompting the authors to be cautiously optimistic regarding the safety of conceiving within 1 year of transplantation, especially where there is careful monitoring by hepatologists

and obstetricians. In a single center report of eight post-liver transplant pregnancies coupled with a literature review, it was concluded that the TCI and the original cause of liver disease could influence the pregnancy outcome and the incidence and type of complications observed during pregnancy, with the resultant recommendation that liver recipients delay conception for 2–3 years post-transplant (dei Malatesta et al. 2006). Kubo et al. (2014) undertook a statistical analysis of maternal factors and pregnancy complications and outcomes in 38 pregnancies after liver transplantation, demonstrating that complications were more common when conception occurred within 3 years of transplantation, and therefore recommended very close monitoring in such circumstances.

The NTPR has analyzed pregnancy outcomes in liver recipients to explore the relationship between TCI and maternal and offspring outcomes. Liver recipients with a first pregnancy were grouped into four categories: Group 1 (TCI <1 year), Group 2 (TCI 1–2 years), Group 3 (TCI 3–5 years), and Group 4 (TCI >5 years). The outcomes of these pregnancies are detailed in Table 1. Significant differences were noted in the incidences of very low birthweight newborn group 1 or 2 versus 4 ($p < 0.05$), rejection during pregnancy group 2 versus 3 ($p = 0.045$), and graft loss within 2 years of pregnancy group 2 versus 3 ($p = 0.04$). The data do suggest better outcomes for mother and newborn when conception occurred more than 2 years after transplantation (Ramirez et al. 2009). Specifically, the TCI <1 year group had more miscarriages and lower birthweight offspring (without a difference in gestational age).

Pregnancy Outcomes

- The majority of post-liver transplant pregnancies have successful maternal and newborn outcomes.
- These are high-risk pregnancies and close collaboration among specialists is mandatory.
- Comorbid conditions should be monitored and treated appropriately.
- Higher incidences of hypertension and preeclampsia are noted compared to the general population.

The larger series reports of pregnancy outcomes after liver transplantation are summarized in Table 2.

In one of the earliest reports (Scantlebury et al. 1990) of pregnancies post-liver transplantation, 17 liver transplant recipients had 23 pregnancies resulting in 19 live births (one set of

Table 1 NTPR pregnancy outcomes in liver transplant recipients with different transplant to conception intervals

	Group 1	Group 2	Group 3	Group 4
No. of recipients	24	23	41	40
Pregnancies/outcomes[a]	24/24	23/24	41/42	40/40
Mean transplant to conception interval (years)	0.54 ± 0.25	1.36 ± 0.19	3.15 ± 0.84	8.84 ± 3.55
Live births	71 %	71 %	83 %	80 %
Miscarriages	21 %	17 %	12 %	13 %
Terminations	4 %	13 %	2 %	3 %
Stillbirths	4 %	0 %	2 %	5 %
Mean gestational age (weeks)	36 ± 4.3	37 ± 3.7	36 ± 3.8	37 ± 2.4
Mean birthweight (g)	2,254 ± 857	2,664 ± 802	2,651 ± 806	2,716 ± 653
Low birthweight (<2,500 g)	59 %	24 %	31 %	38 %
Very low birthweight (<1,500 g)	29 %	18 %	11 %	0 %
Hypertension during pregnancy	42 %	27 %	37 %	25 %
Preeclampsia	32 %	13 %	29 %	27 %
Rejection during pregnancy	13 %	23 %	5 %	8 %
Graft loss within 2 years of pregnancy	8 %	13 %	0 %	5 %

[a]Includes twins; Group 1 TCI< 1 yr, Group 2 TCI 1–2 yrs, Group 3 TCI 3–5 yrs, Group 4 TCI >5yrs

Table 2 Comparison of pregnancy outcomes in liver transplant recipients

	Recipients (n)	Pregnancies (multiples)	Live births (%)	Mean gestational age (weeks)	Mean birthweight (g)	Pre-eclampsia (%)	Acute rejection (n)
USA[a]							
Scantlebury et al. (1990)	17	20 (23)	87	34	1,980	20	1
Jain et al. (2003)	37	49	[b]	36.4 ± 3.2	2,697 ± 775	Not reported	0
Nagy et al. (2003)	29	38	63	36.4	2,762	20.8	6
NTPR (2014)	206	383 (395)	74	36.6 ± 3.4	2,736 ± 781	22 %	15
UK[a]							
Christopher et al. (2006)	45	71	70	37 (median)	2,690 (median)	13	12
Mohamed-Ahmed et al. (2014)	56	62	92	38 (median)	2,698 (median)	13	1
Japan							
Kubo et al. (2014)	30	38	82	Preterm delivery in 10 infants	12 infants born with low birthweight	Not reported	2
Poland							
Jabiry-Zieniewicz et al. (2011)	36	39 (40)	[b]	37.2 ± 2.2	2,877 ± 633	7.7	3
Spain							
Álvaro et al. (2013)	18	30	67	Not reported	Not reported	15	3
France							
Ville et al. (1993)	19	19	58	38.1 ± 1.5	2,990 ± 370	Not reported	0
Germany							
Wu et al. (1998)	16	22 (23)	[b]	38.1 ± 2.2	2,876 ± 589	13.6	1

[a]Potential overlap of cases
[b]Only reported live births

twins) between 1977 and 1988. The mean gestational age was 34 weeks and the mean birthweight 1,980 g. Delivery by cesarean section was undertaken in 63 %. One recipient had an acute rejection during the third trimester which resolved quickly after delivery. At the time of publication, all of the mothers had adequate graft function save for one recipient who died of lymphoma 2.5 years after delivery. The children were reported healthy at last follow-up. The authors concluded that there was no increased risk due to the physical presence of the fetus, and that despite the increased risks of prematurity and cesarean birth, liver transplantation did not contraindicate childbearing, a conclusion endorsed by later published series (Ville et al. 1993; Wu et al. 1998; Mohammed-Ahmed et al. 2014; NTPR Annual Report 2014). Other reports all agreed (Ville et al. 1993; Wu et al. 1998; Nagy et al. 2003; Christopher et al. 2006; Costa et al. 2011; Zegarac et al. 2012; Jabiry-Zieniewicz et al. 2011) that although high-risk, these pregnancies can be successful, especially if they are planned and managed by a multidisciplinary team.

The NTPR has reported 394 pregnancies in 215 liver transplant recipients, most of whom

Table 3 NTPR pregnancy outcomes in female liver transplant recipients

	CsA-based[b]	Tacrolimus-based[b]
Recipients	93	114
Maternal factors (n = pregnancies)	(176)	(200)
Mean transplant-to-conception interval (years)	6.7 ± 6	6.5 ± 5.5
Hypertension during pregnancy	37 %	19 %
Diabetes during pregnancy	1 %	14 %
Infection during pregnancy	30 %	14 %
Preeclampsia	25 %	20 %
Rejection episode during pregnancy	6 %	6 %
Graft loss within 2 years of delivery	5 %	6 %
Outcomes (n)[a]	(179)	(209)
Terminations	6.1 %	1.4 %
Miscarriages	14.5 %	23.9 %
Ectopic pregnancy	0.6 %	1 %
Stillbirths	1.7 %	1.4 %
Live births	77.1 %	72.2 %
Live births (n)	(138)	(150)
Mean gestational age (weeks)	36.9 ± 3.3	36.1 ± 4.2
Premature (<37 weeks)	36 %	43 %
Mean birthweight (g)	2,714 ± 726	2,757 ± 842
Low birthweight (<2,500 g)	30 %	30 %
Cesarean section	41 %	53 %
Newborn complications	30 %	37 %
Birth defects	6 (4.3 %)	6 (4.0 %)
Neonatal deaths (within 30 days of birth)	1 (1 %)	1 (1 %)

CsA-based regimens (brand name or generic formulations of cyclosporine and cyclosporine, USP modified) and Tacrolimus-based regimens (brand name and generic formulations of tacrolimus and brand name tacrolimus extended release); regimens may include azathioprine or mycophenolic acid products and/or prednisone

[a]Includes multiple births

[b]Mycophenolate exposure during pregnancy: CsA (1 %); Tacro (18 %)

were taking CNI-based immunosuppression during their pregnancy. The features and outcomes of those pregnancies are listed in Table 3. As in earlier reports (Christopher et al. 2006; Alvaro et al. 2013), the newborn outcomes were similar and unrelated to the primary immunosuppressant their mothers took during pregnancy (NTPR Annual Report 2014).

In a small series reporting on five liver transplant recipients with six pregnancies and focusing on maternal hemodynamics during pregnancy, there was one stillbirth and five live births, one of which was delivered at 28 weeks due to FGR and superimposed preeclampsia. All of the pregnancies were complicated by some degree of renal insufficiency most significant in the recipients having the stillbirth and the 28 week delivery; both of them having a hemodynamic shift from low to high peripheral vascular resistance during their pregnancy. Although a longer TCI did not appear to protect the recipients from hypertensive complications of pregnancy, the authors did comment that improved hypertensive control preconception may decrease the risk for preeclampsia and poor obstetric outcome in liver transplant recipients (Carr et al. 2000).

An analysis of NTPR data, comparing two groups of liver transplant recipients for graft loss associations (Table 4), revealed that those who lost their graft within 5 years of delivery were significantly younger at transplantation and at the time of conception. Whilst the proportion of live births was similar in those with and without graft loss, gestational age and birthweight were

Table 4 NTPR comparison of pregnancy outcomes in liver recipients with graft loss less than 5 years versus no graft loss greater than 5 years postpartum

	GL5y	No GL5y	RR	*p* value
No. of recipients	16	145		
Caucasian race	46 %	76 %	0.31	0.04
Viral hepatitis as etiology of liver failure	38 %	16 %	2.7	0.047
Age at transplant	18	23		0.001
Age <18 at transplant	44 %	19 %	2.9	0.03
Transplant-to-conception interval (y)	4.3	4.3		NS
Age at conception	22.3	27.7		0.0001
Diabetes during pregnancy	13 %	6 %		NS
Infection during pregnancy	40 %	23 %		NS
Hypertension during pregnancy	31 %	28 %		NS
Preeclampsia	9 %	28 %		NS
Rejection during pregnancy	40 %	7 %	6.1	0.0001
Rejection within 3 months after pregnancy	44 %	8 %	7.0	0.0002
Rejection during or within 3 months after pregnancy	47 %	12 %	4.3	0.004
Cesarean section	30 %	46 %		NS
Live births	69 %	78 %		NS
Gestational age (week)	33.4	36.6		0.01
Birthweight (g)	1,983	2,694		0.02

RR relative risk, non-percent numbers are mean values; GL5y=graft loss within 5 years of delivery, No GL5y=no graft loss within 5 years of delivery

significantly lower in infants born to mothers who would go on to lose their graft within 5 years of delivery. Importantly, rejection during pregnancy was the strongest risk factor associated with graft loss within 5 years, although younger age at the time of conception was also associated with higher risk of such graft loss (Ramirez et al. 2011).

Pregnancy After Living Donor Liver Transplantation (LDLT)

- Successful pregnancy outcomes have been reported after living donor liver transplantation.

There have been few reports of pregnancy after LDLT. One report (Masuyama et al. 2009) described a LDLT recipient who conceived 3 years post-transplant was on tacrolimus, with severe preeclampsia, necessitating hospitalization at 25 weeks, and then delivery by cesarean section 3 weeks later because of increasing proteinuria and evidence of FGR. Her 769 g infant required artificial ventilation for 48 h, but was healthy and developing well at follow-up. Maternal graft function was stable postpartum with hypertension and proteinuria having resolved.

A review of seven LDLT recipients who reported 14 pregnancy outcomes (four miscarriages and ten live births) to the NTPR revealed that pregnancy after LDLT appeared to be well tolerated with no apparent adverse effects on graft function. Unlike the earlier report, there was no hypertension or preeclampsia (Ramirez et al. 2012). The mean gestational age of the ten live born was 37.7 ± 2.5 weeks and mean birthweight 2,906 ± 494 g. One child with exposure to MPA and born with multiple malformations died at 4 months of age (Jackson et al. 2009). The remaining children, at last follow-up (mean 2.8 ± 2.4 years), were reported healthy and developing well although one had pyloric stenosis surgery at 6 weeks of age. Maternal follow-up at 4.3 ± 3.1 years after delivery revealed six recipients had adequate liver function and one reported reduced function due to recurrent primary sclerosing cholangitis 7 years after pregnancy. The authors noted that initial diagnosis and the potential for recurrent disease, apart from

pregnancy related events, must be factored into pre-pregnancy counseling, with regard to long-term maternal survival for LDLT recipients. Interestingly, a survey of pregnancy outcomes after LDLT from 11 centers in Japan (30 recipients, 38 pregnancies, 31 live births) concluded that pregnancy outcomes of LDLT pregnancies were similar to published reports of deceased donor liver recipient pregnancies (Kubo et al. 2014).

Pregnancy After Pediatric Liver Transplantation

- Successful pregnancies have been reported in recipients transplanted in infancy or adolescence.

Data regarding pregnancy after pediatric liver transplantation are accruing as patient survival rates have soared from a 30 % 2-year survival rate in the pre-CsA era to the nearly 80 % 5-year survival rate for pediatric liver recipients transplanted between 1997 and 2000 (Otte 2002, SRTR accessed 09/02/14). A NTPR review (Ramirez et al. 2010) of 111 pregnancy outcomes in 57 female liver recipients transplanted under the age of 21 with a mean age at transplant of 16.6 ± 4.3 years (range 0.8–20.9 years) revealed 83 (75 %) live births, 16 (14 %) miscarriages (seven exposed to MPA), 9 (8 %) pregnancy terminations, 2 (2 %) stillbirths, and 1 (1 %) ectopic pregnancy. Of the 51 recipients available for maternal follow-up (6.8 ± 4.6 years postpartum), 78 % had adequate graft function, 6 % were experiencing reduced graft function, and 16 % had died. Six recipients (10.5 %) lost their graft within 2 years of delivery. The infants' gestational ages and birthweights were slightly lower than the average for all liver transplant recipient deliveries. There were 5 (6 %) birth defects reported: multiple anomalies $n = 2$ (both infants died; both with MPA exposure), total anomalous pulmonary venous return $n = 1$ (MPA exposure), pyloric stenosis $n = 1$, and hypospadias $n = 1$. The majority of the children were healthy and developing well with a mean age of 5.9 years at last follow-up (Ramirez et al. 2010).

In a review of a subset of pediatric liver transplant recipients, the NTPR analyzed the pregnancy outcomes of 13 women transplanted for biliary atresia (Ramirez et al. 2013). Most were transplanted as young children and had years of immunosuppressive exposure before pregnancy. Eleven (85 %) recipients had undergone a Kasai procedure prior to transplantation. The mean age at first transplant was 9.9 ± 8.6 years, the mean age at conception was 24 ± 4.9 years and the mean TCI was 10 ± 6.1 years. Their pregnancies resulted in 17 live births, one miscarriage (MPA exposure), and one stillbirth (placental abruption; no observed birth defects), with gestational ages and birthweights again slightly lower than the average for all liver transplant recipient deliveries. There was one neonatal death due to multiple malformations (MPA exposure). At last child follow-up (mean 5.4 ± 4.0 years), all 16 children were reported healthy and developing well. At last maternal follow-up (mean 5.7 ± 4.2 years), 11 recipients reported adequate function (three had been retransplanted) and two had reduced function.

Another report documented pregnancy in three liver recipients who had four pregnancies after being transplanted during the pediatric period (Ecevit et al. 2012). There were no pregnancy complications and all delivered live births with gestational ages ranging from 32 to 37 weeks and birthweights from 2,160 to 2,400 g. The health of the mothers and children were excellent 2.25 years postpartum with the authors concluding that pregnancy after liver transplantation can be successful, even in those recipients transplanted at an early age. An additional study with similar results pointed out that as pediatric and adolescent transplant recipients are living much longer, with increased quality of life and personal expectations now including the prospect of having children (Spearman et al. 2011).

One pregnancy in a liver recipient transplanted at age 10 for progressive familial intrahepatic cholestasis, type 1 (PFIC-1) was reported (Cash et al. 2010). Following a complicated course during her teenage years, she conceived approximately 11 years post-transplant while taking tacrolimus, MPA, mesalazine, pancreatin,

prednisolone, and warfarin (for extensive external jugular vein thrombosis). MPA and warfarin were discontinued and low molecular heparin was initiated when her pregnancy was discovered at 10 weeks. Her liver enzymes increased slightly at 13 weeks treated with a prednisolone increase. At 37.6 weeks, she delivered a healthy 2,790 g infant with no malformations. Based on managing this case, the authors concluded that pregnancy can be undertaken in liver transplant recipients with PFIC-1, even with other coexisting conditions.

The literature on successful pregnancies in liver transplant recipients transplanted as children is reassuring. When discussing pregnancy with these women, the potential risks for mother and newborn, inheritable disease conditions, and long-term maternal survival need to be stressed with the recipient and/or the parents of the recipient after pediatric liver transplantation. Studies regarding fertility in this population are certainly warranted.

Pregnancy After Combined Liver/Kidney Transplantation

As of 2013, six liver/kidney recipients had reported post-transplant pregnancies to the NTPR, all of which resulted in live births (nine children, one set of twins). Two of the recipients have died since their child was born – one 4.5 years postpartum of a probable accidental drug overdose with functioning grafts and the other lost kidney function 13 years postpartum and died 6 years later. Of the remaining four recipients, one required a kidney re-transplant 9.8 years postpartum (after four pregnancies) and three others reported stable kidney and liver function at last follow-up. All nine children born to these liver-kidney recipients are reported healthy and developing well at last follow-up (NTPR Annual Report 2014).

Breastfeeding

Although breastfeeding while taking immunosuppressive medications is not recommended on product labelling, some transplant recipients have chosen to breastfeed. In a report on the safety of breastfeeding when taking immunosuppressive medications, 23 liver transplant recipients who participate in the NTPR reported breastfeeding their 29 infants while taking either cyclosporine or tacrolimus. Short-term follow-up of the development and health of these children did not reveal any adverse effects due to breastfeeding (Thiagarajan et al. 2013). Over the years, many studies, which measured levels of prednisone, azathioprine, and cyclosporine in maternal or infant serum and in breast milk samples, showed that the amount ingested via breast milk was much less than that to which the fetus had been exposed in utero. Subsequent studies have found that the level of tacrolimus in infant blood drops quickly after birth and at equivalent rates, whether the baby is breastfed or bottle-fed, a finding that led authors to conclude that transplant recipients should not be discouraged from breastfeeding while on tacrolimus, particularly if monitoring of immunosuppressive content in infant blood and breast milk is available (Bramham et al. 2011, 2013). There is a lack of information regarding breastfeeding on MPA, sirolimus, everolimus, and belatacept, and thus breastfeeding should be avoided while taking these agents. Obviously, long-term studies are warranted, but in the meantime, NTPR and other reports are cautiously optimistic that breastfeeding can be considered safe while taking prednisone, azathioprine, cyclosporine, and tacrolimus (Edelman and Schanler 2012; Thiagarajan et al. 2013; Armenti et al. 2013).

Repetitive Pregnancies After Liver Transplantation

Several case reports describe liver transplant recipients with more than one pregnancy after their transplant (Scantlebury et al. 1990; Jain et al. 2003; Christopher et al. 2006). An NTPR review of 125 liver recipients who had a first pregnancy revealed that 61 had between one and four subsequent pregnancies resulting in 217 subsequent pregnancy outcomes. A comparison analysis between the first pregnancy and subsequent pregnancies demonstrated no

significant differences in newborn outcomes, rejection during pregnancy, and graft loss within 2 years of delivery. From this study, it was concluded that female liver recipients who are not experiencing significant recurrent disease or chronic rejection and wish to have more than one pregnancy need not be discouraged from conceiving again (Schiraldi et al. 2008).

Liver Transplantation During Pregnancy

Reports of successful liver transplantation during pregnancy depict variable pregnancy outcomes. The first described a successful liver transplant at 27 weeks gestation with a subsequent neonatal death (Morris et al. 1989). Other non-viable outcomes after successful liver transplantation during pregnancy have also been reported (Thornton and Minns 2012; Franko et al. 2013). Two recent literature reviews, however, noted successful outcomes for both mother and child were possible with highly specialized multidisciplinary care to manage an often stormy clinical course (Maddukuri et al. 2012; Kimmich et al. 2013). For instance, Jarufe and colleagues (2006) reported delivery of a 900 g baby at 27 weeks gestation in a patient who had fulminant hepatic failure at 22 weeks of pregnancy and had received a liver transplant. On postoperative day 14 (3 weeks prior to delivery), the patient underwent Roux-en-Y biliary reconstruction for biliary stenosis, and on day 19 (2 weeks pre-delivery), acute rejection was diagnosed and treated. Despite these complications both mother and child were reported healthy 1 year later (Jarufe et al. 2006).

There are five NTPR participants who had received liver transplants during their pregnancy (Table 5). Four of these recipients went on to have subsequent live births after their intrapartum transplant pregnancy. All of these recipients maintained their graft function for at least 15 years after they delivered their last baby (Armenti et al. 2000).

Management Guidelines

Although pregnancy is well-tolerated by many liver transplant recipients with the majority resulting in a healthy newborn, these women must be considered a high-risk pregnancy group

Table 5 NTPR cases of intrapartum liver transplant

Case	TCI	Immunosuppression	Rejection during	Infection	Outcomes	Current function
1.	−0.35	CsA, pred	N	CMV-ganciclovir	LB GA 29 weeks[a] BW 1,021 g	Adequate-re-transplant; 22 years follow-up
2.	−0.25	CsA, Aza, pred	Y	Port infection	Stillborn GA 26 weeks	Died 15 years postpartum after second pregnancy
3.	−0.41	Tacro, pred	Y	N	M GA 24 weeks	Adequate-with 2 additional pregnancies; 20 years follow-up
4.	−0.33	CsA, Aza, pred, OKT3	Y	CMV-ganciclovir	LB GA 27 weeks[b] BW 927 g	Adequate- had an additional pregnancy; 20 years follow-up
5.	−0.26	CsA	Y	NA	M GA 16 weeks	Adequate-had an additional pregnancy 18 years follow-up

Abbreviations: *TCI* transplant to conception interval (years), *LB* live birth, *GA* gestational age, *BW* birthweight, *M* miscarriage

[a]Case 1 child healthy, age 25 years

[b]Case 4 child had pyloric stenosis repair and broncho-pulmonary dysplasia. Continues with asthma symptoms at age 20 years

requiring very specialized multidisciplinary team care in a tertiary center, with all the necessary facilities to ensure best outcomes for mother, her child and the graft. The clinical guidelines for pregnancy after solid organ transplantation have been derived primarily from studies of kidney recipient pregnancies, but in large part are applicable to liver transplant recipients. As with all transplant recipients, it is recommended that liver transplant recipients use adequate contraception to defer conception for at least 1–2 years after transplantation and that such "active preparation for pregnancy" should be individualized to each woman's needs and involve her partner (Davison 2006).

There should be prepregnancy assessment of liver function, viral status, vaccination history, management of comorbid conditions, kidney function, as well as a consideration of the etiology of the original liver failure and the potential for any genetic predisposition in the offspring. Medications should be reviewed and adjusted as necessary both before and during pregnancy, including attempting to avoid fetal MPA exposure. Monitoring of liver function and drug levels is recommended at 4-week intervals until 32 weeks gestation, then more frequently until delivery (Zheng et al. 2012; Hebert et al. 2013). Comorbidities, as well as infection and graft dysfunction, should be diagnosed appropriately and treated promptly. Hypertension must be taken seriously with optimization of treatment and careful management in pregnancy because of the threat to the health of the mother and compromise of fetal development (Bramham et al. 2014).

Postpartum, vital concerns include maternal medication adherence, measurement of drug levels and dose adjustments, vigilance for postpartum depression, and counselling regarding contraception and sterilization as appropriate (Parhar et al. 2012; Ramirez et al. 2014). For those mothers who had preeclampsia, continued attention to normalizing blood pressure is important, in light of the long term cardiovascular risks which include a 1.8–3.7 increase in the relative risk of cardiovascular disease (hypertension, ischemic heart disease, stroke, venous thromboembolism) (McDonald et al. 2008; Yinon et al. 2010).

Questions continue to be raised regarding pregnancy after transplantation. Continued reports to registries and to the literature are encouraged in an attempt to provide up-to-date and complete information to counsel recipients. Further information from the NTPR can be obtained by contacting their office by email at NTPR@giftoflifeinsitute.org.

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In Memoriam This manuscript is dedicated to Vincent T. Armenti, MD, PhD (1952–2014), the founder and principal investigator of the NTPR. His guidance and leadership allowed the NTPR to flourish and provide countless transplant recipients with scientific based information from which to base their family planning decisions.

Cross-References

- History of Liver and Other Splanchnic Organ Transplantation
- Immunology of Liver Transplantation
- Liver Transplantation in the Third Millennium in North America: The Strategy for Success
- Orthotopic Liver Transplantation: Complications
- Role of the Transplant Coordinator

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Palliative Care in Liver Transplantation: When to Consult a Specialist

27

Alana Sagin and Nina O'Connor

Contents

Abstract

Palliative care is an important part of the care of patients with serious illness, including patients before and after liver transplant. Specialist level palliative care can aid with advance care planning, coordination of care and communication, pain and symptom management, and psychosocial and spiritual support. Palliative care consultation can take place concurrently with curative and aggressive medical interventions and is not only for patients at the end of life.

Keywords

Palliative care • Hospice • Advance care planning • Advance directive • Opioid • Burnout

Introduction

Palliative care is a medical specialty designed to improve quality of life and relieve suffering for patients with serious illness and their families. Palliative care can be initiated at any time during a serious illness alongside disease-modifying and curative treatments (Fig. 1). This is in contrast to hospice care, a service for patients at the end of life who have chosen to forgo disease-modifying treatment for their terminal illness (Table 1). The National Consensus Project states "Palliative care affirms life by supporting the patient and family's goals for the future, including their hopes for cure or life-prolongation, as well as their hopes for

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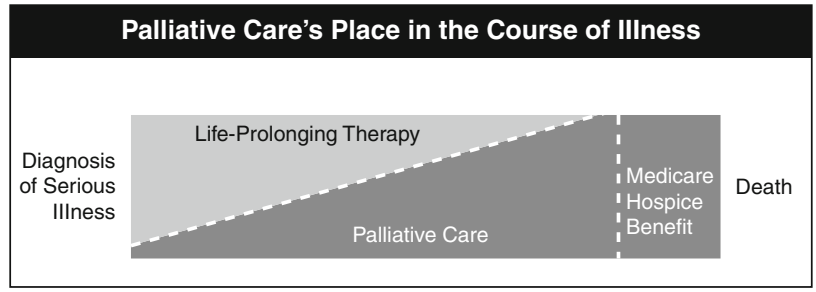

Fig. 1 Palliative care's place in the course of illness (American Academy of Hospice and Palliative Medicine et al. (2004). Reprinted with permission from the National Quality Forum)

Table 1 Comparison of hospice and palliative care

Palliative care	Hospice
A medical specialty that provides interdisciplinary, supportive care for patients with serious illness	A program developed by Medicare to provide comfort care to patients with terminal illness, now available regardless of insurance
Available regardless of prognosis	Must have prognosis of 6 months or less
May continue to receive aggressive care including surgery, chemotherapy, radiation, and transplant. May participate in clinical trials	Must agree with comfort care only. Surgery, chemotherapy, radiation, and transplant generally not available while on hospice

peace and dignity throughout the course of illness, the dying process, and death" (American Academy of Hospice and Palliative Medicine et al. 2004).

The palliative care team functions as an interdisciplinary unit to provide comprehensive care to alleviate a patient's spiritual, social, and psychological suffering as well as pain and other physical symptoms. Surgical patients often struggle with many of these issues and can benefit from palliative care. In a 2005 statement, the American College of Surgeons wrote "The tradition and heritage of surgery emphasize that the control of suffering is of equal importance to the cure of disease. Moreover, by adhering to the standards of professionalism endorsed by the American College of Surgeons, the surgeon is positioned to take a leadership role in advocating for palliative care for all patients" (Task Force on Surgical Palliative Care and Committee on Ethics 2005).

Depending upon the availability of local resources, specialist-level palliative care may be provided in the clinic, in the hospital, or at home. A referral may be helpful to elicit patients and families' goals, to assist with medical decision-making and advance care planning, to provide extra support for patients coping with a serious illness, and to help with difficult pain or symptom management. Because relationship building is an important part of a therapeutic relationship with patients and families, early palliative care referral should be encouraged. The palliative care team is also positioned to provide support for medical providers and staff who cope with the time-consuming and intense work of caring for patients with serious illness on a daily basis. When patients are at the end of life, palliative care providers can help with transitions to hospice care and aid in end-of-life planning and bereavement.

Palliative Care in Liver Transplant Medicine

Palliative care can be helpful at various stages of the transplant process and is currently underused. A recent prospective observational study of palliative care consultation for liver transplant service patients in the surgical intensive care unit demonstrated improved communication and consensus around goals of care. Importantly, palliative care was not associated with any increase in mortality (Lamba et al. 2012). Such integrated interventions and education about palliative care, triggers for palliative care consults, and active case finding are all potential approaches to increase palliative care

services for liver transplant patients (Walling et al. 2015).

Patients waiting for transplant face unique challenges. Health-related quality of life has been shown to be significantly impaired in patients awaiting orthotopic liver transplant (Younossi et al. 2000). While 5,921 liver transplants were performed in the USA in 2013, 1,767 patients died while on the waiting list due to organ shortages (Kim et al. 2015). Patients should be prepared for the possibility that they might not receive an organ or that they might be delisted if their disease progresses and they no longer meet criteria. They also must be prepared for the potentially devastating complications that can occur during or after transplant. It can be difficult to discuss these issues when patients and families are hoping for the long-term survival and improved quality of life that transplant can offer. Palliative care specialists can help facilitate these discussions and introduce a "hope for the best while planning for the worst" approach (Back et al. 2003).

Given the increasing success of liver transplantation, more patients are living for longer periods after transplant. 59,000 patients were living with liver transplants in 2013 (Kim et al. 2015). Quality of life has been shown to improve considerably after liver transplant, and some studies in patients after liver transplant have even found quality of life that approaches that of healthy populations (Karam et al. 2003). However, a 2007 systematic review showed that patients after liver transplant still have significant deficiencies in most quality-of-life domains (Tome et al. 2008). Re-hospitalizations are common in the first few months after transplant, frequently from surgical complications, malnutrition, and infection (Shankar et al. 2011). For these patients, palliative care can offer continued support as they may struggle to adjust their expectations about their health and quality of life.

Palliative care is essential for patients who are ineligible for transplant or do not wish to pursue transplant yet is greatly underused in this population (Poonja et al. 2014). One thousand two hundred twenty-three patients were removed from the liver transplant list in 2013 after becoming too sick to undergo transplant (Kim et al. 2015). Patients who are removed from the waiting list have high symptom burden and may continue to receive aggressive medical interventions despite a poor prognosis. In a retrospective chart review of 102 patients who were removed from the liver transplant list or who declined transplant, median time from denial of transplant to death was 52 days; patients spent a median of 14 days in the hospital. This same study found a high prevalence of pain, nausea, dyspnea, and other bothersome symptoms prior to death (Poonja et al. 2014). Palliative care can assist with symptom management and facilitate transitions to hospice care for this subset of patients.

Hospice care is a program for patients at the end of life that provides medical care and support services. Medicare covers hospice services, as do most other insurance plans, and care frequently occurs at home. Families using home hospice care report higher satisfaction with end-of-life care and fewer unmet needs compared with those experiencing end-of-life care without hospice services (Teno et al. 2004). Patients with liver disease tend to be referred late to hospice care with 22 % dying within 7 days of enrollment (Christakis and Escarce 1996). Though somewhat controversial, a few hospices will enroll patients who are still on the transplant list if they otherwise meet hospice criteria; patients then de-enroll from hospice if they are called for transplant (Rossaro et al. 2004). In one study of 157 patients who were admitted to hospice while still listed for liver transplant, the hospice and transplant teams were able to successfully integrate palliative goals with disease-directed goals. Six of these patients went on to receive a transplant (Medici et al. 2008).

Pain Management

Severe pain is common in patients with advanced liver disease and is comparable to the severity of pain in patients with lung and colon cancer (Roth et al. 2000). In one study, 77 % of liver transplant candidates reported moderate levels of pain in the previous 24 h (Madan et al. 2012). Pain may be due to various causes such as neuropathy, hepatic

capsular stretch, ascites, or arthralgias. After liver transplant patients may experience pain from a variety of causes, such as infection or bleeding. Immunosuppressant therapy may lead to bone pain from osteonecrosis or osteoporosis (Li et al. 2013). Calcineurin-inhibitor-induced pain syndrome, characterized by bony pain and evidence of bone marrow edema on MRI, is theorized to be caused by tacrolimus- or cyclosporine-induced vasoconstriction (Grotz et al. 2001). Compressive peroneal neuropathies have also been described after liver transplant (Singhal et al. 2009). Pain management will depend on the etiology of the pain and a patients' condition at the time of treatment. Adequate pain control can be challenging due to potential side effects of analgesic medications in patients who are at risk for complications such as encephalopathy, nausea, or constipation. History of addiction can pose an added challenge when choosing a pain treatment regimen. Standard approaches to pain need to be modified for patients with end-stage liver disease (ESLD) due to changes in pharmacokinetics and other disease-specific considerations. Further challenges include the lack of guidelines for analgesic use in this population. Because of these barriers, pain is often undertreated for these patients (Imani et al. 2014). However, a limited body of evidence combined with expert opinion can help guide pain management decisions.

Acetaminophen is the preferred analgesic in patients with mild to moderate nocioceptive pain because of its overall safety profile and may be safely used in limited doses for patients with liver dysfunction (Dwyer et al. 2014). Due to the increased half-life of acetaminophen in liver dysfunction, many experts recommend limiting acetaminophen in patients with cirrhosis to total doses of 2–3 g/day. For patients with active alcohol consumption, some experts recommend a dose of 2 mg/day or less, as depletion of glutathione levels in these patients makes them susceptible to increased drug-induced hepatotoxicity (Chandok and Watt 2010). Nonsteroidal anti-inflammatory drugs (NSAIDs) should generally be avoided due to the potential for reduced renal perfusion and antiplatelet effects (Imani et al. 2014). Aspirin and other NSAIDs are associated with GI bleeding and have been associated with first bleeding episode in patients with cirrhosis (De Ledinghen et al. 1999). Furthermore, because NSAIDs are highly protein bound, patients with hypoalbuminemia may also experience increased serum levels and subsequent toxicity (Chandok and Watt 2010).

Patients with more severe pain may require opioid medications (Table 2). Opioids can all cause sedation, constipation, or respiratory depression and can precipitate encephalopathy; patients should be closely monitored during titration of these medications. Tramadol requires metabolism to its active form in the liver and so may not be effective in advanced liver disease; some experts recommend avoiding it entirely in this population (Rhee and Broadbent 2007). Morphine and hydromorphone have increased bioavailability and an increased half-life in patients with cirrhosis and therefore need to be used with caution (Hasselstrom et al. 1990; Dwyer et al. 2014). Codeine, oxycodone, and hydrocodone are metabolized via CYP2d6 enzyme in the liver to their active form and therefore may have decreased efficacy; they also have impaired clearance and can cause drug accumulation and associated side effects (Dwyer et al. 2014). Fentanyl does not have active metabolites, and its half-life is not altered in patients with cirrhosis; it therefore may be better tolerated than other agents; however, it still may require reduced dosing in patients with hypoalbuminemia because it is highly protein bound (Haberer et al. 1982; Chandok and Watt 2010). Methadone also does not have active metabolites but should only be used with expert consultation due to the potential for drug interactions and its pharmacokinetic variability.

In general, when using opioids in patients with liver disease, a useful approach is to start with decreased dosing and increased intervals of administration and to titrate with caution and attention to any side effects such as constipation or encephalopathy (Imani et al. 2014). Avoidance of long-acting formulations of medications may also be recommended (Dwyer et al. 2014). In patients with successful liver transplants, the pharmacokinetics of opioids can be comparable to the pharmacokinetics seen in healthy populations.

Table 2 Opioidsin liver dysfunction

Medication	Normal ½ life	½ life in liver dysfunction	Recommendations for use in liver disease	Suggested starting dose in opioid-naïve patients with liver disease[a]
Fentanyl IV	1–4.4 h	5 h	May be the opioid of choice	25 mcg IV q 4 h PRN
Hydromorphone PO	2.5 h	No data	Reduce dose and frequency	2 mg PO q 6 h PRN
Hydromorphone IV	2.5 h	No data	Reduce dose and frequency	0.2 mg IV q 4 h PRN
Morphine IV	1.7 h	3.4–4.4 h	Reduce dose and frequency	2 mg IV q 4 h PRN
Morphine PO	3.3 h	4.4–6.8 h	Reduce dose and frequency	10 mg PO q 6 h PRN
Oxycodone PO	3.4 h	13.9 h	Reduce dose and frequency	5 mg PO q 6 h PRN
Methadone PO	18.8 h	11.3–35.5 h	Seek expert guidance	Should not be started in opioid-naïve patients
Codeine PO	4–6 h	No data	Avoid use	Avoid use
Tramadol PO	5.1 h	13.3 h	Reduce dose, may be best avoided	25 mg PO q 8 h PRN

References: Tallgren et al. (1997), Sarhill et al. (2001), Rhee and Broadbent (2007), Chandok and Watt (2010), Dwyer et al. (2014)

[a]Clinicians may opt to start lower in patients with encephalopathy, concurrent renal disease, or clinical instability

In a trial involving six patients before and after liver transplant, the metabolism of oxycodone normalized after transplant and was similar to that of healthy adults (Tallgren et al. 1997).

Adjuvant analgesics can be used to treat neuropathic pain. Tricyclic antidepressants, often used as first-line agents for neuropathic pain, may have impaired clearance in patients with cirrhosis and should be up-titrated slowly. Anticonvulsants such as gabapentin and Lyrica are excreted by the kidney and are generally safe for use in patients with liver dysfunction (Dwyer et al. 2014). Other anti-convulsants can also be helpful in neuropathic pain and have varying hepatic clearances.

Symptom Management

Many patients with liver disease awaiting transplant experience symptoms that affect their quality of life. Common non-pain symptoms in liver disease include fatigue, peripheral edema, abdominal distention due to ascites, pruritus, hepatic encephalopathy, and muscle cramps. Symptoms have been found to correlate with disease severity (Kim et al. 2006). Treatment of symptoms should be part of routine medical care in these patients.

Ascites is one of the most common complications of ESLD and can cause significant discomfort. Moderate ascites can be managed with sodium restriction and diuretics, while patients with large amounts of ascites may also require paracentesis. In select patients with recurrent ascites requiring frequent paracentesis, transjugular intrahepatic portosystemic shunting may help to alleviate ascites but can worsen hepatic encephalopathy (European Association for the Study of the Liver 2010). Indwelling peritoneal catheters can be considered but are generally only recommended as a comfort measure for patients at the end of life when the benefits outweigh the risk of infection (Sanchez and Talwalkar 2006).

Hepatic encephalopathy is a debilitating neuropsychiatric syndrome that can be immensely distressing to patients and families. Ranging from mild sleep disturbance to coma, it can be precipitated by constipation, infection, electrolyte imbalances, bleeding, or medications (Sanchez and Talwalkar 2006; European Association for the Study of the Liver 2010). Reversal of the underlying cause is the mainstay of treatment.

Most commonly, nonabsorbable disaccharides such as lactulose are used. Lactulose works by aiding the excretion of ammonia through the GI tract, but high-quality evidence for its use in hepatic encephalopathy is limited. Nonabsorbable oral antibiotics such as rifaximin have also shown benefit (Sanchez and Talwalkar 2006).

Pruritus may be associated with biliary obstruction but is also commonly present in the absence of any obstruction. Factors contributing to pruritus are poorly understood but are likely multifactorial. Endogenous opioids have been suggested to play a role. Rifampin may aid in alleviating symptoms by upregulating the P-450 pathway and increasing the metabolism of endogenous opioids. Rifampin should be used cautiously in patients with ESLD due to its hepatotoxic effects (Sanchez and Talwalkar 2006). Narcotic antagonists such as naltrexone have also been reported to alleviate pruritus but cannot be used in patients receiving opioid medication for pain (Terg et al. 2002). Other cases may respond to antihistamines, and these medications are commonly used due to their relatively low side effect profile. Treatment in the case of biliary obstruction should focus on alleviation of the obstruction if possible. Cholestyramine prevents uptake of bile acids in the terminal ileum and can be helpful. Sertraline has been reported to alleviate cholestatic pruritus in patients with primary biliary cirrhosis (Browning et al. 2003).

Muscle cramps are often overlooked but can be bothersome, may contribute to insomnia, and are highly associated with perception of poor health (Marchesini et al. 2001). The causes of liver disease-related muscle cramps are not entirely understood, but diuretic use may contribute. The presence of muscle cramps has been shown to correlate with severity of liver dysfunction (European Association for the Study of the Liver 2010; Vidot et al. 2014). There is little evidence for optimal treatment of muscle cramping in patients with liver disease, but some benefit has been shown with supplements such as zinc, 1 alpha hydroxyl vitamin D, branched chain amino acids, L-carnitine, and nuiche-shen-qui-wan. Magnesium is often used for this purpose but is yet to be studied for effectiveness (Vidot et al. 2014). Quinine is another drug that is commonly used but has limited evidence (Sanchez and Talwalkar 2006).

Advance Care Planning

One-year mortality rates include 5 % for patients with compensated cirrhosis and 20 % for patients with decompensated cirrhosis (Zipprich et al. 2012). Patients with refractory ascites have a worse prognosis with 50 % 6-month survival (Sanyal et al. 2003). Although survival after liver transplant is greatly improved, the potential for life-threatening complications remains. Given these high mortality rates and risk of complications and hospitalizations, advance care planning should be completed as part of every liver transplant evaluation.

Advance care planning is a process in which a patient's goals, values, and wishes for medical care are discussed. This process may be documented with certain tools or simply noted in the medical record. Advance directives, on the other hand, are formal written documents that outline wishes for care. Examples include a "living will" or designation of a health-care agent.

Advance care planning should occur early, ideally before complications develop, and should take place within the context of the patient's illness and prognosis. Clinicians should normalize advance care planning for patients and explain it as a routine part of the transplant process. Prior to an advance care planning discussion, patients and families need realistic information about prognosis and potential complications, and clinicians should check for understanding. These "breaking-bad-news" conversations may elicit strong emotions, and providers should be prepared to respond in an empathetic manner.

Traditionally, advance care planning has focused on code status and life support. Although specific interventions such as mechanical ventilation or cardiopulmonary resuscitation (CPR) may be discussed, it is often just as helpful to elicit general values, expectations, and concerns, especially during early conversations with healthier patients. As patients get sicker, more specific

scenarios may become important. For instance, patients with severe end-organ failure have poor outcomes after CPR, and discussion of a DNR order may be appropriate. Patients listed for transplant can have DNR status while waiting for an organ if CPR is inconsistent with patient goals (Bramstedt 2008). Health-care agents and potential surrogate decision makers should be involved in these conversations whenever possible, so they can understand the medical issues and the preferences of their loved one.

There are various tools available to facilitate advance care planning conversations and to document care preferences in the form of an advance directive. One of these is the prepareforyourcare.org website, which walks patients through the process of advance care planning (Sudore et al. 2014). Another tool is the Five Wishes, a document which poses questions to patients about their care if they were very ill (Chovan 2007). A completed Five Wishes document is legally acceptable as a living will in most states. For very sick patients with specific preferences about interventions such as cardiopulmonary resuscitation, ventilators, artificial nutrition, or hospitalization, providers can document these wishes as medical orders on a form called Physician Orders for Life-Sustaining Treatment, or POLST (Hickman et al. 2015). POLST forms are recognized in most states and are an expansion of the typical do-not-resuscitate form because they allow more room to document treatment preferences beyond CPR. Transplant teams may have support staff to help with advance care planning, but palliative care consultation can also be useful to facilitate communication and assist patients in balancing hope with prognostic awareness.

Psychosocial and Spiritual Distress

Psychological and social stressors are common in patients with ESLD. 64 % of patients awaiting liver transplant were found to have depression in one study, and depression was independently associated with a higher risk of death while awaiting transplant (Singh et al. 1997). Psychiatric comorbidity has also been associated with relapse of alcoholism after orthotopic liver transplant in patients with a history of alcohol abuse (Rustad et al. 2015). Besides psychiatric illness, patients may be coping with various social stressors. Many patients are unable to work and deal with financial stress. Interpersonal relationships may be affected by changing roles and need for assistance. Patients waiting for a transplant may struggle with the uncertainty of whether they will receive an organ and the very different health outcomes they could be facing. Some patients may struggle with changing self-perception as they cope with serious illness and hope for a cure. Questions of identity, meaning, and purpose are inherently spiritual in nature and may be best attended to by a spiritual counselor.

Hospitalized patients may also deal with challenges intrinsic to their hospitalization. Patients with prolonged ICU stays are at risk for developing post-traumatic stress disorder, as are their family members (Azoulay et al. 2005; Sundararajan et al. 2014). Communication can be difficult if patients are ventilator dependent or have altered mental status. Patients and families may feel frustrated if multiple provider teams or consultants are involved, and good communication can be challenging to achieve.

Palliative care providers often have more time than other medical providers to establish rapport, explore patient and family concerns, and collaborate with multiple care teams. Palliative care teams usually include social workers and chaplains who are well equipped to discuss difficult issues with patients and facilitate communication. Palliative care teams can also help identify patients with psychiatric illness who may need pharmacological treatment or psychiatric consultation.

Caregiver and Medical Team Burnout

Financial and time pressures may be a burden on families as they try to keep up with appointments, keep track of medications, and navigate a complex health-care system and insurance industry. High amounts of care-giving strain are reported both before and after transplant and can impact caregiver mental health and quality of life

(Rodrigue et al. 2011). Caregivers who act as surrogate decision makers for patients who lack decision-making capacity have additional stresses as they make high-stakes decisions for another person.

Burnout is a syndrome with the symptoms of emotional exhaustion, cynicism, and decreased productivity that develops in response to chronic occupational stress (Bianchi et al. 2015). It is common for medical teams caring for sick patients to experience burnout and compassion fatigue. Burnout can lead to psychosomatic complaints, missed workdays, and lower quality of care; early intervention can increase job satisfaction as well as the quality of care for sick patients (Cubrilo-Turek et al. 2006; Kim 2013). For liver transplant teams, burnout may occur when patients have unexpected or poor outcomes or when there are difficult dynamics between team members and patients or family members. By alleviating the perceived suffering of patients through holistic care and symptom management, palliative care providers can also alleviate the secondary suffering of both medical teams and families.

Conclusion

Palliative care is focused on the alleviation of suffering in patients with serious illness. Specialist palliative care can be helpful for patients at various stages of the transplant process and should not be reserved only for patients at the end of life. Palliative care consultation in the SICU does not affect mortality rates for patients on the liver transplant service and improves communication (Lamba et al. 2012). Along with facilitation of advance care planning and medical decision-making, palliative care can offer psychosocial and spiritual support for patients and families, expertise in pain and symptom management, and identification and management of care team burnout. Further research is needed to assess the outcomes of palliative care consultation in liver transplant patients; such research might inspect patient and family satisfaction with care, quality of pain and symptom management, or quality of advance care planning with palliative care intervention.

