

Gebhard Wagener *Editor*

# Liver Anesthesiology and Critical Care Medicine

 Springer

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*To Laurie, Ben, and Anna, who allow me to  
enjoy life and work, and to my parents,  
who contributed so much to what I am.*



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## Foreword

Liver transplantation has made remarkable progress in the 48 years since the first human liver transplant, and especially in the last 30 years since the introduction of cyclosporine made long-term survival after liver transplantation feasible.

A procedure that was initially untested and experimental became routine and is now the accepted treatment for end-stage liver disease in many parts of the world. About 6,000 liver transplants are done in the USA every year, and graft and patient survival is excellent. We are able to administer transplants to children, do living related and split liver transplants, and only the shortage of organs limits the expansion of our field.

This progress is not only due to advances in immunosuppression, surgical techniques or organ preservation, but also to improvements in anesthetic techniques. Anesthesia care initially provided by few experts in a small number of centers proliferated and is now often standardized and protocolized. Advances in anesthesiology enabled the development of surgical techniques such as caval cross-clamp or partial liver transplantation. There are few procedures in which the close cooperation of surgeon and anesthesiologist is as essential for the success of the surgery and liver (transplant) surgery would have never flourished as it did without the teamwork and partnership between anesthesiologists and surgeons.

Within the last 20 years there has been tremendous progress in clinical research of liver transplant anesthesia that aims to reduce blood transfusions, augment organ preservation, and improve overall outcome. Anesthesia for liver surgery has made a similar astounding progress and now extensive resections are conceivable that would have been impossible before. Postoperative critical care medicine as a continuation of the intraoperative care is now frequently in the hands of anesthesiologists and intensivists specialized in hepatic intensive care, reflecting the increasing knowledge in this field.

This book aims to summarize the progress in liver anesthesiology and critical care medicine of the last 20 years and serves as a guide to those who care for patients undergoing liver transplantation and liver resections. The authors are the leaders in the field of liver anesthesiology and critical care in Europe, Asia, and the United States. The foundation of this book is the

increasing fund of knowledge gained through clinical research as well as through the extensive clinical experience of the authors that they share with the readers.

This textbook provides the necessary background to understand the complexity of the liver and its pathophysiology. It summarizes the elaborate logistics involved in donor and recipient matching in Europe and the United States and then describes the routine intraoperative management of liver transplant recipients and patients undergoing hepatic resections. It addresses common comorbidities and complications and how they may affect the preoperative work-up and intraoperative management. The postoperative critical care section describes the routine care after liver transplantation and resection as well as diagnosis and management of possible complications including pain management.

This book aims to summarize our current knowledge of liver anesthesiology and critical care. It will serve as a reference for those who routinely care for patients with liver disease. Those new to our exciting field will gain sufficient knowledge to successfully address many of the complex issues that may arise during liver anesthesiology and critical care medicine. To those who have extensive experience in the care of patients undergoing liver (transplant) surgery this book will serve as an authoritative reference and enable an in-depth immersion into the exciting field of hepatic anesthesiology and critical care medicine.

Pittsburgh, PA, USA

Thomas E. Starz M.D., PH.D.

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## Preface

Liver transplantation and liver surgery have made enormous strides in the last 20 years. It has been transformed from an often heroic operation requiring massive amounts of blood transfusions to almost routine surgery with little blood loss in spite of increasing recipient morbidity. This advancement is reflected in improved long-term mortality rates in the face of preferentially allocating more marginal organs to sicker recipients.

Many little steps and advances are responsible for this achievement, not least improvements of anesthetic techniques and postoperative care. These little steps may not be immediately obvious but were necessary to accomplish such a progress. Clinical and preclinical research in liver anesthesiology and critical care medicine in the last 10 years has thrived, and a new generation of anesthesiologists and intensive care physicians are willing to scrutinize their clinical practice using clinical research tools instead of relying only on experience. This has created a fascinating and productive interaction within the small group of anesthesiologists and intensivists who care for these severely sick patients.

This book summarizes their current knowledge by bringing together the leading experts of our sub-specialty. It not only condenses a large amount of clinical research but also includes opinions and experiences when evidence is insufficient.

It is an in-depth review of the field and presents the current best knowledge. It aims to be the definitive resource of liver anesthesiology and critical care medicine. Experienced and busy practitioners will find essential information to manage complex conditions of liver disease. The novice anesthesiologist or resident will be able to use this book as a thorough and comprehensive introduction to our field and rapidly gain extensive knowledge as well as obtain practical advice for those complex and scary situations that can occur so frequently during liver transplantation.

This book provides a comprehensive review of the pathophysiology of liver disease, pharmacology, immunology, and its implications for the anesthesiologist and intensivist. Anesthesiologic and postoperative care of liver transplant recipients requires a thorough appreciation of the intricacies of liver disease and its complications. Extra-hepatic manifestations of liver disease are addressed in chapters separated by organ systems. Routine management as

well as common intra- and postoperative complications are described in detail to provide the knowledge required to care for these patients.

Liver transplantation is expanding internationally and a large body of work and experience originates from centers in Europe and Asia. Experts from the United States, Europe, and Asia have contributed to this book to give a global perspective of liver transplant anesthesiology.

A separate section reviews the anesthetic and postoperative management of patients undergoing liver resection. New surgical approaches have allowed us to perform more extensive and intricate resections that pose new challenges to the anesthesiologist and intensivists. Surgical techniques and their physiologic repercussions are described in detail and management strategies for routine as well as complex cases and their possible complications are offered.

We hope this book will alleviate the apprehension often associated with caring for these sick patients and encourage many readers to engage in liver anesthesiology and critical care medicine.

New York, NY, USA

Gebhard Wagener, M.D.

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## Acknowledgements

I sincerely thank the authors of this book for their excellent contributions. They have spent many hours of diligent and hard work creating delightful, intelligent, and insightful chapters that were a pleasure to read and edit. I would also like thank their families for the time the authors missed with them while writing these chapters.

This book would not have been possible without the encouragement, support, and advice of my chair, Dr. Margaret Wood, and all my colleagues and friends at Columbia University Medical Center. I am immensely grateful for this.

I would further like to thank my initial editor, Brian Belval, who helped me start this project, Shelley Reinhardt, my editor from Springer Science+Business Media, and Daniel Dominguez, the developmental editor, who have been indefatigable and immensely patient with me. Thank you. I further thank Moury Minhaz, my research assistant, who has helped me with the secretarial and editorial work. A special thank you to Serena and Sharon Mathew, who have done a wonderful job creating some of the illustrations in this book.

I am sincerely grateful to my colleagues, residents, and nurses that I have had the pleasure to work with for many years now and to my patients, who taught me so much about disease, life, and death.





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**Part I**

**Physiology, Pathophysiology and  
Pharmacology of Liver Disease**

Teresa A. Mulaikal and Jean C. Emond

## Introduction

This chapter will review the anatomy and physiology of the liver relevant to anesthetic management during complex liver surgery. Anesthetic management of the patient with chronic liver disease requires an understanding of the alterations induced in cirrhosis that affect many organ systems. Liver surgery for ablation of tumors may reduce the functional mass of the liver resulting in systemic changes that alter hemodynamics and renal function. In liver transplantation, the body is deprived of all liver function during the implantation and may receive a new liver with impaired initial function. All types of liver surgery may accentuate hepatic ischemia with reperfusion, inducing systemic changes both acute and chronic. Thus, an understanding of the liver, and its structure and function, is critical in managing the changes of the liver induced during surgery. This knowledge, applied throughout the perioperative period by anesthesiologists with interest in liver

disease, has been a major factor in the markedly improved outcomes of liver surgery during the past 50 years, and especially since the era of liver transplantation.

The liver is the largest gland in the human body and the only organ capable of regeneration [1]. This unique ability has been both the subject of ancient Greek mythology and modern medicine best illustrated by the Promethean myth in which the injured liver is restored daily as Zeus' eternal punishment to Prometheus. While advances in science allow for the temporary support of renal function in the form of dialysis, and of cardiovascular and pulmonary function in the form of veno-arterial extracorporeal membrane oxygenation (VA ECMO), there is currently no effective substitute for the immune, metabolic, and synthetic functions of the liver other than transplantation (Table 1.1). The absence of artificial liver support makes a strong understanding of hepatic physiology and pathophysiology imperative to the care of critically ill patients with liver injury as management requires careful protection of remnant function while regeneration occurs.

This chapter will review normal liver anatomy, histology, and physiology. The first section covers basic liver anatomy and describes Couinaud's classification, which divides the liver into eight segments as a function of its portal venous and hepatic arterial supply. These segments serve as boundaries for the modern hepatectomy. A knowledge of each segment's vascular supply, proximity to the vena cava, and spatial orientation

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**Table 1.1** Functions of the liver

Metabolic	Synthetic	Immunologic	Regenerative	Homeostasis
Xenobiotic metabolism	Coagulation factor synthesis Pro-coagulants Anticoagulants Fibrinolytics Antifibrinolytics	Innate immunity	Restoration after hepatectomy or trauma	Regulation of intravascular volume Renin Angiotensin Aldosterone
Protein metabolism Ammonia Detoxification	Plasma protein synthesis Albumin	Adaptive immunity		Glucose homeostasis
Lipid metabolism B-oxidation F.A. Triglyceride	Steroid hormone synthesis Cholesterol	Oral and allograft tolerance		Regulation of portal inflow Hepatic arterial buffer hypothesis
Glucose metabolism Gluconeogenesis Glycogenolysis Glycogenesis	Thrombopoietin Angiotensinogen Insulin-like growth factor 1 (IGF-1)			

F.A. fatty acids

is useful in judging the difficulty of resection and use of surgical techniques such as total vascular isolation to minimize blood loss. Lesions located posteriorly and adjacent to the vena cava for example may necessitate total vascular isolation.