Cross-References

- ▶ Fulminant Hepatic Failure: Diagnosis and Management
- ▶ Liver Transplantation: Medical Home
- ▶ Orthotopic Liver Transplantation: Complications
- ▶ Role of Integrative Medicine in Liver Transplantation
- ▶ Role of the Transplant Coordinator

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Artificial Liver Treatment: When and Which One?

28

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Abstract

Patients awaiting liver transplantation often are in critical condition with multi-organ failure accompanying the underlying liver disease. Stabilization and safe bridging of the patient to transplantation is a major indication for liver support methods. Various extracorporeal technologies have been tested clinically since the late 1950s. Currently, methods are divided into artificial, or nonbiological, systems based mainly on filtration and adsorption techniques and biological methods employing liver cells, typically of human, sometimes of animal origin. Examples of currently used liver support methods are the molecular adsorbent recirculating system (MARS) as an artificial system and the extracorporeal liver assist device (ELAD) as a biological liver-cell bioreactor. However, a considerable number of other approaches have been studied before or are currently under investigation. As of today, the best clinical experience exists for the MARS system.

Liver support treatment should be considered early in the course of liver failure. Stabilization of various organ functions including circulatory, hepatic, and renal function, improvement of hepatic encephalopathy, and reduction of elevated intracranial pressure were observed in clinical studies. Modern extracorporeal liver support methods are safe to perform and a valuable addition to the therapeutic armamentarium of liver failure care.

Keywords

Albumin dialysis • Artificial liver • Bridging methods • Detoxification • ELAD • Extracorporeal liver support • Hepatic encephalopathy • Hepatorenal syndrome • Hyperdynamic hypotension • Intracranial pressure • Liver-cell bioreactors • Liver dialysis • Liver support methods • MARS • Multiorgan failure • Transplant-free survival

Introduction

The rationale for an "artificial liver" is obvious in cases of life-threatening failure of the patient's liver. Treatment objectives are the bridging to regeneration of the failing organ or to successful liver transplantation. These aims are not different from initial hopes linked to "artificial kidney" devices that today, more than 50 years after their introduction into therapeutic medicine, form a standard therapy both in the treatment of acute and chronic kidney failure. However, while renal replacement therapies today undoubtedly are a mainstay of organ support medicine, liver support techniques are still in a finding phase with more questions than answers. While the rationale is quite clear and an alternative therapeutic approach to stabilize liver function – except for liver transplantation – is not in sight, we are still lacking sufficient definitions of suitable clinical indications and treatment conditions for various forms of liver failure. Current liver support devices have proven efficacy in the detoxification of various liver failure toxins and the stabilization of different single organ functions that are typically impaired during liver failure, such as circulatory, renal, neurological, and liver function. However, the general assumption is that the validity of liver support devices must be determined by its capability to improve patient survival. This is quite different from, e.g., renal replacement therapies.

The various liver support systems currently in use and all those that have been tested throughout the last 50 years represent a wide range of rather different technologies. Efforts started with renal replacement techniques. Moreover, whole blood and plasma exchange, various hemo- and plasma-adsorption approaches mainly with charcoal and resin columns, and finally biological tissues and cells as whole-liver perfusion, liver slices, and liver-cell bioreactors were applied (Naruse et al. 2007).

The initial intention was to detoxify the patient's plasma. Inspired by the first successes of kidney dialysis, people tried to use hemodialysis and hemofiltration for the removal of liver failure

toxins. We know today that some of the water-soluble liver toxins, such as ammonia, lactate, or aromatic amino acids, are accessible by dialysis and filtration. However, only efficient dialysis techniques with high blood and dialysate/filtrate flow rates reach sufficient clearances for these substances (Slack et al. 2014). Even more importantly, the majority of liver toxins cannot be removed by standard dialysis and filtration, because they are hydrophobic and therefore bound to proteins that are not dialyzable (Please see list below).

Endogenous substrates accumulating in the plasma of liver failure patients. The majority of these potential liver failure toxins are poorly solve in water soluble and are protein bound. Human serum albumin is the most important transport protein for liver failure toxins:

- Water-soluble substances
- Ammonia
- Aromatic amino acids
- Lactate
- Albumin-bound substances
- Benzodiazepinet-like substances
- Bile acids
- Bilirubin
- Diazepam
- Digoxin-like substances
- Indols
- Middle- and short-chain fatty acids
- Nitric oxide
- Phenols
- Prostacyclins
- Thiols
- Tryptophan

Another approach to the field is that of the bioartificial liver. Here the basic assumption is that by using viable hepatocytes or liver tissue, a whole range of liver functions can be replaced, including detoxification, regulation, and protein synthesis. Best clinical evidence stems from the use of cell bioreactors, while whole-liver perfusions or liver-slice perfusions were not followed beyond initial clinical trials. Human and porcine cells were most frequently used for cell devices (Millis et al. 2002; Demetriou et al. 2004). Clinical application of the systems typically appeared to be safe. However, until today, there is no sufficient proof of efficacy, including protein synthesis, organ stabilization, and impact on survival (Wertheim et al. 2012).

A major innovation was the introduction of albumin dialysis in the mid-1990s. The molecular adsorbent recirculating system (MARS) was the first technique combining regular dialysis and adsorption with the use of human serum albumin as a toxin carrier between patient's blood and remotely placed adsorbent columns (Mitzner et al. 2001). Since its introduction, the field of liver support experiences an unprecedented boom with hundreds of preclinical and clinical reports available today and several modifications and further technological advancements being in experimental use. This chapter summarizes currently used liver support systems, their capabilities to remove liver failure toxins and impact on liver and other organ functions, as well as patient survival. Potential clinical indications are reviewed and practical tips for their usage given. The chapter closes with a discussion of future aspects and trends.

Liver Support Methods: Current Status

Currently, three different approaches to extracorporeal liver support are in clinical use: (a) albumin-cleansing methods, i.e., among others the MARS system; (b) therapeutic plasma exchange, mainly with fresh frozen plasma as a substitution fluid; and (c) bioartificial systems, i.e., mainly the ELAD system.

Albumin-Cleansing Methods

MARS

Most of the protein-bound liver failure toxins use human serum albumin as a carrier protein. Albumin-cleansing methods are based on the observation that albumin-bound substances can be dialyzed through a regular dialysis membrane

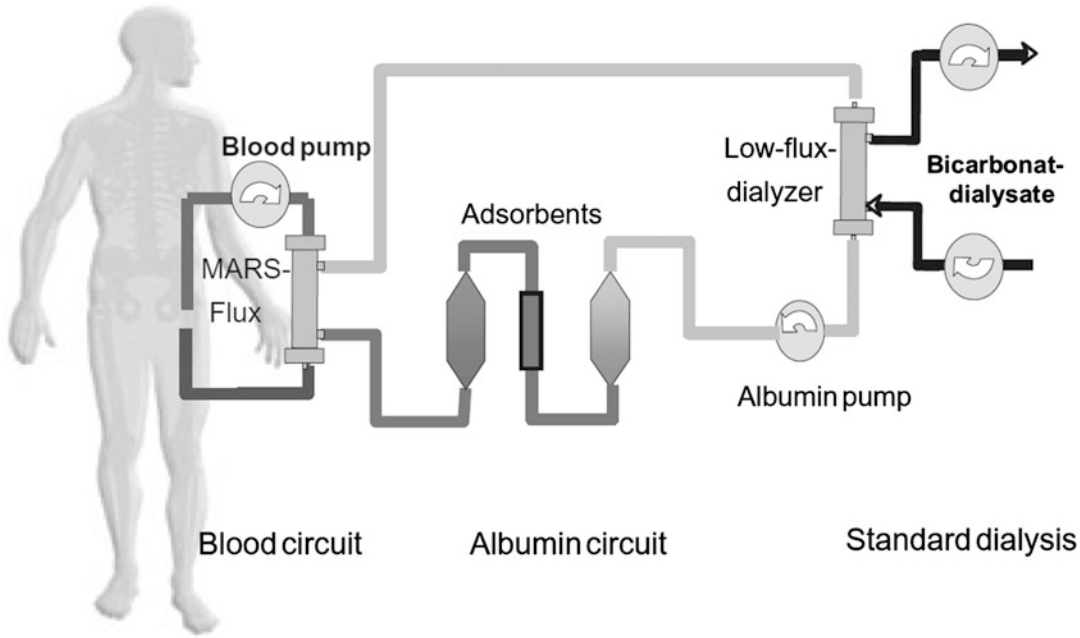

Fig. 1 The molecular adsorbent recirculating system (MARS) consists of a blood circuit, an albumin circuit, and a dialysate/filtrate side (With permission, modified from Mitzner et al. 2006)

if the dialysate contains albumin as a molecular acceptor. To use a more selective membrane with regard to protein passage instead of an open-porous unselective plasma filter might be advantageous with regard to retention of valuable molecules such as hepatocyte growth factor, antithrombin, and others. This approach prolonged survival in an animal model of acute liver failure (Ho et al. 2002). Albumin dialysis was the first membrane-based liver support that allowed maintaining the selectivity of a regular dialysis procedure and the effective removal of even strongly albumin-bound toxins. Two modes of albumin dialysis are available today: MARS and single-pass albumin dialysis (SPAD) (Mitzner et al. 2006).

MARS has been available for broad clinical use since 1998. It is the best-studied liver support method at present time. It comprises a hemodialysis with a high flux membrane permitting passage of albumin-bound toxins and an albumin-enriched dialysate (typically consisting of 15–20 % albumin). This albumin dialysate is online regenerated by passage through a second dialyzer and two adsorber columns (charcoal and anion exchanger). Blood flow is between 150 and 350 ml/min and dialysate flow up to 500 ml/min. The interposed albumin circuit can be run with 100–200 ml/min (Fig. 1). Treatment times are between six and eight hours. Continuous use is possible and was suggested as being effective, especially in bridging patients to transplantation (Kantola et al. 2011).

SPAD

SPAD employs the same blood membrane exchange mechanism as MARS but uses the albumin-containing dialysate in a single-pass mode. This allows for a technical simplification of the system if compared to MARS. On the other hand, for cost reasons the dialysate-albumin concentration needs to be kept low in the range between 1 % and 5 %. Typically, SPAD is used with low blood and dialysate flow rates, comparable to those used in continuous veno-venous hemodialysis or hemodiafiltration (Mitzner et al. 2006) (Fig. 2).

Prometheus

The Prometheus system (also fractionated plasma separation and adsorption, FPSA) consists of the AlbuFlow membrane that allows the passage of a

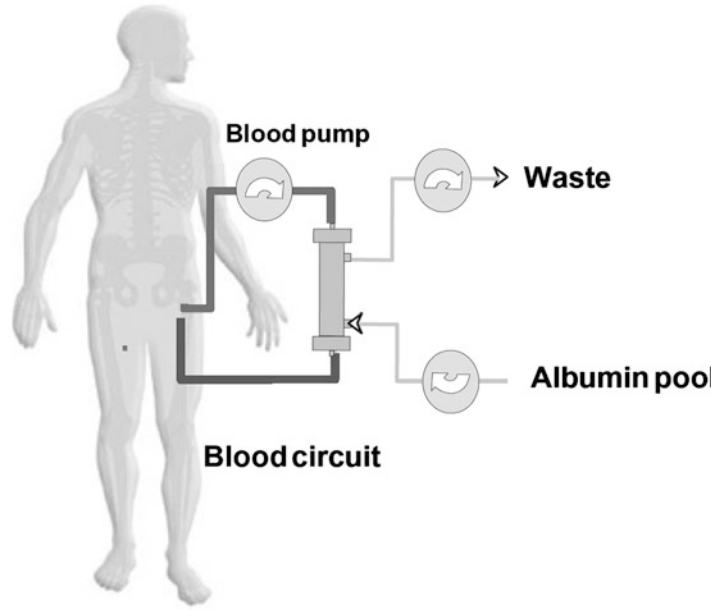

Fig. 2 The single-pass albumin dialysis (SPAD) consists of a hemodialysis setup with an albumin-containing dialysate (With permission, modified from Mitzner et al. 2006)

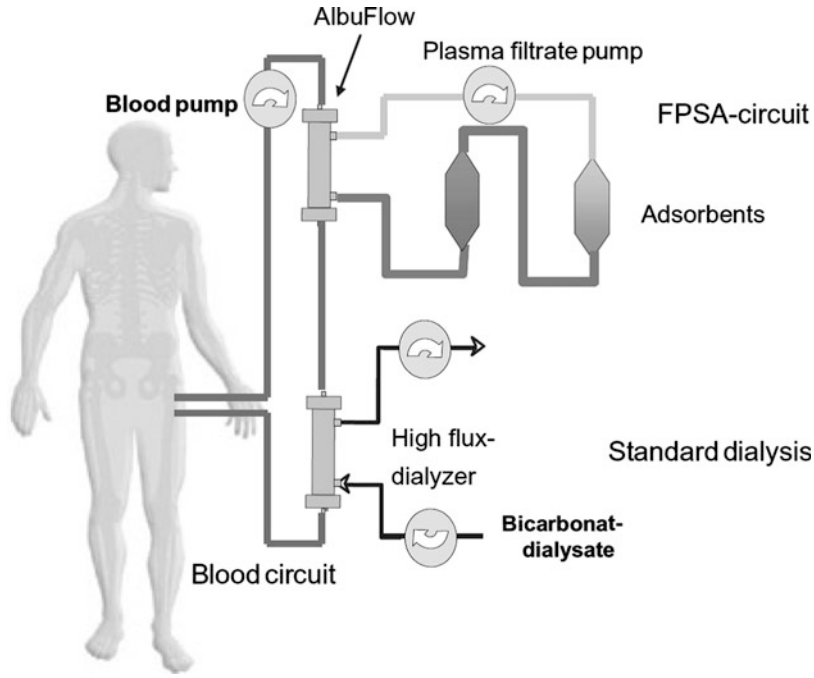

Fig. 3 The Prometheus system consists of a fractionated plasma separation and adsorption (FPSA) unit and a regular hemodialysis unit (With permission, modified from Mitzner et al. 2006)

plasma fraction containing patients' albumin. This fraction is passed over two sorbent columns (a neutral resin and an anion exchanger) to achieve removal of albumin-bound toxins from the albumin. The plasma fraction is then passed back to the blood circuit. The whole blood is then dialyzed while passed through a high flux dialyzer and returned to the patient (Fig. 3) (Falkenhagen et al. 1999; Rifai 2011). The preferred treatment time is approximately 6 h. However, technically longer treatments are possible and were clinically used at least in single cases. The flow rates used

are 150–300 mL/min blood flow depending on the hemodynamic status of individual patients, 300 mL/min FPSA circuit flow rate, and 500 mL/min dialysate flow rate (Mitzner et al. 2006).

Various anticoagulants can be used for all three albumin-cleansing methods. However, typically best clinical performance is reached with citrate.

Therapeutic Plasma Exchange (TPE)

TPE is based on filter or centrifuge separation of patient's plasma with 1:1 volume exchange with either fresh frozen plasma (FFP) or, e.g., a Ringer-lactate solution containing 5 % human albumin. Advantages are the instant availability and easy technical performance. Potential disadvantages are allergic reactions against FFP. Exchange against FFP can help stabilize the coagulation situation of patients with a high risk of bleeding (Stenbøg et al. 2013).

Liver-Cell Bioreactors

These devices utilize hepatocytes from animal or human sources. The most developed systems that have been tested clinically so far are the HepatAssist and the extracorporeal liver assist device (ELAD). The HepatAssist that is not any longer in clinical use utilized a two-step approach consisting of plasma separation and charcoal perfusion followed by perfusion of the plasma through a cell module with porcine hepatocytes immobilized on the outside of a plasma separator membrane. ELAD uses a selective plasma filtration with passage of the resulting plasma fraction through a hollow fiber module carrying up to 450 g of human C3A-hepatoblastoma cells placed on the outside of the hollow fibers (Wertheim et al. 2012).

Clearance of Liver Failure Toxins

Many substances accumulate in the plasma during the course of liver failure. If they can be linked to the development, maintenance, or further aggravation of liver failure, they qualify as "liver failure toxins". One of the key advantages of liver support methods over renal dialysis techniques is that the pattern of harmful substances that can be removed from blood is much broader. Especially a significant removal of albumin-bound metabolites and drugs that accumulate in liver or kidney failure, enzyme defects such as protoporphyria, or drug overdose belongs to this pattern. Substances that are bound to serum albumin and exert damaging effects in higher concentrations are termed albumin-bound toxins (ABT). Rather different groups of biochemicals belong to this group, including steroid acids (e.g., bile acids), open and closed tetrapyrroles (e.g., bilirubin or protoporphyrin), amino acids (especially aromatic amino acids), glycoside derivatives (e.g., indoxyl sulfate), phenols (e.g., para-cresol), lipids (short- and medium-chain fatty acids such as octanoate), and heterocyclic organic compounds (such as furancarboxylic acid). For MARS the range of clearances for ABT was found to be in between 10 and 60 ml/min (Mitzner et al. 2001). Moreover, albumin-cleansing methods allow for removal of water-soluble and thus dialyzable substances such as smaller proteins (e.g., cytokines like interleukin-6 or tumor necrosis factor alpha), ammonia, creatinine, or urea (Gaspari et al. 2006; Stefoni et al. 2006; Yuan et al. 2006; Nadalin et al. 2007; Novelli et al. 2005; Heemann et al. 2002; Lisboa et al. 2012).

The clinical relevance of ABT removal was investigated in detail in a number of animal and clinical trials. Plasmatic nitric oxide (NO), bound to albumin as a nitrosothiol, is responsible for the typical hemodynamic changes of liver failure (hyperdynamic hypotension). NO removal by MARS was demonstrated in several clinical investigations (Guo et al. 2003; Sen et al. 2004a; Kurtovic et al. 2004; Laleman et al. 2006). Capability to remove inducers of hepatic encephalopathy such as ammonia, tryptophan, and endogenous benzodiazepines renders albumin dialysis a valuable tool for this major complication of liver failure (Mitzner et al. 2001; Parés et al. 2009; Donati et al. 2014; Rustom et al. 2014). The Fisher index as the ratio of branched-chain and aromatic amino acids is increasing during MARS treatments (Mitzner et al. 2001; Parés et al. 2009;

Rustom 2014). A constant finding is the removal of bilirubin and bile acids (Huang et al. 2012; Lisboa et al. 2012; Cisneros-Garza et al. 2014; Donati et al. 2014; Rustom et al. 2014). Both fractions the conjugated and, to a lesser extent, the unconjugated bilirubin are removed (Mitzner et al. 2001; Donati et al. 2014). It was found that MARS changes the plasma bile acid composition toward hydrophilic bile acids (Stadlbauer et al. 2007). Moreover, significant clearance of proinflammatory and anti-inflammatory cytokines was observed (Guo et al. 2003; Kurtovic et al. 2004; Auth et al. 2005; Di Campli et al. 2005; Isoniemi et al. 2005; Yuan et al. 2006). However, this did not always result in decrease of blood cytokine levels (Sen et al. 2004a; Ilonen et al. 2006; Stadlbauer et al. 2006). MARS removes copper in the setting of acute Wilson's disease (Mitzner et al. 2001; Rustom et al. 2014). A probably very important effect of albumin dialysis is an increase of the binding capacity of patient's albumin. In a group of patients with acute decompensation on top of chronic liver failure (AoCLF), the median binding capacity was 63 % (compared with healthy controls 98 %, $p < 0.001$). MARS treatments resulted in a significant increase (Klammt et al. 2007, 2008). The impact of this effect remains to be investigated. However, better drug-binding capacity and internal clearance of ABT can be assumed.

Data situation regarding clearance performance of Prometheus, SPAD, and TPE is less complete than for MARS. SPAD removes, among others, bilirubin and copper (Kreymann et al. 1999). Prometheus has proven effect on ammonia, bilirubin, and bile acids (Rifai et al. 2006; Kribben et al. 2011; Krisper et al. 2011). TPE, by definition, can remove virtually every plasma compound. However, the clinical effect is limited by the typically short treatment times. Clinical reports describe among others lowering of ammonia, copper, various exogenous toxins, and drugs (Hilal and Morehead 2014; Stenbøg et al. 2013; Ye et al. 2014).

There is scare data for substance clearances during cell bioreactor treatments. However, removal of bile acids and, to a lesser extent, bilirubin was reported for the HepatAssist system (Krisper et al. 2011; Demetriou et al. 2004).

Indications

Circulatory Failure and Organ Malperfusion in Liver Failure

A key indication for MARS is the improvement of the hemodynamic situation both in acute liver failure (ALF) and in AoCLF. Systemic vascular resistance index (SVRI) increases during MARS treatments (Mitzner et al. 2001; Catalina et al. 2003; Laleman et al. 2006; Yuan et al. 2006). In patients with arterial hypotension, this results in an increase in mean arterial pressure (MAP) (Mitzner et al. 2001; Catalina et al. 2003; Hetz et al. 2006; Laleman et al. 2006; Stefoni et al. 2006). In ALF, Schmidt et al. (2003) found significant increases of SVRI and MAP, resulting in significant decrease of cardiac index and heart rate. In AoCLF patients, the circulatory improvement in the MARS group was paralleled by a decrease in plasma renin activity ($P < 0.05$), aldosterone ($P < 0.03$), norepinephrine ($P < 0.05$), vasopressin ($P = 0.005$), and nitrate/nitrite levels ($P < 0.02$) (Laleman et al. 2006).

The blood perfusion of single organs improved during MARS treatments considerably. A central phenomenon is the decrease of portal pressure in AoCLF (Catalina et al. 2003; Sen et al. 2005) and the improvement of renal blood flow (Mitzner et al. 2001). Increased cerebral perfusion pressure was described in AoCLF (Mitzner et al. 2002). The plasma clearance of indocyanine green increased significantly after MARS treatment (Hetz et al. 2006).

The impact of Prometheus treatments on the improvement of hemodynamics seems to be limited (Laleman et al. 2006; Dethloff et al. 2008).

For TPE, there are reports of improved hemodynamics in ALF patients in the context of high-volume plasmapheresis (mean exchange volume 8.6 l) (Clemmesen et al. 1997). Others could not reproduce the findings with normal-volume plasma exchange (mean exchange volume 3.0 l) (Wiersema et al. 2015). This might hint at the importance of sufficient exchange volume and/or longer treatment times.

The authors are not aware of reports regarding hemodynamic changes during the use of liver-cell bioreactors.

Hepatic Encephalopathy and Cerebral Edema

Hepatic encephalopathy (HE) is a major complication of both chronic and acute liver failure. MARS can improve HE grade and Glasgow Coma Scale (for review, see Mitzner et al. 2002). A multicenter randomized clinical trial studying MARS in 70 AoCLF patients with HE grades III and IV showed significant advantages of MARS versus standard therapy with regard to time to improve and grade of improvement (Hassanein et al. 2007). This was confirmed by other randomized clinical trials (Sen et al. 2004a; Huang et al. 2012; Banares et al. 2013), in several case series (Heemann et al. 2002; Gaspari et al. 2006; Hetz et al. 2006; Stefoni et al. 2006; Yuan et al. 2006; Camus et al. 2009; Parés et al. 2009; Cisneros-Garza et al. 2014), and a meta-analysis (Vaid et al. 2012). Generally, MARS is regarded as a valuable treatment option for HE (Kobashi-Margáin et al. 2011; Leise et al. 2014).

There exist single case reports on positive impact on HE with SPAD (Kreymann 1999) and TPE (Liu 2013; Stenbog 2013). The authors are unaware of significant improvements reported for Prometheus or cell bioreactor treatments.

A drop in intracranial pressure (ICP) during clinical use of MARS was reported by different groups (Mitzner et al. 2001). No randomized clinical trial has investigated this phenomenon so far. However, in a controlled animal study using an ALF-pig model based on devascularization of the liver, MARS, initiated two hours after clamping, significantly attenuated the ICP increase. The MARS group had a significantly lower brain water content and brain ammonia concentration (Sen et al. 2006). Similar results from an animal model of increased ICP were obtained for Prometheus (Ryska et al. 2012). No reports were found for impact on ICP by SPAD, TPE, or cell bioreactors.

Kidney Dysfunction/Hepatorenal Syndrome

Several groups reported improvement of kidney function during MARS treatments. This included decrease in creatinine and urea, increase in urine output, and resolution of HRS (Mitzner et al. 2001; Heemann et al. 2002; Saich et al. 2005; Hetz et al. 2006). In a recent study, of 32 HRS type 1 patients, 13 (40 %) had improved renal function. Among these, nine (28 %) had complete renal recovery. The 28-day survival rate was 47 % (Lavayssière et al. 2013). The positive impact on renal function in HRS type 1 was confirmed in a controlled randomized trial (Mitzner et al. 2000). A possible mode of action is improvement of renal blood flow with subsequent reuptake of organ function (Mitzner et al. 2001). A significant decrease in plasma renin was found in HRS patients treated with MARS that might reflect improved renal blood perfusion (Schmidt et al. 2001; Catalina et al. 2003; Laleman et al. 2006). However, positive effects on kidney function will be most likely if therapy is initiated prior to irreversible ischemic damage to the organs (Wong et al. 2010). MARS is considered as a valuable treatment option for HRS (Cárdenas and Ginès 2006; Moreau and Lebrec 2007).

There are case reports suggesting efficacy of TPE for HRS (Hilal and Morehead 2014; Yu et al. 2014). For all other liver support methods, no clear signals with regard to impact on HRS are available.

Drug Overdose/Intoxication

Accidental or suicidal drug overdose resulting in life-threatening intoxications represents an indication for MARS. The therapeutic goal is either secondary drug removal, if the drug in question is albumin bound and present in the blood circulation, or, more frequently, to treat drug-induced liver failure (for review, see Wittebole and Hantson 2011). Intoxications and liver failure cases induced by various drugs, e.g., acetaminophen or natural toxins, such as amanita toxin, were

successfully treated (Koivusalo et al. 2005; Braun et al. 2006; Pichon et al. 2006; Lee et al. 2005; Sorodoc et al. 2010; Swarnalatha et al. 2013) (Please see list below).

Use of MARS in drug overdose and poisoning caused by various drugs, toxins, chemicals, and other substances (for review, see Wittebole 2011; Mitzner et al. 2001, 2002; Prokurat et al. 2002; Lee et al. 2005; Braun et al. 2006; Pichon et al. 2006; Sorodoc et al. 2010; Swarnalatha et al. 2013; Rustom et al. 2014):

- Acetaminophen/paracetamol
- Amanita phalloides
- Allopurinol
- Amphetamines
- Benzodiazepine-like substances
- Calcium channel blockers
- Chromium
- Copper
- Diazepam
- Diet pills
- Diltiazem
- Disulfiram
- Fentanyl (In animal experiments (Sen et al. 2004b))
- Halothane
- Herbal medicines (Compare Lee et al. 2005)
- Lamotrigine
- Marijuana
- Methylene bis(thiocyanate)
- Midazolam (In animal experiments (Sen et al. 2004b))
- Nimesulide
- Phenytoin
- Theophylline
- Tuberculostatics

With regard to unintended drug removal, there were case reports of relevant removal of piperacillin/tazobactam (Ruggero et al. 2013) and of moxifloxacin and meropenem in an in vitro model (Roth et al. 2013). Only mild impact was found on amphotericin B formulations (Weiler et al. 2011), while no impact on tacrolimus plasma levels was observed (Personett et al. 2014). Accordingly, dose adjustments of affected drugs may be required.

Prometheus was found to be effective in case series of mushroom and ecstasy/cocaine poisonings (Vardar et al. 2010; Kramer et al. 2003). For TPE two cases of drug-induced liver injury following multiple antibiotics and tuberculostatic therapy showed positive results (Liu et al. 2013).

Hepatic Pruritus

Patients with unbearable pruritus resistant to medical therapy respond well to MARS treatments. Underlying liver diseases were cholestatic forms of liver disease such as PBC or primary sclerosing cholangitis as well as chronic viral hepatitis. Typically, two single treatments lowered pruritus impressively as was documented by visual analog scale. The relief lasted between several weeks up to 3 months. However, a number of cases did not respond (Saich et al. 2005; Bellmann et al. 2004; Gaspari et al. 2006; Montero et al. 2006; Parés et al. 2010). MARS was found to be effective as a repeated outpatient treatment (Leckie et al. 2012). It appeared to be safe and effective in children with repeated long-term uses in cases of cholestatic pruritus (Schaefer et al. 2012). The positive clinical effect of MARS on pruritus cannot be explained fully today. However, selective removal of hydrophobic bile acids leading to a longer-lasting shift in the bile acid pattern of the patients was suspected to be a potential mechanism (Stadlbauer et al. 2007; Parés et al. 2010). Protein analysis from MARS column posttreatment revealed a specific removal pattern that might hint at pathophysiologically new traces regarding the cause of hepatic pruritus (Gay et al. 2011). Gene profiling microarray analysis of cytokines revealed the development of an anti-inflammatory pattern resulting from MARS (Lisboa et al. 2012).

Also for the Prometheus system, effective treatment of hepatic pruritus was reported (Rifai et al. 2006). No reports were found describing clinical use of SPAD or cell bioreactors for hepatic pruritus.

Ischemic Hepatitis

Hypoxic situations resulting in ischemic liver failure have been treated with MARS in the context of cardiogenic shock with low-output failure (El Banayosy et al. 2004; Drolz et al. 2011; Zittermann et al. 2013). No reports are available for the other liver support methods.

Bridging of ALF Patients to Liver Transplantation

In ALF patients listed for liver transplantation, MARS can be applied as a bridging method to stabilize the patient's condition. Not only was the treatment reported to be safe, but patient's condition improved markedly in a substantial number to such an extent that sustained liver regeneration was achieved. Koivusalo et al. (2005) report 56 patients with ALF (29 toxic, 22 unknown, 5 other). All fulfilled liver transplantation criteria or had ingested a lethal dose of a known toxic agent (e.g., paracetamol, *Amanita phalloides*). A mean number of 3 MARS treatments were performed per patient; target treatment duration was 22 h/session. The 1-year survival was 84 %. Recovery of native liver function occurred in 30 pats (1-year survival: 79 %). In the transplanted group, 1-year survival was 94 %. In the subgroup of toxic ALF, the recovery rate was 76 % and 23 % in the ALF of unknown origin. Camus et al. (2009) found similar results in their liver transplantation candidates. They treated two times/pat. for 8 h/session and found a transplantation-free survival of 29 %. A number of other groups reported safe and successful bridging to liver transplantation, including anhepatic phases, or even recovery of native liver function (Liu et al. 2004; Choi et al. 2005; Doria et al. 2006; Gaspari et al. 2006; Yuan et al. 2006; Chen et al. 2011; Pőcze et al. 2013), among others in infants and children (Trittenwein et al. 2006; Nadalin et al. 2007; Rustom et al. 2014). However, not all groups saw native liver recovery (Gaspari et al. 2006; Wai et al. 2007). In 2008 a multicenter randomized controlled trial in 102 ALF patients in France investigated the role of MARS as a bridge to liver transplantation. It found the method to be safe and potentially helpful to improve transplant-free 6-month survival (Saliba et al. 2013).

Prometheus was used safely in larger case series of ALF and bridging to transplantation (Grodzicki et al. 2009; Sentürk et al. 2010). For SPAD and TPE, successful cases of bridging to LTx in acute Wilson's disease were described (Kreymann et al. 1999; Hilal and Morehead 2014).

For bioartificial systems, the largest reported randomized controlled trial investigating the impact of the HepatAssist system on the course of ALF and primary non-function after liver transplantation, the bioreactor improved survival in a subgroup analysis (Demetriou et al. 2004). There is no information on the use of ELAD as a bridging tool.

Both MARS and TPE seemed to be safe and feasible for the treatment of post-liver transplant graft dysfunction (Lee et al. 2010).

In children, Lexmond et al. (2015) found MARS safe and efficient even in very sick children. Only the sickest subgroup was bridged to transplantation. They had an outcome comparable to a less severely diseased subgroup. Another study suggested that in children with ALF, TPE combined with hemodialysis may be more advisable than MARS. However, all treatments were tolerated well (Schaefer et al. 2011).

Patient Survival

Influence on survival was evaluated in a number of controlled randomized trials so far. In an HRS type I trial including 13 patients, significant improvement in survival in the MARS group was reported. Seven-day survival was 67 % in the MARS versus 0 % in the control group. Thirty-day survival was 25 % in the MARS group (Mitzner et al. 2000). In another study, in 24 AoCLF patients with severe cholestasis

(mean bilirubin higher than 30 mg/dl), a significant improvement of 30-day survival was found (92 % in the MARS group vs. 50 % in the control group, $p < 0.05$) (Heemann et al. 2002). In the 3-year follow-up of a larger patient group of 149 patients with alcohol-induced AoCLF, a significant survival advantage (33 % vs. 15 %) was found as compared to standard of care (Hessel et al. 2010). A Cochrane Biliary Group analysis of liver support systems from 2003 found a significant 33 % reduction in mortality in AoCLF. This effect was mainly carried by the participating MARS studies (Kjaergard et al. 2003). However, the so far largest study performed with MARS in 189 AoCLF patients did not find a difference in survival (Banares et al. 2013). Also, the HELIOS trial investigating the impact of Prometheus on survival in 145 AoCLF patients found no overall survival benefit. However, in the subgroup of patients with MELD, >30 survival was significantly improved (Kribben et al. 2012).

Regarding acute liver failure, a multicenter randomized trial of MARS in 102 ALF patients fulfilling high-urgency liver transplant criteria in France found a nonsignificant trend toward improved survival in the MARS group and a significantly improved transplant-free 6-month survival in those patients treated with at least three sessions of MARS (Saliba et al. 2013). These results confirm smaller studies that have reported improvement in transplant-free survival in ALF patients treated with MARS (Koivusalo et al. 2005; Camus et al. 2009; Cisneros-Garza et al. 2014). The Helsinki transplant center has reported experience from over 150 ALF patients being treated with MARS. Authors concluded that the implementation of MARS has likely contributed to improve 6-month survival in both non-transplanted (40 % before vs. 66 % after MARS, $P = 0.03$) and transplanted (77 % vs. 94 %, n.s.) ALF patients (Kantola et al. 2011). A meta-analysis found significant impact of extracorporeal liver support on ALF survival (Stutchfield et al. 2011).

There is limited information on survival data for SPAD, TPE, and cell bioreactors. It appears that high-volume TPE can have a positive impact on survival in acute liver failure patients (Larsen et al. 2010). Bioartificial liver support systems have not demonstrated a convincing survival benefit to date (Demetriou et al. 2004). However, clinical trials especially with the ELAD system have been initiated in the last few years (Wertheim et al. 2012).

Cost-Benefit Analysis

The use of MARS both in ALF and in AoCLF was analyzed with regard to its cost utility ratio. In the 3-year follow-up of 149 AoCLF patients, a significant survival advantage (33 % vs. 15 %) was found as compared to standard of care with a favorable cost-benefit ratio (Hessel et al. 2010). Kantola et al. (2010) compared 90 ALF patients treated with MARS from 2001 to 2005 and a historical control group of 17 ALF patients treated from 2000 to 2001. The 3-year outcomes and number of liver transplantations were recorded. Compared to the controls, the average cost per quality-adjusted life year (QALY) saved was considerably lower in the MARS group (64,732 euros vs. 133,858 euros) within a time frame of 3.5 years. The authors concluded that MARS treatment combined with standard medical treatment for ALF in an ICU setting is more cost-effective than standard medical treatment alone.

Last but not least, in an effort to lower treatment costs, Drexler et al. (2009) determined the optimal dialysate albumin amount to be 100 g rather than 120 g per session, as is the clinical standard today.

Treatment Recommendations

Liver support should be considered in AoCLF patients not responding to standard of care within several days. In ALF with a high expected mortality rate, commencement of liver support treatment is recommended as soon as the diagnosis is made. ALF and AoCLF represent rather different

indications for liver support, and therefore, different inclusion and exclusion criteria need to be applied. The absence or presence of sepsis and severe disseminated intravascular coagulation seem to divide AoCLF patients in good and bad candidates for MARS. We recommend early and sufficiently aggressive antibiotic treatment of infections as well as antibiotic prophylaxis in those not infected. In AoCLF, very low platelet count (<50 Gpt/l), high INR (>2,3), and advanced kidney failure needing dialysis or hemofiltration represent high-risk patients that might not take advantage from treatment. An Italian study found that age, male gender, and sequential organ failure assessment score (but not model for end-stage liver disease score) were factors predicting death, whereas the number of MARS sessions and the increase in hepatocyte growth factor proved protective factors (Donati et al. 2014). Inderbitzin et al. (2005) found a critically low plasma disappearance rate of indocyanine green of ≤5 %/min at baseline to be correlated with unfavorable outcome.

In AoCLF, total dosage of treatment should be handled flexible with days of pausing in between, especially if the platelet count is decreasing to values below 50 Gpt/l or INR going above 2.3. The mode should be rather intermittent than continuous with treatment lengths of 6–8 h per day. In ALF the need for treatment is much bigger and probably continuous treatment with few breaks is most efficient. In ALF much worse INR values can be tolerated than in AoCLF, probably due to the different pathogenesis of INR increase (synthetic defect vs. hypercoagulation). Cautious anticoagulation preferably with citrate or small doses of heparin is recommended, whereas no anticoagulation is not advisable for most patients (Faybik et al. 2006; Tan et al. 2007; Yuan et al. 2011; Meijers et al. 2012). Thromboelastography reveals patients at risk for bleeding (via detection of fibrinolysis), while absent thrombocytopenia and elevated plasma fibrinogen predicted clotting of the MARS system (Bachli et al. 2011). For Prometheus, problems with clotting due to direct adsorption of protein C and S to anion exchanger column were described (Meijers et al. 2007). While heparin anticoagulation is not advisable, the use of citrate was found to be safe (Rifai et al. 2008). In patients with high risk of bleeding, addition of TPE before, e.g., albumin-cleansing methods should be considered (Huang et al. 2012; Ince et al. 2013).

In principle removal of both water-soluble and albumin-bound drugs, e.g., antibiotics during the use of liver support therapies, needs to be considered for the planning of the medical treatment. Basic handling recommendations include dosage application posttreatment, therapeutic drug monitoring for blood level surveillance, and dose adjustments (Mitzner et al. 2001; Weiler S et al. 2011; Roth et al. 2013; Ruggero et al. 2013; Personett et al. 2014).

Often liver support is reserved for only the sickest patients that are nonresponders to standard intensive care. Naturally, this approach means that the commencement of liver support treatment is rather late in the course of liver failure (Lexmond et al. 2015). Although not formally studied, it seems to be reasonable to assume that earlier start of treatment would improve chances for a favorable clinical course. This is indirectly supported by the notion that patients that lived long enough to receive a series of MARS treatments (i.e., three and more) had improved survival (Saliba et al. 2013; Donati et al. 2014). In acute liver failure, liver support treatment should be considered as soon as listing for LTx is completed (Kantola et al. 2011). Intensive, in the best case continuous treatment renders the best survival results for ALF patients (33, Koivusalo et al. 2005; Kantola et al. 2011).

Future Needs/Trends

In the future, we need to learn more about the patients we are treating. There are only now first attempts to better understand the syndrome of acute-on-chronic liver failure (Arroyo et al. 2015). Much of this was not known when the larger liver support studies were carried out throughout the last decade. Accordingly, future studies of liver support methods will need to define patient inclusion in more detail. Moreover,

we will need to learn more about indications, timing (start/end), and dosing of treatment. Therefore, in summary we will need more studies.

Current devices will need to improve with regard to detoxification efficacy (Krisper et al. 2011). Central elements of all support methods are the separation membranes used. Future membrane development should consider the critical importance of pore size. They should not be too leaky as open-porous membranes might lose valuable molecules such as antithrombin or hepatocyte growth factor (Ho et al. 2002). On the other hand, regular high flux dialysis membranes might underperform because of size exclusion. Efficacy might be added by further functionalizing the membrane, e.g., as drug-eluting systems (Grabow et al. 2013). A certain amount of albumin loss might be advantageous; as a part of the AoCLF patients, albumin is irreversibly oxidized. The amount of irreversibly oxidized albumin was found to be strongly correlated with mortality in AoCLF (Oettl et al. 2009). Last but not least, comorbidities will have to be considered more thoroughly, especially sepsis. Use of combination devices might be a valuable strategy (such as albumin dialysis and direct hemoperfusion with endotoxin or cytokine sorbents) (Novelli et al. 2011; Frimmel et al. 2014).

Conclusion

Since the late 1950s, experimental artificial liver devices were used in order to support patients with either acute liver failure or end-stage chronic liver disease. In the 1980s, liver transplantation became an established treatment with a major survival benefit. In the 1990s, the concept of albumin dialysis appeared with the capacity to remove toxins, drugs, and molecules strongly bound to albumin. The most widely studied and used system is the MARS. The newer liver support systems have shown in uncontrolled studies and several randomized studies an improvement in the patient condition in terms of clinical symptoms (hepatic encephalopathy, pruritus, jaundice) and in liver and kidney biological parameters bringing these patients safely to liver transplantation. Moreover, for some patients with ALF (mainly paracetamol intoxication), an improvement of spontaneous or transplant-free survival was observed.

However, the performance of these systems needs further improvement. Large randomized trials are still needed in both patients with ALF and AoCLF to establish the indications, the timing, and the real place of liver support therapies. Meanwhile, early use of these devices in patients with AoCLF could be considered as an additional tool among others in specialized liver units. In ALF, treatment is probably useful in acute poisonings to determine if liver function will improve enough to avoid transplant. It may also be indicated in ALF as a bridging strategy in those eligible for transplantation (Hassanein et al. 2011; Kantola et al. 2011; Nevens and Laleman 2012; Gonwa 2014; Willars 2014; Saliba and Samuel 2015).

From today's perspective, the correct timing of liver support treatment is of utmost importance for clinical success. We are starting to learn about clinical and laboratory parameter combinations that describe reliable in- and exclusion criteria and serve as indicators for the monitoring and stopping of therapy. However, this process will be an ongoing one for the years to come.

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Liver Autotransplantation from the Labs to the Ante-situm Procedure: A Long Journey

29

Salvatore Gruttadaria, Duilio Pagano, and J. Wallis Marsh

Contents

Abstract

The use of liver transplantation techniques, including interventional radiology techniques, complete liver vascular control, and liver preservation technique, has contributed to current management of patients with involvement of the inferior vena cava by hepatic tumors or those with large centrally located lesions or lesions in close proximity to the confluence of the inferior vena cava and hepatic veins, which would otherwise be deemed unresectable.

The training of hepatobiliary surgeons must include a familiarity with all such techniques and formal training in liver transplantation. Appropriate decision-making for formal resections in patients who have been treated with systemic neoadjuvant therapies and then require subsequent surgical care is based on a mandatory evaluation of massive lobar or multilobar tumor involvement and intra- or retro-hepatic venous neoplastic lesions.

The transfer of the patient to a transplant center is the gold standard for centers that lack the surgical and medical expertise of transplant referral centers. Technical skills in advanced hepatobiliary surgery, patient hemodynamics and resuscitation, diagnostic multidisciplinary evaluations, operative indications by grade of tumor extension, selection criteria for surgical management, and criteria for the choice of operation are mandatory for indicating formal liver resection as initial therapy and/or excision

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of tumors of the caval confluence and/or all three hepatic veins.

Keywords

Complex liver resection • Anatomic hepatic resection • Oncologic surgical management • Autotransplantation • Liver transplant surgery team

List of Abbreviations

CT	Computed tomography
HCC	Hepatocellular carcinoma
HVE	Hepatic vascular exclusion
ISMETT	Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione (*Mediterranean Institute for Transplantation and Advanced Specialized Therapies*)
IVC	Inferior vena cava
IVCTT	Inferior vena cava tumor thrombus
MRI	Magnetic resonance imaging
PCS	Portacaval shunt
PTFE	Polytetrafluoroethylene
UPMC	University of Pittsburgh Medical Center
VVB	Venovenous bypass

Introduction

The natural tendency of choosing less- or noninvasive treatment in general surgery is also followed in treating oncologic liver tumors and has increased in recent years (Nguyen et al. 2009; Uchiyama et al. 2014). In select patients with limited tumors, laparoscopic liver resection can provide marked perioperative benefits without compromising oncologic outcomes or long-term survival (Schiffman et al. 2014). However, for larger tumors and tumors with difficult locations, this technique seemed to pose an insurmountable problem (Starzl et al. 1963; Sigel et al. 1960). With advances in surgical techniques and the steady increase in the understanding of liver anatomy, together with the advances in anesthesia and intensive care medicine, over 90 % of patients with liver cancer can be offered some form of therapy, with a reduction to less than 0.5 % of the risk of death from elective hepatic resection (Geller et al. 2006). These achievements have allowed surgeons to perform hepatic resection previously thought impossible, with improvements in outcomes.

Current surgical management of patients with involvement of the inferior vena cava (IVC) by hepatic tumors or those with large centrally located lesions or lesions in close proximity to the confluence of the IVC and hepatic veins is focused mainly on the liver preservation technique and can allow a more aggressive approach to tumors of the caval confluence and/or all three hepatic veins, which would otherwise be deemed unresectable (Gruttadauria et al. 2005).

In the UPMC group experience, as in that of others, liver resection is the best possible treatment for hepatic tumors. However, though several significant factors do not seem to influence the short-term outcome of surgery, it is important to be aware of the deleterious effects of the type of resection to be performed and the impact of portal fibrosis on blood loss during partial liver resection (Gruttadauria et al. 2004a, b, 2011). The objective of this chapter is to report the most important troubleshooting areas in the management of liver autotransplantation, for which it is recommended to transfer complex liver cancer patients to tertiary referral centers for salvage resection in order to reduce morbidity and mortality.

History of Surgical Intervention and the Role of Preclinical Procedures

Resection of liver tumors with involvement of the IVC is considered to have a high surgical risk and has been the subject of considerable interest over the last few years, particularly in light of the rise of oncologic care worldwide and the high incidence of primitive liver tumors, especially in the Far East (Zhang et al. 2012; Li et al. 2013).

Though an association between vascular invasion and incidence of worse clinical outcomes in those prone to the disease has been found, there have been conflicting reports on the impact that complex liver surgery has on this subset of patients with regard to survival and surgical outcome (Li et al. 2013).

Other important factors must be taken into account, such as the underlying liver disease, portal hypertension, and associated metabolic syndrome, to clarify the role of extreme surgical procedures in conditioning the prognosis of patients undergoing liver and vascular resection for locally advanced huge liver tumors (Nuzzo et al. 2011).

Several studies have been done in an animal model to obtain a reliable procedure for orthotopic liver autotransplantation that could also be suitable for ex situ liver resection in humans with otherwise unresectable primary liver cancer or metastases, especially large lesions located centrally in the liver or close to the confluence between the intrahepatic IVC and hepatic veins.

The technique of a liver autograft in pigs has been found to guarantee three principal advantages:

1. It provides an excellent training model of liver transplantation.
2. It provides an experimental model for cancer research.
3. It is more economical than liver allotransplant (Gruttadauria et al. 2001; Fondevila et al. 2011; Iida et al. 2007).

Classical orthotopic liver autotransplantation is a very challenging and time-consuming technique. It includes the division of the major hepatic vessels and choledochus and subsequent reconnection by end-to-end anastomoses. Caval end-to-end anastomoses are the most difficult to perform, and the interposition of a prosthesis can be required.

Preclinical experiences have allowed the adoption of innovative surgical techniques, such as total hepatic vascular exclusion (HVE) (Li et al. 2013; Fortner et al. 1974), venovenous bypass (VVB) (Shaw et al. 1984), and ex vivo hepatic resection (Pichlmayr et al. 1990; Yanaga et al. 1993), to render such tumors operable.

Historical series have confirmed that with close collaboration between transplant and hepatopancreatic-biliary surgeons, this type of complicated surgery has become safe and feasible for or replacing the IVC with an autogenous vein graft or prosthetic material (Miller et al. 1991; Yamamoto et al. 1997; Yagyu et al. 1994; Huguet et al. 1995; Sarkar et al. 1998).

Recently, hepatic resection and preservation with sub-euthermic machine perfusion have been proposed to prompt the development of a new model of autotransplantation in pigs, making it possible to perform hepatic resections and vascular reconstructions ex situ while preserving the organ with mechanical perfusion (ex vivo, ex situ surgery) (Gringeri et al. 2011).

Furthermore, resection of the retro-hepatic vena cava has been proposed, with preservation of the caval flow in a large animal during the anhepatic phase by interposing a polytetrafluoroethylene (PTFE) prosthesis. The reconstruction of the vena cava is then performed with a side-to-side cava-prosthesis anastomosis, with lateral clamping of the prosthesis. The procedure is then completed with the classical technique of liver transplantation (Roveda et al. 2009).

Hypothermic liver preservation is a technique in which the future liver remnant is flushed with preservation fluid at 4 °C and packed with ice during the period of total vascular exclusion. This has been shown to attenuate hepatic ischemic injury in large animals and humans (Lodge et al. 2000; Pichlmayr et al. 1990; Guarrera et al. 2010).

Confirmation that translational research is able to apply findings from basic science to improve human health and well-being is strong in this field of surgery. There have been several reports indicating that only resection can offer a chance of long-term survival for patients suffering from primitive or metastatic liver malignancies, such as leiomyosarcomas or colorectal liver metastases involving the IVC (Takatsuki et al. 2014).

A satisfactory cure and disease-free survival in select patients could be proposed with an aggressive surgical approach, which might require a repeat hepatectomy with porcine pericardial patch reconstruction to restore adequate venous return to the IVC after tumor resection (Malde et al. 2011; Hemming et al. 2013; Marangoni et al. 2014).

Resection of the IVC can be performed by applying different reconstructive techniques depending on the location and extension of the lesion, but it must be understood that

perioperative risks are high, with the possibility of massive bleeding and gas embolism. Early and late complications include venous or graft stenosis or thrombosis, graft infection, acute renal failure, and other consequences of hemodynamic instability (Azoulay et al. 2006).

Surgical Decision-Making and Perioperative Monitoring

An important question that skilled hepatobiliary surgeons need to clarify concerns presurgical evaluation. Computed tomography (CT) grading of hepatic lesions and IVC involvement is a key factor in determining the need for surgery. Most patients with a higher grade of oncologic disease that can be managed with extreme surgical intervention have to be transferred to a tertiary referral facility for decision-making.

In the planning stages, the dominant predictors of survival are positive margin status, tumor size, and en bloc radical resection. These can be combined into a risk score that allows prognostication and aids in clinical management (Wachtel et al. 2015).

Noninvasive imaging techniques such as abdominal ultrasound, CT scan, and magnetic resonance imaging (MRI) can aid in diagnosing these tumors, determining their origin, evaluating the presence of local invasion, and excluding pulmonary metastases.

Other imaging modalities include ascending cavography, which can delineate the involvement of major branches (renal and hepatic veins) and allow biopsy of the tumor. Selective arteriography of the celiac trunk can also be done in patients in whom hepatic invasion or metastasis is suspected, and transesophageal echocardiography can exclude or verify intracardiac tumor extension (Sung et al. 2008; Kieffer et al. 2006).

Even with all these modalities, in most cases, it is impossible to confirm the precise origin of these tumors preoperatively. Furthermore, the tumor's location in the anatomical site of the IVC can prevent percutaneous biopsy for definitive histologic diagnosis. Therefore, more often than not, the surgeon is faced with the challenge of a tumor of unknown histologic type and origin at laparotomy.

The type of caval resection and reconstruction varies according to tumor location and extent of IVC infiltration. When the IVC wall involvement is longitudinal and less than 30 % of its circumference, a tangential resection can be performed and closed with a nonabsorbable 3/0 running suture. When involvement of the IVC wall compression is greater than 50 % of its circumference, with lumen occlusion, a caval segment is resected and replaced with a 20 mm ringed polytetrafluoroethylene (PTFE) graft (Nuzzo et al. 2011; Lodge et al. 2000).

According to the location in relation to the IVC, tumors can be divided into three main categories: (1) infrarenal; (2) inter- and suprarenal, up to but not including the main subhepatic veins; and (3) suprahepatic, with possible intracardiac extension.

To evaluate a major hepatectomy with resection of the IVC, the surgical team needs to exclude the presence of inferior vena cava tumor thrombus (IVCTT), which can be seen in 11–23 % of cases associated with hepatocellular carcinoma (HCC) (Sung et al. 2008).

Clinically, IVCTT is classified into three types according to its anatomic location close to the heart: (1) posterior hepatic type, when the tumor thrombus is in the IVC posterior to the liver and below the diaphragm; (2) superior hepatic type, when the tumor thrombus is in the IVC above the diaphragm but still outside the atrium; and (3) intracardiac type, when the tumor thrombus is above the diaphragm and has entered the right atrium (Li et al. 2013).

The principal exclusion criterion for this type of operation is evidence of extra-hepatic metastasis. Experienced anesthesiology teams can be helpful during operative management in achieving hemodynamic stability or in correcting hypothermia, acidosis or severe coagulopathy, and/or reduction of renal function.

An available intensive care unit with continuous pulse and arterial blood pressure monitoring, repeated measurements of blood gas analyzer parameters, and careful clinical follow-up is mandatory.

It bears emphasizing that salvage surgery is usually performed in a highly select group of patients who have undergone previous surgical procedures and advanced chemotherapy schemes and are fit enough to be managed at a transplant referral center.

It is important for the transplant surgeons at the referral center to know the following:

1. What procedures has the patient undergone at the referring hospital, and how much future liver parenchyma did the patient need?
2. What was the tumor's imaging and pathologic picture at the time of patient presentation?

This information is crucial in deciding to indicate the patient for formal complex resection. Obviously, there is a great difference between performing a right hepatic lobectomy in a patient who has a healthy parenchyma, as opposed to one with severe ongoing hemorrhage or reduced regenerative capacity.

Surgical Control of Hemorrhaging and Resection Techniques

The first thing to be taken into consideration for controlling massive hemorrhaging is portal triad occlusion with several surgical maneuvers that can include the Pringle maneuver, which is done by placing a nontraumatic vascular clamp across the hepatic artery, portal vein, and common bile duct at the level of the foramen of Winslow, or total HVE (Li et al. 2013; Nuzzo et al. 2011; Gruttadauria et al. 2001; Fondevila et al. 2011; Iida et al. 2007; Fortner et al. 1974), VVB (Shaw et al. 1984), and ex vivo hepatic resection (Pichlmayr et al. 1990; Yanaga et al. 1993).

HVE is a sequential approach to total vascular exclusion/isolation of the liver, which is achieved by cross clamping both the suprahepatic and infrahepatic IVCs, with hepatic vascular control of the portal vein and hepatic artery without venous bypass (Zhang et al. 2012).

Several reports of aggressive hepatectomy using a back-table procedure for advanced liver tumors have been published, including liver transplantation techniques not only for primary liver tumors – both HCC and cholangiocarcinoma – but liver metastases and IVC tumors as well (Takatsuki et al. 2014; Wen et al. 2013; Gringeri et al. 2012).

The in situ hypothermic liver preservation technique (including supraceliac aortic control) was originally described by Heaney and colleagues in 1966 and Fortner and coworkers in 1974 (Heaney et al. 1966; Fortner et al. 1974). The technique has rarely been reported since because it was widely recognized that total vascular exclusion was not necessary for partial hepatectomy in most patients (Grazi et al. 1997; Torzilli et al. 2001; Nardo et al. 2005).

VVB and hypothermic perfusion should be used to make the liver more resistant for a more prolonged ischemic period. Vascular access for bypass positioning (saphenous vein and left axillary vein) should be achieved in the event of hemodynamic instability during clamping. VVB achieves stable hemodynamics and optimal venous drainage of the kidneys via the preservation of the caval flow (Dubay et al. 2009).

Recently, Azoulay et al. reported the use of a portacaval shunt (PCS) for preventing splanchnic congestion and reducing the specific risks of VVB, which are bleeding from vascular injury, air embolism, hemomediastinum, hypotension, atrial fibrillation, seromas or lymphoceles, wound infections, and nerve injuries (Azoulay et al. 2014; Budd et al. 2001; Sakai et al. 2007).

The technical experience required for ex situ or ante-situm resection is derived from liver transplantation, and some of the problems inherent in these techniques, such as long operation time and remnant liver protection, require the investigation of technical details and potential indications, which can provide guidance for surgeons and increase the safety of its use (Gruttadauria et al. 2005; Lei et al. 2012).

This technique is based primarily on liver transplantation and perfusion with preservation solution under hypothermic conditions via the gastroduodenal artery and portal vein to protect the liver.

The entire obstructed retro-hepatic IVC has to be excised along the liver mass margin.

The remaining free liver parenchyma is reimplanted in situ. The portal vein can be reconstructed with an autologous vein graft, and the hepatic vein directly anastomosed end to end to the infra-hepatic IVC or with a PTFE graft.

Hepatic artery bypass may be required to guarantee adequate oxygen blood supply. The anastomosis of the hepatic ducts usually has to be drained by Roux-en-Y hepaticojejunostomy (Gruttadauria et al. 2005).

All types of resections follow anatomic parameters, independent of the extension of the resection. When initial surgery is performed with a subcostal approach, and in patients in whom abdominal extra-hepatic disease has been excluded, operations can be done with a bilateral subcostal incision, with upward midline extension.

Mobilization of the liver and skeletonization of the retro-hepatic IVC with ligation of all accessory hepatic veins are usually done with the traditional piggyback technique unless the presence of the tumor does not exclude an appropriate cleavage plane (Lei et al. 2012).

Different transection techniques for hepatic resection with or without inflow occlusion have been proposed in select settings for reducing intraoperative blood loss, operative time, and overall surgical quality.

However, there is a lack of consensus in the literature on management of complex liver tumors, and historical studies suggest that the gold standard technique is dependent largely on the surgeon's personal experience, as well as on the kind of resection to be safely and quickly performed (Gruttadauria et al. 2005).

The crush-clamping technique, ultrasonic dissection, vascular stapling, bipolar electrocautery, and radiofrequency can be considered equally safe and effective for transection of the liver parenchyma. All these techniques should be available in a dedicated center for liver surgery and used according to the specific circumstances of the oncologic setting.

The two techniques most frequently used at UPMC and ISMETT are liver resection using stapling devices for unstable patients and hepatic parenchyma transection for stable patients, described elsewhere (Gruttadauria et al. 2004a).

The hepatic parenchyma transection involves:

1. Parenchyma tissue fragmentation and skeletonization of vascular-biliary structures with an ultrasonic dissector (TissueLink, TissueLink Medical Inc, Dover, NH,)
2. Vascular hemostasis and biliostasis of the minuscule biliary ducts through a monopolar floating ball
3. Sectioning of fibrous and vascular-biliary structures with electrocautery
4. Suction of organic and irrigation fluids mixed with parenchyma detritus using a pediatric aspirator and the integrated aspirator in the ultrasonic dissector

Additionally, for all procedures, a presurgical setup of the Cell Saver and the Rapid Infusion System (Haemonetics Corporation, Braintree, MA) is done when needed during the procedures (Gruttadauria et al. 2004b, 2011).

Stapling devices are used when devitalized liver parenchyma around the tumor margin is found, and the TissueLink for major resection is used when the malignancy is found to involve major vessels, such as hepatic veins or portal branches (Gruttadauria et al. 2013).

The role of a liver transplant surgery team can be crucial not only in terms of salvage liver transplantation, which can be used successfully in some cases (Wang et al. 2012; Peitzman and Marsh 2012), but also in managing the potential use of extreme procedures, such as a temporary anhepatic phase using an implantation of human pericardium or a PTFE vein prosthesis to employ back-table repairing surgery or to perform a complex liver resection for hepatic trauma involving the IVC (Gruttadauria et al. 2005; Takatsuki et al. 2014).

In cases of suspected involvement of the suprahepatic IVC, a feasible option is to attempt a direct approach to the juxta-diaphragmatic segment of the IVC by placing the patient on an atrial-caval venovenous bypass.

A complete suprahepatic IVC transection can be done, with the vessel reconstructed by performing an end-to-end anastomosis with 3:0 polypropylene running sutures, using the same

technique as in orthotopic liver transplantation (Marino et al. 2008; Hoekstra et al. 2012a).

When IVCTT is detected during the preoperative imaging evaluation, Type I usually has to be treated with radical hepatectomy and removal of the IVCTT, with total hepatic vascular exclusion. Type II requires treatment with radical hepatectomy and removal of the IVCTT by incision of the diaphragm and Type III by hepatectomy and resection of the thrombus from the right atrium under cardiopulmonary bypass (Li et al. 2013).

As described above, all of these procedures require active hemodynamic support carried out in agreement with the liver transplant anesthesia team.

Postoperative Care

Contrast multi-detector CT scan can be done routinely during the first week or when clinically indicated. Anticoagulant prophylaxis is mandatory and usually consists of low-weight heparin, 5,000 UI every 12 h for patients with PTFE graft during the hospital stay and 5,000 UI once a day thereafter for 3 months. In patients without PTFE graft placement, anticoagulant therapy consists only of subcutaneous heparin 5,000 UI every day during the hospital stay. It is recommended not to place a filter preoperatively. This minimizes the risk of pulmonary embolism after resection (Nuzzo et al. 2011).

Considering the reported independent factors that are correlated with the occurrence of bile leakage, it is clear that autotransplantation with the ante-situm procedure for radical resection is one of the most critical surgical interventions in terms of biliary complications.

The major risk factors (Hoekstra et al. 2012b) include the following:

1. Exposure of Glisson's sheath on the cut surface (caudate lobectomy, central bisectionectomy, and right anterior sectionectomy)
2. Resection of segment 4
3. A cut surface area $\geq$57.5 cm^2
4. Repeated hepatectomy
5. Intraoperative blood loss $\geq$775 ml
6. Intraoperative bile leakage
7. Prolonged operative time $\geq$300 min
8. Peripheral cholangiocarcinoma
9. Preoperative chemoembolization

Nutritional support during this critical period is mandatory for ensuring adequate hepatic regeneration and postoperative recovery. A perioperative nutritional plan has to be devised for each patient based on nutritional status and hepatic function.

Early mobilization, intermittent use of pneumatic compression devices, and pharmacologic agents can be used to prevent venous thromboembolism (Erdogan et al. 2009).

How Do I Do It?

In April of 2014, a 54-year-old woman was worked up because of new onset of abdominal and lower extremity swelling approximately 3 years after laparoscopic cholecystectomy for lithiasis.

A diagnosis of intra-caval thrombus was made at another facility. However, her symptoms progressed, and further work-up found a large mass in the suprahepatic IVC involving the right atrium and infiltrating the liver.

She was started on warfarin and told for the next 7 months that there was no other treatment. After 7 months, she was brought to a Pennsylvania regional hospital for a second opinion and then referred to the UPMC Liver Cancer Center.

The preoperative imaging evaluation with CT scan of the thorax and abdomen showed that the sarcoma was confined to the cava, but extended into the inferior portion of the right atrium. No other abdominal solid organ injuries were detected, with a proper appearance of the spleen, kidneys, pancreas, adrenal glands, and pelvic organs (Fig. 1, Panel A).

MRI allowed detailed definition of the margin of the intracardiac involvement (Fig. 1, Panel B). She was well compensated because her IVC was completely thrombosed above the renal veins, and she had established collaterals.

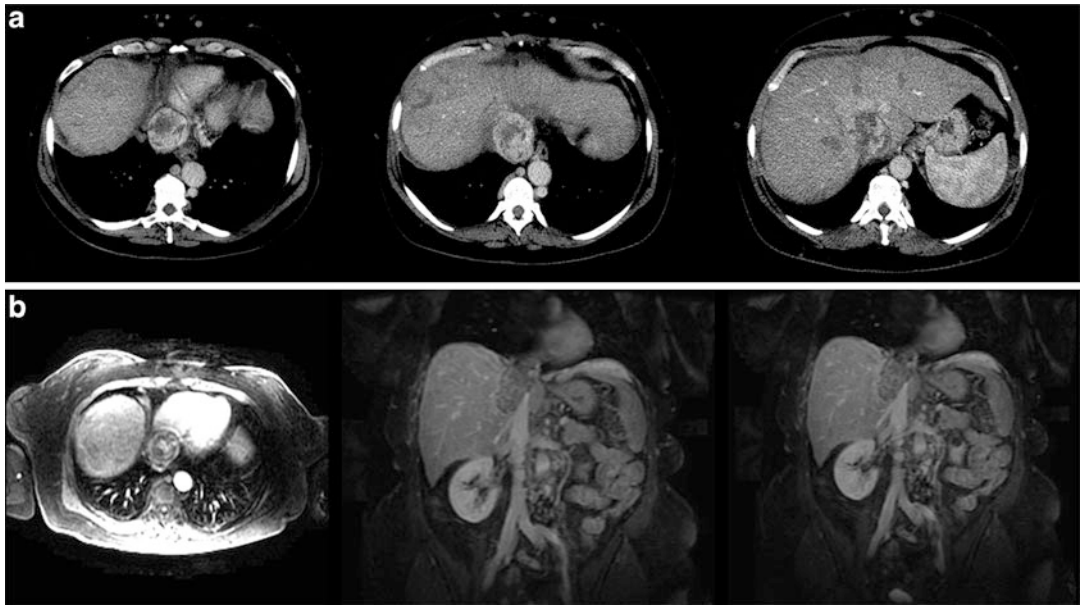

Fig. 1 Admission imaging work-up of a 54-year-old woman. The computed tomography scan confirmed the anatomo-pathologic finding of a biopsy-proven primary leiomyosarcoma of the retro-hepatic vena cava (*Panel A*). Magnetic resonance imaging allowed a detailed definition of oncologic involvement of the heart right atrium (*Panel B*)

After a biopsy-proven diagnosis of primary leiomyosarcoma of the retro-hepatic vena cava due to multiorgan involvement, and the location at the junction of the IVC and right atrium, it was determined that cardiopulmonary bypass and possible circulatory arrest would be necessary to resect the tumor.

A cardiac surgeon was consulted to plan a combined procedure, and the patient was admitted to the hospital for a cardiac catheterization, which was negative for severe pulmonary hypertension.

It was agreed to proceed, and in August 2014 the patient was taken to the operating room of UPMC and put on full cardiopulmonary bypass.

The incision was a long midline from the sternal notch to below the umbilicus. The vena cava was removed with the liver attached from just above the renal veins up to and including the inferior portion of the right atrium (Fig. 2).

The tumor in continuity with the inferior vena cava was resected from the liver on the back table. During this phase, the liver was flushed with 4 l of histidine-tryptophan-ketoglutarate solution (Fig. 3).

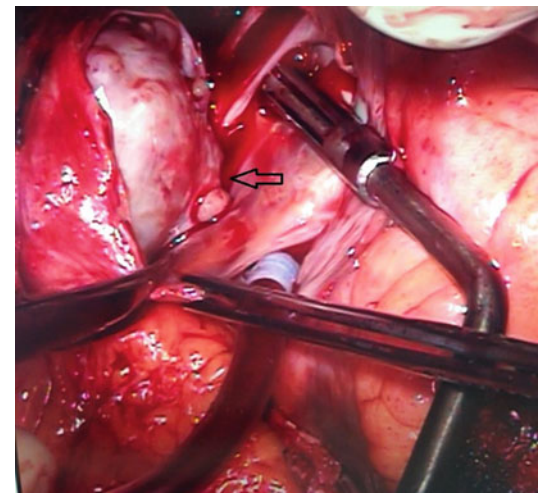

Fig. 2 The right atrium is open and to the left. The inferior portion of the right atrium with sarcoma and IVC to the right (*arrow*). The image shows a cardiac sump pump and one of the bypass cannulas

During the operation, the cardiac surgeons harvested the patient's pericardium, treated it with glutaraldehyde solution, combined it with a small amount of bovine pericardium, and then constructed a tube graft from that.

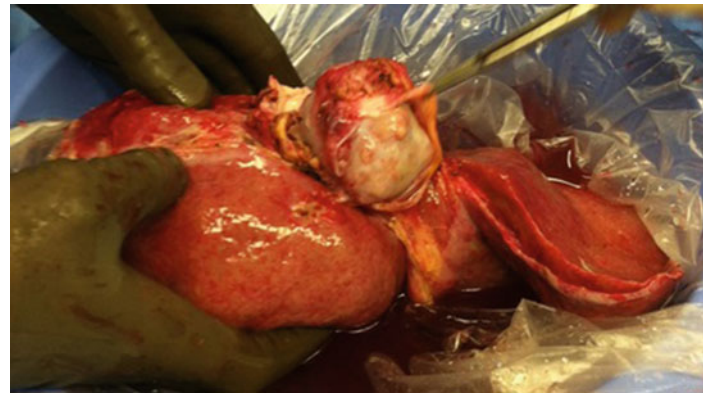

Fig. 3 Explanted liver showing the leiomyosarcoma occluding the retro-hepatic IVC

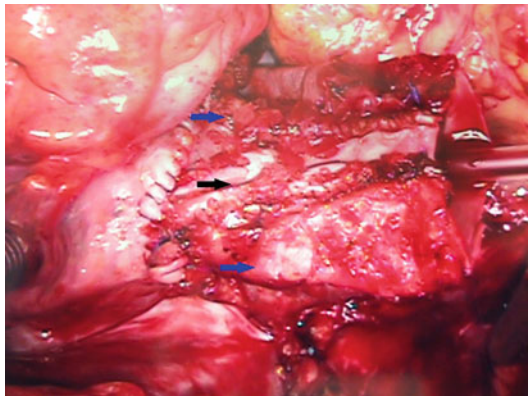

Fig. 4 This image shows the reconstructed inferior vena cava graft reattached to the right atrium (the heart to the left). The graft was constructed from the patient's pericardium (*blue arrows*) plus a small portion of bovine pericardium (*black arrow*)

They then sewed the tube graft to the inferior part of the right atrium so that there was a smaller orifice to sew the liver to. Once the cardiac surgeons had attached the pericardial tube graft, the patient was converted from cardiopulmonary bypass to standard VVB (Fig. 4). The liver was reimplanted using the confluence of the three hepatic veins to the pericardial graft. The artery and portal vein were reconstructed end to end, and the bile duct was reconstructed with a Roux-en-Y.

An intraoperative ultrasound was done to confirm valid flows to and from the left liver. Operating time was 767 min, and 14 units of blood were used during the procedure.

The histology report of the excised surgical specimen confirmed the diagnosis of leiomyosarcoma of the IVC, with a tumor mass of 115 g and 8.8 × 5 × 4.7 cm. The serially parallel sectioning to the long axis revealed a mottled, tan, trabecular cut surface with focal hemorrhage and yellow peripheral necrosis, 1 × 0.8 × 0.6 cm. An irregular rim of the atrium was present on the upper polar side, measuring 0.8 cm in length and 0.2 cm in thickness (Fig. 5).

The patient did well postoperatively, with no complications. She was extubated on the second postoperative day. She was discharged from the hospital on the tenth postoperative day, has had no complications nor required readmission, and is alive and well at the time of this writing.

Uneventful postoperative CT scan to confirm the absence of vascular anatomic complications was done 2 months after surgery, with no complaints (Fig. 6).

Conclusion

Technical skills in advanced hepatobiliary surgery, patient hemodynamics and resuscitation, diagnostic evaluation, operative indications by grade of IVC tumor involvement, selection criteria for operative management, and criteria for the choice of operation are mandatory for indicating formal tumor excision and liver resection as initial or delayed management of patients with involvement of the IVC by hepatic tumors or those with large centrally located lesions or lesions in close proximity to the confluence of the IVC and hepatic veins.

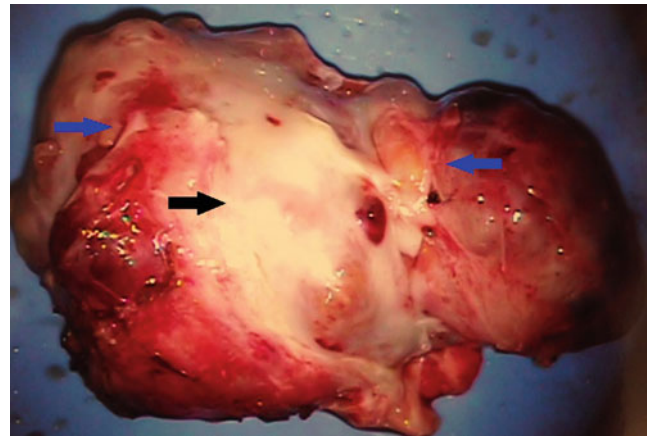

Fig. 5 Surgical specimen after radical tumor excision. Worth noting is the pathologic adhesion between the leiomyosarcoma (*blue arrows*) and the IVC (*black arrow*)

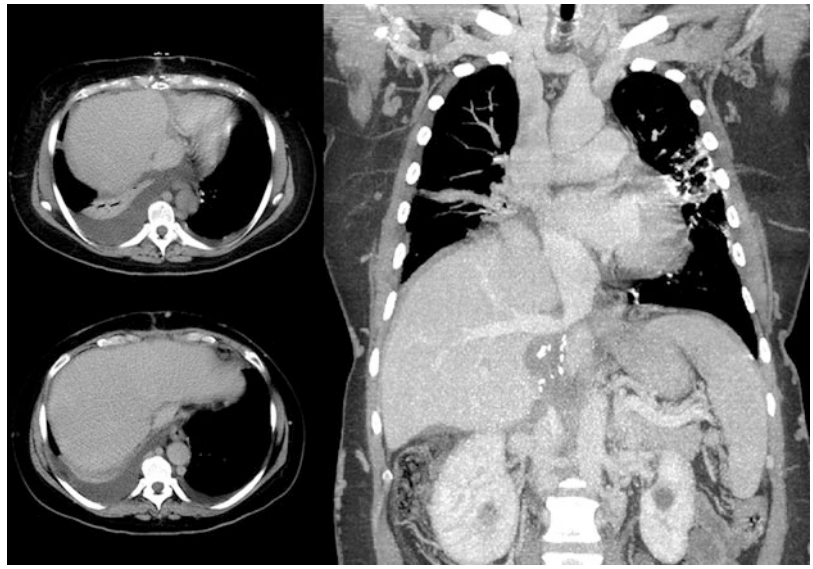

Fig. 6 Follow-up computed tomography 2 months after surgery for IVC tumor, showing resolution of the preoperative pathologic condition

Cross-References

- ▶ Anesthesia Management of Liver Transplantation
- ▶ Artificial Liver Treatment: When and Which One?
- ▶ HCC: The San Francisco Criteria
- ▶ History of Liver and Other Splanchnic Organ Transplantation
- ▶ Interventional Radiology for the Pre-transplant Patient
- ▶ Liver Transplantation in the Third Millennium in North America: The Strategy for Success
- ▶ Orthotopic Liver Transplantation: Indications and Contraindications
- ▶ Orthotopic Liver Transplantation: Surgical Techniques
- ▶ Role of Integrative Medicine in Liver Transplantation
- ▶ Split Liver Transplantation

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Role of Integrative Medicine in Liver Transplantation

30

Anthony J. Bazzan, Andrew B. Newberg, and Daniel A. Monti

Contents

Abstract

Integrative medicine practice includes a combination of current medical therapies in conjunction with practices sometimes referred to as complementary or alternative. Patients undergoing liver transplantation initially are suffering from some type of liver dysfunction pretransplant and also require increased liver support posttransplant. This chapter will focus on current integrative medicine practices such as diet and nutrition, nutritional supplements, acupuncture, and mind-body practices in relation to patients who are planning or have received a liver transplant. The goal is to establish a set of integrative medicine practices that help optimize a patient's diet and exercise regimen, provide appropriate stress management and coping techniques, and consider the pros and cons of various nutritional supplements commonly used to support liver health.

Keywords

Liver disease • Liver transplantation • Integrative medicine • Complementary and alternative medicine • Nutrition • Supplements • Acupuncture • Mind-body practices

Introduction

Integrative medicine practice includes a combination of current medical therapies in conjunction with practices sometimes referred to as complementary

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or alternative. Since much of this textbook is devoted to current medical therapies in patients undergoing liver transplantation, this chapter will focus on the complementary and alternative practices. Such practices include optimizing a patient's diet and exercise regimen, providing appropriate stress management programs to help patients cope better with the stress of liver failure and transplantation, and the potential use of various nutritional supplements to support liver health.

The use of various integrative practices in the management of patients both before and after liver transplantation is not well established. However, many patients report using various complementary and alternative medicine interventions for a wide variety of health issues, and there is some data that show a similar high use among transplant patients. For example, in one study of 100 renal, liver, or combined renal and heart transplant recipients, almost two thirds reported using dietary supplements and a third of these patients used more than one supplement (Foroncewicz et al. 2011). More specific to liver transplant patients, a study of 1,040 patients with chronic liver disease revealed that approximately one quarter used various CAM interventions, most notably nutritional or herbal supplements (Ferrucci et al. 2010). Another study reported that 21 % of chronic liver disease patients used herbal preparations, 27 % used prayer or relaxation techniques, 13 % used manual therapies such as massage or chiropractic, and 8 % took multivitamins (Strader et al. 2002).

This chapter will review what is currently known about integrative medicine practices and liver health, with a particular focus on patients scheduled for or status post-liver transplantation. The existing data can provide some directions as to practices that might be beneficial or detrimental in such patients. Future studies will be required in order to more formally assess the use of such interventions in this patient population.

Diet and Exercise

Maintaining adequate dietary intake of essential nutrients is fundamental to human health in general and liver health in particular. It is important to review current diets with patients in order to determine what foods they are eating and help them to develop an optimal diet that supports their health and liver function. In general, a physician or nurse should review with a patient what their general dietary intake is. Keeping food logs or online diaries can be very helpful to clarify what patients eat on a day-to-day basis.

In the context of liver health, maintaining good nutrition is essential for meeting the patient's physiological requirements as well as providing additional psychological, spiritual, social, and cultural benefits. With this in mind, it is important to assess the specific needs of the liver transplantation patient, both before and after transplantation. Optimal body mass index and body metrics should be assessed and targeted as part of a nutritional evaluation. The health-care team should carefully address the specific caloric needs of each patient throughout the clinical course, in terms of the number and quality of calories.

In terms of the types of foods patients should eat, a diet that contains high amounts of excess sugars is typically regarded as an unhealthy diet. Energy-dense and nutrient-poor foods include refined sugars, candies, fried foods, and so-called junk food. The medical literature is consistent that eating such foods favors the onset of obesity, diabetes, and fatty liver disease, all of which have an impact on liver function and liver transplantation (Sarno et al. 2013; Corey and Kaplan 2014).

Red and processed meat consumption has consistently gained a reputation as a contributor to diseases such as cancer (Corpet 2011; Tang et al. 2012). The data also suggests that red meat, in particular, is proinflammatory and pro-carcinogenic. For example, the European Prospective Investigation into Cancer and Nutrition-Potsdam study of 2,198 men and women found that red meat consumption was significantly associated with higher levels of the inflammatory markers GGT and hs-CRP when adjusted for confounding factors related to lifestyle and diet (Montonen et al. 2012). However, it is important to ensure that patients continue to receive nutrients commonly found in meats such as iron, vitamin B, and essential amino acids. One report

suggested that perioperative enteral and parenteral nutrition have benefits in reducing the morbidity and mortality of liver surgery (Masuda et al. 2013). In particular, branched-chain amino acids appear to promote protein and glycogen synthesis as well as improve immune system function. The administration of branched-chain amino acids, during the perioperative period, to patients undergoing hepatic resection improves liver function more quickly after surgery (Togo et al. 2005). The use of oral branched-chain amino acids might prolong the ability of the patient to wait for a liver transplant by preserving liver function in patients with cirrhosis (Kawamura et al. 2009). Thus, care should be taken to provide nutritional supplements when necessary to augment these requirements. There currently exist several high-quality protein supplements from vegetable sources that are commonly available.

Given the physiological response to liver failure and transplantation, considering diets that reduce inflammation might be helpful in the management of these patients. Inflammation itself is associated with high levels of oxidative stress that can damage both the body's tissues and genetic material. In integrative medicine practice, there is a long tradition of utilizing diets with anti-inflammatory effects to reduce the negative effects of oxidative stress. Ancient cultures also developed and used anti-inflammatory diets, such as in the Ayurvedic medicine (a system of traditional medicine native to the Indian subcontinent that stresses plant-based treatment), which are now investigated using modern scientific methods (Sumantran and Tillu 2012). Proinflammatory foods are those that include refined sugars and starches, saturated fats, and trans fats while having low amounts of omega-3 fatty acids and other natural antioxidants (Giugliano, Ceriello, and Esposito 2006). Anti-inflammatory foods are those that include omega-3 fatty acids, natural antioxidants, and fibers found in fruits and vegetables (Giugliano et al. 2006).

Energy intake, energy density, and energy balance in the body are substantially affected by systemic inflammation. Targeting systemic inflammation is likely to be important in nutritional interventions in liver patients. Wholesome diets rich in fresh and cooked vegetables and lean protein are a usual part of the recommendation from our Integrative Medicine Center (Monti and Bazzan 2008). This combination of foods and appropriate supplements can have a profound anti-inflammatory effect in the gut and body (de Moreno-de LeBlanc et al. 2007; Abd El-Atti et al. 2009; Boleij and Tjalsma 2012). Achievement and maintenance of a healthy body composition via a plant-based diet high in low-glycemic fruits, vegetables, and whole grains and low in saturated/trans fats, red or processed meats, and added sugars/starches should be the guidelines provided to patients from their health-care providers.

Nutritional Supplements

As many as 50 % or more of patients take vitamins, herbal preparations, and other supplements, often without medical guidance (Wanchai et al. 2010). More specifically in the population of patients with liver disease, approximately one quarter to one third report taking some type of nutritional supplement (Strader et al. 2002; Ferrucci et al. 2010). This is important information for the clinician caring for the patient with chronic liver disease as well as those who are pre- or posttransplantation. Physicians need to be aware of the various supplements that might be beneficial in these patients as well as limit potential dangers such as supplement-drug interactions. There are a growing number of research studies upon which to develop a specific approach for utilizing nutritional supplements in patients who are undergoing liver transplantation. While taking supplements must be weighed against other medications that the patient may be on to ensure that there are no potentially adverse interactions, many food-based supplements are safe and can be used along with medications. The health-care provider needs to carefully follow the patient for any adverse effects or drug-supplement interactions.

Data support the use of supplements to provide nutritional support not obtained with the patient's current diet. The goal for using supplements should be to ameliorate the specific

pathophysiological stressors and support the needs of the patient. It should also be noted that good diets do not automatically supplement all aspects of nutrition adequately and therefore nutritional supplements can be considered in many patients. Correcting and augmenting nutritional needs might help address immune function, inflammation, and micronutrient status that can provide health benefits and possibly enable the patient to experience less complications from liver disease and the treatments, including transplantation.

A variety of nutritional supplements have been suggested to be helpful either for liver health or more specifically in the setting of liver transplantation patients. This section reviews the limited data on these supplements. A randomized controlled trial of immunonutrition enriched in n-3 fatty acids, arginine, and nucleotides evaluated 52 patients receiving immunonutrition and 49 patients receiving an isocaloric control diet beginning 5 days post-liver transplant (Plank et al. 2012). There were no significant differences in total body protein levels, rate of infectious complications, or length of hospital stay. Thus, supplementation with the immunonutrition did not affect outcomes in liver transplant patients postsurgery.

A small pilot study of 23 living donor liver transplantation patients were randomly assigned to either an experimental group who received a commercial supplement enriched with antioxidant nutrients for 5 days immediately prior to surgery or a control group (Nagata et al. 2013). Both groups maintained their usual diet. The results showed that the group receiving the supplements had an increased antioxidative capacity in their serum as measured by spectrophotometry using a free-radical analytical system. However, there were no significant differences in terms of nutritional parameters, liver function, immunological parameters, or postoperative outcomes.

CoQ10 is a cofactor for a number of energy-producing pathways within the cell. Generally, it is used to aid in energy production within the body and improve cardiac and immune function. Several studies have explored the use of Coenzyme Q10 in transplant patients.

An early study showed that donor rats or recipient rats which were given an intravenous infusion of CoQ10 1 h before liver transplant had significantly improved survival times, even when the transplanted liver was exposed to heat-related ischemic damage (Sumimoto et al. 1987). Untreated rats all died within 2 days, but almost half of the rats who had received CoQ10 survived at 1 week. Interestingly, it did not matter if the donor or recipient rat was treated with CoQ10 suggesting that once it accumulated in the donor, liver survival was improved along with reductions in liver enzymes.

Another line of evidence suggests that the related molecule, mitoquinone, may reduce inflammation and cell damage in hepatocytes in patients with chronic hepatitis C infection even though HCV levels did not change (Gane et al. 2010). The combination of antioxidants, such as idebenone, melatonin, and arginine were shown to almost completely protect rat hepatocytes from damage related to sodium nitrite-induced hypoxia (Ali et al. 2012).

Thus, while CoQ10 might help support the health of hepatocytes and protect them from various physiological insults, it is unclear whether CoQ10 would be helpful in human liver transplantation. Future studies would be needed to explore such a possibility.

Essential fatty acids are crucial to cellular functions throughout the body. Diets that are rich in omega-3 polyunsaturated fatty acids (ω3-PUFAs) such as alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid have been shown to be associated with lower incidences of several chronic diseases (Vanden Heuvel 2012). Omega-3 fatty acids have known anti-inflammatory effects which might contribute to their beneficial effects. Metabolism of omega-6 PUFAs generally results in proinflammatory mediators. Several specific studies have shown such PUFAs to be beneficial for supporting liver function. For example, one mouse study showed that those receiving a high fish oil diet for 8 weeks had beneficial effects on hepatic insulin resistance, lipogenesis, and beta-oxidation and prevented hepatic tissue from liver damage and NAFLD (Bargut et al. 2014). A limited number of

preliminary clinical trials have suggested that treatment of patients with nonalcoholic fatty liver disease with PUFAs helps improve liver function and outcomes, but larger trials will be necessary (Bouzianas et al. 2013).

Perhaps the most relevant trial was performed on 66 patients with end-stage liver disease or hepatocellular carcinoma who underwent liver transplantation and administration of isocaloric and isonitrogenous parenteral nutrition for 7 days following surgery (Zhu et al. 2012). One group received standard parenteral nutrition while the other group received parenteral nutrition with PUFAs replacing part of the standard lipid emulsion. The results showed that those patients receiving the PUFA nutrition had reduced injury to their hepatic cells. In addition, the PUFA-treated group had slightly reduced hospital stays, reduced complications, and improved 1-year survival. The authors concluded that parenteral nutrition with PUFA may be of benefit in patients receiving liver transplantation.

Alpha-lipoic acid is generally involved in energy metabolism but also acts as a powerful antioxidant, which may help protect hepatocytes from oxidative damage associated with various drugs, toxins, or pathophysiological processes. Several studies have identified specific circumstances in which lipoic acid may help support hepatocytes.

A mouse study of lipopolysaccharide (LPS)/D-galactosamine (D-GalN)-induced fulminant hepatic failure showed that those pretreated with lipoic acid had marked reductions in oxidative damage markers such as iNOS, COX-2, TNF-α, NF-κB, IL-1β, and IL-6 levels (Xia et al. 2014). Lipoic acid also improved apoptotic features in hepatocytes. Taken together, the results indicated that LA plays an important role on LPS/D-GalN-induced fulminant hepatic failure through its antioxidant, anti-inflammatory, and antiapoptotic activities. In both mouse and in vitro cell studies (Yang et al. 2014), alpha-lipoic acid was found to increase nuclear NF-E2-related factor 2 levels and reduce intrahepatic and serum triglyceride content. The studies suggest that alpha-lipoic acid protects against hepatic steatosis by modulating the transcription factors sterol regulatory element-binding protein-1, forkhead box O1, and NF-E2-related factor 2. One study of rats given liver toxic doses of acetaminophen suggested that lipoic acid may help protect the liver in a manner similar to *n*-acetyl cysteine (Elshazly et al. 2014).

NAC is a strong antioxidant and has been used in one particular situation regarding the liver, acetaminophen overdose, or toxicity. The primary mechanism is to help prevent the depletion of antioxidants such as glutathione in the liver in the face of large quantities of acetaminophen. However, it is possible that the antioxidant properties of NAC might be useful in the setting of liver transplantation. For example, a study of rats used for partial liver transplantation showed that when the liver was treated in cold storage with NAC, that NAC treatment resulted in improved microcirculation and functional quality of the partial liver graft. The authors suggest that the use of NAC helped increase antioxidant capacity in the liver graft and also reduced lipid peroxidation.

However, a study of 88 patients undergoing liver resection did not show any significant improvements in patients who had received perioperative NAC. It should be noted that the NAC group did have lower rates of liver failure, but this did not achieve significance (Robinson et al. 2013).

S-adenosyl-L-methionine is an important physiological molecule that participates in multiple cellular reactions. Its primary roles include being a precursor for the synthesis of glutathione and functioning as a principle methyl donor of nucleic acids, phospholipids, histones, biogenic amines, and proteins. SAMe synthesis is typically depressed in chronic liver disease so supplementation has been considered a potentially important therapeutic intervention. However, there have been no conclusive trials or adequate data to support or refute the use of SAMe in patients with chronic liver disease (Anstee and Day 2012). Several examples more specifically related to liver transplantation are described below.

A preliminary study of 81 HCC patients with chronic HBV infection, undergoing partial hepatectomy with inflow occlusion, were treated with SAMe either two hours before surgery or 6 h after surgery and compared to a control group that did

not receive SAMe (Liu et al. 2014). In this study, the preoperative administration of SAMe significantly reduced the plasma levels of alanine transaminase (ALT), aspartate transferase (AST), total bilirubin (TBIL), and direct bilirubin (DBIL) as compared to the other two groups. Administration of SAMe postoperatively resulted in significant reductions in TBIL and DBIL compared to controls. Measures of IL-6 and TNF-α were significantly different between the preoperatively treated group and the other groups. Preoperative administration of SAMe reduced the risk of complications and the hospital stay after surgery.

A rat study evaluated the effect of 5′-methylthioadenosine (MTA), which is a nucleoside generated from *S*-adenosylmethionine, during liver transplantation. The results showed that pretreatment with MTA significantly improved liver function and reduced hepatic ischemia-reperfusion injury by downregulating TNF-α level and suppressing the postsurgical inflammatory response (Tang et al. 2014). Administration of MTA was also associated with the inhibition of IκBα degradation, NF-κB transcriptional activity, and the activation of MAPK signal. Thus, the beneficial effect of MTA in liver transplantation appeared to be mediated by inhibiting the activation of the NF-κB and MAPK signal pathways. However, another study of rats with liver steatosis found no beneficial effect of *S*-adenosylmethionine on ischemia-reperfusion injury during liver transplantation (Pantoflicek et al. 2012).

Taurine derivatives have been evaluated in liver transplant patients. A pilot study of 10 cirrhotic patients awaiting liver transplantation were given tauroursodeoxycholic acid until liver transplantation while evaluating a variety of liver function parameters (Caglieris et al. 2000). For example, liver cholestasis and cytolysis parameters decreased along with serum gamma-glutamyl transpeptidase at the 4th month of therapy compared to pretreatment values and compared to a group of untreated historical controls.

An optimal vitamin D status may benefit liver transplantation (LT) patients by helping them to maintain adequate muscle and bone mass and reduced inflammatory effects. One study evaluated 25(OH)D in banked specimens from 154 human immunodeficiency virus-positive patients with advanced liver disease who were liver transplant candidates/recipients (Branch et al. 2014). The study showed that 71 % of patients had vitamin D deficiency prior to transplantation, and this improved to approximately 40 % of patients posttransplant. The authors also reported that none of the 17 academic medical centers involved in this study routinely recommended vitamin D supplements prior to transplant, and only 4/17 recommended vitamin D supplementation after surgery. However, this study did not evaluate whether the deficiency in vitamin D levels was associated with poorer outcome posttreatment.

Another study evaluated 133 patients who received a liver transplant (Bitetto et al. 2010). Overall, these patients were found to have a median 25-hydroxyvitamin D level that was below normal, and 79 of these patients were treated with supplemental oral vitamin D. The authors found that in the 2 months following transplant, lower pretransplant serum 25-hydroxyvitamin D levels were associated with an increased risk of moderate-to-severe acute rejection episodes. In addition, oral vitamin D supplementation (within the first month after the transplant) was associated with a reduced incidence of acute rejection episodes.

Finally, another study evaluated whether vitamin D levels were associated with cellular rejection in liver transplant patients (Sheikh-Ali et al. 2014). The study evaluated 149 patients who underwent liver transplantation and initially found that 92 % of patients had 25(OH)D levels <30 ng/mL. However, there was no difference in vitamin D levels in patients who had acute cellular rejection compared to those who did not have rejection.