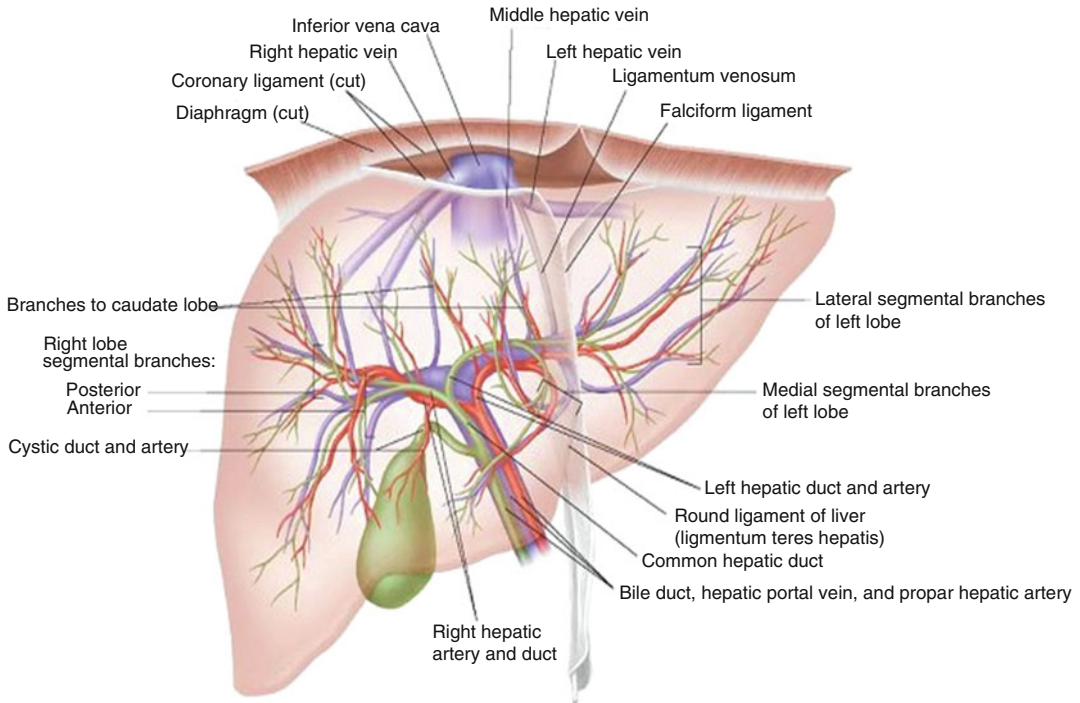
The next section covers basic liver histology, including a discussion of microanatomy and cellular function, which has implications for the regulation of portal blood flow and the pathophysiology of cirrhosis and portal hypertension. The last section focuses on basic liver physiology, including the immunological role of the liver, the regulation of hepatic blood flow and its impairment in small for size syndrome, as well as the metabolic and synthetic functions of the liver.

## Embryology

The liver derives from the ventral foregut endoderm during the fourth week of gestation, responding to signals from the cardiac mesoderm

for hepatic differentiation [2–4]. The ventral foregut also gives rise to the lung, thyroid, and ventral pancreas while the dorsal foregut gives rise to the dorsal pancreas, stomach, and intestines [5]. The ventral endoderm responds to signals from the cardiac mesoderm to generate the hepatic diverticulum that transforms into the liver bud, and hepatic vasculature [6]. The portal vein derives from the vitelline veins [4]. The ductus venosus shunts blood from the umbilical vein, which carries oxygenated blood from the placenta to the fetus, to the vena cava thereby supplying oxygenated blood to the brain. The ligamentum venosum is the remnant of the ductus venosus and the ligamentum teres is the remnant of the umbilical vein.

The extrahepatic and intrahepatic biliary tracts have different origins. The extrahepatic biliary tract, which includes the hepatic ducts, cystic duct, common bile duct, and gall bladder, develops from the endoderm. The intrahepatic biliary tract, however, develops from hepatoblasts [2].



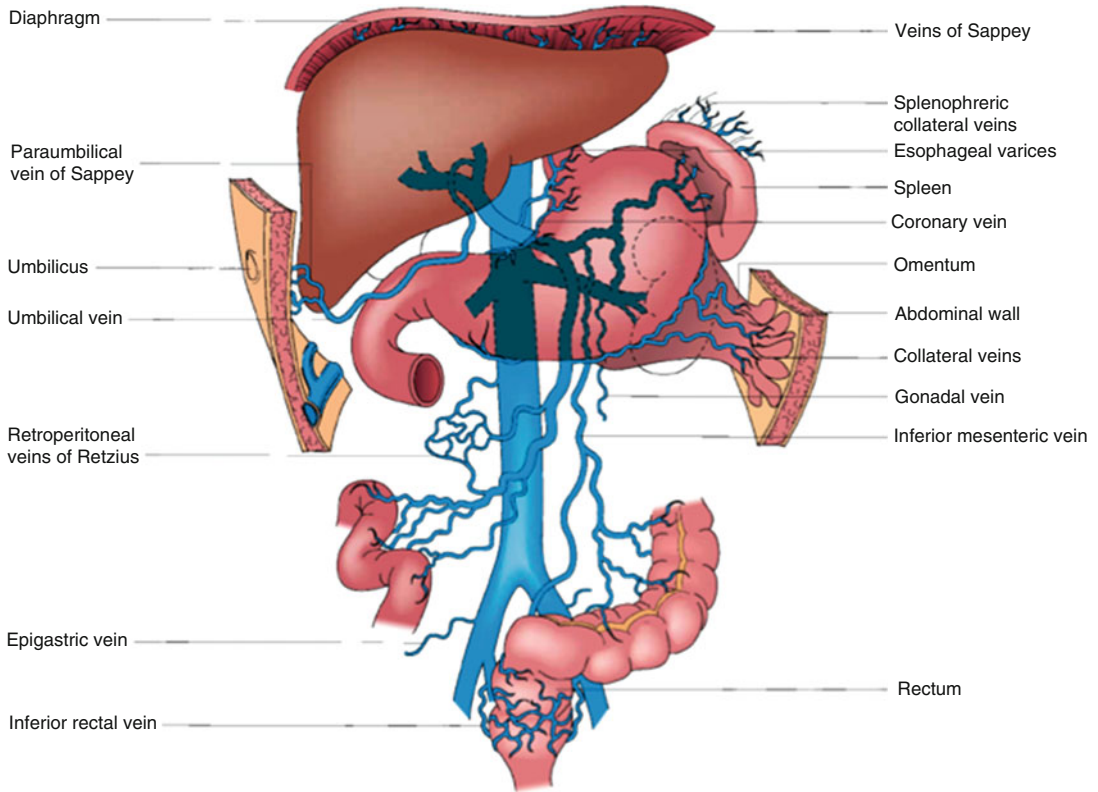
**Fig. 1.1** Arterial and venous circulation of the liver. With kind permission from Lippincott Williams and Wilkins: Tank, Gest, Burket et al.; Atlas of Anatomy 2009 (Chapter 5 “The Abdomen,” plate 5–22, figure A, pg 234)

## Macroscopic Anatomy of the Liver and the Visceral Circulation

Anatomy relevant to surgical management and liver anesthesia includes the blood supply and the intrahepatic architecture of the liver. A much more specific knowledge of liver anatomy is required to plan and execute the operations and is beyond the scope of this chapter. The afferent bloodflow to the liver is composed of both arterial and portal blood and accounts for 20–25% of the cardiac output, and all the blood exits the liver through the hepatic veins (Fig. 1.1). The hepatic artery is derived from the celiac artery in most cases but may receive some or all of its supply from the superior mesenteric artery. The artery divides in order to supply the right and left lobes and the intrahepatic segments, and the anatomy includes several variants that are relevant in

hepatic resections and biliary surgery. These variants do not affect anesthetic management other than the recognition that surgical errors may result in ischemic injury to segments of the liver. Furthermore, since the biliary tree is primarily supplied by the arterial system, bile duct ischemia may result in postoperative complications.

The portal blood accounts for the majority of the hepatic blood flow and unites the venous return from the entire gastrointestinal (GI) tract with the exception of the rectum that drains into the iliac vessels. The foregut, including the stomach, spleen, pancreas, and duodenum drain directly into the portal vein and the splenic vein, while the small intestine and the right colon drain into the superior mesenteric vein. This means that the splenic vein contribution to the portal blood is rich in pancreatic hormones and cytokines while the superior mesenteric vein brings nutrients, toxins, and bacteria that are absorbed



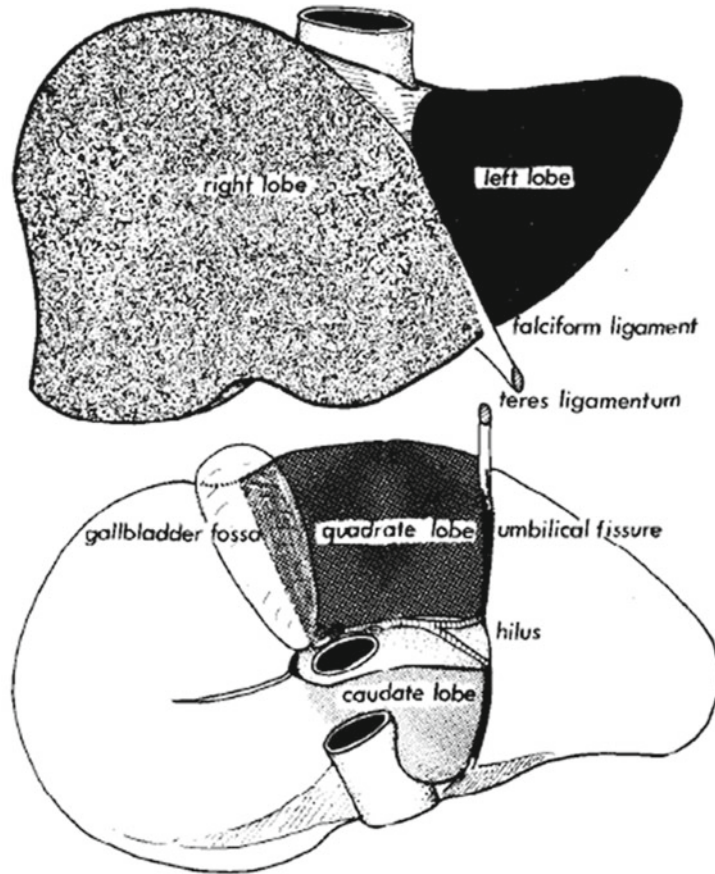
**Fig. 1.2** Sites of collaterals in portal hypertension. With kind permission from Lippincott Williams & Wilkins: Greenfield's Textbook of Surgery, 5th edition 2011 (Chapter 58: "Cirrhosis and Portal Hypertension" (Emond) Figure 58.8, pg 914)

by the gastrointestinal tract. In situations of increased portal vein pressure such as cirrhosis and portal vein thrombosis, collateral veins known as varices can develop as connections between the portal vein and the systemic circulation that become enlarged and shunt blood away from the liver (Fig. 1.2). Shunting results in impaired liver function and is most pronounced in alterations of brain function discussed later in the chapter. Clinically significant varices result in gastrointestinal bleeding, including the esophagus, stomach, and duodenum, as well as the rectum. Other collateral shunts occur in the retroperitoneum and the abdominal wall, and may accommodate large amounts of portosystemic shunting without bleeding but with other consequences of impaired

portal blood flow. In addition to the loss of metabolic transformation, the reticulo-endothelial protective function of the liver is also bypassed in the presence of large shunts and may result in sepsis and contribute to the hemodynamic alterations of cirrhosis discussed below.

The hepatic veins are of great functional significance to the liver and are of surgical and anesthetic importance. They join at the diaphragm and enter the right chest, therefore, unlike the remainder of the abdominal circulation, are exposed to alterations in intrathoracic pressure. The liver is exquisitely sensitive to outflow pressure, and obstruction of the hepatic veins, for example in Budd-Chiari syndrome or right heart failure, causing severe functional impairment of



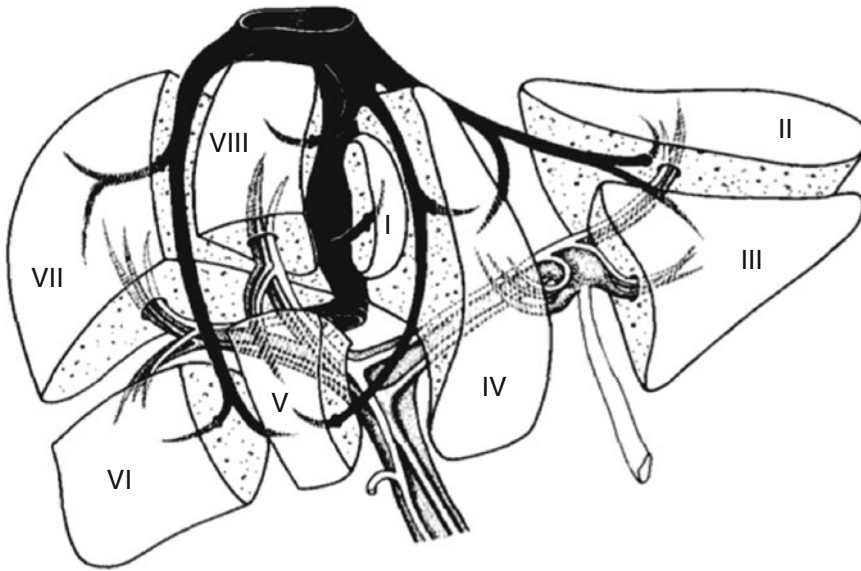


**Fig. 1.3** External anatomy of the liver. With kind permission from Springer Science+Business Media [7]

the liver. During liver surgery, obstruction of the hepatic outflow especially if combined by vena cava clamping or twisting, may result in acute hemodynamic instability. To avoid hemodynamic collapse as the liver is being manipulated, minute to minute communication between the surgeon and anesthesiologist is critical.

The external anatomy is described from gross landmarks including the gallbladder, the vena cava, and the hepatic ligaments (Fig. 1.3) [7]. The internal anatomy is defined by the vessels, and eight functionally independent segments each with an afferent pedicle including artery, portal vein and bile duct, and efferent hepatic vein (Fig. 1.4). From the exterior, the apparent right lobe of the liver is defined by the vena cava and the gallbladder fossa. This is typically 55–70% of

the hepatic tissue and is supplied by the right hepatic artery and the right portal vein, and is drained by the right hepatic vein and comprised of segments V–VIII. The central plane between the right and left lobes of the liver is defined by the middle hepatic vein. The left lobe is more complex. An external left lobe is defined by the falciform ligament (and is termed by some surgeons as the “left lateral segment,” but consists anatomically of two segments, II and III). The medial portion of the left lobe is morphologically described as the quadrangle lobe and is actually segment IV. The left lobe segments are supplied by the left hepatic artery and portal vein, and drained by the left and middle hepatic veins. The caudate lobe (segment I) is central and fully independent of either right or left livers.



**Fig. 1.4** Internal anatomy. With kind permission from Springer Science + Business Media [7]

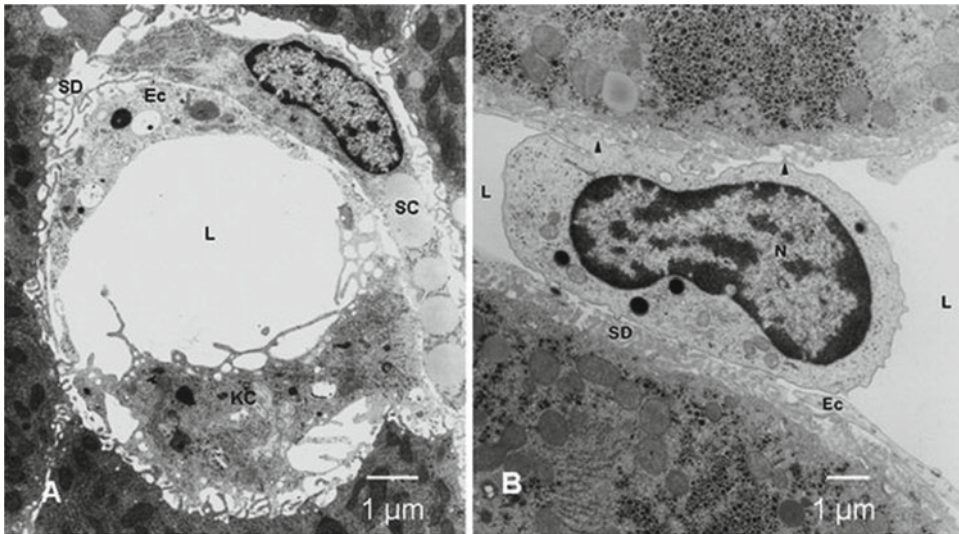
## Histology

### Cellular Classification

The liver is composed of a rich population of specialized cells that permit it to carry out its complex functions, grossly characterized as “parenchymal” cells: the hepatocytes, and “non-parenchymal cells”: all others. The nonparenchymal cells include stellate cells, sinusoidal endothelial cells, kupffer cells, dendritic cells, and lymphocytes (Fig. 1.5, Table 1.2). The hepatocytes or parenchymal cells make up 60–80% of liver cells [8] and carry out the liver’s metabolic, detoxification, and synthetic functions. The hepatocytes have a unique relationship with the sinusoidal endothelium that carefully regulates the exposure of the hepatocytes to the metabolic substrate arriving in the portal blood through fenestrations. The baso-lateral membrane of the hepatocyte absorbs nutrients from the sinusoids, which are then processed with excretion of the metabolic products through the apical cell membrane into the bile duct. Hepatocytes divide under stress and cytokine stimulation and are the princi-

pal components of mass restoration during regeneration. In vitro, hepatic mitotic activity is stimulated by hepatocyte growth factor (HGF), cytokines, and tumor necrosis factor alpha (TNF) clinically observed after hepatectomy, toxic cell necrosis, or trauma [9].

Hepatic stellate or Ito cells are vitamin A and fat storing cells located in the perisinusoidal space of Disse, described by Toshio Ito in 1951 [10, 11] and are of tremendous importance and scientific interest as critical regulators of hepatic function and prime suspects in the pathogenesis of cirrhosis. In the normal liver, stellate cells are quiescent but can become activated by injury and transform into collagen secreting myofibroblasts with contractile properties. This fibroblast-like cellular activity of hepatic stellate cells has a protective function in the generation of scar tissue, promotion of wound healing, and remodeling of the extracellular matrix [12]. Excessive collagen deposition is the underlying mechanism of fibrosis and cirrhosis [13]. Hepatic stellate cell secretion of collagen in the perisinusoidal space of Disse narrows the sinusoidal lumen, thereby increasing hepatic vascular resistance and contributing to portal hypertension [10]. The impact of this dis-



**Fig. 1.5** Transmission electron micrographs of (a) sinusoidal endothelium (Ec) with attached Kupffer cell (KC) encasing the sinusoid lumen (L), and perisinusoidal stellate cell (SC) containing fat droplets in space of Disse (SD); and (b) Pit cell with typical dense granules. This pit

cell is in close contact with the endothelial lining and is seen to contact microvilli of the parenchymal cells (*arrowheads*). Ec endothelial cell; *f* fenestrae; L sinusoidal lumen; N nucleus; SD space of Disse (with kind permission from McCuskey [20], Figure 5 slide A, Figure 6 slide B)

turbance on sinusoidal perfusion creates a secondary ischemic injury, potentially accelerating the destructive impact of an initially limited injury [12]. Stellate cells also have intrinsic contractile function important in the regulation of blood flow and the pathogenesis of portal hypertension. Vasopressin, endothelin-1, and angiotensin II bind to receptors on stellate cells, activating a rho-mediated signal transduction pathway and myosin II contraction [10, 13]. Endothelin-1, angiotensin II, vasopressin, and their receptors have been studied as therapeutic targets for the treatment of portal hypertension and the management of variceal bleeding [14–18].

Hepatic endothelial cells are fenestrated cells that line the sinusoids and also play an important role in the regulation of intrahepatic resistance to blood flow through expression endothelial nitric oxide synthase (eNOS) and release of nitric oxide (NO), a potent vasodilator [19, 20] (Fig. 1.6a). Disruption of sinusoidal endothelial cells in cirrhosis results in a concomitant decrease in the production of NO [21]. This is in contrast to the mesenteric vascular bed that has an increased NO

production in portal hypertension [21]. NO-mediated increase of splanchnic flow is consistent with the *forward flow theory* of portal hypertension that states that portal hypertension is not only due to an increase in hepatic vascular resistance but also due to splanchnic hyperemia [22]. Neoangiogenesis mediated by vascular endothelial-derived growth factor (VEGF) also contributes to splanchnic hyperemia and the hyperdynamic state of end stage liver disease [23, 24].

The kupffer cells are macrophages that reside in the hepatic sinusoids and constitute 80–90% of the macrophages in the human body [25] (Fig. 1.6b). These cells are specialized due to their exposure to high concentrations of endotoxin and oxidative stress in the sinusoids and are critical protectors of the systemic circulation from toxic exposure. They are part of the innate immune system, which is the intrinsic host defense system that allows nonspecific targeting of foreign antigens in contrast to the adaptive immune system that allows specific targeting of foreign antigens. There is a close relationship between the regulation of blood flow and kupffer

**Table 1.2** Cellular microanatomy

	Function	Derivation	Percentage of liver cells
Hepatocytes	Hepatic regeneration Xenobiotic metabolism Protein synthesis and metabolism Lipid synthesis and metabolism APCs—innate immunity	Anterior portion of definitive endoderm	60–80
Stellate/Ito cells	Vitamin A and fat storage Collagen secreting myofibroblasts Scar tissue and wound healing Fibrosis and cirrhosis Contractile cells Regulate vascular resistance APCs—innate immunity	Endoderm or septum transversum mesenchyme	5–15
Liver sinusoidal endothelial cells	Fenestrated endothelial cells Release of nitric oxide (NO) Regulate vascular resistance APCs—innate immunity	Angiogenesis of existing vessels from septum transversum mesenchyme	15–20
Kupffer cells	Macrophages APCs—innate immunity NO, TNF alpha, cytokines Ischemia reperfusion injury Downregulation of APC and T cell activation mediating tolerance	Bone marrow	15
Dendritic cells	APCs—innate immunity	Bone marrow	<1
Lymphocytes			
NK	Nonspecific targeting of tumor and viruses—innate immunity	Bone marrow	5–10
NKT	Target lipid antigens—innate and adaptive immunity	Thymus	
T cells	Cell-mediated adaptive immunity	Thymus	
B cells	Humoral-mediated adaptive immunity	Bone marrow	
Cholangiocyte	Bile duct cells	Hepatoblasts→ intrahepatic biliary tree Ventral endoderm→ extrahepatic biliary tree	<1

Table created from the following publications [8, 10, 12, 92, 93]. *APCs* antigen presenting cells; *NO* nitric oxide

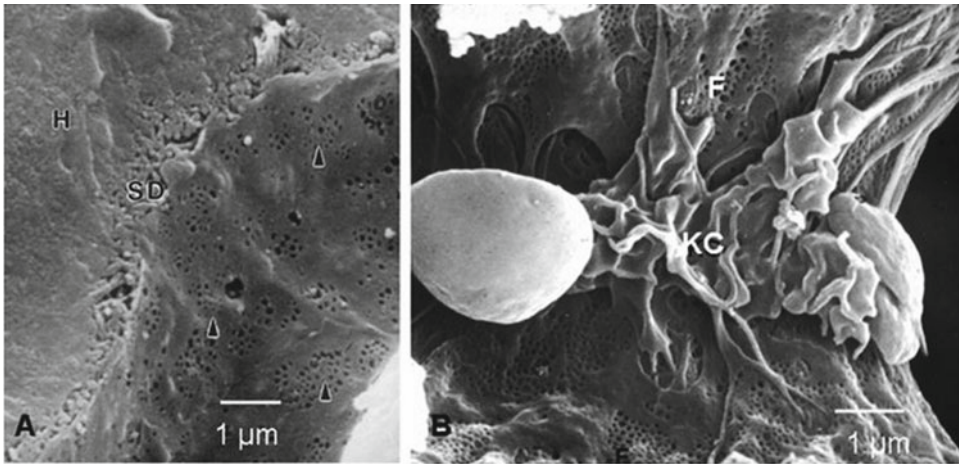
cell macrophage function based on the NO pathway [26] resulting in consistent overlap between ischemic and inflammatory injury to the liver.