Supplements to Avoid

A number of nutritional and herbal supplements have also been observed to be associated with hepatotoxicity (Mullin 2013a, b). Such supplements should be avoided in patients with chronic liver disease or after having received a liver

transplant. A partial listing of some of the more common supplements that might have hepatotoxic effects includes aloe vera, black cohosh, comfrey, germander, green tea extract, Herbalife supplements, hydroxycut, kava, mistletoe, niacin, nicotinic acid, saw palmetto, senna, and valerian (see also a more detailed table in Corey and Rakela 2014). In addition to those supplements that might cause hepatotoxicity, patients should also be cautioned against using supplements that might adversely affect surgical outcome by increasing the risk for complications such as bleeding. Several nutritional supplements may increase the risk of bleeding by affecting platelets or clotting factors such as fish oil, garlic, ginkgo biloba, ginseng, feverfew, vitamin E, and ginger (Stanger et al. 2012; Corey and Rakela 2014). Several supplements might contribute to hypoglycemia such as alpha-lipoic acid and cassia cinnamon. Some supplements such as kava and valerian also have sedating effects which might interact with anesthetics. It is therefore important to obtain a thorough medical history and list of all supplements that a patient is taking prior initially as well as prior to surgery. Patients should be encouraged to discontinue any supplements that might have hepatotoxic effects. Also, supplements that might adversely affect surgical outcomes should be discontinued 2–3 weeks prior to surgery and withheld until several weeks postoperatively depending on the clinical status of the patient (Ang-Lee et al. 2001). In the posttransplant patient, care should be given to any supplements that might interact with immunosuppressive drugs that are necessary for protecting against organ rejection. Oral magnesium is known to inhibit the plasma concentration of the immunosuppressive drug, mycophenolate mofetil, when taken simultaneously (see package insert). Thus, if magnesium is required for the patient, it should be administered at least 2 h after administering the mycophenolate mofetil. Perhaps most importantly in the context of liver transplant patients as well as in relation to immunosuppressive drugs are supplements that interfere with the P450 cytochrome system and P-glycoprotein. The P450 cytochrome system is involved in metabolizing many different drugs. The P-glycoprotein is a membrane transporter that is important in drug absorption and distribution. Immunosuppressants such as tacrolimus, cyclosporine, sirolimus, and everolimus are metabolized by the P450 system and are handled by the P-glycoprotein. Therefore, supplements that increase or decrease the activity of the P450 cytochrome system or P-glycoprotein can affect the concentration of these drugs either reducing their activity or resulting in potentially toxic levels. As a specific example, St John's wort which is frequently used to improve mood, is an inducer of CYP450 3A4 (Mai et al. 2003), the primary enzyme responsible for metabolizing the above mentioned immunosuppressive drugs, thereby reducing their concentration and potentially making the patient more prone to experiencing organ rejection.

Probiotics and Prebiotics

Probiotics are microbiota whose biology is overall symbiotic and favorable to health in humans (Jirillo et al. 2012). Probiotics may play an important role in maintaining overall body health as the human body contains at least ten times more bacterial cells than human cells. Most of these bacterial cells are in the intestinal tract. The gut's microbial community is essential for intestinal, as well as overall, health. Symbiosis in this gut biomass is crucial for maintaining a healthy balance within the host-diet-microbiota triangle. Detrimental changes in any of these three components may lead an individual toward a state of disease or worsening of an existing disease. In addition, disease states are often associated with an imbalance in this triangle. The role of probiotics in the field of liver health is just recently starting to attract attention.

Regarding probiotics, the gut immune system is constantly exposed to multitudes of antigens derived from the environment and food. Peyer's patches and lymphoid follicles respond to the variety of antigenic stimuli by releasing different cytokines or producing antibodies (e.g., secretory IgA). Symbiotic intestinal microbiota generates responses that help reduce inflammation in the gut and body leading to overall better health.

Dysbiotic segmented filamentous bacteria induce Th17 cells to activate and promote inflammation which could be detrimental.

Bacterial infections frequently occur after liver transplantation, and many of the infections are gut derived, most likely through bacterial translocation. In a double-blind study, administration of a specific probiotic preparation markedly decreased the incidence of bacterial infections following liver transplantation. Sixty-six patients undergoing a liver transplant were randomly assigned to receive a combination of 4 probiotic organisms (*Lactobacillus paracasei* ssp. paracasei F19, *L. plantarum* 2362, *Pediococcus pentosaceus* 5–33:3, and *Leuconostoc mesenteroides* 77:1) plus 4 prebiotic fibers (beta-glucan, inulin, pectin, and resistant starch) or just the prebiotic fibers alone as a control group (Rayes et al. 2005). The combination product used for the study was called Symbiotic 2000 (Medi-pharm, Kagerod, Sweden, and Des Moines, IA, USA). Treatment was started the day before surgery and continued for 14 days postsurgery. The incidence of post-liver transplant bacterial infections was 3 % in the group receiving the combination of probiotics and prebiotics and 48 % in the control group.

It should be noted that while probiotics may be of help, they might be not advisable in all clinical settings. For example, probiotics are contraindicated in several in-patient populations (Boyle et al. 2006; Johnston et al. 2012) including (1) patients with neutropenia or other causes of immunosuppression which would be the case in posttransplant patients, (2) intensive care unit patients, (3) patients with central venous catheters receiving parenteral nutrition, and (4) patients requiring administration of the probiotic via a feeding tube or requiring opening of capsules/crushing of medications for drug administration.

However, it is difficult to make general recommendations on when and when not to take specific prebiotics and probiotics in liver patients and transplant patients at this time. Based on the available evidence, it is reasonable that physicians and patients discuss these issues together and come up with an individualized strategy using well-studied and available products along with sound clinical judgment.

Mind-Body Practices

A report from the Agency for Healthcare Research and Quality, Department of Health and Human Services (Ospina et al. 2007), reviewed the current state of research on a variety of meditation-based practices which include meditation, yoga, and others. The report indicated that there are a variety of potentially therapeutic benefits that can be derived from mind-body practices. Such benefits typically are related to psychological symptoms such as stress, anxiety, or depression. Many patients with chronic liver disease, pending transplant patients, and transplant recipients face significant stressors (Bunzel and Laederach-Hofmann 2000; Karaivazoglou et al. 2010). These stressors can include the limitations associated with liver failure, the uncertainly of being on the transplant list, the need to undergo multiple tests and scans, and the need to take a large number medications which can have a variety of adverse effects. Thus, liver disease patients frequently report heightened stress, anxiety, and depression and overall poorer quality of life (Bunzel and Laederach-Hofmann 2000; Karaivazoglou et al. 2010). Thus, mind-body practices might be helpful in reducing the stress and anxiety reported by chronic liver disease patients. While no studies have specifically evaluated the use of such practices in this population, it is worth briefly exploring the effects of mind-body practices.

Mindfulness meditation, the core practice of Buddhist meditation, has been incorporated into several clinically based meditation programs, including mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT). These programs have been well studied and shown to be effective in helping patients with stress, anxiety, and mood disorders (Bishop et al. 2004).

An early study of MBSR in 14 patients with anxiety found a reduction in depression, anxiety, and general psychological distress in patients undergoing MBSR therapy (Kabat-Zinn et al. 1992). However, meta-analyses have come to somewhat conflicting conclusions regarding MBSR's efficacy. One review of 15 studies

found no clear beneficial effect of the MBSR program on depressive symptoms in patients with comorbid medical disorders (Toneatto and Nguyen 2007). Another systematic review and meta-analysis found mindfulness-based therapies to have robust within-group effect sizes in patients with anxiety and mood disorders (Hofmann et al. 2010). These improvements were also maintained on follow-up evaluations. Our group showed a reduction in stress and anxiety in a cohort of cancer patients undergoing a mindfulness-based art therapy program (Monti et al. 2013). Thus, meditation-based practices such as mindfulness programs may be useful for reducing stress and anxiety in liver transplant patients.

Yoga has also been shown to reduce anxiety in different patient populations. A study of women with self-reported anxiety showed that compared to wait-list controls, those in the yoga group had reductions in stress, anxiety, fatigue, and depression as well as increased well-being and vigor, after attending 2 weekly 90 min yoga sessions (Michalsen et al. 2005). Yoga led to improved anxiety in women with breast cancer (Rao et al. 2009). A systematic review of the effects of yoga on anxiety treatment identified five trials of persons with clinically diagnosed anxiety disorders (Kirkwood et al. 2005). While the studies were small and methodologically flawed, the results were consistently positive. It is possible that the potential underlying mechanisms for the positive effects of yoga on psychological and physiological conditions can include the stimulation of pressure receptors leading to enhanced vagal activity and reduced cortisol (Field 2010).

Acupuncture

Acupuncture is the ancient practice of inserting thin needles into different points on the body in order to help elicit specific effects. Acupuncture is most widely used for analgesic purposes in both acute and chronic pain. There are few studies that have evaluated the clinical effect of acupuncture on chronic liver disease or in transplantation patients. Several animal studies have suggested that acupuncture at specific points can help to decrease the swelling of liver cells and improve hepatic microcirculation in rats with hepatic fibrosis (Zhu and Sun 1998). And a few clinical trials often incorporating acupuncture with other elements of traditional Chinese medicine have improved liver function in patients with hepatic fibrosis (Zhou et al. 2012). A small study of patients undergoing liver resection for cancer found that acupuncture might be useful for attenuating postoperative symptoms such as abdominal distention and restoring bowel function (Li et al. 1994).

In addition to its potential effects on the liver itself, like the mind-body practices mentioned above, acupuncture has been effective in the management of anxiety and depression. Several studies have indicated that acupuncture might be useful in reducing pre-procedure anxiety (Wang et al. 2001; Fanti et al. 2003). However, a systematic review of the literature on acupuncture in anxiety revealed generally a poor quality of research studies and many methodological issues that complicate any understanding of acupuncture's effective in anxiety (Errington-Evans 2012). Issues that require further research include the location and types of acupuncture points to be used, the duration and frequency of acupuncture treatment, and the use of adequate control groups. However, given these limitations, sufficient studies do support the potential use of acupuncture in anxiety so more research is required.

Conclusion

As can be ascertained from this review, there is limited data on the use of integrative medicine approaches in the management of patients with chronic liver disease and those either awaiting or having received liver transplantation. Thus, there are no clear guidelines or recommendations that can be made at this time. However, it may be reasonable to consider some of these integrative techniques, particularly a balanced diet and mind-body therapies in the liver patient. Ultimately, future studies will have to explore the specific use of diet and nutrition, supplements, and mind-body practices in this patient population.

Cross-References

- ▶ Orthotopic Liver Transplantation: Complications
- ▶ Orthotopic Liver Transplantation: Indications and Contraindications
- ▶ NASH: The Ethical Dilemma

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Liver Transplantation: Medical Home 31

George Valko

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Abstract

Transplant surgery is by its very nature a medical home to its patients. The transplant team adheres to many of the same principles that the primary care and medical specialties need for their recognition by national organizations, such as first-contact, continuous, coordinated care and an emphasis on excellent patient outcomes. But there is no such recognition yet available under the current definitions of a Patient-Centered Medical Home or Patient-Centered Specialty Practice for surgeons of any specialty. This chapter will discuss the importance and history of the Patient-Centered Medical Home, its evolution to the Patient-Centered Specialty Practice, and the groundwork and effort that will be needed for transplant surgery to be recognized for the similar work it has been doing for years.

Keywords

Transplant surgery • Patient-Centered Medical Home • Patient-Centered Specialty Practice • NCQA

Introduction

Transplant surgery is unique among the surgical specialties that by its very nature must provide long-term or chronic ongoing care to its patients. The transplant team is headed by the surgeon who

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provides first-contact care to the patient. The surgeon leads a team of professionals responsible for continuous care of its patients that may include regulating long-term medications, acute illness management, and even preventive testing and immunizations. The team must arrange care with other qualified professionals, especially with those medical specialties associated with a transplanted organ, as well as the primary care physician and mental health counselors.

The transplant team must coordinate care for its patients across all elements of the health-care system such as social work, case or care management, and even home care and rehabilitation medicine. This may begin from the time a patient is designated for a transplant, to procurement of the organ, to transplant, and years afterward. This comprehensive care is facilitated by registries and information technology. The team also strives for optimal patient-centered outcomes measures and must keep meticulous outcome details for each year of the graft/host survival. As one of the most regulated fields in medicine, this record is mandated for reporting to the Centers for Medicare and Medicaid Services (CMS) and the Health Resources and Services Administration (HRSA) through the Scientific Registry of Transplant Recipients (SRTR) and the Organ Procurement and Transplantation Network (OPTN) (Gaber et al. 2013).

The legacy of transplant surgery is an ongoing and lifelong care for the patient even if co-managed by other clinicians. As such, the role of the specialist, in this case the transplant surgeon, and the primary care clinician might be reversed; the specialist must insure that patients have access to a full range of primary care services, and the primary care team might serve as consultants (Taylor et al. 2011).

Given that transplant surgery carries this enormous responsibility, can the transplant surgery team be considered a true Patient-Centered Medical Home? To understand the answer one must first understand the concept of the Patient-Centered Medical Home (PCMH), the PCMH "neighborhood" (PCMH-N), and finally, the Patient-Centered Specialty Practice (PCSP).

What Is a Patient-Centered Medical Home?

The PCMH is a team-based approach to providing high-quality, comprehensive primary care, improving the patient experience, and reducing costs for the patients and the system – the triple aim of health-care improvement. The team may include medical assistants, nurses, physicians, physician extenders, social workers, pharmacists, and behavioral health providers as well as case managers. The PCMH facilitates and relies on partnerships between individual patients, other physicians, ancillary health-care services, and, when appropriate, the patient's family (Valko et al. 2012). PCMHs are aided by and rely upon robust information technology as they are highly data driven to monitor processes and outcomes for improvement.

According to the Agency for Healthcare Research and Quality (AHRQ) (2012), the medical home model holds promise as a way to improve health care in America by transforming how primary care is organized and delivered. The medical home is not simply a place, but a model of health care that is designed to reliably and reproducibly implement the core functions of primary health care.

The medical home concept was first introduced in 1967 by the American Academy of Pediatrics (AAP) as the way to keep medical records in a central location for all medical specialists' visits (ACP 1967). The concept was expanded in 2002 by the AAP to include principles that all care be accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective (Pediatrics 2002).

In 2004, the American Academy of Family Physicians (AAFP) released its own medical home model to improve patient care (AFM 2004). In 2006, the American College of Physicians (ACP) published and promoted the concept of the "advanced medical home" (ACP 2005).

The American Academy of Pediatrics (AAP), AAFP, and ACP joined with the American Osteopathic Association (AOA) to develop the Joint Principles of the Patient-Centered Medical Home.

In 2007 these four organizations released these seven joint principles to describe the characteristics of the PCMH (ACP 2007):

1. Personal physician:
   - Each patient has an ongoing relationship with a personal physician trained to provide first-contact, continuous, and comprehensive care.
2. Physician-directed medical practice:
   - Personal physicians lead an interdisciplinary team of individuals responsible for the ongoing care of the patient (comprehensive care is a team effort, involving all levels of medical professionals as physician extenders).
3. Whole-person orientation:
   - Personal physician is responsible for providing all of the patient's health-care needs or taking responsibility for appropriately arranging care with other qualified professionals (all stages of life included acute care, chronic care, preventive services, end-of-life care).
4. Care is coordinated and/or integrated:
   - Personal physician ensures care is coordinated across all elements of the health-care system and patient's community (subspecialty care, hospitals, home health agencies, nursing homes).
   - Care is facilitated by registries, information technology, and health information exchange.
5. Quality and safety are hallmarks:
   - Practice advocates for their patients to support the attainment of optimal, patient-centered outcomes.
   - Evidence-based medicine and clinical decision support tools.
   - Physicians accept accountability for CQI.
   - Patients actively participate in decision making.
   - Feedback sought to ensure patient needs are being met.
   - IT used to support optimal patient care, performance measurement, education, and communication.
   - Practices undergo a voluntary recognition process to ensure they have the elements to provide patient-centered care.
   - Patients and families participate in QI activities at the practice level.
6. Enhanced access to care:
   - Practice seeks to create/implement options to improve access (open access scheduling, expanded office hours, new options for communication).
7. Payment:
   - Payment should appropriately recognize the added value of caring for patients in a PCMH.

Several alternative names have been proposed as potential substitutes for the term PCMH, including terms such as "advanced primary care" and "comprehensive primary care." Although these alternative names do provide useful descriptors of the PCMH concept and may be used interchangeably, the term PCMH has been widely embraced by government, insurers, employers, and health-care agencies (CMS 2011).

Developed in part as a response to the fragmented US health-care system, the PCMH addresses the lack of care coordination in a growing population of patients with chronic illness who may seek their care at more expensive episodic emergency room visits rather than improved care at lower costs by a primary care clinician.

The advent of US health-care system reform affected both health insurance and health-care delivery. Delivery reform includes new organizational structures such as the Accountable Care Organizations and other integrated delivery systems (CDC 2014). ACOs coordinate doctors, hospitals, and other health professionals to make sure people get all the care they need while eliminating waste and inefficiency. ACOs also build on a solid PCMH foundation to bring patient-centered care to entire health-care communities. Because of the rigorous practice transformation and ongoing quality improvement required to become certified – and because of the superior clinical outcomes they produce – PCMHs are the key to success in this new environment.

Along with new organizational structures, delivery reform is also associated with payment reform. Payment system reforms include pay for performance, shared savings models, and other quality incentives that reward providers who achieve the triple aim of reduced cost, improved quality, and enhanced patient experience rather than the volume of services they provide (NCQA 2014).

Numerous studies have demonstrated that medical homes improve care and access and reduce unnecessary medical costs:

- A few early studies cited by the Patient-Centered Primary Care Collaborative (PCPCC) (Grumbach et al. 2014)
  - Geisinger, Pennsylvania
    - Fourteen percent reduction in hospital admissions and "trend toward a 9 % reduction in medical costs"
    - Statistically significant improvement in quality of preventive, coronary artery disease and diabetes care
  - Group Health Cooperative, Puget Sound
    - Twenty-nine percent reduction in emergency room visits and 11 % reduction in ambulatory sensitive care admissions
    - Four percent increase in patients achieving target levels on the Healthcare Effectiveness Data and Information Set (HEDIS) quality measures
  - Genesee Health Plan, Michigan
    - Fifty percent reduction in ER visits and 15 % reduction in hospitalizations
    - One hundred and thirty-seven percent increase in mammogram screening rates
    - Thirty-six percent reduction in smoking
- IBC in Philadelphia announced in 2014 that the results of a series of 3-year studies that demonstrate significant reductions in medical costs for patients with chronic conditions such as diabetes, CAD, CHF, COPD, asthma, and hypertension treated in primary care practices that have transformed into medical homes largely attributed to a reduction in hospital and ED costs (IBC 2014).
- Although some more recent studies showed there was no difference in many quality care measures, utilization, or costs of care (Friedberg et al. 2014), issues with that study were raised (Cronholm et al. 2014; Valko and Wender 2014), and a follow-up study of a different segment of the same demonstration project was associated with relative improvements in quality, primary care utilization, and lower use of ED, hospital, and specialty care (Friedberg et al. 2015).
- In addition, in a direct comparison with National Committee for Quality Assurance (NCQA)-Recognized PCMH practices versus non-recognized practices, total Medicare payments, acute care payments, and the number of emergency department visits declined after practices received NCQA PCMH Recognition and was more pronounced in those practices with sicker than average patients, primary care practices, and solo practices (Hasselt et al. 2015).

Other advantages of a recognized PCMH include:

- PCMHs are receiving enhanced payments just for becoming NCQA Recognized as in the case with Independence Blue Cross (IBC) in Philadelphia (Spoeri et al. 2014). Other payers are following this trend with their own plans for enhanced payments.
- Improved market share for the health system: the PCPCC has been the leader in encouraging organizations to develop businesses in areas where there is a high concentration of primary care to help control costs and provide quality care (PCPCC 2008).
- Having a NCQA PCMH Recognition is a seal of approval for that practice; more and more institutions, other providers, and patients recognize the importance of this designation.

Many primary care practices already function as a PCMH, but doing the work to receive certification from and/or by a national agency can be a daunting task. Although recognition by the NCQA is considered by many to be the "gold standard" for PCMH and is the most widely utilized by insurers, other organizations, including

Table 1 Comparison of NCQA Standards 2008–2014

Year	Version	Elements of the program
2003	Physician Practice Connections (PPC)	This PCMH precursor recognized use of systematic processes and health IT to: Know and use patient history Follow up with patients and other providers Manage patient populations and use evidence-based care Employ electronic tools to prevent medical errors
2008	Physician Practice Connections – Patient-Centered Medical Home (PPC-PCMH)	The first PCMH model implemented the joint principles, emphasizing: Ongoing relationship with personal physician Team-based care Whole-person orientation Care coordination and integration Focus on quality, safety, and enhanced access
2011	PCMH 2011	Explicitly incorporated health information technology meaningful use criteria Added content and examples for pediatric practices on parental decision making, age-appropriate immunizations, teen privacy, and other issues Added voluntary distinction for practices that participate in the CAHPS PCMH survey of patient experience and submit data to NCQA Added content and examples for behavioral health care
2014	PCMH 2014	More integration of behavioral health care Additional emphasis on team-based care Focus care management for high-need populations Encourage involvement of patients and families in QI activities Alignment of QI activities with the triple aim: improved quality, cost, and experience of care Alignment with health information technology meaningful use stage 2

the Joint Commission, Utilization Review Accreditation Commission (URAC), and even insurance companies, have certification programs (Valko et al. 2012).

The program by the NCQA has exacting standards which have undergone revisions every 3 years. The primary focus of the 2008 Standards was infrastructure development and introduction of new office processes which emphasized redesigning workflows and roles to support a sustainable new delivery system. The 2011 Standards were intended to leverage the new infrastructure to advance care delivery and test the presence of true systems of care and team-based care as well as promote continuous performance activities within a patient outcome-driven practice. The current 2014 Standards emphasize more coordination of care and patient involvement. The following table (Table 1) from the NCQA 2014 PCMH Recognition Program illustrates these changes over the years.

The PCMH model has been endorsed by multiple medical societies, including the American Medical Association, the American College of Cardiology, the American Society of Clinical Oncology, the American Academy of Neurology, the Society of Critical Care Medicine, as well as the aforementioned four primary care groups. It is strongly promoted by the PCPCC representing employers, consumer groups, and professional societies as well as being a part of CMS national demonstration projects.

The Medical Neighborhood

With the success of the PCMH programs, the non-primary care medical specialties advocated for their role in a PCMH for the appropriateness of specialist-delivered primary care. This was thought by some to be a reaction by those specialties to health-care reform dollars being channeled to the primary care sector at the expense of specialty services, as they were at the start of the health maintenance organizations (HMOs) (Diamond 2010).

The Council of Subspecialty Societies (CSS) of the ACP established a workgroup in 2007 to

specifically address the perceived relationship between the PCMH care model and specialty/subspecialty practices (Kirschner and Barr 2010). They concluded that the PCMH model provides no incentive to limit appropriate referrals to specialists or subspecialists by a patient's personal physician and does not prohibit patients from choosing to see a specialist or subspecialist of their choice. Furthermore, although the PCMH is most compatible with primary care practices, it did emphasize that specialists can participate as long as they provide primary care services, including first-contact and comprehensive care, as well as meet the recognition process requirements of a PCMH. In addition, the PCMH model would appear to be appropriate for the subset of patients in specialty or subspecialty practices who are receiving long-term, principal care for a condition by physicians in that practice, such as a pulmonologist caring for patients with chronic lung conditions or and endocrinology practice caring for complex diabetics.

A later study did corroborate that applying PCMH principles to a specialty clinic improved outcomes: at VA-run HIV clinics, more PCMH-principled HIV clinics largely functioned as PCMHs; patients received integrated, coordinated, comprehensive primary care within a dedicated HIV clinic. In contrast, some clinics were unable to meet the criteria of being a patient's medical home and instead functioned primarily as a place to receive HIV-related services with limited care coordination. Patients from the less PCMH-principled clinics reported less satisfaction with their care (Fix et al. 2014).

Fisher (2008) coined the term medical neighborhood to describe the barriers for PCMHs to reach their full potential. In his article, he states that the medical home has great potential to improve the provision of primary care and the financial stability of primary care practice. Missing so far in the PCMH has been an effort to implement this model in concert with other reforms that more effectively align the interests of all physicians and hospitals toward the improvement of patient care. To deliver on its promise, the medical home needs a hospitable and high-performing medical neighborhood.

Fisher described several approaches to overcome barriers which then would strengthen medical home models:

- Resistance to collaboration because there are few incentives for hospitals and specialists to collaborate with primary care physicians would be balanced by requiring medical homes to specify practice networks for performance measurement and information sharing.
- Institute transparent performance measurements across the continuum of care and reward collaboration through pay for performance or shared savings.
- Foster integrated delivery systems that share savings from improved quality of care and lower costs for patients.

Within a short time, an important position paper outlining criteria to become a PCMH Neighbor (PCMH-N) by the ACP (2010) solidified primary care as the stewards of PCMHs and more realistically clarified the relationship of the non-primary medical specialties to the PCMH with the following points:

1. The ACP recognizes the importance of collaboration with specialty and subspecialty practices to achieve the goal of improved care integration and coordination within PCMH care delivery model.
2. The ACP approves the following definition of a PCMH-N as it pertains to specialty and subspecialty practices:
   - A specialty/subspecialty practice recognized as a PCMH-N engages in processes that:
     - Ensure effective communication, coordination, and integration with PCMH practices in a bidirectional manner to provide high-quality and efficient care.
     - Ensure appropriate and timely consultations and referrals that complement the aims of the PCMH practice.
     - Ensure the efficient, appropriate, and effective flow of necessary patient and care information.

- Effectively guide determination of responsibility in co-management situations.
- Support patient-centered care, enhanced care access, and high levels of care quality and safety.
- Support the PCMH practice as the provider of whole-person primary care to the patient and as having overall responsibility for ensuring the coordination and integration of the care provided by all involved physicians and other health-care professionals.

3. The ACP approves the following framework to categorize interactions between PCMH and PCMH-N practices:
   - The clinical interactions between the PCMH and the PCMH-N can take the following forms:
     - Preconsultation exchange – intended to expedite/prioritize care or clarify need for a referral
     - Formal consultation – to deal with a discrete question/procedure
     - Co-management
       - Co-management with shared management for the disease
       - Co-management with principal care for the disease
       - Co-management with principal care of the patient for a consuming illness for a limited period
     - Transfer of patient to specialty PCMH for the entirety of care
4. The position paper went on to recommend the aspirational guiding principles for the development of care coordination agreements between PCMH and PCMH-N practices to further define the relationship.

Subsequent to the ACP position paper, an AHRQ panel created its own white paper on the PCMH-N (Taylor et al. 2011). This equally important document broadened the view from just the primary care specialist or physician-hospital interactions to incorporate community and social services and a more expansive policy perspective. The AHRQ authors defined the medical neighborhood as a PCMH and the many other clinicians providing health-care services to patients within it, along with community and social service organizations and state and local public health agencies. In this way, they surmised, the PCMH and the surrounding medical neighborhood would focus on meeting the needs of the individual patient but also incorporate aspects of population health and overall community health needs in its objectives.

The PCMH was designated as the center of the medical neighborhood, given its role as the central point of contact for the patient and primary coordinator of the patient's care across various neighbors. Within the PCMH, the primary clinician caring for the patient may be a physician, nurse practitioner, or physician assistant. Importantly, the neighborhood is not necessarily a geographic construct but instead a set of relationships revolving around the patient and his or her PCMH, based on that patient's health-care needs.

For some patients, the authors write, the medical neighborhood may be centered on specific specialists rather than primary care; this might include patients with severe and persistent mental illness, those living with AIDS, and those with a new diagnosis of cancer. In such cases, as noted previously, the role of the specialist and the primary care clinician might be reversed, but the specialist must insure that patients have access to a full range of primary care services, and the primary care team might serve as consultants.

In addition, the AHRQ authors stated that a well-functioning medical neighborhood would include the following:

- Clear agreement on and delineation of the respective roles of neighbors in the system (e.g., through care coordination agreements between PCCs and specialty physicians, agreements on care transitions, pre-referral arrangements, referral and follow-up guidelines from professional societies, or others)
- Sharing of the clinical information needed for effective decision making and reducing duplication and waste in the system, supported by appropriate health IT systems
- Care teams, typically anchored by the PCMH, to develop individualized care plans for complex patients (such as those with multiple

chronic conditions) that describe a proactive sequence of health-care interventions and interactions – followed by tracking and assisting to ensure that this takes place (including care transitions)
- Continuity of needed medical care when patients transition between settings (e.g., when transferred from a hospital to a skilled nursing facility and then to an assisted living facility), with active communication, coordination, and collaboration among everyone involved in the patient's care, including clinicians, patient, and family
- A focus on the patient's preferences with informed or shared decision making – in which patients, families, and clinicians work together to balance scientific evidence and patient preferences to make optimal medical decisions with the patient
- Strong community linkages that include both clinical and nonclinical services (such as personal care services, home-delivered meals, or school-based health care)

The Patient-Centered Specialty Practice (PCSP)

In March 2013, the NCQA, building on the success if its PCMH program, established PCSP Standards for specialty practices engaged in a patient-centered care model (2014).

Development of the PCSP program followed the NCQA product development process and included the use of a multi-stakeholder advisory committee, a literature review, public comment, targeted interviews with practices, and beta testing. NCQA drew from the work of the Agency for Healthcare Research and Quality and the American College of Physicians that were outlined above. PCSP standards were approved by the NCQA Board of Directors in December 2012.

Practices that become recognized as PCSPs will demonstrate patient-centered care and clinical quality through streamlined referral processes and care coordination with referring clinicians, timely patient and caregiver-focused care management, and continuous clinical quality improvement.

The PCSP Recognition Program for clinicians is designed to improve quality and reduce waste and poor patient experiences that result from poorly coordinated care. The program focuses on coordinating and sharing information among primary care clinicians and specialists. It requires clinicians to organize care around patients – across all clinicians seen by a patient – and to include patients and their families or other caregivers in planning care and as partners in managing conditions.

This program recognizes specialty practices that successfully coordinate patient care and communicate with their primary care colleagues, other specialists, and patients. Like NCQA's Patient-Centered Medical Home (PCMH) program, PCSP Recognition has specific expectations for providing timely access to care and continuous quality improvement. Practices who earn recognition have made a commitment to providing high-quality patient-centered care.

The PCSP Recognition Standards are:

1. Track and coordinate referrals: The specialty practice collaborates effectively with other specialists and with primary care practitioners (PCP) to coordinate testing and care of shared patients. Referral communications support the needs of all clinicians.
2. Provide access and communication: The specialty practice offers timely access to appointments, offers timely responses to telephone and secure electronic messages during and after office hours, addresses patients' cultural and language needs, and explains the roles of PCPs, specialists, and the patients in the collaborative relationship. A specialty practice team trains team members to be patient centered and to contribute to the full extent of their license or role.
3. Identify and coordinate patient populations: The specialty practice captures key clinical and administrative data to facilitate reporting on specific populations, uses evidence-based tools to manage care for those populations, and follows up when care is needed.
4. Plan and manage care: The specialty practice develops a patient-centered care plan on its

own or in collaboration with a PCP or other specialists and assesses barriers and progress. The practice manages patients' medications and provides educational resources or refers patients to community services, as needed.
5. Track and coordinate care: The specialty practice coordinates the use of lab, imaging, and other specialty referrals with PCP practices or other specialists caring for a patient and tracks them from the point of request through receipt and patient notification. The practice also tracks patients as they move through transitions of care, such as hospitalizations.
6. Measure and improve performance: The specialty practice measures a number of clinical processes or outcomes and patient experience, showing improvement over time, and demonstrates transparency by sharing data within the practice and with external organizations.

As it is for PCMH Recognition, becoming a PCSP-Recognized practice is a daunting and time-consuming task. Specialties undergoing practice transformation must comply with a rigorous practice redesign to ensure that testing, referrals, and patient care are all highly coordinated and that communication between specialists, primary care physicians, and facilities is efficient, timely, and meaningful.

Again, as it is for PCMH Recognition, the same reasons exist for a specialty practice to make this effort to transform into a PCSP:

- Improved patient care and outcomes
- Changing reimbursement models – although the bulk of specialty care is fee-for-service, with the advent of shared savings, ACO, and other payment models, it is just a matter of time before pay for performance rather than pay for volume is the norm. All physicians must be ready to capture quality care dollars.
- Better market share – as with NCQA PCMH, having an NCQA PCSP Recognition is a seal of approval and may mean more referrals for primary care practices and patients, who value what the designation represents in quality care.

Role of Transplant Surgery

As stated in the beginning, transplant surgery, by its very nature, has many attributes that are used for recognition by the NCQA for either a PCMH or PCSP. Since transplant surgery is not primary care, it does not fit the definition of a PCMH, similar to the medical specialties that originally wanted to be designated as a PCMH. However, transplant surgery would fit nicely into the PCSP model if not for the fact that the NCQA currently recognizes only medical specialties for recognition as a PCSP.

As with the evolution of the PCMH into a PCSP by the efforts of thought leaders and of the medical specialty societies, it may take that type of effort by the surgical specialty societies and others to have transplant surgery recognized for the medical home as it has been for many years. The literature is already illuminating some of this effort from the surgical arena that will further this recognition:

- Talwalkar (2014) states that although innovative models have been directed toward primary care, emerging date suggests that they will also play a major role in the delivery of specialty care, including the clinical practices of general and transplant hepatology. The majority of academic health centers housing major hepatology and liver transplant programs are structured as integrated delivery systems affiliated with a medical school and already attain those principles of PCMHs, PCSP, and ACOs such as multidisciplinary, coordinated care, financing through bundled payments, publicly reported outcomes measures, and shared patient responsibility.
- Although an American Board of Internal Medicine subspecialty, the Advanced Heart Failure and Transplant Cardiology dovetails with transplant surgery to use PCMH and PCSP principles in its care of patients for the long term with improved outcomes (Konstam and Greenberg 2009).
- Innovations such a using telehealth for patient follow-up after liver transplantation is hoped to decrease the 30-day readmission rates (Ertel et al. 2015).

- Using PCMH/PCSP principles, the Perioperative Surgical Home, proposed by the American Society of Anesthesiologists, leverages the abilities of the entire perioperative care team in the service of the patient and may promote standardization and improve clinical outcomes and decrease resource utilization by providing greater patient-centered continuity of care throughout the perioperative, intraoperative, and postoperative periods (Vetter et al. 2013).
- Keck Medical Center has been utilizing a form of the surgical home model for over two decades. Their study compares outcomes for patients under the surgical home model, where patients had the same anesthesiologist for intra- and postoperative management, to the traditional model, where patients have different anesthesiologists. The study finds that both ICU and hospital days were significantly reduced for the surgical home group versus the nonsurgical home group. Further, ICU readmission rates were also lower for the surgical home group. Quantifying the cost savings between the two groups had yet to be determined but is assumed to be significant, especially when assessed on quality of care metrics, namely, LOS and readmission rates (Atoian et al. 2013).
- Besides improved outcomes, the surgical home model can also have a direct economic impact. An abstract submitted by the Department of Anesthesiology at Ochsner Medical Center compares costs of preoperative testing before and after the hospital implemented a variation of the surgical home model. For every 100 patients, they saved close to $18,000 in testing costs. The most unnecessary or redundant tests were EKGs, chest X-rays, kidney function and other chemistry assays, or studies of electrolyte (Carrillo et al. 2012).

Conclusion

The path taken for organizations to create both a Patient-Centered Medical Home and a Patient-Centered Specialty Practice involved years of study and work and trial and error and input from thousands of thought leaders. The work needed for practice transformation to receive a PCMH/PCSP Recognition is no less arduous, but the results of improved patient care and satisfaction and reducing the overall costs of healthcare are certainly worth pursuing. The fact that reimbursement models are starting to change to pay-for-performance will encourage many more to practices to begin to make that practice transformation.

A large segment of the discipline of medicine, especially transplant surgery, is currently left out of this transformation even though the building blocks are already in place for this to happen. By its very nature, transplant surgery truly functions as and meets requirements for a medical home specialty practice by all criteria currently available.

It is time for transplant surgery to be recognized as such a practice.

Cross-References

- ▶ Finance of Liver Transplantation
- ▶ Palliative Care in Liver Transplantation: When to Consult a Specialist
- ▶ Role of Integrative Medicine in Liver Transplantation
- ▶ Role of the Transplant Coordinator

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Part IX

The Contemporary Successful Liver Transplant Program

Regulatory Agencies in Transplantation

32

Belinda Paganafanador

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Abstract

In the early 1960s, transplantation was unregulated. As the science of transplantation has progressed, however, laws have evolved, as is the case in almost all areas of science and technology. Regulatory agencies, such as the Organ Procurement and Transplantation Network and Centers for Medicare and Medicaid Services, now exist to provide all patients with access to transplantation without commercialization, to provide quality outcomes for patients, and to ensure that transplant centers and organ-procuring organizations are in alignment with these goals. Today's health care reform initiatives are focused on quality care and outcomes along with the costs of care. As such, agencies regulating transplantation are closely monitoring transplant centers and organ-procuring organizations to assess quality, to improve performance, and to ensure that they comply with the agencies' requirements. This chapter summarizes the evolution of these regulatory agencies, the changes currently being made, and their implications for the field of transplantation.

Keywords

Regulation • Transplantation • Medicare • UNOS • OPTN

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Introduction

Although transplantation medicine began in the 1960s, its regulation lagged behind. Before 1984, no clear-cut regulations existed regarding transplantation. A shortage of organs led to unregulated organ transplantation and to a lack of proper oversight of organ allocation. Moreover, there was debate regarding the rights of relatives of deceased organ donors. This situation resulted in patients with organ failure seeking organs outside the hospital setting, leading to the commercialization of organ transplantation, as it was becoming clear that with advances in medicine and the introduction of cyclosporine, both patient and organ survival rates were improving significantly. At that time, it was unclear whether the US Food and Drug Administration (FDA) had the authority or capability to regulate organ transplantation. Then, in 1984, Congress formally removed the FDA's authority to oversee deceased and living donor organ transplantation when it passed the National Organ Transplant Act (NOTA).

The most important provisions of NOTA were to (1) provide funding for regional federal organ procurement agencies, (2) establish the Organ Procurement and Transplantation Network (OPTN) to manage and distribute solid donor organs, (3) mandate funding of transplant-related medications and surgical procedures by Medicaid/Medicare, (4) establish a task force to study problems related to the organ allocation process, and (5) specifically prohibit the sale of solid donor organs for transplantation, except for blood, ova, or sperm (National Organ Transplantation Act 1984).

Organ Procurement and Transplantation Network

The OPTN is a unique public–private partnership linking all the professionals involved in the system of donation and transplantation. Under federal law, all US transplant centers and organ procurement organizations (OPOs) must be members of the OPTN to receive funds through Medicare. Other OPTN members include independent histocompatibility laboratories involved in organ transplantation; relevant medical, scientific, and professional organizations; relevant voluntary health and patient advocacy organizations; and members of the general public who have a particular interest in donation and/or transplantation.

The primary goals of the OPTN are (1) to increase the effectiveness and efficiency of organ sharing and equity in the national system of organ allocation and (2) to increase the supply of donated organs available for transplantation. In helping to ensure the success and efficiency of the US organ transplant system, the OPTN's responsibilities include:

1. Facilitating the organ-matching and placement process through a computer system and a fully staffed organ center operating 24 h a day
2. Developing consensus-based policies and procedures for organ recovery, distribution (allocation), and transportation
3. Collecting and managing scientific data regarding organ donation and transplantation
4. Providing data to the government, the public, students, researchers, and the Scientific Registry of Transplant Recipients (SRTR) for use in the ongoing quest for improvement in the field of solid organ allocation and transplantation
5. Developing and maintaining a secure Web-based computer system, which maintains the nation's organ transplant waiting list and recipient/donor organ characteristics
6. Providing professional and public education regarding donation and transplantation, the activities of the OPTN, and the critical need for donation (Final Rule 42 Code of Federal Regulations, Section 121 2005)

Effective March 16, 2000, the US Department of Health and Human Services (HHS) implemented a final rule establishing a regulatory framework for the structure and operations of the OPTN. Based on the final rule, all members of the OPTN must comply with all provisions of the NOTA as amended, 42 U.S.C. 273 et seq.; the

OPTN final rule, 42 CFR Part 121; this charter; the OPTN bylaws; and OPTN policies as in effect from time to time. The OPTN conducts ongoing and periodic reviews and evaluations of each OPO member and transplant hospital for compliance with the OPTN final rule and policies. All OPTN members are subject to review and evaluation for compliance with OPTN policies. All compliance monitoring is performed using processes and protocols developed by the OPTN contractor in accordance with the contract with the HHS, the Health Resources and Services Administration (HRSA), to operate the OPTN (OPTN contract).

Through the NOTA, the HHS solicited proposals to run the OPTN and awarded the initial contract to the United Network for Organ Sharing (UNOS) on September 30, 1986. UNOS, based in Richmond, Virginia, administers the OPTN under contract with the HRSA of HHS, and this contract is overseen by the HRSA OPTN project officer.

As discussed previously, the OPTN brings together medical professionals, transplant recipients, and donor families to develop organ transplantation policy and has instituted various strategic goals that have evolved over time. Currently, its strategic goals are as follows:

1. Increase the number of transplants.
   (a) Ensure that performance metrics for transplant centers and OPOs are aligned and promote increasing the number of effective transplants.
   (b) Measure transplant centers' ability to transplant wait-listed candidates.
   (c) Improve transplant program metrics to remove disincentives for transplanting marginal organs.
   (d) Improve OPO metrics to remove disincentives for pursuing single-organ donors.
   (e) Increase community participation in, and transplants arranged through, the OPTN Kidney Paired Donation (KPD) program.
   (f) Minimize financial disincentives and remove other barriers to living donation.
   (g) Use data to improve the chance of timely offers of organs to centers and candidates most likely to accept.
   (h) Develop decision analytics and support tools to guide OPOs and transplant centers.
   (i) Conduct follow-on research regarding deceased donor potential to assist OPOs in identifying and recovering underutilized categories of donors.
   (j) Identify best practices for donor medical management and share them with donor hospitals.
   (k) Share OPO best practices for maximizing organ utilization and minimizing organ discard rates.
   (l) Increase the number of donation after cardiac death donors.
2. Provide equity in access to transplants.
   (a) Reduce geographic disparity in access to transplantation of livers and other organs.
   (b) Examine the effectiveness of current donor service area (DSA) boundaries and consider developing new methods of distribution.
   (c) Establish clearer rules for allocation of multiple organs to a single candidate, especially liver–kidney candidates.
   (d) Examine ethical issues in retransplantation when a shortage exists.
   (e) Increase the referral of all patients who have a high likelihood of transplant benefit to transplant centers without regard to patient demographics or geography.
   (f) Define other measures of equity to examine system performance.
3. Improve wait-listed patient, living-donor, and transplant recipient outcomes.
   (a) Define alternative measures of positive patient outcomes other than 1-year survival.
   (b) Provide tools to promote self-assessment and improvement by members.
   (c) Examine practices to allocate organs in a way that promotes increased transplant benefit across the population.
   (d) Promote research on long-term (>2 years) living-donor outcomes.
   (e) Develop and distribute educational materials to assist primary care providers with best practices for partnering with transplant centers in the ongoing care of transplant recipients.

(f) Improve transplant patient literacy to facilitate self-management after transplantation.

4. Promote living-donor and transplant outcome safety.
   (a) Increase opportunities for members to exchange best practices and responses to near misses and sentinel events; provide sample forms and other learning tools.
   (b) Facilitate more information sharing among members through "safe harbor" policies.
   (c) Share best practices in developing robust quality programs.
   (d) Deploy technological tools that improve labeling, tracking, and checking in of organs.
   (e) Facilitate improved communication between OPOs and transplant centers.
   (f) Implement the HIV Organ Policy Equity (HOPE) Act while protecting the safety of patients and transplant professionals.
   (g) Expand opportunities for learning about transmission of rare donor-derived diseases.
5. Promote efficient management of the OPTN.
   (a) Align committee proposals with strategic planning goals.
   (b) Consider financial impact on OPTN members as part of the policy development process.
   (c) Employ user-friendly technologies to collect data quickly and accurately and to supplement member-submitted data by integrating other data resources.
   (d) Create stronger connections between committees and board of directors.
   (e) Consider reducing the number of standing committees.
   (f) Identify financial standards and best practices in donation and transplantation.
   (g) Partner with other organizations in donation and transplantation to minimize duplication of efforts (optn.transplant.hrsa.gov/governance/strategic-plan).

The OPTN acts through its board of directors and committees. The current UNOS board also presently serves as the OPTN board of directors. Board members, chosen through an open, comprehensive nomination process, bring a wealth of commitment and technical knowledge to guide the OPTN in establishing and maintaining policies and procedures for the field of transplantation. The OPTN/UNOS committees address issues of concern in the transplant community. They make crucial decisions that shape the national transplant network's ability to serve transplant patients, living donors, family members of deceased donors, and professionals involved in organ donation and transplantation. Committee members identify and discuss issues that may call for a new or revised OPTN policy or bylaw. They review data and share their experiences and views to develop policy proposals or other recommendations to be brought to the OPTN/UNOS board of directors for action. OPTN policies affect US transplant centers, OPOs, and candidates waiting for an organ transplant.

The 21 OPTN/UNOS committees (listed alphabetically) are as follows:

- Ad Hoc Disease Transmission
- Ad Hoc International Relations
- Data Advisory
- Ethics
- Executive
- Histocompatibility
- Kidney Transplantation
- Liver and Intestinal Organ
- Living Donor
- Membership and Professional Standards (MPSC)
- Minority Affairs
- Operations and Safety
- OPO
- Pancreas Transplantation
- Patient Affairs
- Pediatric Transplantation
- Policy Oversight
- Thoracic Organ
- Transplant Administrator
- Transplant Coordinators
- Vascularized Composite Allograft Transplantation

Regulation by OPTN

The OPTN is not empowered by law to enforce OPTN requirements. Only requirements approved by HHS as federal regulations are enforceable. These include the submission of data on forms approved by the US Office of Management and Budget (OMB). The forms provide data on transplant candidates, recipients, and living and deceased donors. The data must be provided by transplant centers, OPOs, and histocompatibility laboratories.

The OPTN also can enforce its requirements through the Social Security Act, which states that for a hospital that performs organ transplants to be eligible to participate in Medicare and Medicaid, it must be a member of the OPTN and abide by its rules and requirements (Social Security Act 42 1987). Any center violating the requirements of the OPTN may become ineligible to participate in the Medicare and Medicaid program in any form, not only transplantation. The Social Security Act requirements are enforced by the government, not by a private entity such as the OPTN.

The HHS has the power to deny membership in the OPTN or the Medicare program to any center that has violated the requirements (54 Federal Register 51802, December 1989). However, the OPTN conducts ongoing, periodic reviews and evaluations of each transplant hospital, histocompatibility laboratory member, and OPO member for compliance with OPTN obligations. Compliance monitoring is performed based on guidelines developed by the OPTN. A member who fails to fulfill all applicable OPTN obligations may be subject to actions as set forth in the OPTN bylaws. The OPTN board of directors or MPSC will require that member to take corrective action to address any potential violation or noncompliance, including root-cause analysis, a corrective action plan, a plan for quality improvement, on-site monitoring, desk monitoring, self-assessments, or external expert consultants (OPTN Bylaws Appendix L, Section 1.A, Section 6).

Transplant centers are responsible for evaluating potential recipients and determining whether they are candidates for transplantation. The OPTN final rule states that once it is determined that a candidate would benefit from transplantation, he or she should be placed on the wait list. If contraindications develop, the center can remove the patient from the list or place him or her in the "inactive" category. The center is responsible for updating candidate and recipient information for the OPTN. The data submitted by the center are analyzed by the SRTR regularly and are published twice a year on a public website. The OPTN also monitors SRTR center-specific data on a quarterly basis, comparing them with expected outcome data after risk adjustment. Using the SRTR program-specific reports (PSRs), the OPTN has adopted three well-defined criteria for quality assurance (Table 1).

Table 1 OPTN noncompliance thresholds to determine transplant center performance

Criterion	Threshold
Observed/expected	>3
Observed/expected	>1.5
P value	Two-sided $P < 0.05$

The criteria identified are used to scrutinize a center's performance and outcomes closely. Oversight is provided by the UNOS Department of Member Quality (formerly the Evaluation and Quality Department) and by the OPTN/UNOS MPSC, which is made up of volunteers from the field of transplantation medicine who donate their time to ensure the integrity of the transplant system in the USA. This strict monitoring, as well as any action necessary to bring a member back into compliance, has fostered a high level of trust among transplant professionals (Abecassis et al. 2015).