Hepatic dendritic cells are antigen presenting cells (APCs) synthesized in the bone marrow that can migrate from the liver to lymphoid tissue, though they are often localized near the central vein [27]. They serve a critical role in antigen presentation and activation of T lymphocytes when encountering an antigen. A subpopulation of den-

dritic cells become resident in the liver and functions in this unique environment as key initiators of innate immunity modulating or in other cases activating acute inflammatory responses [28].

Though small in number relative to other cell populations in the liver, hepatic lymphocytes include natural killer cells, NKT cells, T lymphocytes, and B lymphocytes. Natural killer (NK) cells are part of the innate immune system and are known for their nonspecific targeting of tumor





**Fig. 1.6** Electron micrographs of sinusoidal endothelial cell, hepatic stellate cell, and Kupffer cell. **(a)** Scanning electron micrographs of sinusoid illustrating fenestrae organized in clusters as “sieve” plates (*arrowheads*). *SD* space

of Disse; *H* hepatic parenchymal cell. **(b)** Kupffer cell (*KC*) attached to luminal surface of sinusoidal endothelium by processes that penetrate fenestrae (with kind permission from McCuskey [20], Figure 5 slide A, Figure 6 slide B)

cells and viruses. NKT cells link the innate and adaptive immune systems. They are a subpopulation of lymphocytes with T cell markers and NK cell surface receptors. Conventional T and B lymphocytes are part of the adaptive immune system and play a role in epitope specific cell and antibody mediated destruction of foreign antigens.

### Anatomic Lobules and Metabolic Zones

The microscopic anatomy of the liver can be conceptualized either morphologically as anatomic hepatic lobules or functionally as precise metabolic zones. The hexagonal hepatic lobule is centered around the central vein with the portal triad (hepatic artery, portal vein, and common bile duct) at each corner of the hexagon. These microscopic-ordered aggregations of liver cells are complete and independent units of metabolic capacity that recapitulate on a tiny scale the entire liver. The hepatic artery and portal vein travel together, and transport blood containing oxygen and splanchnic metabolites to the liver, that the functional hepatocytes in the hepatic lobule then process and drain into a common central vein. Bile from each hepatocyte drains into canaculi. These canaculi join to form the ductules that

aggregate to form the inter-lobular bile ducts and eventually the macroscopic segmental ducts. Segmental ducts bring bile to the common bile duct that drains into the gallbladder and duodenum. A more functional histologic classification of the liver defines metabolic zones that form the hepatic acinus [29, 30]. Zone I is known as the periportal zone and is centered around the portal triad, making it oxygen rich given its proximity to the hepatic artery. This periportal zone is the most resilient to hemodynamic stressors, least susceptible to necrosis and the first to regenerate. The cells in zone I also have distinct metabolic capacity and focus on aerobic functions of the liver such as gluconeogenesis and glycogenolysis, generating a fuel source for the body’s extra-hepatic work [30–32]. Zone I also is the site of cholesterol synthesis and beta-oxidation of fatty acids. It is active in the degradation of amino acids in the urea cycle, which is responsible for the majority of ammonia metabolism in the body [30, 31]. While enzymes involved in this periportal zone are expressed throughout the acinus, they are metabolically most active in zone I. Zone II is the intermediate zone between zones I and III. Zone III is the pericentral or perivenous zone and is in close proximity to the central vein. This zone has the lowest oxygen tension ( $\text{PaO}_2$ ), is the most

susceptible to hemodynamic stressors, and the last to regenerate. Zone III is involved in ketogenesis, which generates ketone bodies for the extrahepatic tissues during fasting states. Zone III is also the site of drug detoxification, or phase I and II metabolism [31].

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## Immunological Function of the Liver

### Innate and Adaptive Immunity

The liver is an integral part of both the innate and adaptive immune systems. The innate immune system is the intrinsic host defense system that allows nonspecific targeting of foreign antigens. Of the nonparenchymal cells in the liver, there are four types of APCs that function as immunologic gatekeepers, engulfing bacteria that enter the portal system from the splanchnic circulation, presenting antigenic epitopes to effector T and B lymphocytes, and preventing bacterial entry into the systemic circulation. These four APCs, kupffer cells, dendritic cells, stellate cells, and sinusoidal endothelial cells are all part of the innate immune system.

The innate immune system also includes natural killer (NK) cells and natural killer T (NKT) cells. NK cells play a role in destruction of tumor, bacteria, viruses, and parasites by killing cells that lack “self” major histocompatibility complex I (MHC I) markers [25]. They release granules with perforin that punctures cell membranes and granzymes that lyse internal cellular contents, thereby inducing apoptosis of the target cell. The number of NK cells may comprise up to 90% of total lymphocytes in patients with hepatocellular carcinoma, and diminished function of NK cells has been associated with increased tumor burden [25]. NKT cells link the innate and adaptive immune systems. They are a subpopulation of lymphocytes with NK cell surface receptors and T cell markers [25]. NKT cells target lipid antigens such as glycolipids of mycobacterial cell walls [33].

The adaptive immune system is the acquired host defense system that allows epitope-specific cell and antibody-mediated destruction of foreign

antigens, utilizing memory for fighting subsequent infections. Members of the liver’s adaptive immune system include conventional T and B lymphocytes involved in cell-mediated/cytotoxic and antibody-mediated/humoral immunity respectively. In contrast to the cellular composition in the peripheral circulation, the hepatic circulation has a predominance of nonspecific innate immune cells, which is fitting considering its function as immunologic gatekeeper, regulating the passage of antigens from the splanchnic to portal to systemic circulation [34].

### Oral and Allograft Tolerance

The liver strikes a balance between immunity to infection and tolerance of commensal bacteria and orally consumed antigens, a concept known as oral or systemic tolerance [35]. This immunologic adaptation may underlie the physiologic mechanism of allograft tolerance, the transplantation of organs between the same species of varying genotypes. In 1960 Peter Medawar won the Nobel Prize in Physiology or Medicine for describing the tolerance of skin grafts between dizygotic twin cattle [36, 37]. This observation was thought to be due to the in utero exposure of each twin to erythrocytes of the other [38]. Animal models of porcine allogeneic transplantation illustrate the ability to transplant livers though not kidneys, between unrelated pigs [39]. Pigs, mice, and rats will accept unrelated livers without immunosuppressive therapy and human liver recipients can wean their immunosuppressive regimen over time [28].

This concept of tolerance describes the liver’s ability to downregulate T cell activation or “tolerate” antigens that present no harm. Tolerance is mediated by cytokines such as TNF alpha and interleukin 10 (IL-10). Kupffer cells release these cytokines, which in turn downregulate the activity of antigen presenting dendritic and sinusoidal epithelial cells, thereby decreasing T cell activation [8]. Tolerogenicity is important in liver transplantation and may explain why donor leukocytes can improve hepatic allograft survival [40].

The mechanism underlying enteric tolerance associated with the liver may be mediated by lipopolysaccharide (LPS) endotoxin, a cell wall component of gram-negative bacteria [41]. The portal vein delivers antigens to the liver often in the form of LPS, which complexes with toll-like receptor 4 (TLR 4) and its coreceptors MD 2 and CD14 on APCs. The constitutive exposure of LPS to these APCs is thought to result in a dampening of the immune response or tolerance [41].

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## Hepatic Blood Flow

### Normal Venous Pressure Gradients

The liver receives approximately 1,500 mL of blood per minute or 20–25% of cardiac output, of which three fourths is from the portal vein and one fourth from the hepatic artery [10, 34, 42]. The liver acts as a low resistance reservoir for storage of blood during times of hypervolemia and a source of blood during times of hypovolemia [43, 44]. In a healthy liver blood flows from the portal vein through this low resistance system to the hepatic sinusoids, hepatic veins, vena cava, to the right atrium. The pressure is highest in the portal vein and lowest in the right atrium favoring forward flow to the heart. Directly measuring portal venous pressure is technically challenging and studies have found that in a cirrhotic liver, the wedged hepatic venous pressure (WHVP) is a reliable estimate of portal pressure [45]. In a patient with a healthy liver, however, WHVP is actually a measurement of hepatic sinusoidal pressure. The occlusion of blood flow by a balloon in the hepatic vein transduces the pressure in a static column of fluid from the adjacent vessel [46, 47]. The hepatic venous pressure gradient (HVPG) is the difference between portal vein and hepatic vein pressures, normally 1–5 mmHg and greater than 10–12 mmHg in portal hypertension [47]. This gradient is important in determining the degree of porto-systemic shunting and the likelihood of its complications such as variceal bleeding and hepatic encephalopathy [47].

## Hepatic Arterial Buffer Response

While hepatic outflow may vary, maintaining constant inflow is crucial for optimal drug metabolism and the synthetic functions of the liver. This regulation of hepatic blood flow is achieved by the *hepatic arterial buffer response*. When portal venous flow rises, hepatic arterial flow falls, and when portal venous flow falls, hepatic arterial flow rises thereby maintaining total hepatic inflow constant [42]. This inverse relationship is called the hepatic arterial buffer response since the hepatic artery “buffers” changes in portal venous flow to maintain a steady state [48]. While changes in portal flow affect hepatic arterial tone, the reverse is not true. Hepatic arterial tone does not affect portal venous flow therefore the relationship is not one of reciprocity [48].

In organs such as the brain, vascular tone is determined primarily by oxygen and carbon dioxide tension ( $pO_2$  and  $pCO_2$ ), however, these factors do not seem to affect hepatic arterial tone. Hypoxia and hemodilution do not cause hepatic artery vasodilation rather hepatic artery tone is modulated by portal venous inflow. Experiments that induce hypermetabolic states have found that the liver responds to increased oxygen demand by increasing hepatic oxygen uptake and reducing portal and hepatic venous oxygen content without dilatation of the hepatic artery [49]. This observation is possibly the explanation for necrosis or cell death associated with alcohol intoxication or thyrotoxicosis, in which the liver is unable to respond to increased oxygen demand by hepatic artery vasodilation [49]. Carbon dioxide tension ( $pCO_2$ ), seems to be unaffected [49].