The MPSC generally designates a group of reviewers to investigate the reasons for poor outcomes and report back to the MPSC. This process involves direct communication with the member and, if warranted, a formal interview before the entire committee. The MPSC may take no action, or it may issue a letter of uncontested violation, warning, or reprimand (OPTN Bylaws Appendix L, Section 15D). It also can recommend

adverse actions to be taken by the OPTN board, which may lead to the member being placed on probation, necessitating a formal corrective action plan, or being declared a "member not in good standing," with formal notice to the HHS secretary (OPTN Bylaws Appendix L, Section 15E). The MPSC also can make a recommendation to the OPTN board and HHS secretary regarding higher adverse actions, including but not limited to removal of one or more of the member's transplant programs, termination of the member's reimbursement under Medicare and Medicaid, and termination of the transplant hospital's participation in Medicare or Medicaid. These actions would effectively shut down a program as it no longer would be eligible to attract referrals, patients, and payors.

The MPSC and OPTN must balance the safety of and access to transplantation for patients on a program's transplant waiting list within the OPTN (OPTN Bylaws Appendix L, Section 16). A member in violation is given the opportunity for a formal hearing before the entire MPSC before a formal recommendation is made to the board. In addition, the member may appeal for a review by the OPTN board of directors if the MPSC proceeds with the recommendation (OPTN Bylaws Appendix L, Section 18). HHS approval is required for any of the higher-level adverse actions.

The peer review process is rigorous, and members understand its importance and consequences, as even lesser adverse actions require members to develop a corrective action plan, implement the plan, and undergo follow-up before regular membership status is restored. MPSC, along with OPTN, has addressed the concerns of patient safety aggressively and adopted recommendations in 2006–2007 from its review initiated in 2005.

Centers for Medicare and Medicaid Services and Transplantation

The Centers for Medicare and Medicaid Services (CMS) is the largest single payor in the USA for health care services in general and for transplant services in particular. It also acts as a regulator. As CMS plays an important role in end-stage renal disease (ESRD), it also plays an important role in transplant services. All individuals in the USA who develop ESRD are eligible for Medicare benefits, including kidney transplantation, at a center approved by CMS to perform kidney transplants. For nonrenal transplants, individuals in need of transplantation should show evidence of permanent medical disability or be at least 65 years of age to qualify for Medicare benefits.

Transplant centers must be certified by CMS for each organ type. Certification is based on meeting a certain volume and patient and/or graft survival rate requirements. Nonrenal transplant centers are required to submit an application to CMS for review by an expert panel. In 2005 and 2006, the media highlighted inadequacies in the oversight of transplant centers by OPTN and CMS with respect to patient safety and patients not receiving transplants despite being allocated organs. These reports resulted in a congressional review, leading CMS to propose Conditions of Participation (CoPs) in 2005 for the transplant centers. A joint task force comprising members of the American Society of Transplant Surgeons (ASTS), the American Society of Transplantation, and the International Society for Heart and Lung Transplantation examined the proposed CoPs and met with CMS; subsequently, a final rule was published in the *Federal Register* in 2007 (Federal Register: Center for Medicare and Medicaid 2007). Under this final rule, the CMS CoPs comprise several sections, including notification of transplant program changes, data submission, outcome review, initial approval, patient and living-donor selection, organ recovery and receipt, patient and living-donor management, quality assessment and performance improvement (QAPI), human resources, organ procurement, and patient and living-donor rights (Abecassis et al. 2008). QAPI is mandated and detailed by CMS, and transplant centers are required to track and monitor performance and also to take action for performance improvements. The CMS CoPs follow the same three criteria used to assess centers but with one difference: it uses a one-sided *P* value, which is more stringent (Table 2).

Table 2 CMS noncompliance thresholds to determine transplant center performance

Criterion	Threshold
Observed/expected	>3
Observed/expected	>1.5
P value	One-sided $P < 0.05$

CMS conducts on-site reviews and looks for detailed documentation of policies and procedures, as well as medical records documenting that the center is following those policies and procedures. It uses the SRTR-generated PSR to determine whether a transplant center should be allowed to continue to perform transplants. CMS has two levels of response in cases in which a transplant center is not meeting outcome standards. A "condition"-level citation is grounds for termination of a center's certification and is issued if two of the past PSRs, including the most recent report, show failure to meet standards. However, a center may request consideration of mitigating factors, which may provide a temporary reprieve from meeting the CoPs. Moreover, CMS allows up to 210 days for a center to demonstrate program improvements. CMS expects the center to have an effective internal quality improvement process in place that would help the center show evidence of improvement in graft and patient outcomes before the effective date of scheduled Medicare termination. Because there is a 1-year lag in the 2.5-year cohort within each PSR, it takes a prolonged period for the poor outcomes to disappear. Therefore, CMS has proposed a legally binding Systems Improvement Agreement (SIA) that focuses on an on-site multidisciplinary peer review over a 12-month period, allowing a center to come into compliance if additional time is required.

Indeed, findings indicate that since the implementation of CoPs, the programs cited have shown significant improvement in 1-year patient and graft survival, albeit at the expense of a decline in transplant volume (Hamilton 2013). Some centers may become risk averse, which has implications for high-risk patients who might benefit from transplantation, especially those with characteristics not captured by the risk-adjustment methodology used by the SRTR.

Debate exists in the transplant community regarding the unfunded burden of data collection, duplication of regulations and its burden on transplant centers and OPOs, and inefficient use of federal funds. With the intense QAPI process mandated by the CMS CoPs, 1-year outcomes likely will improve, but there is less focus on longer-term outcomes. Moreover, centers likely will become more risk averse, stifling innovation and causing them to avoid transplantation in high-risk patients, especially those with cardiovascular morbidity and malignancy, as they are not included in the risk adjustment for liver transplantation. The same holds true for the ABO and cross-match–positive desensitization populations in kidney transplantation (Abecassis et al. 2015). As a result, many patients are at risk of losing access to transplantation as well as for experiencing longer wait times. In addition, incentives exist for poor-quality data within the SRTR risk-adjustment models, especially with regard to missing data. Centers can pick and choose covariates that maximize expected risk and underreport covariates that lower the expected risk, as in some cases, missing data are computed to have average risk.

Conclusion

Regulatory agencies have played an important role in improving organ allocation; increasing equity, information sharing, and multidisciplinary interaction; and establishing quality metrics for outcomes, policies, procedures, and decision analytics, which help transplant centers and OPOs. However, multiple agencies are doing the same work, there is significant duplication of efforts, and demands are placed on the transplant centers as they try to remain compliant with oversight by both the OPTN and CMS. CMS and OPTN must work together to establish regulations that are complementary without overlapping. This would allow transplant centers and OPOs to focus on their primary goal, providing quality care and equitable access to transplantation for all patients.

Cross-References

- ▶ Finance of Liver Transplantation
- ▶ Quality Measure of a Contemporary Liver Transplant Program

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Quality Measure of a Contemporary Liver Transplant Program

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Maria McCall and Natalie Doria

Contents

Abstract

In the era of increasing oversight of transplantation, which includes a prescriptive framework for quality monitoring, transplant centers have been provided some necessary blueprints for developing a basic quality assurance/assessment and performance improvement (QAPI) program. Missing from the regulatory framework for the QA portion of QAPI is the inclusion of structure and value as quality indicators in addition to process and outcomes. A meaningful and effective method of both measuring and monitoring quality in a liver transplant program involves incorporating structure and value as additional quality measures. This achieves monitoring of minimum program requirements as well as program efficiency, and it meets the goals of multiple stakeholders such as payers, providers/programs, regulators, and patients. In order to make the QAPI program successful and to establish ownership with the transplant team, goal setting and benchmark establishment should be a collaborative process.

In effective QAPI programs, the PI portion is equally critical. Meaningful PI not only meets minimum regulatory requirements of established methodologies for monitoring but also incorporates PI monitoring secondary to adverse event occurrences and the recognition of negative trends. All QA measures and PI methodology, along with pertinent policies

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and documentation, should be incorporated into the program's annual quality plan.

Keywords
Adverse events • Performance improvement • QAPI • SPO paradigm

Introduction

Quality in healthcare is often defined based on the constructs of outcomes, process, or structure. These constructs are measured either individually or in combination. In organ transplant, quality was historically based on only outcome measures. Specifically, a quality program was based on patient and graft survival indicators. A more recent paradigm shift, driven by regulatory requirements, has expanded quality measurement to include processes. In addition, structural requirements set forth by regulators have necessitated the addition of monitoring of this construct. Further, commercial payers and the shift toward accountable care have redirected hospitals and transplant programs to focus on efficiencies and cost relative to outcomes and add value as a fourth construct in defining quality. This chapter will describe best practices in the measurement and monitoring of quality in a modern liver transplant program which will satisfy the priorities of all stakeholders involving hospitals/programs, patients, regulators, and payers. In addition, this chapter will review the steps necessary for establishing an effective and compliant QAPI program starting with best practices in choosing quality measure. This chapter will also provide guidelines for developing performance improvement plans that meet regulatory guidelines and provide structure for adverse event reviews.

Regulatory Oversight Driving Transplant Quality Monitoring

Transplant programs have experienced sweeping regulatory changes in the past 10 years. These regulatory requirements, high-profile media stories, and the era of online research and the educated consumer have been the impetus for the development of comprehensive QAPI programs in solid organ transplant. The federal government has recently begun surveying transplant programs strictly for the purpose of assessing their QAPI program amid known outcome issues. This process has been coined fQAPI and has driven transplant programs to dedicate significant staffing and resources to their transplant-specific QAPI programs. The emergence of the fQAPI on-site survey has placed even further emphasis on the importance of a quality program to the extent that there are multiple annual QAPI webinars hosted by the transplant professional organizations and an annual conference dedicated strictly to transplant quality management. The new level of sophistication in QAPI development and awareness has not only driven changes in staffing models, it has also encouraged true multidisciplinary collaboration and bridged the gap between programmatic quality programs and hospital administration-level quality management.

Prior to 2007, hospitals had minimal oversight of organ transplantation in terms of maintaining quality. The Organ Procurement and Transplant Network (OPTN) required maintenance of outcomes as a quality measure; however, the remainder of oversight was documentation driven and no requirement for a formalized QAPI program existed. On June 28, 2007, the Centers for Medicare and Medicaid Services (CMS) published the final rule on organ transplant certification and oversight in the Code of Federal Regulations. Among the requirements was a specific Condition of Participation for QAPI. Upon publication of these regulations, Thomas Hamilton, the Director of the Survey and Certification Group of CMS Division of Medicaid and State Operations, described the QAPI Condition of Participation as one of the most important aspects of the new era of oversight in transplantation (Hamilton 2008). Hamilton explained that the requirement was meant to be action oriented, and feedback systems for adverse events will be analyzed for effectiveness along with the data-driven measurement aspect of QAPI.

The QAPI Condition of Participation (42 CFR § 482.96) states that "Transplant centers must develop, implement, and maintain a written, comprehensive, data-driven QAPI program designed to monitor and evaluate performance of all transplantation services, including services provided under contract or arrangement." It further lists a standard that requires the QAPI program to measure "outcomes" as well as a standard requirement for adverse event monitoring. The Condition is very broad overall and provides little specific guidance to maintaining this requirement. One year after the regulations were effectuated, CMS released a formal guidance letter to the state survey agency directors, which included the Interpretive Guidelines for all of the Transplant Conditions and Standards (CMS 2008). This provided some further assistance for transplant programs wishing to develop and enhance their QAPI programs. This guidance was necessary as 24 % of all programs surveyed by the state agencies were found to be out of compliance for the QAPI Condition at that time (Abecassis et al 2008). Transplant programs, however, continued to struggle with the QAPI Condition and inconsistent application of the rules by state and contract surveyors. In 2009, CMS awarded a contract to Catapult Consultants, LLC, to develop guidance meeting three goals including "1. The national need to ensure transplant surveyors understand the QAPI regulations and survey guidelines; 2. Further describe CMS expectations for a comprehensive transplant QAPI program; and 3. Provide surveyors with a tool that provides/promotes a consistent application of the QAPI regulation (Catapult Consultants 2010)." The consulting group released a 37-page guideline and accompanying work sheet in 2010 which provided delineated steps for transplant centers to craft meaningful QAPI programs aimed at not only meeting CMS expectations but also at measuring and maintaining quality in a way that is objective and provides proven results. Figure 1 describes the steps necessary for development of an effective QAPI program that takes into account the consultant's recommendations and also incorporates best practices pertinent to a modern transplant program and its strengths and challenges. These further recommendations are described in the sections below.

Quality Assessment Beyond the Regulatory Requirement

The historical monitoring of just survival outcomes to monitor program quality is outdated and insufficient. The Catapult Consultants report provided specific instructions for ensuring that transplant programs also analyze process measures. They further describe the need to implement quality measurement at all phases of transplantation including the pretransplantation phase (during evaluation and while waitlisted), the inpatient and perioperative phase, and the posttransplantation phase. Their guidelines necessitate a minimum of nine quality measures per organ program with at least three measures per phase of transplant, at least one of which is an outcome measure and at least one of which is a process measure. This guideline, although tremendously helpful for both transplant centers and surveyors in setting forth clear expectations, is not exhaustive of all necessary quality assessment practices for Transplant Centers, nor does it provide practical guidance to transplant programs for building their quality plan in a collaborative and meaningful way. For example, their guidelines cover process and outcome requirements but do not encompass structure monitoring or value monitoring.

Avedis Donabedian's work on the structure, process, and outcome (SPO) paradigm has been frequently cited as the necessary comprehensive framework for quality measurement in healthcare (Donabedian 1988). Specific structural parameters have long been required in order for a transplant program to obtain and maintain institutional membership in the OPTN. In addition, the majority of the CMS Conditions for Coverage can be categorized as either structure, process, or outcome requirements. Given that both the OPTN rules and CMS rules are required (OPTN for membership and CMS for reimbursement), it is a worthwhile safeguard to include measurement of

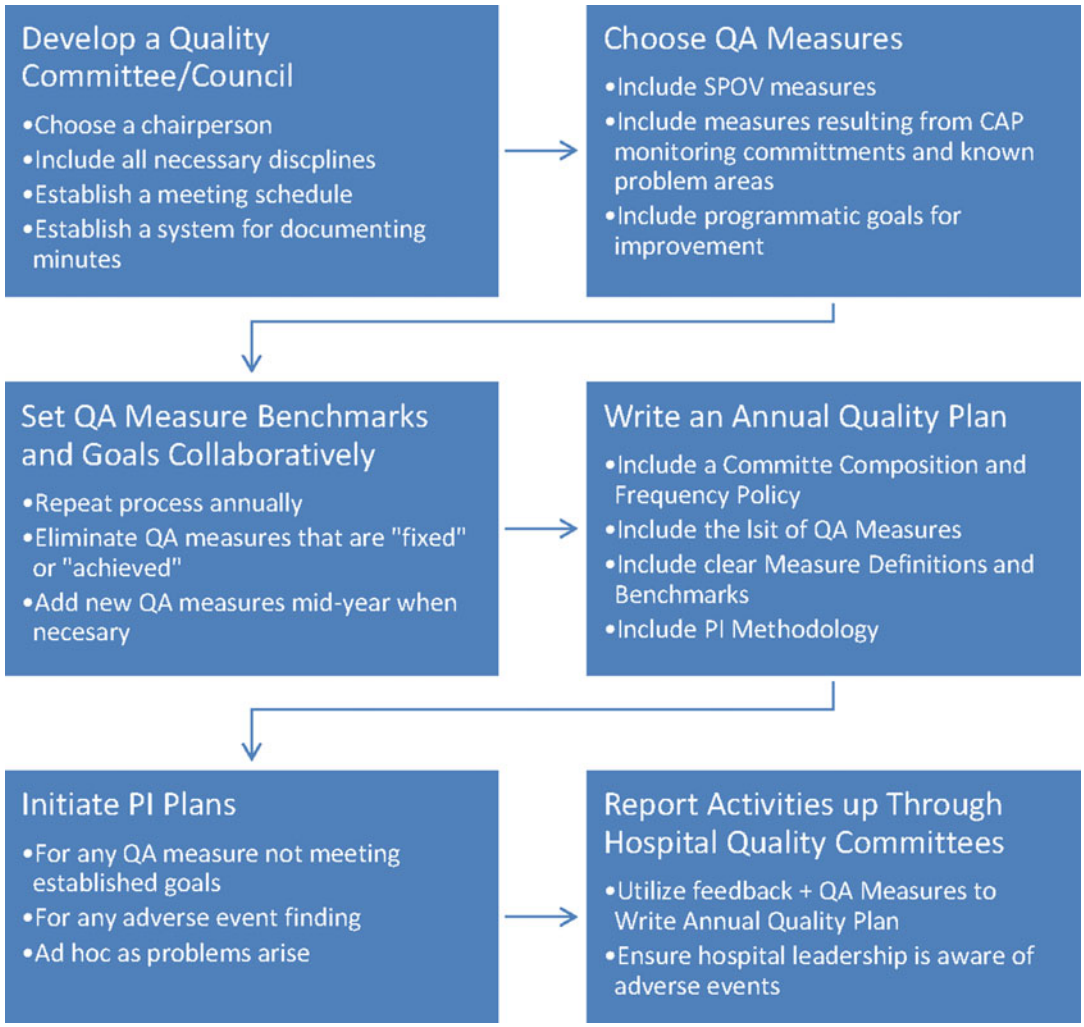

Fig. 1 Steps for successful quality plan development and implementation

these rules as part of a comprehensive QAPI program. Donabedian (1988, 2005) describes structure variables/measures as the setting in which care is delivered including adequate facilities and equipment and qualifications of personnel. This data is often readily accessible and objective making it an easy opportunity for data gathering. For example, it should be relatively easy for a transplant program to gather and monitor data on maintenance of competencies for personnel (a CMS requirement), monitor appropriate personnel on nursing units (a CMS requirement), and monitor appropriate vessel storage units (an OPTN requirement).

Value in healthcare is defined as outcomes relative to costs (Porter and Teisberg 2010). Value has been recognized as the one goal that is overarching for all stakeholders involved in transplantation: hospitals and healthcare providers, regulators, payers, and patients (Porter and Teisberg 2010). As organ transplantation costs are very closely monitored within the hospital setting due to Medicare cost report requirements, obtaining this data should be practical and accessible for transplant programs. Monitoring costs as the denominator in the value equation can assist a program in ensuring that care is delivered efficiently and responsibly. In organ transplantation,

Table 1 Sample of quality assessment measures for a liver transplant program meeting the SPOV suggested framework

Liver transplantation phase	Example quality measures	Measure type	Regulatory required minimum?	Additional measure for best practice?
Pretransplant	Average time from referral to waitlist	Process	**X**	
	Psychosocial assessment complete before waitlisting	Process	**X**	
	Waitlist mortality rate	Outcome	**X**	
	Transplant coordinators maintain annual competencies	Structure		**X**
	Average cost of fast-track evaluation for high-MELD patients	Value		**X**
Peri-op/ inpatient	Pre-implant ABO verification completed accurately	Process	**X**	
	High-risk donor consent completed	Process	**X**	
	Unplanned return to OR	Outcome	**X**	
	Multidisciplinary discharge planning documented	Structure		**X**
	Average cost of inpatient stay for patients with infections	Value		**X**
Posttransplant	Removal from the waitlist occurred within 24 h	Process	**X**	
	1-year graft survival	Outcome	**X**	
	1-year patient survival	Outcome	**X**	
	Average wait time for patient clinic appointments	Structure		**X**
	Average cost of readmission within 30 days	Value		**X**

process measures are very telling indicators of efficiency, and utilizing a process measure relative to cost will also be an effective tool for measuring value in this setting. For example, if the liver transplant program utilizes a fast-track option for high-MELD patients, it may be an area they wish to analyze to explore cost savings with this option. Therefore, looking at the average cost for fast-track evaluations is a useful value measure. As an additional example, graft survival at 1 month is a common outcome measure. To look at this in terms of value, a simplified measure would be 1-month graft survival relative to a cost measure such as posttransplant costs at 1 month. Having an understanding of costs at different phases of transplant and relative to different processes and outcomes from within the program is very useful in understanding how the program provides high value to the patients.

In summary, utilizing the Donabedian SPO paradigm plus the addition of V (value) as a more modern construct, a best practice for a transplant program is to have SPOV quality assessment measures at all phases. Please refer to Table 1 as an example of quality measures to meet minimum regulatory guidelines for QAPI (at least three measures per organ per phase with at least one process and one outcome) while also capturing structural indicators and value-related indicators.

Development of the Quality Plan and the Quality Committee

Although the examples illustrated in Table 1 may be useful for a program, it is important for transplant programs to have a quality committee or council tasked with collaborative agreement on quality measures. The CMS guidelines recommend establishing a quality committee whose membership is clearly defined in terms of disciplines, roles, and format and frequency of

Table 2 Functions of the quality committee

1. Hold routine meetings in accordance with program QAPI policy/plan
2. Maintain and update quality plan annually and as needed
3. Form consensus on quality measures being analyzed
4. Establish goals and benchmarks for all quality measures
5. Provide a format for report out of performance improvement plans
6. Assign performance improvement plan owners and provide feedback on determining new plans
7. Provide a format for reporting adverse events and results of root cause analyses
8. Document meeting minutes
9. Provide a member to report to higher-level hospital quality committees

meetings. Table 2 lists the recommended functions of a quality committee (Norris 2008). CMS requires that key personnel be included on the quality committee. Key personnel are defined as medical and surgical directors and all key members of the multidisciplinary team such as transplant coordinators, etc.

The quality plan developed by the quality committee should be updated annually to ensure that it is effective. It should be considered a program "policy" and adhered to as such. CMS defines in its Interpretive Guidelines what the quality plan should include. In addition to defining the team members by title and role, the quality plan should include explanation of decision-making methodology such as committee vote, subcommittee vote, etc. The plan should list the measures you choose, list the benchmarks and goals chosen, and list the methodology by which data will be analyzed to obtain each measure. For example, the quality plan associated with the example measures above in Table 1 would list the measures and the numerator and denominator for each one established. Average time from referral to waitlist, for example, should include information in the plan as to what date is considered the referral date and where the referral date is being obtained. The purpose of this is to ensure that measures are truly objective data driven and are not estimates or subject to collection bias.

The quality plan should also list the frequency with which the quality committee will meet and how often new measures will be established. Reporting methodology from the quality committee to the hospital-wide QAPI program or quality committee is important to be defined in the plan as well. Specifically the plan should include what is being reported, how often it is being reported, and to whom. The program should be prepared to have available documentation to demonstrate that this is happening. Any recommendations from the hospital-wide QAPI committee should be documented.

CMS requires that a person be designated to be responsible for monitoring the quality plan and this person should be listed within the plan document. Commonly this position is considered a quality coordinator or a QAPI coordinator. This person also does not need to be the same as the QAPI chairperson. The chairperson's role can be a clinical lead or a decision maker. The trend nationally, as demonstrated by the UNOS staffing survey of 2015, is for this position to be embedded within the transplant program and for at least one full time equivalent be dedicated to the program in this capacity. The QAPI coordinator should ensure that data required for analysis is readily available, valid, and comprehensive. The QAPI coordinator should coordinate quality committee meetings, maintain the quality plan, represent the program for hospital-level quality meetings, and work toward bringing consensus to the team on matters of quality decision making. The QAPI coordinator should have readily available all documents related to the quality plan for immediate dissemination in the event of an on-site visit from CMS. These documents, although accessible to the transplant team, should be kept in a secure location due to the sensitivity and peer-protected nature of the information.

Also required within the quality plan is evidence of tracking and implementing recommendations for improvements, evidence of ongoing compliance with changes as recommended by the committee, and broad representation of transplant program issues across disciplines. In order for the quality committee to achieve all that is laid

Table 3 Quality plan recommended table of contents

1. Quality committee composition
2. Member roles and responsibilities
3. Meeting frequency
4. Plan year's QA measures
(a) Definitions
(b) Goals
(c) PI plan triggers
5. PI methodology
6. Methodology for reporting up through hospital quality committee
7. Adverse event's policy
8. Complaint's and incident's tracking policy
9. Appendix – prior year's meeting minutes
10. Appendix – prior year's adverse event's reports
11. Appendix – prior year's QA measures and PI plans
12. Appendix – add on/new measures for plan year
13. Appendix – ongoing PI plans with responsible parties' plan year

out in the plan, plus meet the SPOV framework, choosing measures is the next step.

Additional quality plan items include the program's adverse event policy and policy for tracking of complaints and incidents. A recommended table of contents for the quality plan can be found in Table 3.

How to Choose Quality Measures

Quality measures meeting the SPOV framework should be chosen based on areas in which the program is struggling, issues for which the program has been cited by a regulatory agency, and programmatic goals that include major changes or shifts in activities or processes.

Because QAPI is aimed at continuous improvement, quality measures should not be chosen based on what is a known programmatic strength. For example, if the program has the resources to utilize a fast-track evaluation that has had years of proven success in evaluating patients expeditiously, it is not helpful to measure program evaluation timeliness as a pretransplant process. Conversely, if a program is struggling in any area, this should be a target for quality measurement. Whenever possible, cited deficiencies from regulatory agencies should be monitored as QA measures. A commonly cited deficiency by the OPTN is the use of incorrect labs for MELD scoring. As part of a corrective action plan (CAP), a program must often commit to monitoring that this error is remedied. Adding this monitoring to the program quality plan as a QA measure is an effective way to achieve this. MELD labs at the time of listing can be analyzed in an objective way, utilizing readily available data, to fulfill a pretransplant process QA requirement as well as ensure that a past deficient practice is being monitored.

In addition to areas of struggle for the program, QA measures should be chosen based on broader programmatic goals for improvement. For example, if volumes are a key growth goal for a liver transplant program, QA measures can be chosen with ambitious goals and benchmarks in order to achieve success. A liver transplant program may have a goal of a percentage increase in transplant growth for a given fiscal year. To achieve this growth, the program may surmise that outreach events are key to engaging referring physicians. Therefore, a measure of outreach events per month could be utilized to achieve this programmatic goal. This particular measure is more effective than a referral count measure because a related PI plan can be put in place to achieve the number of outreach events.

QA measures should not be permanent. As numbers improve and are consistently "good," the quality committee should consider eliminating the measure and replacing it with a new measure. Also, as issues crop up throughout the quality plan year, a program should not feel as though they are trapped with their list of chosen measures. The program can and should add new measures in an ad hoc manner as issues arise that require monitoring.

Critical to any measure chosen, whether it be a result of a deficiency citation, a CAP commitment, or a programmatic goal, is quality committee participation and collaboration. The process of QAPI can be intimidating for the team in particular if measures are specifically related to individual work functions. It is critical that meetings are conducted in a collaborative and encouraging

format for programmatic betterment as opposed to a tone that is punitive when goals are not met. That is not to say that team members are given a "free pass" when it comes to QAPI and for measures that require them to perform at a high level. However, team members who are directly affected by measures (and PI plans) should be part of the planning and goal setting in order to feel ownership rather than intimidation.

Collaboration is also key in establishing the QA numerator and denominator, the data source, the personnel responsible for collecting the data, and the goal or benchmark.

Defining Measures and Setting Goals

The quality plan should have each QA measure chosen clearly defined. For example, if length of stay is a concern for a liver transplant program and it is chosen as a perioperative/inpatient outcome measure, it should be clearly defined. The QA measure should indicate if this is measured in days, if it is an average, during which time period is the data collected, for which population of patients, when the time period begins and ends, and if there are any patients who should be eliminated from the measure due to outlier scenarios. Collaboration in defining these measures so specifically is important as it often uncovers how team members may interpret the use of a data field differently.

The QA measure definition in the quality plan should resemble the following example in Table 4 which uses the University Hospital Consortium (UHC) as a goal benchmark.

Once a measure has been defined clearly, then a goal must be set by the quality committee. The purpose of the goal is to determine when a PI plan must be initiated. In Table 3 a goal is defined based on a numeric trigger. It is not uncommon for the team to wish to alter the goal after a QA measure results unfavorably. And although it is permissible to change goals, all efforts should be made to adhere to the original goal established collaboratively by the team. Situations in which changing the goal would be permissible include known errors in the QA measurement or benchmark and major shifts in priorities (where goals become stricter or more ambitious).

Table 4 Examples of QA measures defined in quality plan

Measure name: Ratio of length of stay for transplant admission versus goal
Measure type: Peri-operative/inpatient outcome measure
Definition: Average number of inpatient days per transplant admission, starting with admission date and ending with discharge date at (transplant) hospital divided by UHC number, for the same population, for patients discharged during the prior (measured) quarter
Exclusions: Transplants occurring on patients who were already admitted, i.e., admission was not specifically for the transplant event, current inpatients
Goal: Less than or equal to 1.0. A PI plan is necessary when (1) this measure is at least 0.1 above the established goal or (2) the measure shows an increase in ratio in three sequential quarters
Data source: Inpatient EMR, admission date, and discharge date fields. UHC quarterly report using predefined DRGs

QA measures must also be objective and data driven. For example, lab values, dates, time frames, etc. are objective data elements that can be utilized in setting measures.

Performance Improvement

When a QA measure goal is not met and a PI plan is triggered, the quality committee should choose a responsible party/PI champion to develop the plan. Oftentimes a team member will volunteer for this role, especially if the measure not meeting the goal is pertinent to their role. However, for some PI plans, it will be necessary for a responsible party/champion to be assigned. The QA committee chairperson can take on the role of assigning someone. To avoid overwhelming any one individual, work should be distributed as much as possible. Further, to encourage participation, it is recommended that participation in QAPI be incorporated into the job descriptions of team members and team members and participation be assessed as part of an annual performance appraisal. As recommended by CMS, hospital-wide methodology should be utilized for the performance improvement (PI) portion of the quality

Table 5 Using DMAIC methodology for transplant QAPI

1. Quality committee meeting reports QA measure – readmissions within 30 days is not meeting the committee's previously established goal (define and measure of DMAIC)
2. A PI responsible party/PI champion is assigned, and suggested PI plans are discussed at the committee meeting (analyze of DMAIC)
3. The PI responsible party/champion establishes a plan for calling patients at defined time points after discharge
4. The PI responsible party/champion presents the plan to quality committee for consensus, necessary resources, and comment. Plan is implemented (improve of DMAIC)
5. The QA measure of readmissions within 30 days is remeasured to evaluate effectiveness of the PI plan, and this is repeated and refined (control of DMAIC)

Table 6 Sample of PI plan using DMAIC resulting from deficiency citation

1. CMS cites transplant program for lack of consistently documenting a comprehensive psychosocial evaluation prior to waitlisting (D of DMAIC)
2. Transplant program submits a plan of correction or CAP committing to ensuring that (a) psychosocial assessment documentation is measured as part of the QAPI process (M of DMAIC) and (b) a checkbox is developed for the listing work sheet which triggers a check of the psychosocial assessment prior to listing (AI of DMAIC)
3. The PI process continues with remeasuring the completeness of psychosocial assessments and adjusting the PI plan if not found to be an effective remedy (C of DMAIC)

plan. Common in most hospital settings today is the use of six sigma, Failure Modes and Effects Analysis (FMEA), plan–do–study–act (PDSA), and define, measure, analyze, improve, and control (DMAIC) methodologies. It is critical for the quality committee to have a working knowledge of the approved methodology. It is useful for hospital quality or PI staff to conduct a training session for the transplant quality committee before embarking on the program's first PI planning.

Using the DMAIC methodology as an example and assuming a QA measure of readmissions within 30 days with an unmet established goal, the quality committee would assign a PI responsible party/champion. After potential PI plans are suggested during the meeting, the PI responsible party would initiate DMAIC for this measure. Table 5 is a demonstration of this in action.

Throughout the stages of the PI plan, quality committee meetings should take place, and progress with the plan should be clearly documented in the meeting minutes. A sophisticated and proven quality methodology allows for alteration of plans as needed and ensures that plans are monitored for effectiveness. Implementing a "fix" for a problem without analysis and remeasurement risks the "fix" not working without brining awareness to the program.

Similar to how QA measures should be chosen based on regulatory deficiency citations, PI plans can also be chosen based on CAP commitments. For example, a CMS citation may include a lack of consistently documenting a comprehensive psychosocial evaluation prior to addition to the liver transplant waitlist. A transplant program will be required to demonstrate a plan of correction or CAP and would commonly include a commitment to measuring and auditing this as well as a commitment to a new process to mitigate this. The new process can be converted to a PI plan. Table 6 demonstrates this in action.

Similar to how QA measures can and should be added to the quality plan in an ad hoc format given issues that arise throughout the plan year, PI plans can and should be added this way as well. Adverse event occurrences are a good example of where a PI plan is required and is not associated with a particular QA measure.

Adverse Events

CMS requires that transplant programs not only track and trend patient complaints and incidents but also have an established policy on transplant-specific adverse events. The policy should define what an adverse event is, include specifics related to the phase of transplantation, and include how adverse events will be analyzed, e.g., process for root cause analyses.

The CMS definition of an adverse event is

> . . .an untoward, undesirable, and usually unanticipated event that causes death or serious injury, or the risk thereof. As applied to transplant centers,

examples of adverse events include (but are not limited to) serious medical complications or death caused by living donation; unintentional transplantation of organs of mismatched blood types; transplantation of organs to unintended recipients; and unintended transmission of infectious disease to a recipient.

The transplant program's quality plan adverse event policy should specifically address this adverse event definition. Further, the policy must (1) address the procedure for reporting an adverse event by transplant program personnel, the hierarchy of reporting, and for conducting analysis based on the reports; (2) the required time frame for reporting, investigating, and analyzing adverse events; (3) the corrective action process after the completion of the analysis and the time frames for the action; (4) the use of analysis of reported adverse events in prevention; (5) external reporting of events to external agencies as required and applicable; (6) reporting to, or inclusion of, the Institutional Review Board (IRB)/Western Institutional Review Board (WIRB) if the adverse event occurred within the context of an approved study; (7) for suspected medical device-related deaths or serious injury, reporting to the Food and Drug Administration (FDA) and the device manufacturer as required by federal law; (8) reporting to the OPTN if the adverse event caused, or may have caused, transmission of an infectious disease and reporting to the Centers for Disease Control (CDC), if CDC requires such reporting to them; and (9) reporting to the organ procurement organization (OPO) if the adverse event was related to an infectious disease present in a recovered organ from a deceased donor that could have been transmitted to other recipients who received organs from that same donor or an otherwise compromised organ that was not detected either through the donor screening or organ transport processes (CMS 2008). This can be placed in the policy verbatim with the Interpretive Guidelines from CMS. An example of incorporating the CMS definition into a program's policy is found in Table 7.

Table 7 Example adverse event policy definition by phase of transplant

An untoward, undesirable, and usually unanticipated event that causes death or serious injury
Pretransplant/pre-donation:
1. Serious complications or death of an intended living donor
2. Any error/omission/action causing death or harm to a pretransplant recipient while at transplant hospital
Transplant/peri-op:
1. Any error/omission/action causing death or harm to a patient during the transplant or donation procedure and immediately following including but not limited to:
(a) Unintended ABO incompatible transplant
(b) Hyperacute rejection
(c) Unintended disease transmission
Posttransplant:
1. Any error/omission/action causing death or harm to a patient during the posttransplant/post-donation phase while at transplant hospital including but not limited to:
(a) Medication errors
(b) Serious infections acquired in the hospital that have the potential to cause death or graft failure
2. Notification by an OPO of a (previously not known) disease transmission to a transplant recipient

CMS also requires that the analysis used for adverse events be described in the policy. Root cause analyses in transplantation are especially challenging given the multidisciplinary nature of the process and the multiple phases throughout which errors can occur. Successful root cause analyses for transplant adverse events address all areas. Table 8 lists a recommended work sheet to be used while conducting a root cause analysis. This work sheet allows for all disciplines to be addressed and all hospital areas throughout which the transplant recipient could have "touched" to be covered. The checklist also ensures that associated PI plans are documented as the plan is approved. Following adverse event root cause analyses, any PI plans established should be reported back to the next quality committee for documentation in the meeting minutes.

When an adverse event occurs that meets policy criteria, the work sheet should be utilized to work through a root cause analysis meeting. The meeting should be coordinated by the QAPI coordinator and should be chaired by the quality chairperson or his/her delegate. Preparation is necessary for a successful root cause analysis meeting. In advance, a lead clinician responsible

Table 8 Sample adverse event root cause analysis work sheet

Transplant RCA work sheet report (confidential and peer protected)		
Organ		
Meeting date		
Attendees		
Patient name		
MRN		
Transplant date		
RCA event trigger (death, graft failure, disease transmission, etc.)		
Date of event		
Case description, presentation		
RCA contributing factor summary – each contributing factor category must be completed and enter "no findings" if the category is found to be not applicable)		
Contributing factor	**Findings**	**Action/ follow-up plan**
Recipient selection/ waitlist management		
Donor selection		
Surgical/peri-op		
Anesthesia		
Patient medical management (includes infection)		
Patient pharmacological management		
Post-op follow-up care		
Psychosocial		
Nursing		
Nutrition		
Support staff		
Communication		
Competency/training		
Equipment/resources		
Policies and procedures		
Others		
Approval		
Surgical director	Medical director	Administrator

for care of the patient should assist in preparing a brief case summary. This should be presented at the beginning of the meeting. All disciplines should be present and be prepared to speak to their portion of care of the patient. For example, a death that is linked to medical complications may not appear as though a social work representative be necessary to the meeting; however, the complications could stem from a psychosocial high-risk patient who did not meet criteria for inclusion. At this point, a follow-up may be necessary to revise selection policies, and social work representation is important for this step. Similarly, a patient death may be linked to an error at the bedside. The outpatient team may be responsible for reinforcing education or educating the inpatient team, and their participation, although initially may not seem important, now becomes critical for understanding all processes related to the evaluation and care of the patient through all stages. Although all disciplines should be represented, it is not necessary for all team members to be present, and limiting the root cause analysis meeting to only representatives for each discipline can help set an environment for candid sharing and critical dialogue.

Follow-up actions are usually required after a root cause analysis. The work sheet should list the individuals responsible for the follow-up and required dates. Follow-up meetings may be required to reconvene as well. Usually an adverse event will necessitate PI plans. The same methodology used for QA measures not meeting goals should be used for PI plans related to adverse events. Finally, when the root cause analysis is complete and PI planning and follow-up actions are underway, this should be reported to the quality committee and up through the hospital-level quality committee.

The adverse event requirement does not address near misses. A near miss can be defined as an event or occurrence that, if not detected and/or abated by a staff member, could have readily resulted in an adverse event. Near misses, along with substantiated patient complaints, and unfavorable trends should be indicators for an ad hoc meeting of the quality committee to discuss the occurrences and determine if a PI plan or after action is necessary. A near miss can be treated like an adverse event for analysis purposes. An unfavorable trend or patient complaint can be treated this way but more often will necessitate a focused

review with a smaller group. For example, if waitlist mortality is not a programmatic QA measure and it is indicated that waitlist mortality has been trending unfavorably, a meeting should be convened or a portion of the quality committee time should be dedicated to discussing this and mitigating further issues with this.

Conclusion

In order for a modern liver transplant program to ensure quality, a quality plan must be developed. The composition of the quality plan is driven heavily by regulatory factors but also requires further diversity in quality measurement development to develop best practices. Specifically, quality measures should be chosen following a structure, process, outcome, and value format. QA measures should be chosen based on areas of struggle, deficiency citations, and programmatic goals. QA measure goals and benchmarks should be established via committee and in a collaborative nonintimidating manner to ensure that team members have a sense of ownership. PI planning should be conducted in a format that is consistent with the hospital-wide methodology. Team members should have a working knowledge of the PI planning methodology. The annual quality plan should include detailed descriptions of the QA measures, the PI planning methodology, the program's adverse event's policy, and all pertinent changes made throughout the year. Also, the quality plan should contain previous year's meeting minutes and documentation pertaining to all interventions taken throughout the year. It is important for a QAPI program to go beyond the regulatory required minimum and include best practices for actual quality improvement that resonate with team members, payers, and patients.

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Role of the Transplant Coordinator

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Jerita Payne

Contents

Abstract

The transplant coordinator plays a pivotal role in the care of patients during all phases of the transplant process: pre-transplant evaluation, waitlist management, transplant admission, and discharge/posttransplant follow-up. The ability to perform this role is dependent upon organizational and critical thinking skills, utilization of evidenced-based practice methods, and the most recent research, as well as interpersonal skills to work with patients, families, and their support systems, transplant team members, and referring providers. Liver transplant coordinators are well versed in medical and surgical management. Medical management of patients with end-stage liver disease includes dealing with symptoms, managing medication side effects, and maintaining the appropriate waitlist status. The surgical management of posttransplant patients incorporates medication management and not only immediate postoperative issues such as infection and bleeding but also the ability to recognize potential life- or graft-threatening issues. General issues the transplant coordinator must manage are radiologic imaging for those with tumors, MELD score updates with detail including exceptions, appropriate vaccinations, and, in some instances, living donor candidates.

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Introduction

Coordination is the process of organizing people or groups so they work together properly, causing things to follow the same or similar process. For example, the human body is coordinated, different parts of the body move together well or easily (Merriam-Webster 2014). The same is true for the liver transplant coordinator. This nurse is responsible for keeping patients on track, no matter the phase of transplantation: from reviewing medical records, to arranging appointments and procedures, to understanding the pathophysiology of chronic liver disease, knowledge of immunology, transplant pharmacology, and infectious diseases. As the cornerstone of the transplant process, the coordinator uses evidence-based nursing to care for patients through all phases of transplant in order to optimize outcomes and provide for an optimal quality of life all the while maintaining the role of patient advocate (American Nurses Association and International Transplant Nurses Society 2009; North American Transplant Coordinators Organization 2009a, b). This chapter will discuss the role of the registered nurse (RN) and advanced practice nurse (APN) transplant coordinator as it relates to each phase of transplantation. The phases of transplant referenced in this chapter are:

- Phase 1: Pre-transplant evaluation
- Phase 2: Patient accepted and listed with the United Network for Organ Sharing (UNOS). Now in maintenance or candidacy phase
- Phase 3: Admitted for transplant procedure and inpatient stay
- Phase 4: Discharge and posttransplant follow-up care (Table 1)

Table 1 Four phases of transplantation

Phases of transplantation	
Phase 1	Pre-transplant evaluation
Phase 2	Patient accepted and listed with UNOS. Now in maintenance or candidacy phase
Phase 3	Admitted for transplant procedure and inpatient stay
Phase 4	Discharged and posttransplant follow-up care

Rogers (2013)

Registered Nurse Pre-transplant: Phase 1

During this phase of the liver transplant process, the RN transplant coordinator is responsible for the transplant candidate from referral to selection committee presentation. The RN coordinator is an integral part in assuring appropriate records are obtained and reviewed prior to the patient's first visit and throughout the evaluation process, as records become available. Upon review of the records, utilizing critical thinking skills and protocols, the RN coordinator determines if additional information is needed and requests as necessary. Because the RN coordinator is an expert in the inclusion and exclusion criteria for liver transplantation, he/she has the ability to determine the need for additional records. The goal for the RN coordinator prior to the patient being seen is to assure that as complete a medical record as possible is available to the physician – this saves time for the patient and provider and avoids any unnecessary duplication of tests.

Once the patient is determined as an appropriate candidate, the RN coordinator manages the transplant evaluation, similar to a project management. Upon receipt of the physician's order for evaluation, the RN coordinator works with various departments to schedule appointments and testing. This data is reviewed and prioritized to determine immediate needs and follow-up versus long-term or ongoing needs. For example, a lab value may be abnormal and require immediate action by the coordinator, or an abnormal cardiac test may require follow-up with a cardiac

catheterization, which the RN coordinator will then assure, as scheduled, follow-up on those results and report to the appropriate provider. As the evaluation process continues, the RN coordinator collects data in a systematic manner assuring inclusion of the patient and family in this process. While scrutinizing the data, the coordinator identifies patterns in the patient's history and status providing for a comprehensive assessment of the patient.

Patient education is one of the most important functions of the pre-transplant coordinator. Education of this population is not limited to the patient only but includes the family and others of the support system. Patient education focuses on disease processes; signs and symptoms of liver disease, including those that should be reported to the transplant program; symptom management; and specific information about the transplant process – from evaluation to long-term follow-up. This education is extremely important to the patient and family. Not only does it provide vital information to the patient but allows the formation of the nurse-patient relationship. This bond is vital in transplantation since these relationships are lifelong. The transplant education piece should include an overview of the transplant program, indications and contraindications of liver transplant, the evaluation process, selection committee, candidacy determination (accept, decline, defer for listing), and expectations for remaining or being removed from the list and issues that may lead to inactivation (status 7). Risks and benefits of the surgery should be part of the education process; however, these will be reviewed in depth during the surgical evaluation (American Nurses Association and International Transplant Nurses Society 2009; North American Transplant Coordinators Association 2009b). During this period the Model for End-Stage Liver Disease (MELD) score is described. The MELD score can be confusing to patients, so special attention is taken to explain and assure a basic understanding. Logistical information such as what to do when a liver becomes available, what to bring to the hospital, and expectations for the hospital stay is outlined. While patients and their families may not remember this information in detail, this discussion can help to serve as a reminder when the time comes for the actual transplant. A broad overview of the surgical procedure is provided as are expectations for the family before, during, and immediately after the transplant procedure. Potential complications are reviewed while it is suggested that the patient discuss these in detail with the surgeon.

The designation of a primary support and additional support persons is the most important part of patient education the transplant coordinator can discuss. Based upon programmatic considerations, the transplant coordinator has an in-depth educational session with the support person(s) to assure they have an adequate understanding of their expectations during all phases of the transplant process. The RN coordinator consults with the social worker regarding any issues that may have arisen during this education session providing continuity of care during the evaluation phase.

Medication plans and complications of immunosuppression are addressed at this time as well. Again, this provides an overview in order to manage expectations posttransplant (American Nurses Association and International Transplant Nurses Society 2009; North American Transplant Coordinators Organization 2009b).

There are regulatory requirements mandated by the Centers for Medicare and Medicaid (CMS) and/or UNOS that must be addressed during the pre-transplant phase. Often, it is simpler and more efficient to address these during the educational sessions. The first requirement is the consent for evaluation. The consent for evaluation must be signed by the patient or designee and includes acknowledgement of receipt of information from the transplant team concerning:

- Overview of the entire transplant process, including required tests and evaluation
- The donation process and waitlist
- The surgical procedure and associated risks
- Recovery expectations
- Psychosocial risks
- Emotional and personal stress
- Financial implications
- Compliance with a complex medical regimen
- Alternative treatments to transplant

- Right of refusal for testing, the transplant itself
- Information about how recipients are selected (selection criteria)
- Information about organ donor risk factors
- Ability to be listed at multiple transplant centers at the same time
- Ability to transfer waitlist time to another transplant center
- Survival outcomes for the specific transplant center and nationally
- Medicare-approved transplant facility
- Acknowledgement of receipt of educational materials

Health Resources and Services Administration, Organ Procurement and Transplantation Network (2014a).