Adenosine, a potent vasodilator, modulates this physiologic response. Adenosine is produced in smooth muscle and tissues in the space of Mall surrounding the hepatic vasculature and is able to diffuse locally to exert its effect [42]. When injected into the portal vein, adenosine causes significant hepatic arterial dilation [50]. Elevations in portal venous flow “wash out” locally produced adenosine, thereby decreasing hepatic arterial flow. Conversely, low portal flow causes

an accumulation of adenosine and hepatic arterial dilatation [50]. This concept is described as the *adenosine washout hypothesis* [50, 51].

### Small for Size Syndrome

This peculiar situation occurs after massive hepatic resection or in transplantation when extremely small livers are used either from liver donors or whole organ donors much smaller than the recipient. In brief, the hepatic mass is not sufficient for the needs of the host. The study of this complication arose in the early work with living donor liver transplantation and raised some fundamental physiologic questions about the limits of adaptation of the liver and the extent of regeneration in the clinical setting [52]. Small for size syndrome is characterized by coagulopathy, cholestasis, hyperbilirubinemia, and ascites that results from transplantation with a donor graft to recipient weight ratio of less than 0.8–1% [53]. The adenosine-mediated regulation of hepatic inflow as described by the hepatic arterial buffer response has implications in the pathogenesis of small for size syndrome. Portal hyperperfusion of the relatively small-sized recipient results in graft dysfunction. Sinusoidal congestion, endothelial damage, obliteration of the space of Disse, and hepatocyte apoptosis are the histologic markers of this syndrome [54]. High portal venous pressures in the first week following living donor liver transplantation in small for size grafts result in increased patient morbidity and mortality [55]. Furthermore, elevation of portal venous pressure is associated with a decrease in hepatic arterial flow, more pronounced in split liver transplantation of left compared to right liver grafts. The lower the graft to recipient volume ratio (left lobe ratio lower than right lobe ratio), the higher the portal vein flow and pressure and therefore the lower the hepatic arterial flow [56]. The hepatic arterial buffer response, as measured by hepatic artery flow in response to portal vein occlusion remains intact in split liver grafts shortly after reperfusion, however, the hepatic arterial flow is much less in split liver grafts compared to whole grafts [56]. Evidence in animal models suggests

that while the hepatic arterial buffer response may be preserved immediately after reperfusion, postoperative normalization of portal venous blood flow is not accompanied by a concomitant elevation or normalization of hepatic arterial flow [57]. An impaired hepatic arterial buffer response characterized by hepatic arterial vasospasm is important in the pathogenesis of small for size syndrome. Clinically, a sustained postoperative reduction in hepatic arterial flow can result in centrilobular tissue necrosis, biliary ischemia, and hepatic artery thrombosis. In the porcine model, intra arterial injection of adenosine can reverse these histopathologic findings and improve graft survival [57].

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## Hepatic Drug Metabolism

### First Pass Metabolism

Drugs administered intravenously have 100% bioavailability because the original form of the drug reaches the systemic circulation unchanged. Drugs ingested orally, however, undergo first pass metabolism. The intestines and liver absorb and process drugs thereby decreasing the effective dose that enters systemic circulation. Drugs with a high bioavailability are minimally metabolized by enzymes of the enterohepatic system. In contrast, drugs with a low bioavailability are extensively metabolized by enterohepatic enzymes. Drugs that undergo extensive first pass metabolism are particularly susceptible to fluctuations in blood levels if their enzymatic metabolism is altered by co-ingestants [58].

### Phase I and II Reactions

The enzymes involved in drug metabolism in the liver are part of the P450 cytochrome family, located in metabolic zone III. Cytochrome P450s catalyze phase I reactions. Phase I reactions are oxidation, reduction, and hydrolysis reactions that increase the polarity of substances for excretion or for further metabolism by phase II enzymes [59]. Phase II enzymes, such as uridine diphosphate



glucuronosyl transferases (UGTs), sulfotransferases, and glutathione-S-transferases, conjugate phase I metabolites to substances such as glucuronate, sulfate, and glutathione [59]. These conjugation reactions transform drugs into hydrophilic substances, thereby increasing their solubility in bile and blood for excretion. Absence or dysfunction of these phase I or II enzymes can result in hyperbilirubinemia and encephalopathy.

In Gilbert's syndrome, there is a mutation in the promoter region of bilirubin-UGT that leads to decreased levels of normally functioning enzyme, reduced conjugation of bilirubin with glucuronide, and an unconjugated hyperbilirubinemia. In Crigler-Najjar syndrome, there is a mutation in the coding region of bilirubin-UGT that results in absent or defective bilirubin-UGT, unconjugated hyperbilirubinemia, and in some cases kernicterus [60].

Similarly, depletion of molecules involved in these conjugation reactions can result in liver injury. Acetaminophen toxicity for example occurs because of the relative depletion of glutathione and the accumulation of *N*-acetyl-*p*-benzoquinone-imine (NAPQI), the unconjugated toxic acetaminophen byproduct. The accumulation of NAPQI leads to zone III or centrilobular necrosis. *N*-acetylcysteine, a precursor to glutathione and a free radical scavenger, may be of benefit in the treatment of acetaminophen toxicity [61]. Some studies have also suggested its use in decreasing ischemia reperfusion injury, primary graft dysfunction, and acute kidney injury in liver transplantation [62, 63]. These findings, however, are controversial and not all studies have proven definitive benefit of *N*-acetylcysteine in the perioperative transplant setting [64].

### **Substrates, Inducers, Inhibitors of P450 System: Implications for Toxicity and Therapeutic Failure**

Many commonly used drugs in the clinical setting interact with P450 enzyme substrates either as inhibitors or inducers. Inhibitors slow down P450 enzyme activity, thereby increasing the substrate bioavailability. This can result in drug

toxicity, which has profound implications for medications with a narrow therapeutic index, such as the P450 substrate warfarin. Initiating treatment with inhibitors such as azoles, macrolides, beta blockers, calcium channel blockers, and proton pump inhibitors may lead to a supratherapeutic INR and clinically significant bleeding. Conversely, initiating treatment with a P450 inducer such as phenobarbital, phenytoin, rifampin, or dexamethasone may cause therapeutic failure.

Substrate competition can also lead to therapeutic failure as demonstrated by the interaction between clopidogrel and proton pump inhibitors. Recent studies have suggested that the use of proton pump inhibitors may decrease the efficacy of clopidogrel resulting in an increased incidence of hospitalization for recurrent myocardial infarction or percutaneous coronary intervention (PCI) [65, 66]. Cytochrome 2C19 (CYP 2C19) is the enzyme that activates the prodrug of clopidogrel and the enzyme that metabolizes proton pump inhibitors [67]. Competition for this enzyme causes a decreased activation of clopidogrel and an increased risk of acute coronary syndrome. There are over 50 P450 enzymes and numerous drug interactions. A knowledge of clinically relevant substrates, inducers, and inhibitors is useful in predicting these types of enzyme interactions [68–71].

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## **Hepatic Glucose, Amino Acid, and Lipid Metabolism**

### **Glucose Homeostasis**

The liver has the ability to produce glucose during fasting states to preserve euglycemia. It is the main site of gluconeogenesis, the synthesis of glucose from pyruvate, lactate, glycerol, and amino acids. The liver also stores glucose in the form of glycogen which can be converted back to glucose during fasting states in the glycogenolysis pathway. Epinephrine stimulates glycogenolysis during states of stress. Both gluconeogenesis and glycogenolysis take part in the periportal metabolic zone I of the liver, the zone closest to the portal triad.

During nonfasting states the liver is able to store glucose by glycogenesis or convert glucose to pyruvic acid and ATP by glycolysis. These processes take place in metabolic zone III, or the pericentral zone. This zonal heterogeneity or differential expression of metabolic enzymes prioritizes crucial metabolic functions that provide energy or glucose to the body during fasting states by placing them in close proximity to the oxygen and nutrient rich environment of the portal triad [30]. The minute to minute regulation of glucose homeostasis is clinically relevant in that hypoglycemia is the most dramatic manifestation of liver failure and generally implies a terminal state of hepatic failure.

### **Protein Metabolism and Hepatic Encephalopathy**

When the body has sufficient protein stores, the liver transforms additional amino acids to ammonia in the urea cycle. Ammonia detoxification involves the degradation of proteins to their amino acid components, the breakdown of amino acids to alpha ketoacids and ammonia, and the generation of urea. This process occurs in the oxygen rich periportal zone I. The enzyme glutamine synthetase located in the perivenous zone III, then transforms ammonia and glutamate to glutamine. Liver dysfunction of any etiology results in hyperammonemia from both a decreased ability to produce urea and glutamine, and diminished first pass metabolism from portosystemic shunts [72]. Ammonia is neurotoxic, as is the excitatory neurotransmitter glutamate when present in excess [72]. Ammonia diffuses into brain astrocytes, causing edema and hepatic encephalopathy. Cerebral astrocytes can convert some ammonia to glutamine but supraphysiologic levels of glutamine result in an osmotic intracellular gradient and subsequent edema, elevated intracranial pressure, and at its worst herniation [72]. This is the basis of the ammonia-glutamine hypothesis of intracranial hypertension in fulminant hepatic failure.

There are two types of cerebral edema: cytotoxic edema that results from cellular swelling

due to an increase in osmotic load and intracellular water absorption, and vasogenic edema from the increased permeability of solutes and solvents through a disrupted blood brain barrier [73]. Cerebral edema due to fulminant hepatic failure is predominantly cytotoxic with a preserved blood brain barrier and responds to osmotic diuretics such as mannitol and hypertonic saline [73, 74]. Intracranial hypertension is less common in chronic liver failure due to a compensatory intracellular increase in solute load.

### **Lipid Metabolism and Nonalcoholic Fatty Liver Disease**

The liver is the principal site of lipid metabolism, both in absorption of dietary fats and their de novo synthesis. Dietary fats are emulsified by bile salts and absorbed in the form of micelles by the intestine and delivered to the liver via enterohepatic circulation. Fatty acids can be hydrolyzed by beta-oxidation to generate energy or ATP for the body's extrahepatic metabolism. During fasting states, starvation, or diabetic keto-acidosis (DKA) when glucose is not available to the body, the liver can generate ketone bodies (acetoacetic acid, beta hydroxybutyric acid, and acetone) from fatty acids that can be used by organs such as the brain [75]. Conversely, in nonalcoholic fatty liver disease (NAFLD) when hepatic lipid content or steatosis constitutes 5% of liver weight, there is an increase in triglyceride synthesis and defective insulin-mediated inhibition of lipolysis [76, 77]. Metabolic syndrome, defined as visceral obesity associated with hypertension, dyslipidemia, and hyperglycemia may also be associated with NAFLD by a similarly impaired insulin-mediated inhibition of lipolysis [78, 79]. This metabolic derangement of lipid metabolism has striking clinical implications since NAFLD is the most prevalent liver disease and can progress to nonalcoholic steatohepatitis (NASH) [77]. Close to half of patients with NASH develop fibrosis and one sixth develop cirrhosis, which may eventually lead to liver failure requiring transplantation [80].

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## Liver Coagulation and Fibrinolysis

The liver is a major organ involved in hemostasis since it is the primary synthetic site of procoagulants, anticoagulants, fibrinolytics, and antifibrinolytics [81]. While extrahepatic sites such as the endothelium contribute to synthesis of some coagulation factors such as factor VIII and von Willebrand factor (vWF), the liver remains the principal synthetic site of coagulation cascade components. Primary and secondary hemostasis requires the formation of a platelet plug and fibrin clot, triggered by tissue trauma or endothelial damage [82]. While platelets are made in the bone marrow, they are often sequestered in the spleen of patients with portal hypertension and splenomegaly [83]. This platelet sequestration contributes to thrombocytopenia and bleeding in those with end stage liver disease. The liver synthesizes fibrinogen (factor I), prothrombin (factor II), factor V, and factors VII–XIII. It also synthesizes anticoagulants such as antithrombin III, protein C, protein S, selected fibrinolytics such as plasminogen, and antifibrinolytics such as alpha 2-antiplasmin and thrombin activatable fibrinolysis inhibitor (TAFI) [81]. The balance between procoagulants and anticoagulants in liver failure determines the risk of bleeding or thrombosis. In end stage liver disease, the balance may be tipped towards anticoagulant and fibrinolytic factors predisposing patients to bleeding, though cases of venous thrombosis can occur secondary to venous stasis or hepatocellular carcinoma [84]. Traditional laboratory makers of coagulopathy such as prothrombin time (PT) and partial thromboplastin time (PTT) may not accurately portray the balance between procoagulant and anticoagulant factors in liver disease. PT and PTT reflect the degree to which pro-coagulants factors are depressed but not whether anticoagulants such as protein C can offset this deficiency since reagents used in these laboratory assays do not contain enough thrombomodulin to activate protein C [85].

Hyperfibrinolysis has traditionally been associated with chronic liver disease as demonstrated by elevated levels of tissue plasminogen activator (tPA) and plasmin, both involved in the degradation

of fibrin clots, as well as decreased levels of alpha 2 plasminogen inhibitor and thrombin activatable fibrinolysis inhibitor (TAFI) [82]. Whether or not these markers of fibrinolysis correlate with a clinical bleeding risk remains unclear [86, 87].

Other factors that can contribute to clinically significant bleeding include renal failure with platelet dysfunction, portal hypertension, endotoxemia with fibrinolysis, and disseminated intravascular coagulation [86, 87]. Patients with isolated hepatic coagulopathy usually have normal to elevated levels of factor VIII and vWF in contrast to patients with DIC, though both conditions may coexist [82]. Endotoxemia is associated with both fibrinolysis and a procoagulant state. Sepsis-induced hypercoagulability occurs by the inhibition of activated protein C and S, as well as by increased tissue factor expression [88]. This is the basis of therapeutic use of activated protein C in sepsis [89].

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## Hepatic Endocrine Function

The liver acts as an endocrine organ, producing hormones such as insulin like growth factor (IGF-1), thrombopoietin, angiotensinogen, and steroid hormones. The liver produces 75% of IGF-1, which is a peptide hormone, mediating the effects of human growth hormone (GH). Growth hormone activates the release of IGF-1, which stimulates tissue growth. Levels rise during puberty, are abnormally high in conditions such as acromegaly and may be low in patients with short stature.

Thrombopoietin is a peptide hormone produced in the liver that stimulates megakaryocytes and platelet production. Low levels of thrombopoietin in liver failure may contribute to thrombocytopenia since these levels as well as platelet counts are restored with orthotopic liver transplantation [90, 91].

Angiotensinogen, the precursor of angiotensin, is produced in the liver as well. This precursor peptide hormone is activated by renin in the renin-angiotensin-aldosterone pathway, the target of antihypertensives such as ACE inhibitors, angiotensin receptor blockers (ARBs), and

diuretics such as spironolactone, which antagonizes aldosterone, and is used to manage ascites in liver disease.

Lastly, the liver is the site of cholesterol synthesis therefore crucial in the genesis of endogenous steroid hormones such as cortisol, aldosterone, and testosterone. While these hormones are synthesized in the adrenal gland, their precursors are hepatic in origin.

## Conclusion

This chapter is broad in its scope though we have attempted to provide relevant anatomic and functional information to enhance the management of patients with liver disease undergoing major surgical and anesthetic challenges. This chapter is not meant as an exhaustive review of liver disorders, portal hypertension, and functional hepatic impairment associated with extreme liver resections or the limits of transplantation in the ability of the liver to compensate under stress. However it provides the basis for understanding specific disease conditions and therapies presented in detail later in this volume.

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## Introduction

Acute liver failure (ALF) is an unpredictable and rapidly progressive, life-threatening multisystem condition that ensues when an insult causes diffuse necrosis of liver parenchyma disrupting hepatocyte function in patients who have no pre-existing liver injury. The subsequent development of encephalopathy and coagulopathy within days or weeks represents the key features of ALF, but critically often culminates with multi-organ failure (MOF), which impacts significantly on mortality. Timely referral to specialist centres with expertise in the management of ALF and liver transplantation is crucial.

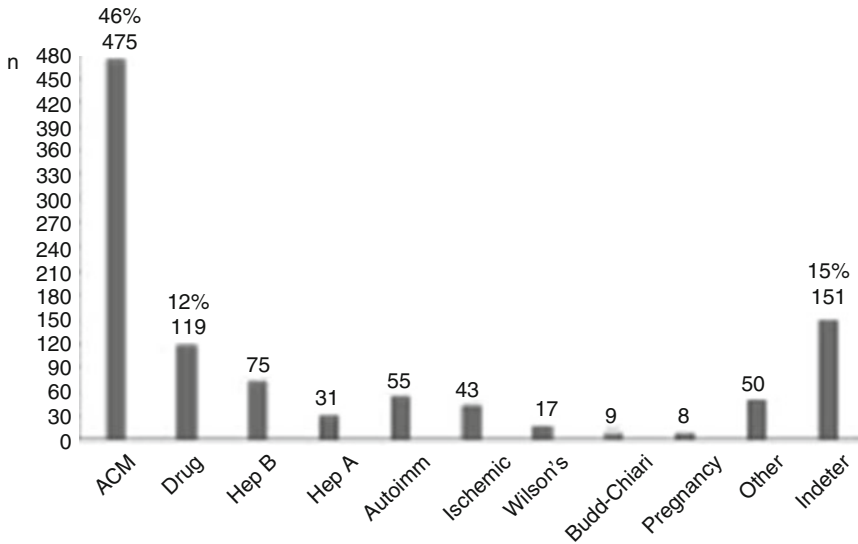
ALF is rare with around 2,800 and 400 cases of ALF per year in the United States (US) and the United Kingdom (UK), respectively [1]. There are multiple etiologies of ALF that vary in worldwide geographical location, clinical presentation, time course, and prognosis. In the developing world the leading cause of ALF are the viral hepatitises, particularly hepatitis B. In the US and the UK, viral hepatitises are no longer the most common cause of ALF; in recent years, paracetamol (acetaminophen) overdose, idiosyncratic drug reactions, and sero-negative hepatitis have

emerged as the leading causes of ALF (Fig. 2.1) [1, 2].

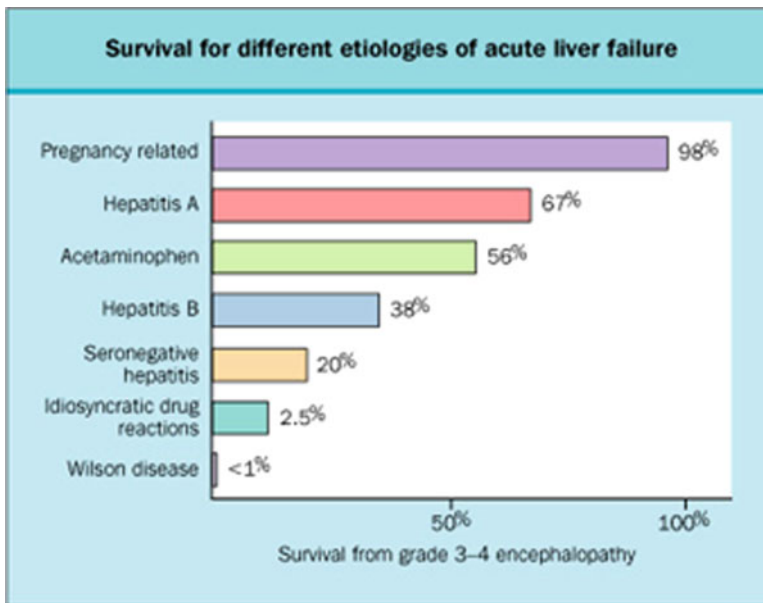
The prognosis of ALF depends on age, etiology, and the time course over which the disease evolves. In the most severe cases the mortality of ALF without transplantation ranges from 10 to 90%; in recent years, survival has improved to around 40–90% [3]. This is related to improved critical care management, better prognostic assessment, and the timely prioritisation of patients for liver transplantation (LT). The management of ALF is focused on the support of all organ systems and the prevention and treatment of complications, particularly sepsis. Liver necrosis acts as a focus of inflammation, driving vasoplegia and leading to cardiovascular collapse, which exacerbates dysfunction of other vital organs, particularly the kidney and brain. The identification and treatment of the cause of the underlying liver injury should be the primary goal, with a concurrent focus on the optimization of the circulation to promote hepatocellular regeneration and to prevent further insult due to ischemic injury. However, despite such endeavours timely recognition that hepatic regeneration will ultimately not be sufficient is crucial. Liver transplantation with removal of the necrotic liver mass offers the best chance of survival. The decision to prioritise for transplantation requires a multidisciplinary team approach incorporating specialist liver transplant surgeons, hepatologist, and intensivists who can utilize established prognostic criteria along with the daily assessment of the levels of

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**Fig. 2.1** Overall comparison of etiologies observed among 1,033 patients with acute liver failure (ALF) in the ALD study Group registry, 1990–2004. A preponderance of acetaminophen cases is observed approaching 50%



**Fig. 2.2** Survival for different etiologies of ALD

organ support to best determine which patients are likely to benefit from being listed for transplant with high priority and indeed proceeding to OLT if levels of organ support permit (Fig. 2.2) [4].