Multiple listing (wait-listing for transplant at more than one center) is acceptable according to UNOS policy (United Network for Organ Sharing 2008). However, UNOS allows each center to make the determination as to whether or not they will allow it. Therefore, documentation that multiple listing has been discussed with the patient is mandatory. This is the responsibility of the RN coordinator during the pre-transplant phase. Documentation that education has taken place is required as well and is completed during the pre-transplant phase.

After the evaluation is completed, the transplant coordinator gathers and reviews the testing data. Abnormal results are reported to the provider and a plan is created. It is typically the RN coordinator who implements and follows up on this plan. The evaluation data is collated into a standard format and is reviewed at the selection committee. At this committee, all members of the transplant team speak about their interactions with the patient and family. Once a decision is made, the RN coordinator is responsible for relaying the decision to the patient and for implementing any plans or recommendations brought forward by the committee. This ongoing process can last for months; therefore, organizational and follow-up skills are imperative in this position.

The pre-transplant coordinator lists the patient with UNOS via UNet (United Network for Organ Sharing 2014). The listing is based upon blood type, body size, and MELD score. Per UNOS policy, two identical ABO results with sign-off by two team members are required. Following listing, the transplant coordinator documents in the medical record and sends correspondence to the patient and referring provider. Additionally, the UNOS patient education letter is included in the correspondence (Health Resources and Services Administration, Organ Procurement and Transplantation Network 2014b).

Registered Nurse Pre-transplant: Phase 2

Once the determination of the selection committee is complete, the waitlist management begins. This may be done by the same RN coordinator or some programs have separate waitlist managers. In either scenario, the main focus of the waitlist coordinator is to manage those patients who are awaiting transplant (American Nurses Association and International Transplant Nurses Society 2009; North American Transplant Coordinators Organization 2009b). This can be a daunting task as there are many moving parts to keep a patient activated on the waitlist. Native MELD scores, MELD exceptions, appropriate x-rays, and lab data within required time periods along with symptom and side effect management are some of the main foci of this coordinator.

MELD Score

The MELD score is a numerical scale for patients aged 12 or older, with scores ranging from 6 to 40. A score of 6 indicates a less ill patient, while a score of 40 indicates serious illness. Calculation of this score determines how urgently a patient needs a liver transplant within 3 months of the calculation. The calculation for this score uses a formula with three lab tests: total bilirubin, INR/prothrombin time, and creatinine (Health Resources and Services Administration, Organ Procurement and Transplantation Network 2014c).

Each of these lab tests are routinely measured in patients awaiting liver transplantation.

Total bilirubin measures how well the liver is excreting bile; INR is a measurement of the body's ability to make clotting factors; creatinine is a measurement of kidney function (United Network for Organ Sharing 2008; Taber's 2005). Of note in this situation, an elevated creatinine is an indication of poor kidney function; poor kidney function is often associated with liver disease.

For pediatric liver transplant patients, the PELD (pediatric end-stage liver disease) scoring system is in place for patients 11 years and under. While similar to MELD, the PELD score uses different lab values and other measures to determine the score – total bilirubin, INR/prothrombin time, albumin, growth failure – and is the child less than 1 year of age (United Network for Organ Sharing 2008; Health Resources and Services Administration, Organ Procurement and Transplantation Network 2014b).

Albumin measures the nutritional ability of the liver (Taber's 2005); growth failure and age recognize the developmental needs associated with children of this age category (Health Resources and Services Administration, Organ Procurement and Transplantation Network 2014). Both MELD and PELD scores increase and decrease over time as the patient's liver disease may improve or worsen. The goal is for the donated organs to be transplanted into those patients who are the sickest (i.e., in greatest need at the time).

The formulae are:

$$\begin{aligned}\text{MELD} = {} & 0.957 \times \text{Log}_e(\text{creatinine mg/dL}) \\ & + 0.378 \times \text{Log}_e(\text{bilirubin mg/dL}) \\ & + 1.120 \times \text{Log}_e(\text{INR}) + 0.643\end{aligned}$$

$$\begin{aligned}\text{PELD} = {} & 0.436\,(\text{Age}(< 1\text{ year})) - 0.687 \\ & \times \text{Log}_e(\text{albumin g/dL}) + 0.480 \\ & \times \text{Log}_e(\text{total bilirubin mg/dL}) + 1.857 \\ & \times \text{Log}_e(\text{INR}) + 0.667(\text{Growth failure} \\ & (< -2\text{standard deviations present})).\end{aligned}$$

The MELD/PELD system was implemented in 2002. Prior to that time, liver transplant candidates were categorized into four groups according to medical urgency. Those groups included some laboratory test results as well as symptoms of liver disease. The area of concern for this system was using symptoms as a means to gauge severity of liver disease because different physicians interpret symptom severity in different ways; therefore, this was not viewed as equitable. Because of this concern, this manner of scoring candidates could not categorize patients according to severity of liver disease and therefore those who were in greatest need of the transplant. Research studies were undertaken and showed that MELD and PELD scores more accurately predict patients' short-term risk of death if they do not receive a transplant. The MELD/PELD scores are objective and can be easily verified, providing an equitable, consistent means for determining severity of illness and need for transplant (United Network for Organ Sharing 2008).

The MELD/PELD scoring system requires that the RN transplant coordinator have exceptional organizational and follow-up skills in order to maintain accurate MELD scoring. The transplant coordinator is notified by UNOS that a listed patient's laboratory results require updating. If the update is not completed in the allotted time, according to UNOS policy, the patient's MELD score drops to 6 which is the lowest applicable score and basically provides few to no options for organ offers. The most recent lab results, along with the result date, are entered into UNet and the patient's score is updated or recertified. Those patients with MELD scores of 25 or above (for ages 18 or above) must have new lab results submitted every 7 days. Additionally, the lab results can be no more than 48 h old. For MELD/PELD scores off 25 or above (for those under 18 years of age), the lab results must be submitted every 14 days and can be no more than 72 h old. For MELD/PELD scores 19–24, the lab values must be resubmitted monthly and can be no more than 7 days old. MELD/PELD scores of 11–18 must be updated every 3 months with lab results no more than 14 days old and MELD/PELD scores of 10 or less must have lab tests resubmitted annually with lab data no more than 30 days old (Health Resources and Services Administration, Organ Procurement and Transplantation Network 2014c; Table 2).

Table 2 Liver status update schedule

If the candidate is:	The new laboratory values must be reported every:	And when reported, the new laboratory values must be no older than:
Status 1A or 1B	7 days	48 h
MELD 25 or greater (ages 18 and older)	7 days	48 h
MELD/PELD 25 or greater (less than 18 years old)	14 days	72 h
MELD/PELD 19 to 24	1 month	7 days
MELD/PELD 11 to 18	3 months	14 days
MELD/PELD 10 or less	12 months	30 days

Health Resources and Services Administration, Organ Procurement, and Transplantation Network (2014c)

Exceptions

As with most rules, there are exceptions. Liver transplant candidates may be assigned to a 1A status (high priority) if the following criteria are met: 18 years of age or older and life expectancy of 7 days or less without a transplant **plus one** of the following:

1. Fulminant liver failure. There must be no preexisting liver disease, the patient must be housed in the intensive care unit, there is development of encephalopathy within 8 weeks of the first onset symptoms associated with liver disease, **and one** of the following:
   (a) Ventilator dependent
   (b) Dialysis: Either continuous veno-venous hemofiltration or continuous veno-venous hemodialysis
   (c) INR greater than 2.0
2. Primary nonfunction within 7 days of a previous liver transplant according to **one** of the following criteria:
   (a) Anhepatic
   (b) AST equal to or greater than 3,000 U/L **plus one** of the following:
   Lactate greater than or equal to 4 mmol/L
   Venous pH less than or equal to 7.25
   Arterial pH less than or equal to 7.30
   INR greater than or equal to 2.5
3. Primary nonfunction within 7 days of a segmental liver transplant from a deceased or living donor according to **one** of the following criteria:
   (a) Anhepatic
   (b) Lactate greater than or equal to 4 mmol/L
   (c) Venous pH less than or equal to 7.25
   (d) Arterial pH less than or equal to 7.30
   (e) INR greater than or equal to 2.5
4. Hepatic artery thrombosis within 7 days of transplant according to **either** of the following criteria:
   (a) Anhepatic
   (b) AST greater than or equal to 3,000 U/L and one of the following criteria:
   Lactate greater than or equal to 4 mmol/L
   Venous pH less than or equal to 7.25
   Arterial pH less than or equal to 7.30
   INR greater than or equal to 2.5
   If the patient's hepatic artery thrombosis is within 14 days of the transplant, then the patient receives a MELD score of 40, not 1A status.
5. Acute decompensated Wilson's disease

Pediatric patients also have the option to be assigned a 1A status. The following criteria must be met: the patient is under 18 years of age at the time of *initial* listing **and** the patient has one of the following:

1. Fulminant hepatic failure in the setting of no preexisting liver disease with encephalopathy within 8 weeks of the first onset of liver disease symptoms and one of the following criteria:
   (a) Ventilator dependent
   (b) INR or 2.0 or greater
   (c) Requires either CVVH or CVVHD
2. Primary graft nonfunction within 7 days of transplant **and two** of the following criteria:
   (a) ALT equal to or above 2,000 U/L
   (b) Total bilirubin of 10 mg/dL or above
   (c) INR of 2.5 or greater
   (d) Acidosis defined as one of these criteria:
   Lactate of 4 mmol/L or greater

Venous pH of 7.25 or greater
Arterial pH of 7.30 or greater

3. Hepatic artery thrombosis within 14 days of transplant
4. Acute decompensated Wilson's disease

Pediatric liver transplant candidates also have the options of being assigned to a 1B status when all of the following are met: the potential recipient is under 18 years of age at the time of *initial* listing **and one** of the following criteria:

1. Organic academia or urea cycle defect with a MELD or PELD exception score of 30 for 30 days
2. Non-metastatic hepatoblastoma proven by biopsy
3. Chronic liver disease with a MELD of greater than 25 (for ages 12–17) or a PELD of greater than 25 (for ages under 12 years) **and one** of the following:
   (a) Mechanical ventilation
   (b) Renal failure or insufficiency necessitating CVVH or CVVHD
   (c) GI bleed necessitating at least 30 mL/kg of red blood cell transfusion within the previous 24 h
   (d) Glasgow coma score less than 10 within 48 h prior to the assignment or extension of 1B
4. Chronic liver disease requiring a combined liver-intestinal transplant with an adjusted MELD or PELD of 25 or greater **and one** of the following:
   (a) Mechanical ventilation
   (b) Renal failure or insufficiency requiring CVVH or CVVHD
   (c) GI bleed necessitating transfusion of at least 10 mL/kg of red blood cells within the previous 24 h
   (d) Glasgow coma score less than 10 within 48 h prior to the assignment or extension of 1B

Each time a patient is either assigned or recertified as a status 1A or 1B, a status justification form must be submitted to UNOS. If the patients was less than 18 years of age when initially listed, and remains listed after turning 18 years old, that patient may continue in the assigned pediatric classification by exception only after the transplant program had applied for and received approval by the regional review board. This determination is based upon urgency and the potential benefit for the patient when compared to other pediatric patients with the same issues (Health Resources and Services Administration, Organ Procurement and Transplantation Network (2014b) Policy 9: Allocation of Livers and Liver-Intestines).

Specific MELD/PELD Exceptions

Specific exceptions are directed to the Regional Review Board (RRB) or each UNOS region.

Cholangiocarcinoma is cancer of the bile ducts (Taber's 2005). Patients with this diagnosis will receive a MELD score of 22 points or a PELD score of 28. If the patient is not transplanted, the score will be adjusted to a 10 % point increase in the risk of 3-month mortality. This will occur every 3 months until the patient is transplanted or dies. This can only take place within transplant programs that have submitted a written protocol to the Liver and Intestinal Organ Transplantation Committee discussing candidate selection criteria, use of chemotherapy prior to radiation or surgical treatments, surgical staging that would exclude those with regional hepatic lymph node, and intrahepatic or extrahepatic metastases. Additionally, the Liver and Intestinal Organ Transplantation Committee can ask for any sort of information to assist them in making a determination. The liver transplant program must also provide documentation that the patient meets diagnostic criteria for hilar cholangiocarcinoma with a malignant appearing stricture as shown on cholangiogram along with biopsy or cytology results showing malignancy *OR* CA 19–9 results greater than 100 U/mL (without cholangitis) *OR* aneuploidy. To maintain a candidate on the waitlist, chest and abdominal cross-sectional imaging must show no metastases every 3 months.

Cystic fibrosis candidates must show signs of decreased pulmonary function with FEV_1 below

40 %. These candidates will receive an initial MELD of 22 or PELD of 28. Every 3 months, the score equivalent to a 10 % point increase in the risk of 3-month mortality will be assigned.

Familial amyloid polyneuropathy (FAP) candidates must be mobile with a well-defined diagnosis, an echocardiogram showing an EF of greater than 40 %, the TTR gene mutation (Val30Met vs. non-Vale0Met), **and** amyloid in the organ proven by biopsy. The receipt of MELD and PELD exception points is the same as discussed for cystic fibrosis patients.

Hepatopulmonary syndrome (HPS) is a combination of liver disease, decreased arterial oxygenation concentration, and dilatation of the blood vessels of the lung (Taber's 2005). In order to receive exception points, the candidate must have clinical evidence of portal hypertension, confirmation of a shunt, no primary pulmonary disease, **and** a PaO_2 less than 60 mmHg on room air. MELD score of 22 and PELD of 28 will be provided at the initial exception. In order to receive the score equivalent to a 10 % point increase in the risk of 3-month mortality every 3 months, the patient's PaO_2 must remain under 60 mmHg.

Patients with portopulmonary hypertension must have a mean pulmonary arterial pressure (MPAP) below 35 mmHG after intervention. The diagnosis should include an initial MPAP level, an initial PVR level, an initial transpulmonary gradient to correct for pulmonary overload, treatment documentation, MPAP less than 35 mmHg, **and** PVR less than 400 dyn/s/cm^{-5} after treatment. The same scoring system applies to this MELD/PELD exception as long as repeat heart catheterization done every 3 months confirms that the MPAP remains below 35 mmHg.

Primary hyperoxaluria is an inherited metabolic disease due to a glyoxylate metabolism defect. This defect leads to an increased secretion of oxalate in the urine, renal stones, and renal failure (Taber's cyclopedic medical dictionary 2005); therefore, this patient is a candidate for a liver-kidney transplant. This patient is deficient in AGT which must be proven by liver biopsy. The GFR must be 25 ml/min or less for 6 weeks or more. MELD score will be 28 and PELD score will be 41 for the initial exception, and the score will be adjusted every 3 months in the same manner as the other exceptions previously discussed.

Pediatric patients with metabolic diseases receive an initial MELD/PELD of 30. If these patients are not transplanted within 30 days of this exception, then the status may be changed to 1B (Health Resources and Services Administration, Organ Procurement and Transplantation Network (2014b) Policy 9: Allocation of Livers and Liver-Intestines).

The majority of MELD exceptions are due to hepatocellular carcinoma (HCC). Hepatitis C is most associated with HCC although anyone with liver disease can develop this cancer. Because hepatitis C makes up the majority of those transplanted annually, it follows that these patients most often develop HCC and require MELD exceptions, and the work of the RN coordinator increases. Patients with stage T2 lesions receive MELD or PELD scores equal to a 15 % risk of 3-month mortality. Stage T2 lesions are:

One lesion 2 cm or greater and 5 cm or less in size and 2 or 3 lesions that are 1 cm or greater and 3 cm or less in size

Before the exception request is submitted to the RRB, the following must occur:

1. Determination of the number and size of lesions using a "dynamic contrast-enhanced computed tomography (CT or magnetic resonance imaging (MRI)" (Health Resources and Services Administration, Organ Procurement and Transplantation Network (2014d) Policy 9.3.g.ii).
2. CT or MRI in order to exclude any extrahepatic or macrovascular metastases
3. CT of the chest to exclude metastases
4. Documentation that a resection of the lesion (s) is not possible
5. Alpha-fetoprotein blood level

In addition to these criteria, the RN transplant coordinator must assure that the imaging is performed on specific scanners. Attention to detail of the orders presented by the provider assures that the patient will not need to repeat unnecessary imaging.

For example, CT scan results must show the late arterial, portal venous, and delayed phases. MRI results must show pre-contrast T1W, late arterial, portal venous, and delayed phase images. Transplant centers obviously maintain this sort of equipment, but often smaller hospitals do not provide such imaging; therefore, the RN must coordinate the appropriate timing of scans in order to submit data to the RRB in a timely manner to prevent downgrading of the MELD score.

Furthermore, the RN transplant coordinator responsible for managing wait-listed patients must also be aware of class 5 lesions. These lesions are further divided into classes from 0 (inadequate study to make a determination) to 5X (lesions outside stage T2). A single nodule between 1 and 2 cm, showing enhancement on the late arterial phase and washout during the later contrast phases and peripheral rim enhancement on delayed phases, is considered to be class 5A. A biopsy could also be done but is not necessary to meet 5A classification. Class 5A-g nodules are also between 1 and 2 cm, show increased enhancement on late arterial phase, and have increased by 50 % or more on MRI or CT within 6 months. 5B class is a single nodule between 2 and 5 cm. Again, increased contrast enhancement must be noted on late hepatic arterial phase of the scan. Additionally, the imaging must show either washout on the delayed phase, late capsule, or pseudocapsule enhancement or increase in diameter by more than 50 % on imaging less than 6 months apart or biopsy. 5 T nodules are those that have been treated but must meet class 5 criteria prior to treatment. And finally 5X lesions are those that are outside of and of the previously defined criteria.

Class 5B and 5 T lesions can be wait-listed at a higher MELD score (22) automatically (without RRB approval). A single 5A nodule that is consistent with T1 staging does qualify for the automatic higher MELD score; however, if the 5A nodule meets stage T2 criteria, then the higher MELD score is applicable. Patients whose tumors are in the class 5X criteria may be listed with their native/calculated MELD score only (no additional points or priority). If the transplant program believes the patient is appropriate for additional points, then the RN coordinator is responsible for submitting information to the RRB for review and possible approval (Health Resources and Services Administration, Organ Procurement and Transplantation Network (2014b) Policy 9: Allocation of Livers and Liver-Intestines).

The necessity of an RN transplant coordinator with organizational skills is most apparent when managing these HCC patients on the waitlist. In order for these patients to continue on the waitlist with the appropriate MELD score exceptions, the RN transplant coordinator must manage the moving parts of lab results, appropriate scanning, treatment regimens, and timely submission to the RRB since these exceptions may not be automatically upgraded. Without organizational skills, the patient is at risk for MELD score downgrading which may result in the loss of an organ offer.

Compliance for these exceptions/rules is imperative as any noncompliance can put the program at risk for corrective action by UNOS and/or CMS. Therefore, the RN transplant coordinator must maintain appropriate documentation, specifically radiologic documentation. This must include reports of imaging that include documentation of the current nodule size as well as all previous size monitoring.

While patients remain on the waitlist, they are in the maintenance phase of transplantation. During this time, the RN transplant coordinator is again the hub of communication and coordination managing patients with chronic liver disease including management of symptoms, medications and side effects, lab data, imaging, and social issues. The RN is expected to communicate with patients on a regular basis as well as triage any issues that arise. The RN can manage most issues that arise according to established protocols but is expected to elevate issues that are above his/her scope of practice to other providers (American Nurses Society and International Transplant Nurses Society 2009; North American Transplant Coordinators Organization 2009b).

RN Transplant Coordinator: Phase 3

During the transplant hospitalization, the RN coordinator is responsible for moving the patient toward discharge. Important components of this

phase are medication and side effects, wound care, and diabetes teaching for the patient and support person(s) and reportable signs and symptoms emphasizing infection and rejection, nutrition, and follow-up expectations (American Nurses Society and International Transplant Nurses Society 2009; North American Transplant Coordinators Organization 2009b).

Medication administration and side effect education is one of the most important functions the RN transplant coordinator is responsible for. The education process includes all medications the patient will take at discharge but focuses on immunosuppressive therapy, antibiotics, antifungals, antiviral agents, and diabetes medications. In some instances, this may also include training about antihypertensive medications. Typically, this information includes dosage, frequency, and duration of specific medications. An important point about the calcineurin inhibitor is that the medication must be held prior to having blood samples drawn in order to obtain an accurate trough level. The trough level in combination with other lab test results allows for appropriate adjustment of dosage of these medications. Diabetes education includes blood glucose monitoring, determination of appropriate insulin dose based upon blood glucose results, or standing dosage for other forms of insulin, drawing up the appropriate dose into the syringe, and then injection. Signs and symptoms of hypo- and hyperglycemia are taught during this time as well. Side effects such as increased appetite and weight gain, mood changes, bone and joint pain, stomach ulcers, edema, insomnia, headaches, tremors, hair loss or increased growth, kidney dysfunction, low red and white blood cell counts, and increased risk of infection.

Wound care education includes how to clean the wound; change any dressings; inspection of the wound to assess for redness, swelling, drainage, and bleeding; and again reportable signs. The connection between immunosuppressive therapy and infection is an important component of this part of the education process since immunocompromised patients are at higher risk for infection including the surgical wound area.

Reportable signs and symptoms are those that are related to the recent transplant but long-term issues as well. Due to the suppression of the immune system by medications, there is an increased incidence of infection, particularly in the first 90 days after transplant. An elevated temperature should always be taken seriously and evaluated if persistent. Redness, swelling, or heat from the surgical site, diarrhea, blood in the stool, nausea, and vomiting are all symptoms that should be evaluated in a timely manner. Long term, there is an increased risk of cancer, particularly in former smokers (lung, head, and neck) and in those patients transplanted for liver cancer (recurrent disease). Skin cancer is also more prevalent among transplant patients. The importance of sunscreen, protective clothing, and annual skin examinations by a dermatologist is an area that should be incorporated into education early on in order to hardwire these lifelong expectations.

Nutrition education by the RN is an extension of the education already provided by the nutritionist. This includes specific dietary requirements such as diabetic or low-sodium diets, foods to avoid and those that are encouraged, and appropriate supplements.

Follow-up expectations include laboratory tests several times per week but with the expectation that this will decrease over time and keeping clinic appointments which can be several times per week as well. Posttransplant patients require assistance in taking care of themselves for several weeks after surgery. The support person(s) is an integral part of this process and must be committed to performing oversight and administration of medications, wound/incision care, transportation to and from clinic appointments, blood draws, and other procedures as needed. This is typically one person but can be a combination of family and close friends who will all undergo training of these tasks.

By beginning these educational opportunities as soon as possible after transplant, the patient and support system are well prepared to leave the hospital in a safe manner. The goal is to equip the patient and family with the knowledge they will need to have a good outcome (American Nurses Society and International Transplant

Nurses Society 2009; North American Transplant Coordinators Organization 2009b).

RN Transplant Coordinator: Phase 4

After discharge, the RN again becomes the center of communication and care for the patient. In some instances, the RN coordinator may attend clinic to assess the patient's progress and report issues to the appropriate provider. Following these visits, the RN coordinates any follow-up issues that may have arisen including contacting the patient about lab results, medication changes, and next appointments (American Nurses Association and International Transplant Nurses Society 2009: North American Transplant Coordinators Organization 2009b).

For this phase of transplantation, the RN coordinator manages the patient similarly to the pre-transplant phase by triaging phone calls, reporting signs and symptoms, obtaining results of lab tests and procedures, managing imaging requirements, and communicating with the appropriate provider. The RN requires critical thinking skills and can manage some issues according to protocol. These patients require frequent lab testing to assess for rejection. Once results are received, the RN either manages the medication changes or, if rejection is suspected, coordinates liver biopsies and other tests to make that determination. If rejection is diagnosed, the RN then coordinates the treatment and appropriate follow-up. The same is true for issues such as cytomegalovirus and any infection requiring intravenous infusions.

In summary, the RN transplant coordinator is the cornerstone of the transplant process. These nurses that have experience in nursing and transplantation use their experience, critical thinking, and assessment skills to review a situation and make plans accordingly, think intuitively, provide education to patients and support person(s), serve as a patient advocate, and focus on long-term patient goals (American Nurses Association and International Transplant Nurses Society 2009; North American Transplant Coordinators Organization 2009b; Table 3).

Table 3 Roles of the RN transplant coordinator

Phase of transplant	Responsibilities	Required skills
1: Pre-transplant evaluation	Educator Consultant Project manager Collaborator Communicator Patient advocate Regulatory/ compliance manager	Organization Critical thinking Attention to detail Communication Compliance/ regulatory
2: Maintenance or candidacy	Waitlist manager Triage nurse Communicator Patient advocate Regulatory/ compliance manager	Organization Follow-up Critical thinking Attention to detail Communication Compliance/ regulatory
3: Transplant procedure and inpatient stay	Educator Consultant Collaborator Patient advocate Discharge planner	Organization Critical thinking Attention to detail Communication
4: Posttransplant follow-up	Educator Consultant Collaborator Triage nurse Communicator Patient advocate	Organization Follow-up Critical thinking Attention to detail Communication

The APN transplant coordinator may perform similar functions to the RN coordinator in addition to those more advanced components of nursing according to education (master's degree or higher) and scope of practice. This includes advanced assessment, differential diagnosis and treatment, ability to order and interpret diagnostic tests, and prescriptive authority (American Nurses Association and International Transplant Nurses Society 2009; North American Transplant Coordinators Organization 2009b).

APN Transplant Coordinator: Phase 1

During this phase of transplantation, the APN is involved in the assessment, diagnosis, and determination of transplant candidacy. The APN provides initial review of the candidate's records and physical assessment, orders and interprets testing, forms

differential diagnoses, and in collaboration with the hepatologist and/or surgeon makes recommendations regarding the patient's transplant options or for other forms of treatment. During selection committee the APN may provide the history and physical findings and discuss concerns or further testing needed to determine the patient's appropriateness for transplant. It is then the APN's responsibility to obtain this additional information and provide follow-up to the appropriate physician (s) (American Nurses Association and International Transplant Nurses Society 2009; North American Transplant Coordinators Organization 2009a).

APN Transplant Coordinator: Phase 2

After acceptance and listing, the APN transplant coordinator works with the RN transplant coordinator to maintain patients on the waitlist. The APN manages the patients in the clinic or inpatient setting with physical assessment, review of symptoms and medication side effects, differential diagnoses, medication reconciliation, and review of data such as labs and imaging. Formulation of the treatment plan is completed and communicated to the attending physician(s). This process is maintained during the wait-listing period and occurs on a regular basis, allowing the APN to develop an ongoing relationship with the patient and support system and providing continuity of care. Any issues that are outside the APN's scope of practice are elevated to the attending physician (American Nurses Society and International Transplant Nurses Society 2009; North American Transplant Coordinators Organization 2009a).

APN Transplant Coordinator: Phase 3

During the transplant hospitalization, acute care APNs manage the patient in concert with physicians. Depending on the institution, APNs may replace surgical residents and provide day-to-day care in the intensive care unit(s) and the non-ICU care areas. This includes management of fluid status, need for blood products, adjustment of medications, invasive monitoring, and pulmonary toilette. These APNs round regularly with other transplant team members, including the RN transplant coordinator, thus providing care across the continuum (American Nurses Society and International Transplant Nurses Society 2009; North American Transplant Coordinators Organization 2009a). The APN coordinator also has the opportunity to provide education to the patient and support system. This is the golden opportunity to add emphasis to the education provided by the RN coordinator.

APN Transplant Coordinator: Phase 4

Once the patient is discharged, the APN coordinator is responsible for continuity of care by providing lifelong medical management. In phase 4, the APN coordinator provides management similar to that discussed for phase 2 but in the posttransplant population. This management includes history and advanced physical assessment, symptom and medication side effect management, ordering and interpreting lab and diagnostic testing, determination of differential diagnoses, and creation of the plan of care. This can include treatment of infection, rejection, biliary complications, recurrent hepatitis C, monitoring for recurrent hepatocellular carcinoma, and general medical issues such as hypertension, bone disease, diabetes, cholesterol considerations, vitamin deficiencies, and skin cancer assessment. Some of this management can be coordinated with the patient's primary care and other providers such as dermatologists and gynecologists. Many times it is the APN coordinator who recognizes psychosocial issues and can provide medication and refer to appropriate providers. The APN coordinator works closely with the RN to coordinate care across the continuum since these patients can be complicated. This lifelong connection again provides for continuity of care in establishing rapport and partnership with this patient population (American Nurses Society and International Transplant Nurses Society 2009; North American Transplant Coordinators Organization 2009a; Table 4).

Table 4 Roles of the APN transplant coordinator

Phase of transplant	Responsibilities	Required skills
1: **Pre-transplant evaluation**	Educator Consultant Collaborator Communicator Provider Patient advocate Regulatory/ compliance manager	Organization Critical thinking Attention to detail Communication Compliance/ regulatory Order and interpret tests Determine differential diagnoses Prescribe medications
2: **Maintenance or candidacy**	Waitlist manager Communicator Provider Patient advocate Regulatory/ compliance manager	Organization Follow-up Critical thinking Attention to detail Communication Compliance/ regulatory Order and interpret tests Determine differential diagnoses Prescribe medications
3: **Transplant procedure and inpatient stay**	Educator Consultant Collaborator Patient advocate Discharge planner Provider	Organization Critical thinking Attention to detail Communication Order and interpret tests Determine differential diagnoses Prescribe medications
4: **Posttransplant follow-up**	Educator Consultant Collaborator Communicator Patient advocate Provider	Organization Follow-up Critical thinking Attention to detail Communication Order and interpret tests Determine differential diagnoses Prescribe medications

Living Donation

There is another coordinator who follows patients in the same manner as those listed above, but does so for the living donor. These coordinators manage potential and actual donors in order to avoid any hint of coercion. The phases of transplantation are the same but are for potential donors instead. During phases one and two, the coordinator focuses on the needs of the donor only and assures that there is no coercion associated with donation.

In the pre-transplant phase, the living donor coordinator is obtaining and reviewing medical records, history and physical, to determine if the donor has any issues that would rule him/her out as a potential donor. Once the donor has been cleared by the first review, the donor coordinator then arranges for testing. This is often done in a stepwise fashion performing the least invasive procedures first in order to rule out potential donors prior to the more invasive procedures. The donor evaluation includes many of the same tests that recipients undergo but includes other special testing such as volumetric CT scans and a rigorous psychosocial evaluation. It is the responsibility of the coordinator, in collaboration with the donor team and the independent living donor advocate, to provide an "out" at any time the potential donor changes his/her mind. It is also their responsibility to safeguard the donor's medical issues and reasons for non-candidacy or deciding not to donate, no matter the reason.

Phase 2 is a bit different because it is maintenance of a healthy donor to the point of donation. This can be an anxiety-provoking time for the donor as he/she continues to contemplate a procedure that is not without risks. It is imperative that the donor coordinator be available to the donor to reassess mental and physical health issues and refer to other providers as necessary and again to provide an "out" if needed.

During phase three, the coordinator is responsible for discharge planning. The education for the donor and support person(s) includes wound care, pain management, medication administration,

reportable signs and symptoms, and follow-up care. Wound care management for the donor is simpler because there are no medications to alter their immune system and they were healthy at the time of surgery which should allow for faster wound healing. The pain management regimen should be determined prior to discharge in order for the patient to avoid emergency department or additional clinic visits. Reportable signs and symptoms are of particular importance since this was a healthy individual who has undergone a partial hepatectomy. Monitoring for jaundice, itching, abdominal or shoulder pain, and fever should be included in the discharge education. It is important for these patients to maintain their follow-up schedules. Serial laboratory tests will provide an early indication of poor liver function, imaging will take place in order to assess regeneration of the liver and look for any complications that are not overt, and assessment for hernias will take place in phase 4. While it is preferred that living donors maintain lifelong follow-up with the transplant center, this often does not occur. Post donation, patients return to normal health and do not see the need to return to the transplant center (American Nurses Society and International Transplant Nurses Society 2009; North American Transplant Coordinators Organization 2009a; Table 5).

Table 5 Roles of the living donor transplant coordinator

Phase of transplant	Responsibilities	Required skills
1: **Pre-transplant evaluation**	Educator Consultant Collaborator Communicator Provider Regulatory/ compliance manager	Organization Critical thinking Attention to detail Communication Compliance/ regulatory
2: **Maintenance or candidacy**	Communicator Provider Regulatory/ compliance manager	Organization Follow-up Critical thinking Attention to detail Communication Compliance/ regulatory
3: **Transplant procedure and inpatient stay**	Educator Consultant Collaborator Discharge planner	Organization Critical thinking Attention to detail Communication Prescribe medications
4: **Posttransplant follow-up**	Educator Consultant Collaborator Communicator	Organization Follow-up Critical thinking Attention to detail Communication

General Considerations

Vaccinations

Vaccines are an important consideration of care in the pre- and posttransplant phases. The response to immunizations can be suboptimal in patients with end-stage organ disease and those receiving immunosuppressive medications; therefore, a thorough vaccination history should be obtained early on in the transplant evaluation and initiation of vaccines should be undertaken as soon as possible. In general, vaccines given prior to transplantation produce more of an immune response than those given after transplantation (Avery and Ljungman 2001; Duchini et al. 2003; Ballout et al. 2005).

There are two types of vaccines to consider in the transplant populations: live and killed. Live vaccines are those that contain live, attenuated microorganisms that can cause a primary infection (Avery and Ljungman 2001; Ballout et al. 2005). Killed vaccines are also known as inactivated vaccines. The disease-causing microorganism has been killed with chemicals, radiation, or heat. These vaccines are more stable and safer than live vaccines because they are not able to mutate back to cause a primary infection.

Influenza

The influenza vaccine should be given annually, at the appropriate time of year, while awaiting transplant. This vaccine provides

prophylaxis against developing influenza, either a severe primary infection or a secondary bacterial pneumonia, either of which could delay transplantation. The vaccine is also indicated after transplant, again in the appropriate season annually. While antibody titers may not reach those of healthy adults, the benefits outweigh avoiding the vaccine. Children should also receive this vaccine. The first receipt of this vaccine should be given in a series of 2 doses, each 1 month apart. Also, all family and household contacts should receive this vaccine (Avery and Ljungman 2001).

Pneumococcal Pneumonia

Prevention of pneumococcal pneumonia and sepsis can be achieved by receipt of the pneumococcal polysaccharide vaccine. It should be administered prior to transplantation and again at 2–3-year intervals while awaiting transplant (Avery and Ljungman 2001).

Hepatitis A (HAV)

This virus can lead to severe liver dysfunction and fulminant hepatitis, especially for patients with preexisting liver disease. Havrix® and Vaqta® are two vaccines that have proven effective. This series should be administered prior to transplant (Avery and Ljungman 2001; Duchini et al. 2003; Ballout et al. 2005).

Hepatitis B (HBV)

Engerix-B® and Recombivax HB® are recombinant HBV vaccines that should be administered to seronegative patients. The response to this series of immunizations is again more effective in the pre-transplant phase rather than after transplantation. A dose of 40 40 μg mu;g at 0, 1, 2, and 6 months is most effective for pre-liver transplant patients. A fourth dose may be administered at 12 months for patients with diabetes (Avery and Ljungman 2001).

Tetanus-Diphtheria Toxoid (Td)

This booster should be given if the patient has not received it in the preceding 5 years. However, if the patient has never received the initial series, it should be administered prior to transplant. In children the primary DTP or DTaP (diphtheria-tetanus-pertussis or diphtheria-tetanus-acellular pertussis) should be administered before transplant, according to standard practice (Avery and Ljungman 2001).

Measles-Mumps-Rubella (MMR)

Live viruses such as the MMR are not recommended after transplantation; therefore, completion of the primary series should take place prior to transplantation (Avery and Ljungman 2001; Duchini et al. 2003).

Polio Virus

Another live virus, the oral polio vaccine (OPV) should not be administered after transplantation. Inactivated poliovirus vaccine (IPV) is safe following transplant. The IPV is acceptable for household contacts as well since there is a small likelihood of transmission of live virus (Avery and Ljungman 2001; Duchini et al. 2003).

Meningococcal Vaccine

The quadrivalent form of this vaccine should be considered for college-age patients or those who plan to attend within 1–2 years (Avery and Ljungman 2001; Duchini et al. 2003).

Haemophilus Influenzae Type B Conjugate Vaccine (HIB)

This series should be completed in children awaiting transplantation. In adult recipients who have undergone a splenectomy or are

Table 6 Vaccinations

Immunization	Dosage	Considerations for adults	Considerations for children (if indicated)
Influenza (trivalent inactivated)	Double dose	Annual during appropriate season After transplant	Annual during appropriate season
Pneumococcal pneumonia (Pneumovax®)	23-valent polysaccharide, heptavalent protein conjugated	Prior to transplantation and at 2–3-year intervals while waiting. After transplant	
Hepatitis A (inactivated)	1,440 ELISA	Series prior to transplant at 0 and 2 months After transplant	
Hepatitis B (recombinant)	40 μg	Series at 0, 1, 2, and 6 months After transplant	
Tetanus-diphtheria toxoid		Primary series or Booster if not received in previous 5 years After transplant	Primary DTP or DTaP according to standards
Measles-mumps-rubella		Complete series pre-transplant only Controversial	
Polio		OPV or IPV AFTER transplant only. IPV ONLY for household contacts	
Meningococcal		Quadrivalent form for college age or those entering college within 1–2 years pre-transplant	Quadrivalent form for college age or those entering college within 1–2 years pre-transplant
Haemophilus influenzae type B conjugate vaccine		Adults: post-splenectomy or other immunosuppressive therapy check HIB titers and then determine necessity After transplant	Complete series according to standards
Varicella		For seronegative, consider administration of vaccine Controversial	Prior to transplant

Avery and Ljungman (2001), Duchini et al. (2003), Ballout et al. (2005)

immunocompromised for other reasons, HIB titers should be measured after which consideration of revaccination is based on these results (Avery and Ljungman 2001; Duchini et al. 2003).

Varicella

Primary varicella infection after transplantation leads to morbidity and mortality in this population. Assessment of varicella titers should be reviewed at which time administration of the live attenuated vaccines should be considered (Avery and Ljungman 2001). In children and adolescents, vaccination prior to transplantation is suggested (Ballout et al. 2005; Table 6).

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Finance of Liver Transplantation

35

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Contents

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Abstract

Organ transplantation, particularly liver transplantation, is one of the most expensive and complicated services that a hospital can provide. There are varied disciplines involved in the daily operations of a liver transplant program. There are numerous payment methodologies, contract types, and reimbursement methods due to transplant being more complicated than most medical procedures. Private commercial insurers and Medicare are the primary sources of payment in liver transplant. Medicare's payment system is a threefold process, consisting of a diagnosis-related group payment, the Medicare Cost Report, and ambulatory payment classifications. Commercial payers work through managed care organizations that contract with specialty transplant networks. While a majority of liver transplants are covered by Medicare and private payers, Medicaid and self-pay are other payment sources. The expansion of health coverage through the Patient Protection and Affordable Care Act has greatly impacted the finances of transplant programs in the United States. Patients who are candidates for a transplant will have increased access to transplant care; however, the Medicare reimbursement will be reduced through decreased payments of the diagnosis-related group and organ acquisition cost. A transplant program must increase focus on quality and efficiency while understanding the costs involved in providing liver transplantation.

Keywords

Liver transplant • Medicare • Managed care • Diagnosis-related group • Cost report • Affordable Care Act

Introduction

Organ transplantation is one of the most expensive and complicated services that a hospital can provide. Based on the Organ Procurement and Transplantation Network data of 2013, there were 137 centers in the United States that performed adult and/or pediatric liver transplantation. The Organ Procurement and Transplantation Network also stated that as of August 2014, there was a median volume of 40 adult liver transplants and eight pediatric liver transplants performed in 2013 in adult and pediatric liver transplant programs, respectively.

Medicare was among the first national payers to reimburse for liver transplantation in 1991. Following this Medicare approval for liver transplant coverage, commercial payers developed coverage plans for providing liver transplantation benefits for their covered members.

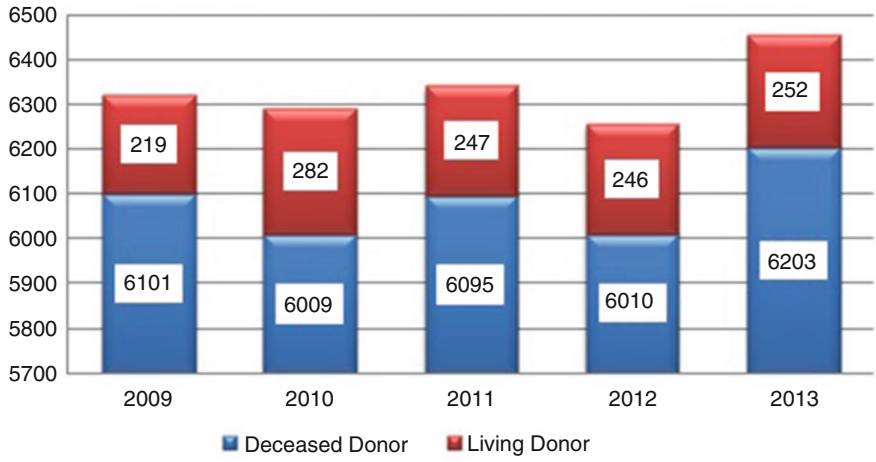
The evolution of public and commercial payers covering liver transplantation has created numerous payment methodologies, contract types, and reimbursement methods. Revenue management in liver transplantation is a highly complex yet crucial process needed to stay viable in such a specialized environment.

Reimbursement and contracting vary among payers and can have an adverse economic impact if not managed appropriately. Therefore, it is imperative to be aware of the liver transplant financial environment, including types of payers, contracting terms, and opportunities to optimize overall reimbursement, as well as managing costs.

Organ Supply

The supply of donated livers comes from two sources, deceased donors and living donors. Ninety-six percent of the liver transplants performed in the United States in 2013 were from deceased donors. As illustrated in Fig. 1, living liver donation from 2009 to 2013 ranged from 3.5 % to 4.5 % of the total liver transplants performed in the United States.

The Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) requires separate policies and procedures for management of living donors, including separate quality assessment practices and performance improvement processes. Centers for Medicare and Medicaid Services (CMS) and



Based on OPTN data as of August 1, 2014.
This work was supported in part by Health Resources and Services Administration contract 234-2005-37011c. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Fig. 1 Deceased and living donor liver transplants performed annually, calendar year 2009–2013

Table 1 Four phases of transplantation

Phases of transplantation	
Phase 1	Patient evaluated for transplant
Phase 2	Patient accepted and listed with OPTN/UNOS and is now in the maintenance or candidacy phase
Phase 3	Patient admitted to hospital for organ transplant procedure and subsequent inpatient stay. This is typically the diagnosis-related group (DRG) component of the transplant process
Phase 4	Patient discharged from hospital and posttransplant follow-up care period starts

OPTN/UNOS both audit living donor programs for specific criteria. It is difficult for small volume transplant programs to maintain sufficient volume to be proficient and attain acceptable outcomes to perform living donor liver transplants.

Four Phases of Transplantation

The process of transplantation involves four phases of care (Table 1).

Phase One: Pre-transplant Evaluation

This phase includes all pre-transplant clinical visits, multiple tests, and evaluations to determine a patient's candidacy for liver transplant. All work involved in screening the patient for candidacy to the point of a decision by the patient selection committee is considered to be part of the pre-transplantation evaluation phase.

Phase Two: Candidacy and Maintenance Phase

The patient selection committee approves the patient to be placed on the liver transplant waiting list. While on the liver transplant waiting list, patients may have to undergo minimal maintenance testing and other procedures to ensure a continuation of transplant candidacy. Liver transplant patients receive a Model for End-Stage Liver Disease (MELD) score to determine how urgently he/she needs a transplant. To maintain updated MELD scores, a patient needs to have the appropriate lab tests every 1–4 weeks on a continuous basis until the time of transplant. There may be

additional tests that are required to confirm the candidacy of the patient (OPTN 2014).

Phase Three: Day of Transplantation

The patient is admitted to the hospital for the liver transplant procedure. This phase comprises all services related to the transplant episode itself and includes such items, based on the payer, as the hospital and professional fees, organ acquisition, and transportation costs. This phase usually begins 24 h prior to the transplant and concludes the day of discharge.

Phase Four: Posttransplant

This phase begins the day after discharge and ends after a contractually predetermined amount of time. Patients are followed closely to ensure proper organ function.

Living donation follows similar phases for pre-donation, acceptance as a living donor, donor surgery, and post-donation follow-up (Table 2).

These phases of transplant and living donor care are important as they directly relate to payer methodology.

Transplant Payers

Medicare

Medicare is one of the major payer sources for transplant services. Medicare is a federally funded program that provides health insurance to those aged 65 and older, certain younger individuals with disabilities, and individuals with end-stage renal disease. For transplant patients, Medicare also covers immunosuppressive drugs for 3 years posttransplant only if the patient is transplanted at a CMS-approved facility (Norris 2014). Medicare also covers healthcare costs for living donors. There are four main parts of Medicare:

Part A – Hospital insurance that covers inpatient services, outpatient diagnostic services, and extended care after hospitalization
Part B – Medical insurance that covers physician services and outpatient services
Part C – Medicare Advantage Plans that allow private health insurance companies to provide Medicare benefits
Part D – Prescription drug insurance that covers outpatient prescription drugs

CMS approves transplant programs that wish to participate in the Medicare program. The final rule, with an effective date of June 28, 2007, established for the first time Medicare conditions of participation for kidney, pancreas, liver, intestine, heart, lung, and heart-lung transplant centers. This rule sets forth clear expectations for safe, high-quality transplant service delivery in Medicare-participating facilities. Medicare will not pay for the organ acquisition transplant event under Part A or immunosuppressive medications under Part B unless the transplant is performed at a Medicare-certified transplant hospital. All medications can be paid under Part D if the transplant is performed at a non-Medicare-certified center. The program must perform at least 10 liver transplants within the 12 months prior to initial approval.

Medicare can account for as much as 26 % of the liver transplant payer attribution when Medicare fee-for-service and Medicare Advantage Plans are combined. Based on the OPTN data of June 6, 2014, Medicare fee-for-service and Medicare Advantage Plans numbered 1,050 and 630, respectively, of a total number of 6,455 liver transplants.

Table 2 Four phases of living donation

Phases of living donation	
Phase 1	Patient evaluated as transplant donor
Phase 2	Patient accepted as living donor and now in candidacy phase
Phase 3	Patient admitted to hospital for living donor procedure and subsequent inpatient stay
Phase 4	Patient discharged from hospital and post-donor follow-up care period starts

There are three components of cost: physician services, hospital services, and organ acquisition costs. Medicare's payment system is a threefold process. The process consists of a diagnosis-related group payment, the Medicare Cost Report, and ambulatory payment classifications.