The availability of donor organs is under continued pressure in the UK and worldwide. Patients

with ALF must fulfil a strict set of selection criteria based on published risk factors for prioritisation before being established on the national super-urgent transplantation waiting list (Table 2.1). These patients are then stratified by blood group and time while on the super-urgent waiting list. In most cases a donor organ should



**Table 2.1** Classifications of ALF (time from jaundice to onset of encephalopathy)

Definition	Time (days)	Most common etiologies	Definition	Time (weeks)
Hyperacute	<7 days	POD, hepatitis A and B	Fulminant	<2
Acute	8–28 days	Hepatitis A, B, E, idiosyncratic drug reactions		
Subacute	29 days to 8 weeks	Idiosyncratic drug reactions, sero-negative hepatitis	Subfulminant	>2

be available within 48–72 h. Occasionally the option of an ABO incompatible donor organ has to be considered in light of the unavailability of an ABO compatible organ weighed against the projected deterioration of the clinical condition. It is widely accepted that the currently available selection criteria are imperfect with up to 10–20% of patients surviving without a transplant. The option of an auxiliary transplant graft is sometimes considered as it allows native regeneration and withdrawal of immunosuppression, but due to the increased risk of early postoperative complications it necessitates careful scrutiny of appropriate potential candidates.

### Classification of ALF

The classifications for ALF have evolved since the initial definition by Trey and Davidson in 1970 in an attempt to reflect the impact that both etiology and the existence of chronic liver disease have on prognosis. The two most commonly used definitions concentrate on the time period from jaundice to the onset of encephalopathy [1]. This classification is important, because the hyperacute forms of ALF including acetaminophen overdose and Hepatitis A are associated with mortality due to cerebral edema and kidney injury. However survival without transplantation for this group is superior to the more indolent subacute causes, including sero-negative and idiosyncratic drug reactions that are not as frequently complicated by the cerebral and renal insults, but carry a higher mortality burden compared with hyperacute causes (Table 2.1).

### Etiologies of ALF

#### Paracetamol (Acetaminophen) Overdose

Paracetamol overdose (POD) in the UK had been increasing steadily likely due to its easy availability [5]. In 1998 the Medicine Control Agency in the UK sought to limit the availability of paracetamol. Legislation was changed in line with World Health Organisation recommendations and data from other countries with similar restrictive policies that had lower rates of paracetamol-induced hepatotoxicity. Suicidal or parasuicidal actions are usually impulsive acts in reaction to crises; therefore, it was postulated that limiting supply would result in reduced availability of paracetamol, thus reducing the quantity ingested and lowering rates of hepatotoxicity. The general sale of paracetamol was restricted to 16 500 mg tablets, a total of 8 g per packet. Studies have sought to demonstrate whether these restrictions have indeed been associated with a reduction in admissions to hospital and liver units, and in the need for liver transplantation. However, both short follow up periods and a diverse range of outcomes evaluated have hampered these studies in quantifying any change with certainty. Despite this, there is a trend towards an overall reduction of paracetamol-related hepatotoxicity and hospital admissions following the change in legislation [6].

In the UK POD comprises up to 50% of all poisoning admissions and around 10% in the US [7]. Due to a combination of the small doses absorbed and the efficacy of early antidote therapy, only

0.6% of these cases result in hepatotoxicity in the UK. Studies assessing the rate of deliberate vs. accidental POD display geographic variation. In Europe, studies have reported around 86% of POD cases were deliberate and 14% were accidental [8], while US poisons centre data have reported rates of 35% and 65%, respectively [9]. Additionally, paracetamol medications combined with narcotics have been shown to pose a potential for unintentional hepatotoxicity when addiction to the narcotic within such combined analgesics leads to a gradual increase of the ingested dose [2]. There has been the suggestion that this is a significant reason for the discrepancy between the US and the UK with regard to deliberate and unintentional overdose. The assessment of the risk of developing ALF from POD, whether accidental or deliberate, is closely related to the total dose ingested, as well as the time from ingestion to presentation and treatment with *N*-acetylcysteine (NAC).

The pathophysiological reasons behind this relate to the length of time exposed to the active unstable paracetamol metabolite, *N*-acetyl *p*-benzoquinone imine (NAPQI). NAPQI depletes hepatic glutathione levels, with ensuing hepatocellular damage, unless the antidote, glutathione precursor NAC or methionine is given in a timely fashion. NAC acts to augment the glutathione reserves in the body, which directly bind to toxic metabolites and protect hepatocytes in the liver from NAPQI toxicity. When administered within 12 h of an unstaggered ingestion of paracetamol, NAC can prevent hepatocellular damage.

A clear history regarding the timing and quantity of paracetamol ingested is important, as is establishing whether the ingestion was staggered. However, the circumstances that surround any para-suicidal event can make this information difficult to establish, especially if patients have ingested opiate-based medication combined with paracetamol or are intoxicated with alcohol. Additionally, an assessment of potentiating factors that lower hepatic glutathione levels or increase cytochrome P450 enzyme activity and increase hepatotoxicity should be undertaken. These factors include anorexia nervosa, malnutrition, chronic alcohol consumption, and enzyme inducing drugs such as phenytoin and carbamazepine.

In an unstaggered overdose presenting within 24 h a paracetamol level should be measured and applied to one of the nomograms, based on the Prescott nomogram. A paracetamol level of more than 150 mg/kg is generally considered to be hepatotoxic, though strong evidence ratifying this is lacking. In a staggered overdose the paracetamol level cannot be interpreted and one must assess the risk of hepatotoxicity based on dose alone. If any doubt regarding timing exists or there has been a delay in presentation treatment should be commenced until it becomes clear that hepatotoxicity is unlikely. Patients presenting within 24 h of ingestion without signs of hepatotoxicity can be managed on the wards, while those with features of paracetamol-induced hepatotoxicity should be managed in a critical care environment.

## Viral Hepatitis

All hepatitises except for Hepatitis C have been implicated in cases of ALF [1]. Viral hepatitis A and B are the most common causes of ALF worldwide including France and Japan; Hepatitis E is predominant in India.

The risk of ALF is lowest with Hepatitis A at less than 0.35%, but this risk increases with age at the time of exposure. In the western world, it appears that native immunity to Hepatitis A is decreasing. In the US the incidence of ALF due to Hepatitis A is around 3.1% with around 0.12% of all cases listed for liver transplantation. In the developed world the incidence of Hepatitis A has been decreasing since 1995 and this is thought to be related to high risk patients being vaccinated, improved sanitation, and improved food preparation techniques [10]. The treatment is largely supportive.

Hepatitis B infection is the cause of ALF in around 1% of all cases with over 50% associated with hepatitis D co-infection, mortality for those developing ALF ranges from 70 to 80% [11]. Hepatitis B has eight genotypes A–H and all have been associated with different clinical presentations. In Japan, Hepatitis B genotype B predominates and one study has shown increased efficacy

with lamivudine therapy and improved the survival of patients treated early in the course of the disease [11].

Hepatitis E is common in Asia and Africa with the risk of ALF greatest in pregnancy at greater than 20%, particularly during the third trimester. In the general population, Hepatitis E carries a low mortality of 0.5–4%, but this figure approaches >75% in developing countries like Bangladesh especially during the second and third trimester. It is transmitted by the fecal-oral route, often through contaminated water supplies. Consequently, it has been the cause of epidemics in Asia, China, and Eastern Europe especially after heavy rainfall. The first documented of these epidemics occurred in New Delhi, India in 1955 and affected 29,000 people [12].

Viruses including cytomegalovirus (CMV), Epstein barr virus, herpes viruses type 1, 2 and 6, and varicella zoster have all been implicated in case reports of ALF, frequently in patients with profound immunocompromised states. Falciparum malaria has also been reported as a cause of ALF, primarily in India. The mortality associated with atypical viral hepatitis is around 76% and for falciparum malaria 24% [1]. Antiviral therapies that have been shown to be of benefit in some cases of ALF include, as mentioned, lamivudine for hepatitis B, valganciclovir and acyclovir for herpes 1, 2, and CMV disease.

## Idiosyncratic Drug Reactions

The administration of drugs directly affects the liver because it is the primary site of metabolism and elimination. This exposes the liver to the potential toxicity of many drugs. In the US, hepatotoxicity is the main cause for halting drug development and withdrawal from the market. Drug-induced liver injury (DILI) including cases of acetaminophen toxicity, is the leading cause of ALF and indication for liver transplantation. The remainder of DILI cases are idiosyncratic reaction, which occur in around 1 in 10,000 of exposed patients. However, more than 1,000 drugs and herbal remedies have been implicated in DILI and altogether comprise 10% of ALF

cases [13]. Idiosyncratic DILI is a complex phenomenon, which appears to be integrally related to how cell mitochondria balance cellular injury and regeneration. Idiosyncrasy defines the unpredictable and non-dose dependant fashion with which liver injury can occur. There are non-allergic and allergic idiosyncratic DILI, the latter characterised by fever, skin reactions, eosinophilia with the formation of autoantibodies, one such example is drug-related eosinophilic syndrome (DRESS). Several risk factors for DILI have been identified and include age, female gender, concomitant diseases, and drugs. There are DILI algorithms and clinical scales that can be used to improve the consistency, accuracy of causality of adverse drug reactions [14].

Genetic polymorphisms have been associated with increased risk of DILI, for example, cytokine polymorphism and diclofenac hepatotoxicity. The same applies to genetic variations involving mitochondrial function with a genetic deficiency of mitochondrial long-chain 3-hydroxyacyl-CoA dehydrogenase associated with acute fatty liver of pregnancy, presumably related to the increased levels of female sex hormones. DILI tends to be diagnosed primarily by increased levels of alanine transferase (ALT) and gamma-glutamyl transferase (GGT). Currently metabolomic studies are being conducted to identify biomarkers of DILI that will detect injury prior to elevations in ALT.

## Malignancy

There are numerous case reports in the literature that have documented a wide range of solid and hematological tumours as a rare cause of ALF. A literature review in 2005 cited 34 cases of primary and metastatic neoplastic infiltration of the liver resulting in ALF [15]. The pathophysiology of ALF in neoplastic infiltration is multifactorial. Parenchymal ischemia and infarction can be caused by diffuse tumour cell infiltration or vascular occlusion from tumour thrombi. It has also been postulated that diffuse tumour cell infiltration renders the remaining liver parenchyma highly susceptible to ischemic injury. A case series of three patients with metastatic disease demonstrated

biopsy-proven hepatic ischemia, which was in the absence of any discernable episode of systemic hypotension [15, 16]. Additionally, cytokine-mediated liver injury has been implicated in lymphomatous infiltration [17]. Clinical suspicion and features suggestive of malignancy such as enlarged lymph nodes on physical examination along with computer tomography (CT) findings suggestive of an infiltrative process should prompt an attempt to obtain a biopsy for a definitive histological diagnosis. Furthermore, radiological imaging including both ultrasonography and triple phase computer tomography should not be relied on due to the poor sensitivity for metastatic and lymphomatous infiltration of the liver. The only serum markers of tumour infiltration are alkaline phosphatase (ALP) and aspartate and alanine aminotransferase (AST), though elevation of these is usually below levels seen in ischemic hepatitis. Both appear to have greater sensitivity in the presence of hyperbilirubinemia. However, jaundice does not always manifest in the setting of tumour infiltration with cases of over 90% liver infiltration without jaundice in the literature. A trans-jugular liver, bone marrow aspiration, and trephine or lymph node biopsy can all prove to be invaluable tools for establishing a diagnosis. The diagnosis of malignancy is a clear contraindication for liver transplantation and establishing the diagnosis therefore crucial.