Diagnosis-Related Group Payment

The diagnosis-related group (DRG) payment is derived through a specific formula based on disproportionate share (DSH), Graduate Medical Education (GME), Indirect Medical Education (IME), and labor index, among others. Liver transplant was originally listed as DRG 480 (Acute Care Hospital 2013). In 2007, the DRG system was further refined to include medical severity, which is labeled as MS-DRG. The MS-DRG for liver transplant is divided into two categories based on transplants with and without major complications and comorbidities (MCC):

MS-DRG 005 – Liver transplant with MCC and intestinal transplant
MS-DRG 006 – Liver transplant without MCC

Some common complications and comorbidities related to a liver transplant are hepatitis, diabetes, acute hepatic failure, and primary liver cancer. The MS-DRG must cover all costs directly related to the transplant surgery and inpatient hospital stay following the surgery (Files for FY 2008; FY 2014 Final Rule Tables 2014).

Medicare Cost Report

The Medicare Cost Report is a payment arrangement in which additional reimbursement is made to a transplant program for all appropriate Medicare allowable pre-transplant expenses in phases 1 and 2 to the point of admission for transplantation. These expenses are known as the organ acquisition costs (Fig. 2). The organ acquisition costs are comprised of the cost of the organ and transportation, plus direct and indirect expenses that are allocated to the pre-transplant portion of activity prior to the admission of the patient for transplant (Fig. 3). However, treatment and disease management of the transplant patient are not considered organ acquisition costs.

Additionally, the salaries and benefits of administrative and clinical liver transplant staff that have pre-transplant responsibilities and have documented their pre-transplant time through monthly time studies (alternating 1 week time studies each month) are considered an organ acquisition expense. The time studies must be

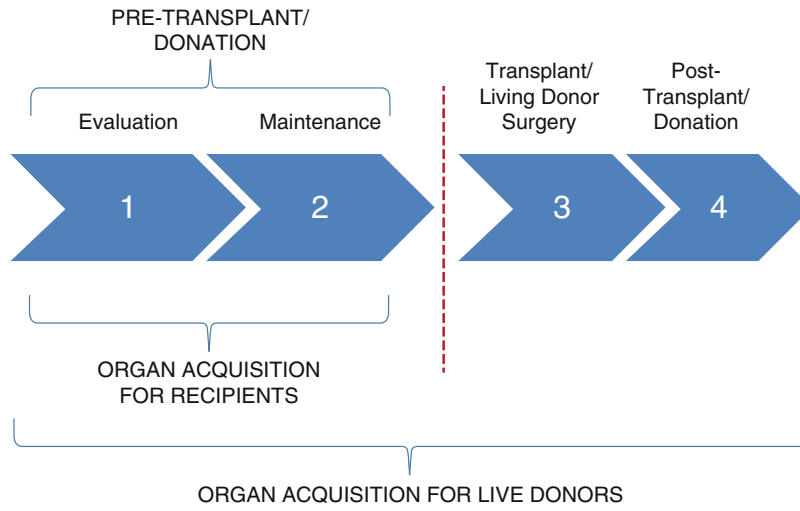


Fig. 2 Organ acquisition phases 1–4 for transplant recipients and living donors

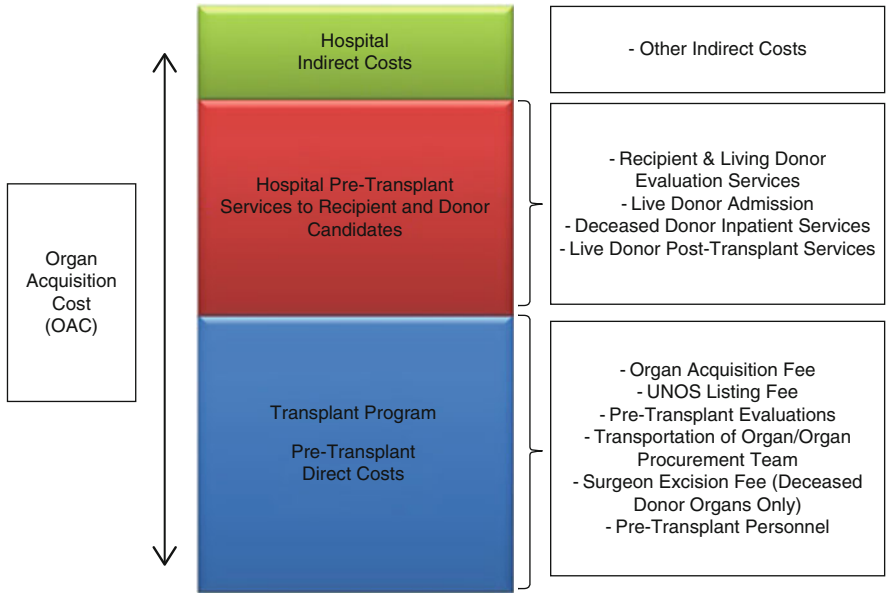


Fig. 3 Components of direct and indirect costs accounted for in organ acquisition

completed by, but not limited to, medical directors, transplant coordinators, social workers, financial coordinators, dieticians, pharmacists, and administrative personnel (Rogers 2013).

For physicians, only the time spent on pre-transplant administrative tasks relating to their medical or surgical director roles may be included on the cost report. The physician's pre-transplant clinical time is not included on the cost report, as physicians already bill separately for this time. Medicare will reimburse for administrative tasks based on the reasonable compensation equivalent (RCE), which is based on physician specialty (Levinson 2006 and Norris 2014). The RCE limits were designed with metropolitan location adjustments, but CMS will eliminate these adjustments and increase the RCE limits overall as of January 1, 2015 (CMS/HHS 2014). For example, a liver transplant surgical director is compensated a total of $50,000 for administrative duties. The surgical director logs 200 h of pre-transplant time annually. The surgery 2015 RCE limit rate is $246,400 (CMS/HHS 2014). The following calculation illustrates the amount that can be reimbursed under the Medicare Cost Report:

$$\text{RCE limit rate } (\$246,400/2,080 \text{ h per year}) = \$118.46 \text{ per h}$$

$$\$118.46/\text{h} \times 200\,\text{h} = \$23,692$$

Therefore, only $23,692 would be placed on the cost report for the physician's administrative tasks (in comparison to$50,000), and the Medicare Cost Report ratio would be applied.

Living donors for liver transplant are also included in the Medicare Cost Report. The costs for living donors include donor evaluation provided by the physician or hospital, donor liver resection, post-donation complications, and routine follow-up provided by the hospital (Fig. 2). All other services are billed fee-for-service on the account of the recipient; the hospital may not bill the donor. Additionally, travel and lodging for pre-donation needs are not included in the Medicare Cost Report for recipients, donors, or family members (Rogers 2013).

To determine if a cost is considered an organ acquisition cost, please see Fig. 4.

Transplant programs maintain an organ acquisition cost center or account to accumulate these charges during any given year and report these charges on the hospital's Medicare Cost Report at

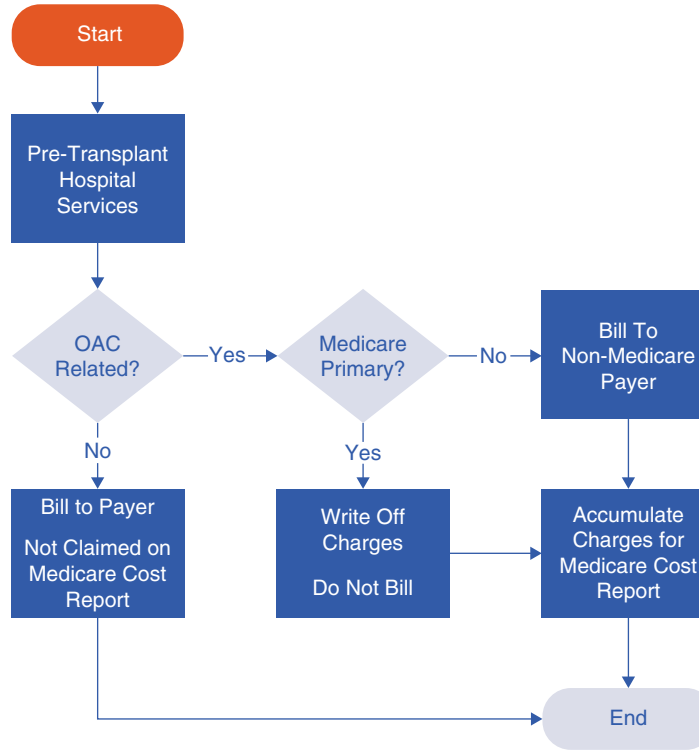


Fig. 4 Algorithm to account for organ acquisition costs

year end for reimbursement at the level of the hospital's costs. The Medicare ratio is applied to all allowable pre-transplant expenses placed on the cost report. There are three fundamental determinants to calculate a transplant program's Medicare Cost Report ratio and reimbursement. The first is the number of liver recipients transplanted with Medicare as the primary payer. The term "Medicare primary" refers to a program's number of transplants with Medicare as the primary payer. The second ratio determinant is the number of liver recipients that Medicare has paid as a secondary payer, which refers to the number of transplants that had Medicare as a secondary payer to the patient's employer insurance. The third determinant is the number of deceased donor livers procured in the transplant hospital. Taking these factors into account creates the following ratio:

$$\frac{\text{Medicare primary} + \text{Medicare secondary} + \text{Donor organs}}{\text{Total liver transplants} + \text{Deceased donor livers}}$$

An example of what these Medicare ratio determinants mean to a transplant program's Medicare reimbursement is shown using an example of a liver program that performs 50 transplants per year with hypothetical pre-transplant costs for 1 year of one million dollars (see Tables 3 and 4). Accurately accounting for these Medicare ratio determinants is critical to ensure that all allowable cost reimbursements are received by the transplant hospital. In this hypothetical example, the Medicare ratio is 10 % greater, and the cost-based reimbursement is$100,000 greater than if the transplant hospital used Medicare primary liver transplant patients as the only determinant in the formula.

Table 3 Determinants to calculate Medicare ratio

Medicare organs	Ratio
Annual liver transplants = 50	N/A
Medicare primary payer transplants = 15	15/50 = 30 %
Medicare secondary payer transplants = 2	17/50 = 34 %
Liver donation in transplant hospital = 5	22/55 = 40 %

Table 4 Medicare ratios from Table 3 applied to one million dollars of organ acquisition costs

Medicare ratio	Reimbursement
Medicare primary = 30 %	$300,000
Medicare primary + secondary = 34 %	$340,000
Medicare primary + secondary + in-house deceased donor livers = 40 %	$400,000

If pre-transplant services are appropriately captured, the Medicare Cost Report can result in significant cost reimbursement for a transplant program (Marshall and Swearingen 2007; Beach-Langlois and Yankasky 2011).

The Office of the Inspector General (OIG) may audit a transplant program's compliance with CMS regulations. A transplant program needs to accurately support and verify all cost submissions, as overreporting on the cost report can result in heavy fines. Common noncompliance findings by the OIG include posttransplant- and non-transplant-related costs inappropriately included in the organ acquisition costs, inadequate documentation of unsupported costs, medical director fees exceeding reasonable compensation equivalent limits, and Medicare organs not properly documented (Abecassis 2006; Rogers 2013).

Ambulatory Payment Classifications

The third Medicare payment mechanism is Ambulatory Payment Classifications (APCs) that cover posttransplant outpatient services. Each APC has an established payment rate. The transplant program may be reimbursed for more than one APC in a single patient case, unlike DRGs. APCs apply only to hospitals. If a transplant patient seeks posttransplant care at a physician's office, the physician will be reimbursed based on Medicare Part B.

Medicare Advantage Plans

Medicare Advantage Plans (MAP) are designed to allow individuals that meet the age requirement, of 65 years, and receive Medicare, to have the option of assigning their benefits management to a Medicare Advantage Plan. These plans are typically managed by a commercial payer and, as such, are considered a commercial plan. The transplant benefits in these MAPs may differ from plan to plan. Additionally, the payments for transplant services to transplant hospitals are negotiable just like a commercial managed care plan. The traditional Medicare payment mechanism of pre-transplant costs, organ acquisition, DRG, and posttransplant outpatient reimbursement (APC) is not relevant in the MAP model of reimbursement. Additionally, the MAP transplant patients cannot be used in calculating the Medicare ratio for the annual Medicare Cost Report.

Managed Care

For the most part, transplant reimbursement from commercial payers is based through managed care in which the financial risk is shared between the payer and the provider. Managed care organizations (MCOs) develop transplant-specific contracts that provide access to transplant services regardless of the referring physician's affiliation. Based on OPTN/UNOS data as of June 6, 2014, private insurance companies covered 53 % of liver transplants in 2013. A transplant program's main goal of MCO business is to obtain consistent volume on a long-term basis that reimburses at a satisfactory rate.

Centers of Excellence

MCOs contract with specialty transplant networks that have a high clinical and financial competitiveness. MCOs will rate institutions on their clinical, administrative, and financial competence and designate programs that meet these criteria as centers of excellence. Transplant programs want this designation because it typically leads to an increase in volume and better reimbursement rates. To be designated as a center of excellence, a transplant program must be an OPTN/UNOS member in good standing and certified by CMS.

The transplant program must also complete an OPTN/UNOS standardized request for information (RFI), meet an annual volume of liver transplants ranging from 25 to 40 depending on the MCO, and have acceptable patient and graft survival outcomes as verified by the Scientific Registry of Transplant Recipients (SRTR). The OPTN/UNOS RFI requires a transplant program to provide information on its facility, quality, volumes, outcomes, staff coverage, and credentials. The transplant program also needs to include descriptions of its unique qualities and initiatives on the RFI. When the MCO has received this information, most organizations will require a site visit to assess the facility in its entirety. Once a program meets the MCO's criteria, it is deemed a center of excellence, and the program can begin the contract negotiations through its managed care department.

Managed Care Contracts

In transplantation, MCOs reimburse all services based on the predetermined case rate unless the services have been "carved out." These carved out rates are usually specified for services that are either very costly, that do not occur in a majority of cases, or that the hospital does not provide. Transplant services that are typically carved out are high-cost pharmaceuticals and organ acquisition (Scharlin 2014). In regard to reimbursement, services that are carved out should be included in the managed care contract, but should not be included in the stop loss or outlier calculation.

Popular Models of Transplant Contracting

1. Pre-transplant services for hospital and physicians paid at a percentage of charges. Transplant procedure paid at a case rate, inclusive of hospital and physician services. Posttransplant services for hospital and physicians paid at a percentage of charges
2. Pre-transplant outpatient services for hospital and physicians paid at a percentage of charges. Pre-transplant inpatient services paid at an all-inclusive per diem rate. Transplant procedure paid at a case rate, inclusive of hospital and physician services. Posttransplant outpatient services paid at a percentage of charges. Posttransplant inpatient services paid at an all-inclusive per diem
3. Four-phase global (pay includes some carve-outs). Phases 1–4 with a defined posttransplant time period (i.e., 3–12 months) of risk for transplant-related routine care and complications. One fixed price for hospital and physicians
4. Hybrids of the previous three and other nuances from the payer

The nature of trying to financially manage the typical models for managed care reimbursement in the four models described is complex and needs strong data systems and transplant-trained business staff to monitor closely. Figure 5 shows the hybrid model of commercial reimbursement reflecting the different billing processes by phase of care and hospital or physician services.

Single-Case Agreements

A transplant patient may be referred to a program that does not have a managed care contract with the patient's insurance company. If a transplant program is considered out of a managed care network, the transplant program can establish a single-case agreement with the payer. If the provider and payer can negotiate a reasonable rate, the single-case agreement can be beneficial to both parties because the local transplant program is usually much more cost effective for the insurance company based on the savings on travel and lodging.

Medicaid

While a majority of liver transplants are covered by Medicare and private payers, Medicaid also reimburses for transplant services. As seen in Fig. 6, nearly 16 % of liver transplants were covered by Medicaid in 2013. Medicaid provides health insurance to low income individuals. It is dually funded by the federal and state's

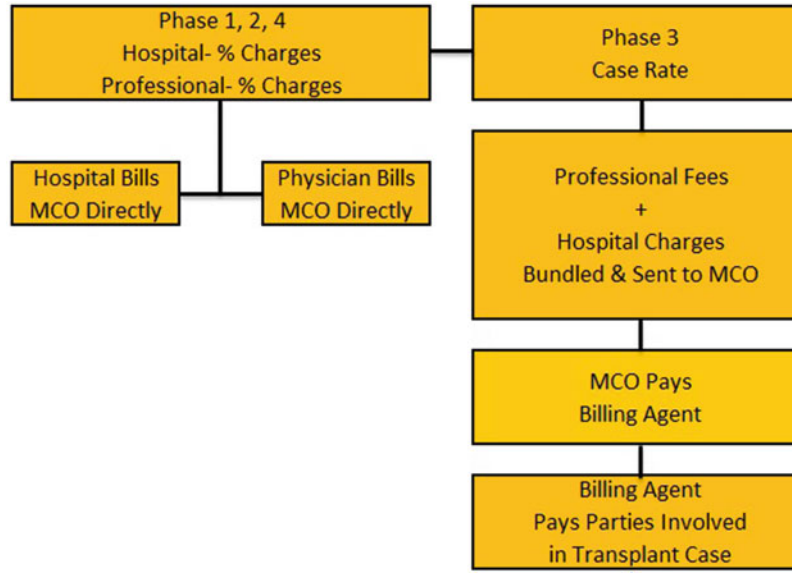
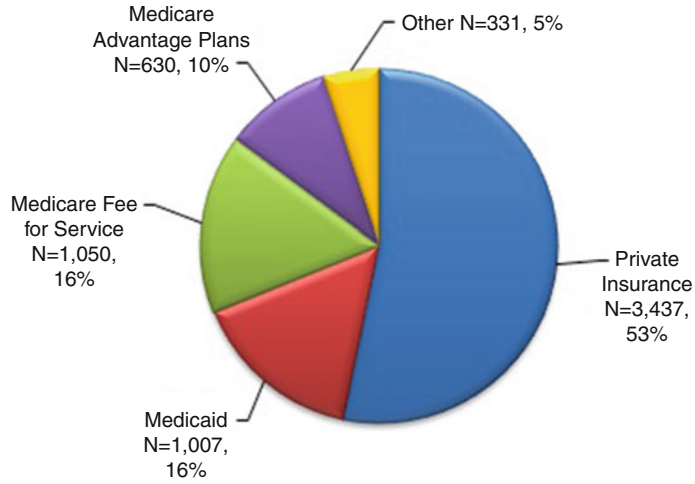


Fig. 5 Hybrid model of commercial reimbursement using percentage of hospital and physician charges pre- and posttransplant and a case rate for all charges during transplant admission



Based on OPTN data as of June 6, 2014.

This work was supported in part by Health Resources and Services Administration contract 234-2005-37011C. The content is the responsibility of the authors alone and doesnot necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Fig. 6 Primary source of payment for liver transplantation in 2013

government and is administered by individual states. Each state determines whether Medicaid will pay for organ transplantation and by how much. This payment varies from state to state.

States typically provide Medicaid reimbursement on a fee-for-service system. Within the past 15 years, however, states have been more likely to implement managed care systems to provide

Medicaid benefits (Managed Care 2014). States can either require or allow individuals to choose to enroll in the state-managed care program. It is typically a lengthy process to determine if a Medicaid patient will be covered for transplantation. Additionally, most states' Medicaid plans will not cover a transplant if a patient receives the transplant out of state (Norris 2014).

Self-Pay

Some patients may choose to pay out of pocket for the transplant procedure. This is particularly true for international patients, as well as those who are uninsured, underinsured, and self-insured. To ensure complete payment, transplant programs usually require self-paying patients to put down a deposit for evaluation and then pay the full balance prior to wait-listing the patient. Sometimes transplant programs offer a discounted rate for the procedure for self-paying individuals (Marshall and Swearingen 2007).

Stop Loss

The reimbursement agreement between the provider and payer has a large impact on the transplant program's profitability. Every contract must have a payment specified for the case rate and some type of stop loss, also known as an outlier protection, which is a protection method to help programs recover from outlier cases. Some patients may have long lengths of stay or a procedure complication, which creates additional unanticipated costs. Stop loss provides additional monetary compensation when normal reimbursement is insufficient to cover all costs of the transplant procedure.

For Medicare, once the charges exceed the specified DRG payment, the reimbursement converts from a fixed payment to a percentage of charges, which is set at a national level each fiscal year. MCOs also establish a stop loss provision within their contracts that takes effect when a specified cost is reached above the global case rate. Some common stop loss methodologies that MCOs use are first dollar, second dollar, per diem outlier, and floor outlier (Scharlin 2014). These methodologies reimburse the transplant program at a percentage of the total cost. This percentage is typically set at a lower rate prior to stop loss so that profit is unlikely, but the hospital is still able to recover its costs.

While this additional reimbursement does help with the extra costs, there is typically a gap between the case rate and the stop loss payment threshold. The costs that fall within this gap remain unpaid, and the transplant program must assume this financial burden. Additionally, even when the payment threshold is met, the program is only reimbursed a percentage of the total charges, which still leaves the transplant program at a financial loss.

Within the global case rates, a certain percentage is set aside to pay for unforeseen costs. Transplant programs can use this consultant/risk pool account to help cover the stop loss gap. If the pool reaches the predetermined upper limit, no more money can be added from additional accounts until the pool decreases. This pool can be applied to outlier arrangements or individual agreements (Marshall and Swearingen 2007).

Multiple-Payer Complexity

As a liver transplant program develops and grows, it will see the addition of multiple payers. The major primary payers for liver transplant are commercial and Medicare. The complexities of Medicare reimbursement for a transplant recipient and living donor from hospital inpatient, outpatient, professional fees, and organ acquisition, among others, are shown in Tables 5 and 6. Although Medicare has its complexities, they are consistent. In the commercial payer area, there are multiple commercial payers, and each has their own way of contracting and payment methodology. A liver transplant program could have upwards of 8–12 payers for liver transplant that all have their own individualized billing and payment methodology.

Table 5 Multiple-payer complexity for transplant candidate/recipient Medicare and commercial reimbursement

Phases of transplantation		Medicare		Commercial	
		Facility	M.D.	Facility	M.D.
Phase 1	Patient evaluated for transplantation	Organ acquisition	Organ acquisition	Based on contract	Based on contract
Phase 2	Patient accepted and listed with OPTN/UNOS and is now in the maintenance or candidacy phase				
Phase 3	Patient admitted to hospital for organ transplant procedure and subsequent inpatient stay. This is typically the DRG component of the transplant process	DRG	Part B		
Phase 4	Patient discharged from hospital and posttransplant follow-up care period starts	APC			

Table 6 Multiple-payer complexity for living donor Medicare and commercial reimbursement

Phases of donation		Medicare		Commercial	
		Facility	M.D.	Facility	M.D.
Phase 1	Patient evaluated as transplant donor	Organ acquisition	Organ acquisition	Based on contract	Based on contract
Phase 2	Patient accepted as living donor and now in candidacy phase				
Phase 3	Patient admitted to hospital for living donor procedure and subsequent inpatient stay		Part B		
Phase 4	Patient discharged from hospital and post-donor follow-up care period starts				

Transplant Physician Billing

Physician reimbursement differs based on the payer. For Medicare, the physician is reimbursed differently based on the phase of care. The physician is reimbursed for phases 1 and 2 through the organ acquisition costs and through Medicare Part B for phases 3 and 4 (Tables 5 and 6).

Managed care organizations may not require that the contract specify the actual amount of the case rate that should be directed to the hospital and to the physicians. However, it is efficient if the managed care contract includes the breakdown of the costs in the contract so that reimbursement teams are able to appropriately allocate the payments. In general, the case rate split between the physician and hospital varies by payer and organ. To determine this case rate split, the transplant program needs to review multiple years of data based on volumes and organ type. Upon this analysis, the percentage of total charges attributable to hospital services and to physician services for each type of organ can be determined and included in future contracts or used to develop a negotiated case rate split between hospital and physician services.

Liver Procurement and Surgeon Recovery Fee

Approximately 60 % or more of the 58 organ procurement organizations (OPOs) in the United States pay liver surgeon recovery fees. Some OPOs pay the fees of surgeons only for their own affiliated transplant centers in their donation service area (DSA) and not other transplant centers outside their DSA. Some OPOs offer to pay all the surgeon fees regardless of the transplant center's home DSA. Typically, the OPOs will use data gathered from the Association of Organ Procurement Organizations (AOPO). Using this data, and what nearby or contiguous OPOs pay, each OPO will then set its own fee. For liver surgeon recovery fees that are not paid by the OPO, the transplant center will typically develop a method

and amount to pay the liver surgeon for organ recovery. Payment of liver surgeon recovery fees is not consistent in the United States. According to the Medicare Provider Reimbursement Manual, the only consistent surgical recovery fee is for deceased donor kidneys, which is set at $1,250 (2771.3 2014).

Estimated Charges for Liver Transplantation

The estimated US billed charges for liver transplantation are shown in Table 7 from the 2011 Milliman triennial summary of estimated billed charges. Charges in this report refer to the amount billed, which may not be the actual amount paid for transplant services due to the presence of case rates, discounts, or other negotiated reimbursement arrangements (Bentley and Hanson 2011).

These estimated billed charges may not be the actual amount paid for transplant but do indicate the significant expense involved in liver transplantation. It is critically important that a transplant program understands and knows the costs involved in providing liver transplantation to better manage the finances of transplantation, as well as to be able to contract effectively with managed care organizations.

Table 7 US organ and tissue transplant charge estimates per 2011 Milliman research report

Liver transplant		
Inpatient services	Procurement	$71,000
	Hospital transplant admission	$316,900
	Physician during transplant	$46,600
Subtotal		$434,500
Outpatient services	180 days posttransplant discharge (includes physician professional fees)	$93,900
	30 days pre-transplant	$25,400
	Immunosuppressants and other Rx	$23,300
Subtotal		$142,600
Total		**$577,100**

Increased Cost for Liver Transplantation

When patients are evaluated for a liver transplant, transplant programs calculate a MELD score for each patient. A MELD score is a numerical scale which is based on how urgently the patient needs a liver transplant within the next 3 months. The MELD score does not alter the Medicare reimbursement rate. The Medicare DRG stays the same, and the reimbursement rates do not change if the patient has a complication or a longer length of stay. This means that the transplant program must assume the financial risk for sicker patients. According to Axelrod et al. (2005) and Axelrod et al. (2007), transplant programs across the United States have seen an overall increased MELD score in their liver transplant patients. These patients tend to have longer hospital stays resulting in an increased cost for the transplant program. The increase in sicker patients leads to reductions in net income and may lead to net loss for transplant programs.

Affordable Care Act's Impact on Liver Transplant Finance

On March 23, 2010, President Obama signed the Patient Protection and Affordable Care Act (ACA) into law. The ACA is changing the organization and financing of the American healthcare system to increase coverage and affordability for all Americans. The law strives to expand access to both private insurance and Medicaid. The ACA affects all providers, including transplant programs.

Expanded Coverage

Patients with end-stage organ failure will have improved access to transplant services through the expansion in healthcare coverage. Patients with chronic conditions will have increased access to healthcare because insurance companies can no longer deny patients with preexisting conditions. Additionally, young adults are eligible to remain covered under their parents' health plan

until the age of 26. According to Axelrod et al. (2010a), it is particularly critical that prospective liver transplant recipients have access to health insurance, especially those that are only covered by Medicaid. When compared to recipients with private insurance, Medicaid liver transplant patients are less likely to be evaluated for transplantation and have higher MELD scores and a decreased graft survival rate. The increased access to private health insurance can potentially benefit these liver transplant candidates.

This expansion of coverage will lead to a rise in the number of patients on the transplant waiting lists, which will put a further strain on the already limited organ supply. The increase in the waiting list number may also expand the use of marginal organs, which could result in poor outcomes for posttransplant patients (Axelrod et al. 2010a).

Effects on Patient Costs

In addition to the expanded coverage, the ACA limits insurers from establishing lifetime limits on the dollar amount of coverage. This is particularly significant for those transplant patients who require a longer length of stay or have complications posttransplant that require further care or even a re-transplantation, since many times these patients have already hit their spending caps.

Medicare beneficiaries covered by Part D medication coverage will also benefit financially from the ACA. Currently, Part D beneficiaries are expected to cover the complete costs of annual drug expenses between $2,251 and $5,100, known as the "donut hole." The ACA aims to close the current donut hole by decreasing the payments by 25–75 % by 2020. This decrease in costs is particularly beneficial for transplant patients whose immunosuppressive medications range from $13,000 to $25,000 annually (Axelrod et al. 2010b).

Impact on Reimbursement

The expansion of Medicaid will lead to an increase in the number of patients who need transplant care. However, Medicaid typically offers inadequate reimbursement that often does not cover organ acquisition costs, resulting in insufficient funding for transplant programs.

Medicare reimbursements will decrease in effect of the ACA, as well. According to Axelrod et al. (2010b), large academic centers that serve less affluent communities will receive reduced Medicare payments through the decrease in disproportionate share payments by 75 %.

The ACA also has an increased emphasis on quality of care. To encourage the delivery of high-quality care, the ACA has reduced Medicare payment in hospitals with high rates of readmissions and for patients with hospital-acquired infections. This reduced payment is especially harmful for transplant programs because readmission rates are common in the transplant population. Additionally, the immunosuppressive medication that patients must take posttransplant increases the risk for hospital-acquired infections.

Decreased Medicare Reimbursement for Liver Transplantation

Medicare pays for transplant through two primary mechanisms, the DRG and the cost report. The first is the actual surgical procedure or DRG payment (MS-DRG 005 and 006). The DRG amount is billed to Medicare at the time of transplantation. The ACA will impact Medicare reimbursement by reducing DRG hospital payments. Zavala et al. (2014a) show a national modeled approach to determine the estimated decrease in liver transplant MS-DRGs 005 and 006. For MS-DRG 005, the decrease is $8,381; for MS-DRG 006, the decrease is $3,063 (Table 8).

The second mechanism is the organ acquisition cost center. This cost center is comprised of the cost of the organ from the OPO plus direct and indirect expenses that can be allocated to the pre-transplant portion of activity prior to the admission of the patient. Under this mechanism, the hospital maintains an organ acquisition cost center or account to accumulate these charges during a given year and reports them on the hospital's Medicare Cost Report at year end for

Table 8 Transplant DRG modeled payment reductions

DRG/organ	Total Medicare DRG payment pre-reductions	Total Medicare DRG payment post-reductions	Modeled reduction	Percentage decrease
005 Liver w/ MCC	$87,175	$78,794	($8,381)	−7.80 %
006 Liver w/o MCC	$39,850	$36,787	($3,063)	−5.80 %

Table 9 Transplant cost analysis template for the transplant admission

Patient ID	1	2	3	4	5	6	Averages
Length of stay	0	0	0	0	0	0	0.00
ICU length of stay	0	0	0	0	0	0	0.00
ICU cost	$0	$0	$0	$0	$0	$0	$0
Medical/surgical cost	$0	$0	$0	$0	$0	$0	$0
Laboratory cost	$0	$0	$0	$0	$0	$0	$0
Radiology cost	$0	$0	$0	$0	$0	$0	$0
Operating room cost	$0	$0	$0	$0	$0	$0	$0
Pharmacy cost	$0	$0	$0	$0	$0	$0	$0
Organ acquisition cost	$0	$0	$0	$0	$0	$0	$0
Blood transfusion cost	$0	$0	$0	$0	$0	$0	$0
Other department costs	$0	$0	$0	$0	$0	$0	$0
Phase 3 transplant cost	$0	$0	$0	$0	$0	$0	$0

reimbursement at the level of the hospital's costs. The Budget Control Act sequestration will reduce Medicare reimbursement for organ acquisition hospital payments by two percent projected through 2023 (Zavala et al. 2014a).

Healthcare reform will affect all aspects of the American healthcare system. The expansion of health coverage through the ACA has significant risk for transplant programs. Transplant patient candidates will have increased access to transplant care; however, the reimbursement rates are likely to be reduced. Transplant programs will need to create systems that focus on quality and efficiency to maintain profit margins.

Reducing Costs of Liver Transplantation

The impending decrease in Medicare reimbursement through the Affordable Care and Budget Control Act will impact liver transplant programs significantly. Liver transplant programs must work as a clinical and administrative multidisciplinary team and identify opportunities for meaningful cost reductions. At the same time, quality patient outcomes must be maintained. As noted by Zavala et al. (2014b), key areas in reducing substantial costs in liver transplantation have been shown in blood utilization, induction therapy, and liver procurement aviation. Zavala et al. (2014b) documented annual sustainable savings to the liver transplant program of over $1.8 million dollars.

Analyzing the Costs of Liver Transplantation

To be cost effective, liver transplant programs should review and analyze their costs for performing liver transplant. The key information needed to perform a review is noted in Table 9. This is not an all-inclusive list, but does contain many of the cost categories for performing liver transplant. Reviewing these costs in detail, patient by patient, may reveal opportunities to reduce costs without affecting the patient outcome.

Aviation for Liver Procurement

Many transplant centers must use charter aviation for nonlocal liver donor runs. The aviation costs in some transplant centers can be a significant part of the organ acquisition expense. The cost of charter aviation can vary by type of aircraft, distance flown, and aircraft repositioning. Safety and insurance coverage is also a very important issue when transplant center surgeons and staff fly out for an organ recovery.

A review performed in 2009 by Zavala et al. shows that a turboprop aircraft can meet the cold ischemic time demands for livers at a distance of less than 400 miles at an average cost of $1,200/h. For distances greater than 400 miles, the jet is the most effective, but at a cost of $2,200/h.

Any aircraft that is being used by transplant center staff must meet, at the minimum, the Federal Aviation Administration Part 135 aviation maintenance requirements. Compliance with the transplant program's Risk Management Department is critical to ensuring that all staff in a fly-out situation are covered by the organization's accidental death and dismemberment insurance (Zavala et al. 2009).

Conclusion

The finances of liver transplantation are a complex array of multiple reimbursement processes by both government and private payers to transplant programs and providers. This is made more challenging by the Medicare reimbursement reductions through the Affordable Care Act. The complexity of the transplant financial processes requires transplant-trained and dedicated business professionals to work in a multidisciplinary approach to ensure the continuum of costs and revenue management are regularly optimized.

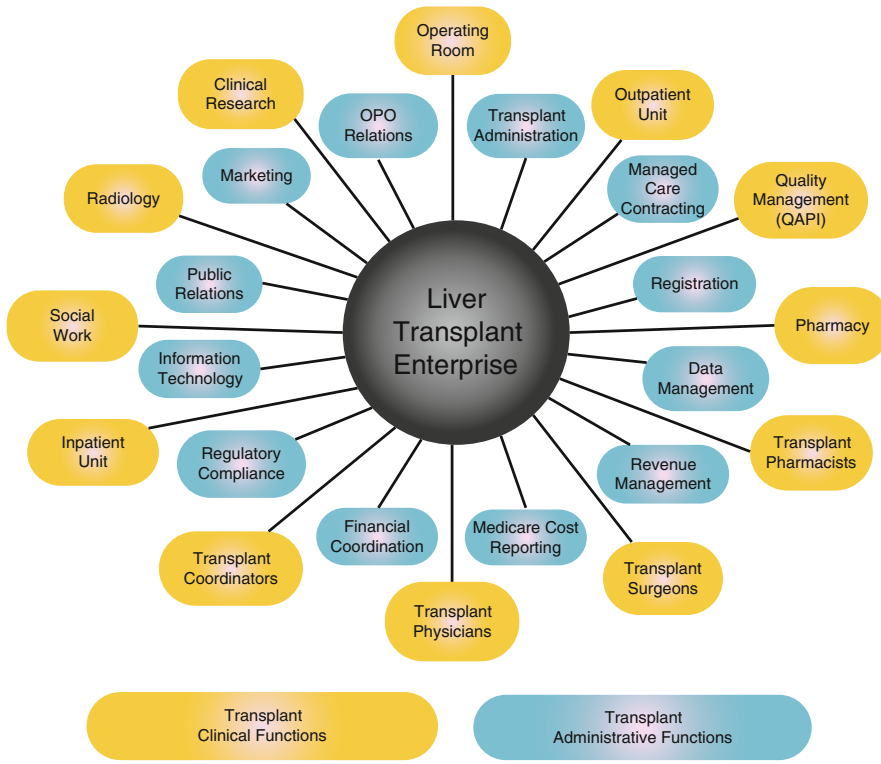


Fig. 7 The liver transplant enterprise showing the multidisciplinary clinical and administrative functions

The integration of both the multidisciplinary clinical and business teams is imperative in managing within the new healthcare era of liver reimbursement and doing more with less. The varied clinical and business disciplines encompassed in liver transplantation are shown in Fig. 7. The figure is not intended to identify all the varied clinical and business disciplines associated with liver transplantation, but merely to provide an overview of the many and varied disciplines involved in the daily operations of a liver transplant program.

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Cross-References

- ▶ Quality Measure of a Contemporary Liver Transplant Program
- ▶ Regulatory Agencies in Transplantation

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Liver Transplantation in the Third Millennium in North America: The Strategy for Success

36

Richard B. Freeman

Contents

Abstract

Delivery of liver transplantation care has evolved, out of necessity, as programs have developed knowledge and expertise beyond the initial surgical challenges. This evolution has brought professionals from many different medical specialties together and has recognized the important contribution that other professions such as nursing, social work, pharmacy, psychology, and others that have resulted in a model for team-based care that today is applicable to other areas of medicine. In the third millennium, these teams will need to integrate further to become more efficient and cost conscious while they expand their attention to patient-centered quality of life outcomes in addition to the more traditional patient and graft survival results.

Keywords

Transplant programs • Team-based care • OPTN program requirements • CMS Final Rule • Value-based care • Patient-reported measures

Introduction

From the time of the first successful human transplant performed at the Peter Bent Brigham Hospital in 1954 (A Science Odyssey PBS 2014), physicians, surgeons, and other providers have come together as teams to deliver the highly

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complex care that transplantation embodies. As the field moved from the experimental to the routine, these teams also evolved from loosely knit groups into organized programs. More recently in the USA, governmental and payor oversight has further influenced the shape and function of these programs under the goal of delivering better-coordinated, high-quality care. Today, the highest functioning programs are complex, multi-professional, cross disciplines, and include contributors from medicine, surgery, anesthesia, critical care, nursing, laboratory, pharmacy, blood bank, social work, psychiatry, ethics, home care, rehabilitation, and many other professionals. These programs, in many ways, serve as examples of how any form of complex care can be coordinated and delivered in our burgeoning accountable care marketplace and can provide some insight into what the future holds for care of patients with complex health problems as health-care reform progresses. In this chapter, we will briefly review the evolution of transplant programs, with some discussion of the forces that compelled their development and maturation. We will then outline some of the characteristics of current highly functioning programs in order to set the stage for exploring what characteristics are likely to be desirable or necessary for success in the future.

Transplant Program Beginnings

The first team to perform a human transplant successfully consisted of a plastic surgeon, Joseph Murray; a nephrologist, John P. Merrill; a urologist, J. Hartwell Harrison; an anesthesiologist, Leroy Vandam; and many others (Fig. 1). This team, as with other teams in Cambridge, England; Denver, Colorado; and elsewhere, worked together in the laboratory developing the techniques for transplantation and understanding the medical and surgical challenges that needed to be overcome to make transplantation a viable treatment option. With the early successes and because of early setbacks, teams further coalesced becoming increasingly focused on the selection of appropriate candidates and developing surgical techniques that were reliable (Starzl et al. 1964). With the discovery of six mercaptopurine and introduction of oral immunosuppressive agents such as corticosteroids and azathioprine in 1962 (Schwartz and Dameshek 1960) and cyclosporine in 1970 (Calne et al. 1978), more members of the team such as pharmacologists, and infectious disease experts, became necessary. These drugs, along with the acceptance of brain death as a legal and social norm, made deceased donor transplantation feasible. Now, experts in tissue typing,

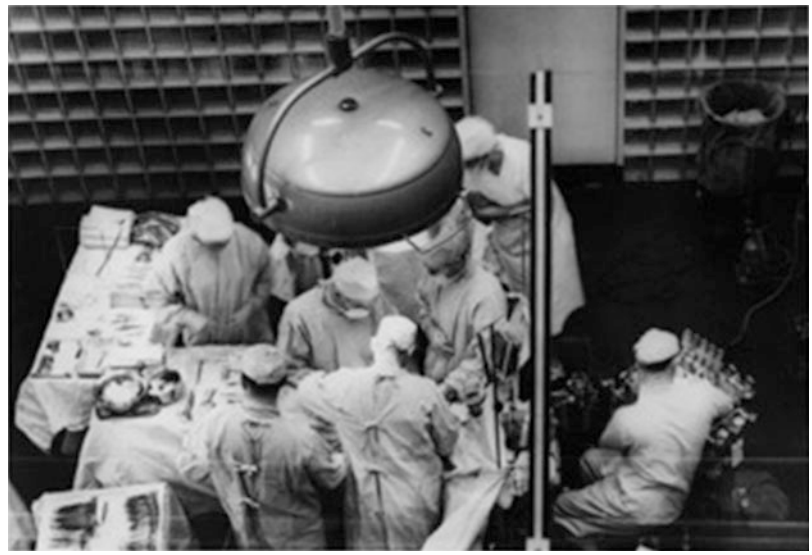

Fig. 1 Photograph of first kidney transplant. L–R. Miss Rhodes (Scrub Nurse), Dr. Daniel Pugh (Assistant Surgeon), Dr. Joseph E. Murray, Dr. John Rowbotham (Assistant Surgeon), Dr. Edward B. Gray (Assistant Surgeon), Miss Edith Comisky (Circulating Nurse), Dr. Leroy D. Vandam (Anesthetist) (From https://www.countway.harvard.edu/chm/archives/iotm/iotm_2004-11.html Accessed 1 Sept 2014)

blood banking, and clinicians knowledgeable (there were few training programs at this early stage) in the immunologic response to allogeneic tissues became necessary for a transplant program to function successfully. The advent of the immunosuppressive drugs also helped to enable liver transplantation to become a viable option (Calne et al. 1979). In addition to the nephrologists and surgeons familiar with care of end-stage renal disease (ESRD) patients, growing liver transplant programs required similarly trained experts in the care of patients with end-stage liver disease (ESLD) or hepatologists. Liver transplantation also stimulated development of specialized expertise in anesthesiology, critical care, hematology, infectious disease, and others so that patients with decompensating liver disease with complications such as ascites, variceal hemorrhage, and encephalopathy had experts available for their care. Cardiac transplantation also evolved in parallel, with its own requirements for medical and surgical specialists in the treatment of heart failure along with critical care, anesthesia, and other providers. More interestingly, these teams have had to become facile with extracorporeal mechanical support and other devices that are routinely used now as bridge therapy to get patients to transplantation (Kanter et al. 1988).

As living donation grew mostly in kidney transplant programs and then in the late 1990s for liver transplantation, many programs realized that evaluation of the potential donors' motivation was an important aspect for ethical and surgical success. The success of transplantation drove more patients suffering with end-stage organ failure to seek care, making the evaluation and management of candidates and potential donors, as well as the follow-up care of the growing numbers of survivors more complex. Consequently, psychological and social work evaluation increasingly became a routine part of assessment of donors and potential transplant candidates. Particularly because lots of liver disease is referable to behavioral issues, experts in assessing and treating addictions and personality disorders became critical collaborators for liver transplant programs. Moreover, because the patients and their care became much more complicated, nursing personnel became first skilled and, later, essential for the coordination of the care these patients received. These professionals became integral parts, as did the many other providers in pharmacies, blood bank, and laboratories and financial and administrative paramedical roles.

Recognizing that training and certification for transplant professionals was an important part for ensuring quality transplant care, professional societies developed programs to provide for these growing and increasingly complex programs. The American Society of Transplant Surgeons developed training program criteria for transplant. Soon afterward training program criteria for medical specialists in transplant nephrology, hepatology, cardiology, nursing anesthesia, and organ procurement were put into practice.

In 1972, an amendment to the US Social Security Act provided federal funding for the care of patients with end-stage renal disease including those who are candidates for, and/or receive renal transplants (CMS, Medicare.gov 2015). This introduced the beginning of governmental oversight of transplantation. As success mounted in the clinical arena and more and more patients sought the lifesaving treatment that was now possible with successful organ transplantation, the public and policymakers increasingly recognized the need for a national system that would provide policy for procuring and allocating organs and collecting data for the purpose of assessing the results of the allocation policies. As experience accumulated, it became clear that some standards defining characteristics of successful programs were necessary to ensure quality and coordinated care. This compelling need to be sure programs are delivering the highest quality care was propelled by the need to ensure that the precious donor organ resources are used wisely and with the utmost expertise. This has been the driving force for the evolution of the regulations around what the minimum standards should be for organ transplant programs in the current era. While these do not necessarily ensure success, they do set the standard across the USA. Most other countries where transplantation is well developed have created similar regulations that aim to define

transplant center compositions. In 1984, the US Congress passed The National Organ Transplant Act (NOTA) in which the Organ Procurement and Transplantation Network (OPTN) was established. One of the many functions authorized by NOTA for the OPTN was to define minimum criteria for transplant programs. Centers were required to meet these in order to participate in the OPTN and thereby gain access to the deceased donor pool. In 1999, the Final Rule promulgated by the Centers for Medicaid and Medicare (CMS) also adopted regulations defining standards for transplant programs wanting to receive payment for transplant services delivered to Medicare beneficiaries. Subsequently, the CMS Conditions of Participation (CoP) clearly defined CMS expectations for transplant center structure (Federal Register 2007). A comparison of the UNOS and CMS program standards is provided in Table 1. (a link to the full table with references to OPTN and CMS survey methods can be found at http://optn.transplant.hrsa.gov/governance/compliance/crosswalk-guide/).

Current State of Liver Transplant Program Structure

Personnel

In this section, the various requirements outlined in Table 1 will be discussed and the rationale for why they should be part of a transplant program. The principles outlined here are also generally applicable to other solid organ transplant programs although there are procedure-specific and medical specialty-specific considerations for each organ type. Later, we will build on these to outline how they need to function together and discuss how this framework provides a model for the delivery of complex multidisciplinary care in the future.

Surgeons explored the first liver transplants; however, as outlined above, in order to progress and mature, successful programs all had to seek out and gain input from many disciplines. The OPTN, in order to oversee the efficient use of organs, defined personnel requirements for transplant programs in the early 1990s (OPTN Web site 2015). In addition to the transplant surgeon, policymakers recognized the need for medical specialists trained in the care of patients with end-stage organ failure in each of the kidney, liver, and heart disciplines. Recognition for the need for coordination of all of the transplantation services, and the significant social and psychological burden that end-stage disease can pose for patients and their families, led to both CMS and the OPTN including the need to have dedicated personnel with skills in nursing, social work, and psychology readily available. Similarly, as immunosuppressive treatment became more complex and additional drugs became available, along with more refined antibiotic prophylactic regimens, regulations to include pharmacologic expertise arose. Payors, policymakers, and researchers all stipulated the need to collect data so data managers and registry operators became necessary. In addition, insurance coverage and complexities of reimbursement models as well as the costs of long-term medications all posed significant financial risks to patients, programs, and payors that drove the need for dedicated financial planners and analysts to assist. Transplant programs and their hospitals are required to have adequate facilities to care for patients, to have an agreement with the organ procurement organization designated to serve their area, to have adequate histocompatibility laboratory services available, and to have adequate blood banking services. Formal requirements defined by the OPTN for transplant hospitals and programs are documented at http://optn.transplant.hrsa.gov/ContentDocuments/OPTN_Bylaws.pdf#nameddest=Appendix_D.

Data

The severely constrained organ resource has driven the development of standards for liver transplant programs. Several important characteristics for data collection and measurement of programmatic performance are required above and beyond the regulations themselves, and I will argue similar kinds of efforts are required to for the success of any program that endeavors to

Table 1 A comparison of the UNOS and CMS program standards. Adapted from http://optn.transplant.hrsa.gov/governance/compliance/crosswalk-guide/

Requirement description	Applies to deceased donor component reviews?	Applies to living donor component reviews	Applicable organ programs	Oversight entity
Membership in the OPTN	Yes	Yes	All	CMS; OPTN
Getting approval for a pediatric program if the majority of transplants performed at your program are for adults	Yes	Yes	Pediatric programs	CMS
Getting approval for an adult program if the majority of transplants performed at your program are for pediatrics	Yes	Yes	Pediatric programs	CMS
Data submission requirements (initial approval)	Yes	Yes	All	CMS; OPTN
Living donor forms: data submission requirements	No	Yes	All (CMS); kidney (OPTN)	CMS; OPTN
Organ procurement	Yes	No	All	CMS
End-stage renal disease service requirements	Yes	Yes	Kidney	CMS
Inpatient dialysis services	Yes	Yes	Kidney	CMS
Participation in the ESRD network activities	Yes	Yes	Kidney	CMS
Vessel storage	Yes	Yes	Liver	OPTN
Patient and living donor selection/OPTN routine referrals and candidate selection procedures	Yes	Yes	All	CMS; OPTN
Psychosocial evaluation for transplant candidate	Yes	Yes	All	CMS
Living donor: medical and psychosocial evaluation	No	Yes	CMS: all; OPTN: kidney	CMS; OPTN
Social services	Yes	Yes	All	CMS
Nutritional services	Yes	Yes	All	CMS
Human resources condition	Yes	Yes	All	CMS
Director of a transplant center	Yes	Yes	All	CMS; OPTN
Transplant center director responsibilities	Yes	Yes	All	CMS
Director of a transplant center responsibilities coordinating care adequate training of nursing	Yes	Yes	All	CMS
Director of organ procurement services	Yes	Yes	All	CMS; OPTN
Director of transplantation tissue typing	Yes	Yes	All	CMS; OPTN
Director ensuring transplant surgery is performed under the direct supervision of a qualified transplant surgeon	Yes	Yes	All	CMS
OPTN designated transplant surgeon and physician	Yes	Yes	All	CMS
Clinical transplant coordinator	Yes	Yes	All	CMS; OPTN

(*continued*)

Table 1 (continued)

Requirement description	Applies to deceased donor component reviews?	Applies to living donor component reviews	Applicable organ programs	Oversight entity
Transplant coordinator is licensed RN or clinician	Yes	Yes	All	CMS
Living donor advocate/team knowledge and understanding	No	Yes	CMS: all living donor programs; OPTN: kidney	CMS; OPTN
Transplant team	Yes	Yes	All	CMS
Director of anesthesia	Yes	Yes	Liver	OPTN
Financial coordinator	Yes	Yes	All	OPTN
Mental health and social support	Yes	Yes	All	OPTN
OPTN program approval requirements – primary surgeon/physician, general facilities, and resources	Yes	Yes	All	OPTN
Primary program administrator	Yes	Yes	All	OPTN
Transplant pharmacist	Yes	Yes	All	OPTN
QAPI program	Yes	Yes	All	CMS

deliver complex care successfully and efficiently in the future.

The organ shortage has driven the need to have data for the design of transparent and evidence-based policy to allocate organs. Because the goal of transplantation is to provide the organ resource to patients most likely to benefit while avoiding futile transplants where no benefit is derived, it is essential to understand likely outcomes for various types of patients with end-stage liver disease. In order for standards to be based on evidence, adequate, accurate, and timely data are necessary to define quality metrics and track positive and negative deviants from the expected outcomes. For these reasons, Congress recognized at the time of the passage of the National Organ Transplant Act (NOTA: P.L. 98–507) (NOTA) that a system was necessary to collect information for patients along the timeline of their organ failure from the time they are identified as potential transplant candidates through their transplant and following up for their complete posttransplant survival. Consequently, Congress authorized creation of the Scientific Registry of Transplant Recipients (www.SRTR.org 2015) (SRTR) as the repository of this population-based data. Over the years as data accumulated, the SRTR has been used to inform design of organ allocation policy. More recently with the advent of the CMS Conditions of Participation for Transplant Programs (Federal Register 2007) (CoPs), the SRTR data have been used as the basis for assessing the quality of the transplant programs' results on a center-specific basis, the so-called center-specific reports (CSRs) (SRTR Web site 2015). All transplant programs today and in the future will need to capitalize on this wealth of data to help inform their local programmatic decision-making to be sure their results remain in the statistically accepted range, especially since these data are publically displayed and failure to meet the standards can lead to adverse action by CMS and the OPTN. Not surprisingly, because programs must continue to meet the CoP for Medicare and other payor outcomes as well as UNOS criteria, there is increasing pressure to maintain outcomes that are as good as expected. Consequently, transplant programs need to devote resources to paying attention to their outcome results.

Much scrutiny has been focused on these outcome measures. As with all data registries, there are some inadequacies, and since program success

and ongoing certification for payment by both government and private payors are defined by these data, much attention has focused on the risk adjustment methodology for these CSR. Because the stakes are high for accurate risk prediction for patients and programs, many risk models have been developed to help predict outcomes (Elsayed et al. 2015; Cardoso et al. 2015; Pan et al. 2014; Briceño et al. 2014; Parker et al. 2014). For example, transplant programs have made many attempts to develop accurate prediction of liver transplant outcome, but most of these require use of data inputs that are only obtainable after the transplant is performed and therefore of little practical utility for clinical decision-making (Freeman 2007). More recently, policymakers have employed risk models for allocation of livers making it necessary for transplant programs to have good working understanding of how these models function for their individual patients. In the future programs will have to become more sophisticated in their ability to interpret risk models to better inform their patients about the probability of receiving an organ offer (Freeman et al. 2002) and the likely probabilities for survival after transplantation. To address this need, statistical tools have been developed to prospectively predict likely outcomes for given candidates to help programs more accurately assess candidate and donor organ risks at the time of registration for transplant and/or at the time of acceptance of a donated organ offer (Reichert et al. 2012; Avolio et al. 2013; xyn Web site 2015). Successful programs will need to refine and exploit these predictive models to maintain outcomes as good as or better than expected. As health care in general becomes more outcome driven, this type of risk assessment and prospective, patient-specific decision-making based on population-defined data is likely to become increasingly more necessary within and outside of transplantation. Transplant programs will be excellent resources for other specialties facing this reality to help them better function in the future health-care reform world.

Financial success is, and will remain, an imperative for all health-care endeavors, including transplant programs. In some ways, the history of payment models for transplant services has preceded other reforms in accountable care, and this experience should help transplant programs transfer to the accountable care models of the future more easily. Programs have, and will need, to continue to look for process improvement in refining their best practice protocols and look to reduce cost in terms of the overall transplant care they deliver. Since much of reimbursement, particularly for liver and heart transplantation, has been in the form of bundled payments, programs already have experience with aggregating their costs and revenues across inpatient and outpatient venues (Habka et al. 2015; Buchanan et al. 2009). These efforts have brought increased resolution to the understanding of the relative contributions of the severity of disease at the time of transplant surgery, the quality of the donor organ, and the treatments patients receive before and after the liver transplant procedure (Stahl et al. 2015; Mathis 2015; Soárez et al. 2015; Salvalaggio et al. 2011). All health systems across the world are interested in these cost questions so transplant centers, regardless of their home country, will need to be increasingly sensitive to these pressures and equipped to assess them (Younis et al. 2015; Weeks and Blais 2011; Rosselli et al. 2015). Pharmaceuticals are also important cost drivers over the long term of liver transplant survival. Many of the important immunosuppressive drugs are available in generic form now. However, the new antiviral drugs now licensed for use to treat hepatitis C are still extremely expensive (Shah and Younossi 2015; Soárez et al. 2015; Owens 2015). This is one example of newer therapies coming on line that will need to be evaluated in the context of the overall cost of liver transplant care by programs and payors going forward. There are ample data documenting the cost-effectiveness for transplantation from many areas around the world (Habka et al. 2015; Soárez et al. 2015; Li et al. 2015; Chang et al. 2014; Lim et al. 2015; Kensinger et al. 2013). To some degree, society will determine whether the incremental cost-effectiveness ratio for various forms of transplantation remains worth the price (Talwalkar 2014). As transplant programs develop new ways that may decrease costs, it is likely that this ICER may improve. Importantly, at least for kidney

transplantation compared with dialysis, transplantation is already more than cost-effective; it is cost saving (Younis et al. 2015; Jassal et al. 2003; Schnitzler et al. 2005).

Future

As advances in organ preservation, and potentially even organ restoration are realized, these costs too will need to be factored into the overall value proposition for transplantation. Programs will need to gain expertise in the various approaches to improving donor organ function to help best utilize the resource. Similarly, as efforts to develop operational tolerance improve, liver transplant programs will have to factor these into their overall costs of care. Immunosuppressive minimization and/or withdrawal protocols will also have to withstand cost-effectiveness analyses. Investigators will need to include the increased expenditures for potential organ rejection and/or graft loss into these trials to make the ultimate cost-effectiveness determinations where there may be a great benefit but where costs of failure are also high. Successful programs of the future will want to have a data infrastructure capable of performing all of these sophisticated analytics to assess the *value* – quality/cost – of the services they provide. Simple patient and graft survival data are already incomplete in assessing patient outcomes. Transplant centers will need to become even more adept in thinking about the cost-effectiveness of their therapies for the population they serve. This will require robust financial information linked directly to the clinical and operational data so that the cost of interventions are adequately assessed and folded into the clinical results. Again, these attributes for success are not unique to liver transplantation or to organ transplantation alone, but they will be necessary components of any successful health system. Moreover, liver centers will have become much more adept and committed to collecting patient-reported measures as the patient experience and quality of life already play important roles in how patients choose their health care. Increasingly, payment for transplant services will incorporate these patient-centered outcomes along with the traditional patient and graft survival parameters.

Conclusion

The evolution of liver transplantation and the programs that have developed to successfully deliver this highly complex and increasingly patient-centered care can help to inform the way forward for health systems trying to advance in our current health-care reform world, as many lessons apply more broadly today. The formation of a multi-professional, multidisciplinary team directly focused on the medical surgical and psychosocial care of the patient and his/her family, with all team members bringing different expertise and training to improve outcomes across all domains of health, is the essence of the medical home concept today. Population health programs, widely quoted but not well implemented, will need to use many of the methods transplantation employed to develop allocation policy and to be sure programs were meeting outcome standards. Bundled payments and close accounting of cost per outcome that are widely prevalent today are ideas that transplant programs have wrestled with and succeeded in mastering for decades. These are all attributes and successful liver transplant programs and will be attributes of successful health delivery systems in the not-too-distant future as well.

Cross-References

- ▶ Finance of Liver Transplantation
- ▶ Role of Integrative Medicine in Liver Transplantation
- ▶ Role of the Transplant Coordinator

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Transplant Program Liability and Risk Factors for Litigation

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Abstract

While providing an introduction to and explanation of the four crucial elements of a medical malpractice claim, this chapter discusses the most common theories of transplantation liability and related issues facing surgeons and other practitioners. Causes of action are considered within the broader context of the current medical malpractice environment. Drawing upon factual examples of litigation concerning organ transplantation, this chapter explains the physician's legal duty, circumstances constituting breach of duty, proximate causation of injury, and damages caused by breach. Possible areas of liability and triggers of litigation in the transplantation setting, including the unique challenges posed by the legal need to obtain the informed consent of donors and recipients, shall be explored before reviewing the ways in which diligent documentation and clear communication by the medical team can constitute the crux of a case. Having discussed the resolution of transplantation conflicts between parties via litigation, this chapter ends by considering the various means by which patients and doctors can come to terms outside of the courtroom.

Keywords

Alternative dispute resolution • Arbitration • Breach • Causation • Clinical practice guidelines • Communication • Damages • Documentation • Duty • Expert witness • Informed consent • Injury • Liability • Litigation • Mediation • Medical malpractice • Negligence • Proximate cause • Standard of care • Transparency • Transplant program • Transplant surgeon

Introduction

Almost 155,000 payments were made to claimants in medical malpractice cases, and slightly under 400,000 adverse actions were taken against physicians in the United States between 2004 and 2014 (NPDB 2014). Though national trends reveal a decrease in the numbers of cases settled by or decided against treating physicians since 2009, medical malpractice lawsuits carry significant consequences for defendant physicians, including the impact on insurance premium levels and insurability, reputational effects, and issues related to hospital privileges and managed care contracts (Sage 2014). And of course, the emotional exhaustion and anxiety attendant to litigation may not be denied (Chen 2011).

This chapter will discuss the various elements of claims for "medical malpractice" and "failure to obtain informed consent," the two most common professional liability claims brought against surgeons. In doing so, actual cases where courts have construed these elements will be examined, and the impact of those decisions on the future practice of medicine, particularly in the field of transplant surgery, will be considered. Possible strategies that transplant surgeons may employ in an effort to diminish their chances of being sued or to increase their odds of prevailing in litigation will also be discussed. Finally, this chapter will examine the various alternatives to litigation that are available to resolve disputes that arise between surgeons and their patients.

The Four Legal Components of Medical Negligence

Malpractice has been defined as "the failure of one rendering professional services to exercise that degree of skill and learning commonly applied under all the circumstances in the community by the average prudent reputable member of the profession with the result of injury, loss, or damage to the recipient of those services" (Barnes v. Schlein 1984). To state a prima facie case of medical malpractice, a plaintiff must prove that (1) the physician owed a duty to the patient; (2) the physician breached that duty; (3) the breach of that duty was the proximate cause of, or a substantial factor in, bringing about the patient's harm; and (4) the damages suffered by the patient were a direct result of that harm (Hrynkiw v. Trammell

2012; Dickhoff v. Green 2012; Mitzelfelt v. Kamrin 1990; Eaddy v. Hamaty 1997).

Legal Component No. 1: Duty

In medical malpractice actions, there typically is no dispute regarding whether a physician owes a duty to a patient. When a physician agrees to provide medical care to a patient, he/she implicitly assumes a duty to supply such treatment in a manner consistent with the applicable standard of care. Of course, physicians are not charged with a duty to provide perfect care. Rather, "[a] doctor must exercise the degree of skill and care ordinarily possessed and exercised by a reasonably skillful and careful practitioner under the same or similar circumstances" (Syfu v. Quinn 2005).

Although the existence of a duty is rarely contested in most medical malpractice cases, in the context of organ transplant litigation, courts have occasionally been called upon to decide difficult and unusual issues concerning whether a surgeon owes a duty to an organ donor. For instance, in Moore v. Shah (1982), the court held that a kidney donor did not have a cause of action against a physician whose alleged negligence in diagnosing and treating the recipient necessitated the transplant. The donor argued that New York's rescue doctrine, which held that a wrong perpetrated on a victim was also a wrong perpetrated on his rescuer, should be extended to an organ donor who agreed, after deliberation, to donate a kidney to the victim of alleged malpractice. However, the court declined to do so on the grounds that "[s]ince [the donor] was never [the physician's] patient, no duty to him originally existed." The court further observed: "[i]t is obvious that extension of liability of a physician to every person who conceivably might come forward as a kidney donor could create a group beyond manageable limits."

Similarly, in Malik v. William Beaumont Hospital (1988), an organ donor sued the organ transplant team for the loss of his kidney after the recipient suffered postoperative cardiorespiratory arrest and lapsed into a coma. The donor alleged that the transplant team's postoperative negligence caused the recipient's injuries and rendered the donor's sacrifice of his kidney needless. However, the Michigan Court of Appeals held that the donor did not have a viable claim against the surgeons who implanted the kidney in the recipient because those surgeons did not owe a duty to the donor. The court explained that there was one physician-patient relationship between the donor and the surgeon who removed his kidney and a separate physician-patient relationship between the organ recipient and her surgeons. The court then determined that "[n]o physician-patient relationship arose between [the recipient's surgeons] and [the donor] as a result of surgery they performed on [the recipient]" and that the donor "voluntarily agreed to give up his kidney no matter what the outcome of the transplant operation." Therefore, the court affirmed the trial judge's dismissal of the donor's claims against the kidney recipient's surgeons, effectively nullifying the litigation prospects of donors trying to sue when their donation fails to bear fruit in the form of the improved health of the recipient. Taken in tandem, these cases underscore that transplant surgeons owe separate duties to both organ donors and recipients, and a breach of a surgeon's duty to one of these patients generally will not give rise to a cause of action by the other.

The Role of Expert Witnesses in Defining the Standard of Care

While the existence of a duty is generally not contested in medical malpractice actions, the parties in most such cases regularly dispute the requirements of that duty – i.e., the standard of care. No law rigidly defines what this medicolegal standard entails; instead, the essential elements forming the standard of care are forged anew in the crucible of each case and its individual circumstances by the trier of fact. Because jurors lack the requisite education, training, or experience to determine the applicable standard of care on their own, expert medical testimony is required in the vast majority of cases to define the appropriate standard of care (Morlino v. Medical Ctr. of

Ocean Cnty. 1998). The minimum criteria that must be met to qualify as a medical expert on the issue of a physician's standard of care can vary from state to state, but generally include an unrestricted physician's license to practice medicine in at least one state or the District of Columbia and active involvement in, or recent retirement from, clinical practice or teaching (e.g., 40 P.S. § 1303.512). Reasonably, some states also require a medical expert testifying on the issue of standard of care to share the same expertise and board certification of the physician whose care they are critiquing (40 P.S. § 1303.512, MCLA § 600.2169). However, other states are much more liberal in allowing an expert to testify on this issue by requiring only that he/she has a reasonable pretension to specialized knowledge about the subject matter (Caviglia v. Tate 2012; McDonald v. Memorial Hosp. at Gulfport 2009; Staccato v. Valley Hosp. 2007).

Of course, just as physicians often disagree on the best course of treatment for a patient, they likewise frequently differ on what the standard of care in treating a patient requires. Accordingly, plaintiffs and defendants in medical malpractice actions typically identify medical experts to testify on their behalf who possess sharply differing opinions concerning the applicable standard of care. After considering matters such as the experts' qualifications and the reasons for their opinions, the trier of fact must then determine which medical expert's opinion is more worthy of belief. The ultimate result of a lawsuit often hinges on which side's expert witness(es) the jury finds more credible. Therefore, this battle between plaintiffs and defendants to define the standard of care is almost always critical in medical malpractice litigation.

The Standard of Care, Clinical Practice Guidelines/Policies, and Medical Literature

Practitioners facing possible litigation often question what role, if any, clinical practice guidelines and policies created by specialty societies play in defining the standard of care. The Organ Procurement and Transplantation Network, the American Association for the Study of Liver Diseases, and the American Society of Transplantation are among several groups that have developed clinical practice guidelines and policies governing organ transplantation covering, among other elements, the procurement, allocation, and transportation of organs for transplant and the postoperative care of patients. While such societies develop these policies and guidelines via the review and analysis of published world literature on organ transplantation, the examination of previous surgical guidelines, and the clinical experience of experts in this field, these policies and guidelines are not intended to establish the legal standard of care. Rather, they usually suggest preferred, yet flexible, approaches to diagnostic, therapeutic, and preventive components of care (Lucey et al. 2013). The use of such policies and guidelines in medical malpractice litigation primarily depends upon each state's evidentiary rules (Mackey and Liang 2011). Generally speaking, adherence to or divergence from a learned society's guidelines will not definitively exculpate or inculpate a treating physician.

Although rules regarding the use of policies and clinical practice guidelines created by specialty societies as evidence can vary from state to state, the US Supreme Court has held that medical treatises can be used to cross-examine expert witnesses in federal cases. In Reilly v. Pinkus (1949), the Supreme Court reached this holding by reasoning: "[i]t certainly is illogical, if not actually unfair, to permit witnesses to give expert opinions based on book knowledge, and then deprive the party challenging such evidence of all opportunity to interrogate them about divergent opinions expressed in other reputable books." Accordingly, "impeachment with a learned publication is a valid tactic in all jurisdictions" (United States v. Coleman 1994 citing Giannelli and Imwinkelried 1993). However, the great weight of authority has held that the publication must be authenticated as authoritative either by the witness being examined or by another witness, such as the proponent's

own expert, in order to use a learned treatise to impeach an expert witness (Flanagan v. Wesselhoeft 2001 citing Carroll v. Morgan 1994; Fed. R. Evid. 803(18); Wigmore 1976).

Some commentators have suggested that specific clinical practice guidelines and policies should be adopted to delineate a uniform standard of care for every case. These proponents argue that the adoption of uniform clinical practice guidelines and policies will improve the quality of patient care by eradicating regional variation in clinical practice, balancing the overuse and underuse of medical services, and providing a means of communicating outcome-based and cost-efficient clinical practices to physicians. Moreover, some tort reform advocates have theorized that the adoption of standardized clinical practice guidelines and policies will reduce healthcare costs by decreasing defensive medicine practices and malpractice claims. However, others have observed that the use of uniform clinical practice guidelines and policies may also restrict physician autonomy and impose inflexible or impractical standards on clinical practice (Mackey and Liang 2011). One transplant surgeon argues against agencies taking a larger role in guiding the clinical decision-making of medical professionals, stating, "'[t]his is an external agency practicing medicine. . .[y]ou don't see my patient, and you don't see my donor, and you're going to tell me who I can and can't use?'" (Meckler 2007). Furthermore, "[m]andated [clinical practice guidelines] may unduly compel physicians to comply with such guidelines due to liability considerations even if they conflict with clinical judgment, potentially leading to adverse outcomes for patients" (Mackey and Liang 2011). Alternatively, doctors might follow guidelines to insulate themselves from negligence claims, possibly endangering the health of their patient while seeking a so-called safe harbor for themselves (Mello et al. 2014). No consensus on the safe harbor concept exists among practitioners, but current law is clear: practice guidelines alone do not establish the applicable standard of care in a malpractice trial.

The Term of a Surgeon's Duty

How long after an organ transplant operation does a surgeon's duty of care continue? As with any surgeon, a transplant surgeon's duty of care to his patient does not end at the moment the patient leaves the operating room. All surgeons have an ongoing duty to manage their patients' postoperative recuperation until either another physician assumes the patient's care or the patient is properly discharged after making a suitable recovery.

In the context of liver transplantation, the length of time in which that duty will continue is likely to be of significant duration. Despite considerable strides in organ transplant surgery, studies demonstrate that a substantial number of recipients will incur a complication that will require treatment after surgery. As transplant recipients uniformly require lifelong postoperative care in the form of liver function tests, immunosuppressive drugs, and other treatments, transplant surgeons should likewise expect their duty of care to continue for the lifetime of their patients unless and until another qualified surgeon assumes a patient's care. Ending the physician-patient relationship prematurely could not only have dire medical consequences but also lay the physician bare to strong claims of negligence.

Legal Component No. 2: Breach

After presenting evidence regarding what the standard of care requires, a plaintiff must then establish that his/her treating physician breached that standard of care. Again, this generally requires the presentation of medical expert testimony. In rare cases, courts may determine that a physician's allegedly negligent conduct is so obvious that the plaintiff need not present expert testimony to establish that the physician breached the standard of care (Syfu v. Quinn 2005). However, application of this exception, known as the res ipsa loquitur ("the thing speaks for itself") doctrine, "is limited to situations in which the physician's conduct is so obviously substandard that one need not possess medical expertise in

order to recognize the breach of the applicable standard of care." Examples of situations where courts have applied the res ipsa loquitur doctrine include an operation where a surgical instrument was inadvertently left inside a patient's body and a case where a quadriplegic patient fell off an examination table (Ripley v. Lanzer 2009; Quinby v. Plumsteadville Family Practice, Inc. 2006). Regardless of whether a plaintiff is required to present expert testimony to support his/her claim that a physician breached the standard of care in treating him/her or the doctrine of res ipsa loquitur applies, it is the trier of fact who must ultimately decide whether a doctor breached the standard of care in treating the patient. Common reasons for lawsuits involving transplant include the following:

- Inadequate pretransplant evaluation
- Infection in living donor
- Cancer in living donor
- Complications of immunosuppression
- Inadequate management of posttransplant complication
- Failure to detect rejection

(Campobasso et al. 2005; Doe v. University of Chicago Medical Center 2014)

Program-Wide Breach

Entire programs themselves can come under fire for breaching the collective care owed to their transplant patients, in any 1 year or over an unspecified period. For example, one state recently investigated a hospital for its failure to achieve the 80 % 1-year survival rate required by that state's regulations. CMS also conducted its own investigation since the transplant program did not meet that institution's mandate of a 77 % survival rate (FreeAdvice 2015). Additionally, the liver program at another hospital paid millions of dollars to settle 35 cases involving patients who waited for livers without knowing that the hospital was refusing procured organs and lacked the requisite staff to operate the program (Berthelsen 2007).

Legal Component No. 3: Causation

While the existence of plaintiff's injuries may not always be contested in medical malpractice cases, the cause of those injuries often is. Indeed, even in cases where the parties agree on the full extent and likely duration of a plaintiff's injuries, they may sharply disagree over whether those injuries preexisted the defendant physician's care of the patient or occurred after the physician treated him due to factors unrelated to the treatment. Moreover, it is not sufficient for a plaintiff to merely prove that a physician breached the standard of care in treatment and that the patient suffered an injury. Rather, the plaintiff must establish that the physician breached the standard of care and that *the deviation* caused the plaintiff's injuries (Hamilton v. Good Samaritan Hosp. of Suffern, N.Y. 2010; Jennings v. Badgett 2010; Joyce v. Boulevard Physical Therapy and Rehabilitation Ctr. 1997; Mitzelfelt v. Kamrin 1990). In other words, the plaintiff must prove a clear causal link between the physician's negligent conduct and the injury suffered. "[E]xpert medical testimony is necessary to establish the causal nexus of the injury to the tortious conduct in those cases where the connection is not obvious" (Maliszewski v. Rendon 1988). The trier of fact must then determine whether the plaintiff has met his/her burden of proving that the physician's alleged negligence caused the plaintiff's alleged injuries.

In determining whether a physician's negligence was the proximate cause of a patient injuries, the plaintiff need not establish that the particular injury suffered was specifically foreseeable by the treating physician (Lubbers v. Anderson 1995). Rather, if the injuries that the patient ultimately suffered fall within the general umbrella of adverse medical possibilities of the provider's negligence, then the plaintiff is entitled to redress. Thus,

> for a party's negligence to be the proximate cause of an injury, the act must be one which the party ought, in the exercise of ordinary care, to have anticipated was likely to result in injury to others, *though he could not have anticipated the particular injury which did happen*. There must also be a showing that the defendant's conduct was a substantial factor in bringing about the injury.

(emphasis added). Stated differently, "negligence is tested by foresight, but proximate cause is determined by hindsight" (Dellwo v. Pearson 1961). If a physician is negligent in his/her care and treatment of a patient, then he/she is liable for all of the natural and proximate consequences, notwithstanding whether he/she could have foreseen their occurrence.

Legal Component No. 4: Injury/ Damages

In most medical malpractice cases, the parties do not dispute that the plaintiff suffers from a physical injury. Many patient injuries can be objectively verified and are generally documented in the medical records of either the defendant healthcare provider or a subsequent treating physician. Moreover, because the defendants can, and often do, compel the plaintiff to undergo a medical examination to assess the existence and extent of the plaintiff's injuries, the odds of a patient successfully feigning a physical injury are greatly diminished. In the transplantation setting, patient injuries are often too serious to be feigned.

However, the extent of a plaintiff's injuries, including whether they are temporary or permanent, is an issue upon which parties frequently disagree. In addition, parties often dispute the treatment necessary to remedy those injuries, including the cost thereof. Therefore, except in cases where the extent of a patient injuries is obvious, a plaintiff must generally present expert medical testimony to establish that his/her injuries may be permanent and his/her need for future treatment. If a plaintiff contends that he/she will require lengthy or lifelong treatment for his/her injuries, he/she may be required to present evidence in the form of a medical life-care plan, which is typically prepared by a nursing expert specializing in this field.

Moreover, a plaintiff claiming lost wages, due to death or long-term disability, must demonstrate that his economic horizon has been shortened (Kearns v. Clark 1985). To satisfy this burden of proof, the plaintiff must establish more than simply a permanent injury (ibid citing Carroll v. Pittsburgh Rys. Co. 1962). Rather, "[t]here must be some evidence from which a jury can reasonably infer that earning power will probably be reduced or limited in the future" (Kearns v. Clark 1985 citing Baccore v. Mennella 1976; Turner v. Heston 1983). "[W]age losses cannot be presented to the jury on mere conjecture" (Gloffke v. Robinson 2002 citing Kearns v. Clark 1985). Hence, to recover damages for lost earnings and lost earning power, the plaintiff must provide sufficient reliable evidence from which the jury can determine that the plaintiff has suffered a diminution in his/her earnings and future earning potential and that such losses were the proximate result of the defendant's act or omission (Kearns v. Clark 1985; Gordon v. Trovato 1975; Gunn v. Robertson 2001). This evidence must generally come in the form of expert testimony from a physician and an actuary or economist.

Informed Consent

The doctrine of informed consent is a medical-legal tenet that originated more than 200 years ago and is of vital importance to any surgeon (Largey v. Rothman 1988 citing Slater v. Baker and Stapleton 1767). The doctrine stems from the notion that every adult patient who is mentally and physically able to consult about his condition has the right to be free from an unknown or unwanted operation, which constitutes a trespass on his body (Largey v. Rothman 1988 citing Schloendorff v. Society of the N.Y. Hosp. 1914). Future Supreme Court Justice Benjamin Cardozo summarized this concept more than a century ago by stating: "Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages" (Schloendorff v. Society of the N.Y. Hosp. 1914).

However, simply obtaining a patient's consent to undergo an operation will not suffice to fulfill a surgeon's duty to a patient under the doctrine. Rather, to satisfy this duty, in the absence of an emergency, a surgeon must obtain his/her patient's *informed* consent to undergo surgery or

the informed consent of a family member if the patient is a minor or is mentally or physically incapacitated.

Accordingly, "[t]o obtain a patient's informed consent, doctors must provide patients with 'material information necessary to determine whether to proceed with the surgical or operative procedure or to remain in the present condition'" (Valles v. Albert Einstein Med. Ctr. 2002). While surgeons are not required to disclose all information they may know about a procedure, they are required to inform the patient "of those material facts, risks, complications and alternatives to surgery that a reasonable person in the patient's situation would consider significant in deciding whether to have the operation" (ibid quoting Gouse v. Cassel 1992). (For a thoughtful consideration relating to the issue of whether a physician can provide too much information, see Rosenbaum 2015.) Although some jurisdictions allow the surgeon to delegate the task of providing patients with this information to a nurse or intern with knowledge of the procedure, including its risks and alternatives, the ultimate responsibility for accurately conveying this information to the patient remains with the surgeon and cannot be delegated (Stalsitz v. Allentown Hosp. 2002).

Informed Consent in the Transplantation Setting

In the context of transplantation surgery with a live donor, the surgical team's duty to obtain informed consent is complicated by the fact that the informed consent of two patients must be obtained. If the harvesting of the donated organ is performed by a different surgeon than the surgeon performing the transplant, this situation will result not only in duties *owed to* two different patients but also in the creation of duties *owed by* two different surgeons. Of course, while each procedure includes common surgical risks such as bleeding, infection, and death, there are also different risks inherent in both procedures that must be thoroughly explained to each patient.

Any transplant surgery involving a living donor is essentially putting a relatively healthy person at risk of injury with the hope that the donor and recipient will each recover. It is because of this very real risk that the informed consent of the donor is paramount. The need to apprise live organ donors of the potential risks of surgery is critically important. Most of the more than 6,000 living organ donations that occur each year in the United States (ASTS 2012) are made by close friends or relatives of the recipient – slightly over 74 % according to a 2012 article (Cohen 2012) – and the decision to donate a portion of one's liver is nearly always an emotional one. While such altruistic behavior is commendable, the donor often may not fully appreciate the potential consequences of his/her decision, including the very serious risks that accompany surgery and the complications that occasionally arise. Indeed, accidents and adverse events do, at times, occur. Living organ donors bear a low but finite and well-documented risk of mortality and morbidity (Miller et al. 2013). As the American Society of Transplant Surgeons (ASTS 2010) indicated in a 2010 position paper, "[l]iving donor procedures are not without risks to the donor, even in experienced hands and programs." The ASTS further acknowledged in a 2012 position paper that "serious complications including death are always possible in living donor surgery and do occur, even when performed by skilled surgeons in very experienced transplant centers." Accordingly, the donor must be thoroughly apprised of not only all surgical risks and complications but also the alternative of refraining from organ donation altogether. The surgeon should also fully explain the distinct possibility that the organ transplantation may not be successful so that the donor understands that his/her heroic altruism may ultimately be for naught.

The Role of Expert Testimony in Informed Consent Cases

To establish a prima facie case on an informed consent claim, a plaintiff must typically show that the operating surgeon failed to advise the patient of those material facts, risks, complications, or

alternatives to surgery that a reasonable person in the patient's situation would consider significant in determining whether to undergo the operation (Cline v. Kresa-Reahl 2012; Giles v. Brookwood Health Servs., Inc. 2008; Flatt v. Kantak 2004; 40 P.S. § 1303.504; Southard v. Temple Univ. Hosp. 2001). Although the issue of what information in material is a question that the jury must generally decide, to assist the jury in making this determination, the plaintiff must usually produce expert testimony identifying the risks of the procedure, the alternatives to that procedure, and the risks of those alternatives (Cline v. Kresa-Reahl 2012; White v. Leimbach 2011; Whittington v. Mason 2005; Flatt v. Kantak 2004; 40 P.S. § 1303.504(c); Moure v. Raeuchle 1992). Such testimony is essential for the plaintiff to prove the nature of risks inherent in a particular procedure, the likelihood of therapeutic success, the frequency with which particular risks will occur, and the nature of available alternatives to the treatment (Garcia v. Robinson 2015; Festa v. Greenberg 1986). Expert testimony is also necessary for the plaintiff to show a causal connection between the surgeon's allegedly tortious conduct and the patient injuries (White v. Leimbach 2011; Maliszewski v. Rendon 1988).

An expert testifying at trial regarding a donor informed consent issue would likely testify that, in addition to traditional informed consent, a donor should be provided with a patient advocate. The advocate would be described as an independent physician, who interacts face to face with the donor, to ensure lack of coercion and observe donor suitability (Campobasso et al. 2005).

The Importance of Documentation/ Communication for Medical Care and Malpractice Cases

Documentation remains critically important to safe and effective medical care. Careful documentation of a physician's findings and recommendations facilitates the accurate recall of prior treatment and plays a vital role in promoting continuity of care.

However, accurate documentation can also play an important role in avoiding potential medical malpractice lawsuits and defending against those that arise. Plaintiff's attorneys are fond of the old adage that runs, "if it isn't documented, it wasn't done." While this familiar maxim may be passé and is often inaccurate, the fact remains that the best way to prove that a certain medical finding, recommendation, or treatment decision was made is to document that information in a patient's medical records. Taking a few extra minutes to thoroughly and accurately document one's findings and treatment plan can prevent hours of anxiety later when a plaintiff's attorney asks a defendant physician during his deposition to point to the portion of the chart that supports his recollection of events. Moreover, since juries are charged with the often difficult task of determining which side's witnesses appear more credible when deciding the outcome of medical malpractice trials, they generally find it easier to accept a surgeon's version of events if it can be demonstrated by thorough, accurate, and contemporaneous documentation in the records.

Furthermore, thorough and accurate documentation plays a vital role in defending against claims of failure to obtain informed consent to surgery. When a patient suffers an operative complication, even a surgeon who spent considerable time with the patient discussing the nature, risks, and alternatives of surgery over multiple preoperative office visits may find himself/herself defending against a claim of failure to obtain informed consent to surgery. To protect oneself against such claims, a wise practitioner should meticulously document the discussion in the patient's medical chart and have the patient and a witness sign a detailed consent form setting forth the operation to be performed and all material risks and complications of the procedure. The consent form should include a patient acknowledgment that these matters were thoroughly discussed with him/her, he/she was given ample opportunity to ask any questions he/she had concerning the operation, and the surgeon sufficiently answered any questions that he/she posed. Many surgeons use a consent form initialed by the patient on every page and signed several days or

even weeks before the operation takes place to defend against claims that the patient did not have time to read the document, independently investigate the procedure, or consider the risks and alternatives to surgery.

While litigation cannot always be avoided, establishing policies and procedures founded upon best practices can go a long way toward shielding physicians from liability. The importance of constant communication and meticulous documentation cannot be overstated in the general context of a medical negligence matter and the specific setting of liver transplantation. Moreover, being remiss in communicating can have consequences stretching beyond the individual surgeon. For example, when Medicare closed a hospital's liver program in 2005, its rationale was based, in part, on the program's failure to communicate changes to liver transplant candidacy to patients on their waitlist (Bernhard 2005).

Clear communication among the transplant team members remains critical for passing information along to the layperson, for whom understanding such a complex surgery can be difficult enough (Gordon et al. 2015). When the patient receives mixed messages from team members, litigation can result. Transplant programs must also pay close attention to the break points in its team's treatment of donors and recipients. That is, transplant surgeons and their team members need to be extremely clear in accepting and discharging patients to their service. Lapses in communication or documentation during these hand-off moments between medical disciplines can easily lead to negative outcomes for the patient and future litigation for the treating physician.

Nor can solid communication between the surgeon and the patient be ignored, regardless of the stage of surgery and of the medical outcome. In fact, lack of sufficient communication has been identified as one of the four motivations underpinning causes of action (Bismark and Dauer 2006), and plaintiffs sometimes sue not primarily because of a surgeon's negligence, but because of his silence or failure to explicitly communicate compassion (Rowe 2002, 2003). After all, the patient's perception of his care plays just as large a role as the care itself in the decision to pursue litigation (del Barrio et al. 2004). In fact, a 2002 study linked the increased likelihood of a lawsuit against a physician to, among other elements, the "patients' dissatisfaction with their physicians' ability to establish rapport. . .administer care and treatment consistent with expectations, and communicate effectively" (Hickson et al. 2002). In other scenarios, a physician's sudden silence can lead the patient to suspect medical error and consider commencing litigation (Berlinger 2003). Without question, the risk of a lawsuit can be reduced by appropriately communicating with donors and recipients (Campobasso et al. 2005).

Transparency and Its Effects

Perhaps the most appropriate response to an unexpected outcome of any kind is complete transparency with the patient and her family. This is true whether the physician commits an error or the patient experiences a complication that occurs in the absence of negligence. Conversations with the patient and family regarding the event should occur as soon as possible, and all subjects should be up for discussion. Apologies should be offered. Questions should be answered as completely and frankly as possible. Physicians should document all interactions, noting the substance and time of the discussion as well as all participants.

Some commentators believe that prompt and complete disclosure will deter litigation (Kachalia 2013). If a lawsuit should be brought, timely, properly documented transparency will be well received by the trier of fact. And many states now have statutes which preclude the admission of benevolent gestures, including apologies, as evidence of an admission of negligence (e.g., 35 P.S. §10228.3). Perhaps more importantly, prompt and thorough disclosure has been associated with benefits to patient safety (McDonald et al. 2010) and addresses the ethical imperative to initiate transparent discussions with patients and families when errors and adverse events occur (Kowalczyk 2013; Kachalia 2013).

Possible theories of liability for organ transplantation litigation		
Suits by donor	*Suits by recipient*	*Suits against transplant center*
Improper timing of procurement failure to obtain informed consent (understating or failing to explain real possibility of risks, neglecting to mention elective nature of donation, etc.) Prioritizing recipient's care failure to treat postoperatively or inadequately managing posttransplant complication wrongful death	Improperly timing recommendation for surgery (i.e., too early or too late) inadequate pretransplant evaluation failure to obtain informed consent Discharging patient too soon or failing to hand off care to competent physician Inadequate management of posttransplant complication Failing to protect against infection treatment errors, especially regarding immunosuppression, leading to organ rejection Failure to detect rejection	Improper manipulation of waitlist (e.g., unjust criteria or their inconsistent application) Failing to communicate with patients on waitlist and/or obscuring practices (e.g., turning down organs without informing patients on waitlist) Failing to ensure matching blood types between donor and recipient Transplanting diseased, infected, or cancerous organs needless wasting of organs

The transplant surgeon can protect himself/herself from the prospect of litigation by doing his/her utmost to avoid the above mistakes during the transplant process and by meticulously documenting the patient's treatment and the transplant team's thorough communication to coordinate care.

Is Litigation Inevitable? Types of Alternative Dispute Resolution (ADR)

On average, the life of a malpractice claim is over one and a half years, with cases that see the inside of a courtroom taking over 2 years to conclude. Surgeons are especially likely to find themselves in court (Jena et al. 2012). According to a 2002 study, almost two-thirds of all surgeons had been sued at least once, compared to under one-third for nonsurgical practitioners (Hickson). What holds true for surgeons generally is likely to be even more applicable to transplant surgeons specifically, as such complex operations rank toward the top in medical difficulty. In light of these facts – the significant duration of medical malpractice cases and the prevalence of suits against surgeons – considerable interest exists in the viability of alternative dispute resolution.

ADR Type No. 1: Binding Arbitration

Arbitration can take different forms as an alternative dispute resolution mechanism for medical malpractice litigation. It can be ordered by the court, agreed upon with the patient at the time of treatment, or decided upon by parties during litigation (McCullough 2006).

Court-ordered arbitration is often seen as less than helpful in the resolution process (McCullough 2006). State constitutional provisions often mitigate the effectiveness of mandatory arbitration in this setting (Mattos v. Thompson 1980). Despite the expertise a panel might bring, the process does not take the place of a jury trial, and litigants retain the rights thereto. Such arbitration can be viewed as simply adding an extra step to the process, resulting in lengthier, more costly, and more complicated litigation.

Some practice groups, health systems, and hospitals have asked patients to sign contracts at the time of the provision of service agreeing to arbitrate any professional liability matter that may arise. (Disputes outside the realm of traditional malpractice might also be the subject of these contracts.) A contract from a case litigated in Tennessee included the following language:

> The parties to this agreement are Physician and Patient. It is understood that any dispute as to medical malpractice, that is as to whether any medical

> services rendered under this contract were unnecessary or unauthorized or were improperly, negligently or incompletely rendered, will be determined by submission to arbitration and not by a lawsuit. . .Both parties to this contract, by entering into it, are giving up their constitutional rights to have any such dispute decided in a court of law before a jury and instead are accepting the use of arbitration.

The Tennessee Supreme Court found the agreement enforceable. They noted that the agreement was considered a contract of adhesion because of the superior bargaining power of the healthcare provider. Such contracts are unenforceable if the terms are beyond the reasonable expectations of ordinary persons or are oppressive or unconscionable. Here, the court found the contract was fair (Buraczynski v. Eyring 1996).

The Tennessee Court also rejected the argument that these types of arbitration agreements are void as against public policy (Buraczynski v. Eyring 1996). However, not all courts agree. Many courts have struck down these agreements as contrary to policy considerations. In addition, problems regarding enforceability may arise if there are parties to the lawsuit or insurers who are not parties to the contract.

Parties may also agree to binding arbitration as an alternative to jury trial after litigation has begun. These sessions are held before a single arbitrator or panel. They are almost always shorter in duration than a jury trial and thus less expensive. Evidence is presented just as if the parties were litigating in court. Agreements may be reached as to whether experts testify in person, by prerecorded video deposition, via videoconferencing, or simply by submitting a written report. The arbitrator or panel serves as judge and jury, making evidentiary rulings and returning a verdict. The verdict is final and non-appealable.

Parties in arbitrations of this sort sometimes contract in advance of the arbitration regarding the parameters of the award. Thus, the defense may agree that the plaintiff will be paid some amount even if the arbitration results in a verdict for the defendant, in exchange for plaintiff's agreement to accept an upper limit on an award, even if that limit is exceeded by the verdict. These "high/low" agreements have an added benefit for the defendant physician – namely, if a defense verdict is returned in a high/low arbitration, no report to the National Practitioner Data Bank is required even though a payment to the plaintiff by the physician's insurer will be made pursuant to the agreement (NPDB 2001).

ADR Type No. 2: Mediation

Mediation is a voluntary, nonbinding process using an impartial third party to assist the parties toward a mutually acceptable resolution of their dispute. Communications in mediation are generally privileged and cannot be used as evidence if the case proceeds to arbitration or trial.

Currently, some of the most successful mediation programs are combined with early intervention, pre-litigation concepts, and patient safety initiatives. One of the earliest such programs was instituted at Rush Presbyterian–St. Luke's Medical Center in Chicago. The Rush Project began in 1995. It emphasizes the prompt and thorough disclosure of adverse events to patients. Two mediators are used at each mediation session. Rush reports that, as a direct result of its mediation program, defense costs have been reduced by 50 %, and indemnity payments have been lowered by 40–60 % (Meruelo 2008).

Similar models are in place in many jurisdictions around the country. Many systems are designed to make the mediation option as attractive as possible to patients with potential claims by ensuring the patient understands that no rights are surrendered, the healthcare provider will pay for arbitration, the right to sue is preserved, and the statute of limitations will be extended by the time spent in the mediation process. Despite these apparent concessions, hospitals, healthcare systems, and insurers find that a patient-friendly program, combined with early and thorough disclosure of adverse events, leads to a decrease in costs with the added benefit of improved patient safety. (Insurance industry sources predict that mediation programs could result in a reduction of indemnity payments by 25 % and a reduction

in defense costs by 60 % (Meruelo 2008).) In the current climate, voluntary, nonbinding mediation seems to offer the most realistic opportunity to affect savings in all aspects of the litigation process, with a concurrent and continuing focus on patient safety.

Conclusion

Although medical professionals and laypeople desire ideal outcomes for both donors and recipients, history and common sense teach us that such perfection is often neither possible nor attainable. Complications will invariably arise despite the valiant treatment efforts of qualified physicians in many outstanding transplant programs. Litigation can be the result of such unfortunate realities, and surgeons often find themselves sued for medical malpractice, frequently for allegedly failing to obtain informed consent. Nonetheless, transplant surgeons can insulate themselves from potential litigation and improve their own defenses when cases do arise by employing several strategies. Carefully procuring the informed consent of donors and recipients equally protects patients and surgeons. Meticulous documentation not only enables continuity of quality care but also bolsters the surgeon's credibility at trial. Lucid communication among the transplant team helps eliminate treatment errors and heads incipient lawsuits off at the pass. Moreover, increased transparency and forthrightness in the immediate aftermath of an adverse event spell both better care and fewer negligence claims. Put into everyday practice in the transplantation setting, these approaches very well may improve patient safety, decrease costs, and reduce the volume of litigation in the years to come.

Cross-References

- Cell Therapy for Liver Failure: A New Horizon
- Downstaging Hepatocellular Carcinoma for Liver Transplantation
- Immunology of Liver Transplantation
- Live Donor Liver Transplant
- Liver Transplantation in the Third Millennium in North America: The Strategy for Success
- Orthotopic Liver Transplantation: Complications

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