## Vascular

ALF following vascular insults are uncommon; however, causes include ischemic hepatitis, which is often associated with low cardiac output states with variable degrees of left and right ventricular cardiac dysfunction. The veno-occlusive disorders, such as Budd-Chiari (BC) are also uncommon with the incidence of BC quoted at 1 in 2.5 million [18]. It is characterised by hepatic venous outflow obstruction and presents with ALF in around 20% of cases. In the western world occlusion of the hepatic veins is commonly due to thrombosis whereas in Asia a membranous web is the most frequent cause. Both inherited

and acquired procoagulant conditions have been implicated in Budd-Chiari and often two conditions coexist. Veno-occlusive disorders have been associated with inherited conditions such as Factor V Leiden, Protein C, S and antithrombin deficiency and acquired conditions including paroxysmal nocturnal hemoglobinuria and anti-phospholipid syndrome. The recently discovered Janus Kinase 2 mutation (JAK2) has also been detected in around 40–59% of cases with BC [19]. Myeloproliferative disorders also need to be ruled out as a cause with an examination of the bone marrow function using a trephine biopsy and aspiration as these disorders are most commonly associated with both BC and portal vein thrombosis [18].

## Metabolic

ALF secondary to inherited and acquired metabolic disorders are uncommon, though remain important and include acute fatty liver of pregnancy, fructose intolerance, galactosemia, lecithin-cholesterol acyltransferase deficiency, Rye's syndrome, tyrosinemia, and Wilson's disease (WD).

WD is a rare autosomal recessive condition caused by a mutation to the WD gene ATP7B, which encodes a copper transporting P-type ATPase leading to insufficient copper excretion into bile with subsequent copper accumulation in brain, liver, and cornea. The incidence of WD is around 1 in 30,000 and can present acutely, usually in pediatric or young female patients, or chronically in adult patients sometimes into their eighth decade of life. ALF in WD is unique in so far as there is usually some degree of preexisting liver disease at the time when ALF ensues. WD is diagnosed by measuring indices of copper metabolism, although in ALF these investigations can be misleadingly normal. Serum copper and caeruloplasmin, as an acute phase protein, can both be normal or elevated in other causes of ALF. Elevated levels of urinary copper are a good indicator of WD, but the high incidence of anuric acute kidney injury in ALF can extinguish the availability of this diagnostic tool. Ophthalmic

interrogation of corneas can be useful to detect the presence of Kayser-Fleischer rings, which together with evidence of liver disease and copper metabolism abnormalities strongly support the case for the diagnosis. Additionally, Coomb's negative hemolytic anemia and low serum cholinesterase levels can be a feature of WD [20]. The ALP/bilirubin and aspartate AST/bilirubin ratios are often significantly lower in fulminant Wilson's disease than in other categories of fulminant liver failure, but distinction between diagnostic categories on this basis is not possible [21].

## Miscellaneous

Other rare but also important causes of ALF include HELLP (Hemolysis, elevated liver enzymes, and low platelets) syndrome of pregnancy. The amphetamine derivative, 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") has caused a number of cases of ALF requiring OLT. Toxins of mushrooms such as *Amanita phalloides* or foodborne illnesses by *Bacillus cereus* are also causes of ALF.

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## Clinical Features and Management

### General

The diagnosis of the underlying insult is crucial in determining potential therapies that could halt the injurious process and reverse liver failure. Investigations should include those for: hepatitis and atypical viral serology; autoantibodies, such as antinuclear, anti smooth muscle, anti-liver kidney microsomal, anti-soluble liver antigen, anti-mitochondrial antibodies; an illicit drugs screen, paracetamol levels; and urine and serum copper. A negative paracetamol level does not rule out paracetamol as a cause of ALF. Additionally, ultrasonography of the liver and its vasculature is important. Where possible, if the history and investigations do not suggest a viral or drug-induced insult, axial imaging with computer tomography is advisable. Patient outcomes are largely determined by the severity of the underlying

ing liver insult and the development of organ failure and episodes of sepsis have a strong impact on mortality. Early recognition and treatment of sepsis and the prevention and support of organ dysfunction is therefore key to increasing the potential for hepatic regeneration. Finally, a timely decision regarding super-urgent liver transplantation is required when it becomes sufficiently clear that hepatic regeneration will not occur. This decision carries particular importance given that the median time from listing to transplantation is around 48 h. Consequently, 24% of patients listed will fail to proceed to transplantation with 92% of these patients dying [22]. Those that are not transplanted have a median time from listing to death of 2 days (2–4), with several pre-transplant factors associated with poor outcomes such as age <45 and escalating vasopressor requirement [22]. There are several other factors that should prompt discussion regarding the suitability to proceed to transplantation. These include fixed dilated pupils for greater than 2 h, necrotizing pancreatitis, severe adult respiratory distress syndrome (ARDS), moderate to severe pulmonary hypertension, culture proven bacterial or fungal sepsis requiring more than 24 h of antimicrobial therapy before transplantation. All these conditions need to be evaluated in relation to age and the degree of associated organ failures.

The complex nature and progression of ALF requires the involvement of wide array of expertise to form a cohesive multidisciplinary team. Such teams include critical care nurses, physiotherapists, pharmacists, transplant surgeons, and liver intensivists.

### Cardiovascular

The circulatory hallmarks of established ALF mirror the hemodynamic changes of sepsis with an elevated cardiac output and vasoplegia. The main vasoactive mediator, nitric oxide, causes regional vasodilatation primarily in the splanchnic bed, but it also acts globally resulting in a cumulative reduction in oxygen consumption, despite demonstrable increases in oxygen delivery,

as indicated by higher central and mixed venous saturations. The management goals for the circulation in established ALF should intuitively, follow the initial resuscitation recommendations outlined in the Surviving Sepsis Campaign (SSC), in view of the similarities and despite formal validation. The early use of hemodynamic monitoring is recommended as it often forms a vital aspect of management providing important additional clinical indices about central circulating volumes and cardiac output. Furthermore, a cardiac output in the normal range or particularly elevated central venous pressures should prompt further interrogation of myocardial function with echocardiography to evaluate left and right ventricular filling and function.

The SSC recommends commencing resuscitation in any patient who is hypotensive, MAP <70 mmHg, or with an elevated serum lactate >4 mmol/L with due consideration that management is conducted in a critical care environment. There are problems associated with some the SSC parameters as mentioned ScvO<sub>2</sub> are often significantly elevated reflecting the hyperdynamic circulation and microvascular shunting. The SSC threshold for lactate is 4 mmol/L; in ALF this is unlikely to reflect sole circulatory disarray, but it should be assumed to be so until adequate volume resuscitation has been implemented. Hyperlactemia broadly reflects liver, circulatory and cellular dysfunction, although the liver does have large reserves for lactate metabolism. The normal lactate levels encountered after hepatectomy with more than 50% of the liver resected supports this [23]. However, high circulating blood lactate levels are frequently encountered in ALF where inadequate fluid resuscitation has led to circulatory and cellular metabolism dysfunction. Overall hyperlactemia and the speed of resolution acts as an important predictor of outcome in both critical illness and ALF [24]. It is now recognised as an important prognostic variable. Consequently, elevated serum lactate has been incorporated into the Kings College Criteria (KCC) adding statistical strength to the original O'Grady criteria [25], when persistently elevated >3.0 mmol/L despite aggressive fluid resuscitation [26].

In ALF relative adrenal insufficiency (RAI)—defined as a total cortisol (TC) level less than 248 nmol/L after corticotropin administration—has a reported prevalence of 62% and steroid replacement therapy is associated with reductions in vasopressor requirements, albeit without any mortality benefit [27, 28]. The diagnosis and treatment of RAI in critical illness was first encountered in sepsis with the demonstration that low dose hydrocortisone could accelerate the reversal of shock, despite a lack of significant mortality benefit [29]. The high prevalence of RAI in ALF can be explained by factors that affect cortisol metabolism. Firstly, both ALF and sepsis often coexist and ALF represents an additional stress that can lead to RAI. Secondly, patients with ALF have low circulating cortisol levels for several reasons: the effects of low levels of HDL cholesterol that is central to cortisol production, increased conversion of cortisol to the inactive form cortisone and the negative effect of cytokines such as tumour necrosis factor alpha (TNF- $\alpha$ ) on hypothalamic function all contribute to the low circulating TC levels [30].

The diagnosis of RAI is often established by performing the short synacthen test; however, during critical illness and ALF this is fraught with problems of interpretation as highlighted by the CORTICUS study [29]. It is largely related to the fall in both albumin and cortisol-binding globulin (CBG), which leads to increases in free cortisol levels (FC), despite low measured TC level implying RAI. Therefore, to improve interpretation various alternative measures or calculations have been explored to better assess FC levels. The use of salivary cortisol has been shown to correlate well with FC, although in ventilated patients this may be difficult to obtain. Alternatively, the free cortisol index (see equation below) can be calculated by measuring both CBG and TC levels, which has also been shown to correlate well with FC levels [31]. These alternative measures of FC may prove to be better methods of assessing RAI rather than relying on TC levels alone. However, hydrocortisone therapy is frequently initiated empirically after a short synacthen test has been performed to impact on escalating vasopressor levels. The results of



the short synacthen test to limit the duration of hydrocortisone therapy and potential adverse effects of steroids.

The free cortisol index:  $(\text{Unbound cortisol } (\mu\text{mol/L}) = (0.0167 + 0.182 (\text{CBG} - \text{TC}))^2 + (0.0122 \times \text{TC})^{0.5} - (0.0167 + 0.182 (\text{CBG} - \text{TC}))$  [32].

## Respiratory

The development of hepatic encephalopathy in ALF is one of the primary indications for intubation and ventilation to establish a protected airway. A significant proportion of patients will also develop a spectrum of respiratory complications. Acute lung injury (ALI) and ARDS complicate up to 30% of paracetamol-induced ALF cases [33]. It affects primarily those with significant vasopressor requirements and evidence of intracranial hypertension (ICH). The mechanisms involved of ALI in ALF include the directly toxic effects of acetaminophen and the pathophysiological overlap of changes involving vasoactive mediators that affect not only the brain and circulation, but also the lung with increased vascular permeability and capillary leak. This is further exacerbated by the additional fluid accumulation within extravascular compartments, due to large cumulative volumes of fluid administered to support the vasoplegic circulation. Additionally, there is a high incidence (around 51%) of cultured tracheal aspirates with gram-negative organisms in intubated ALF patients [34], which has a direct impact on the development of ventilator-associated pneumonia and ALI. Hepatic encephalopathy and ICH are also implicated in the development of ALI. The risk of pulmonary and extrapulmonary sepsis and indeed ARDS are specifically associated with aspects of ICH management. These include deep sedation, induction and maintenance of hypothermia and limited endotracheal suction, which all contribute to limited tracheo-bronchial toilet and retention of secretions. In ALF commonly encountered respiratory complication associated with both mechanical ventilation and critical illness have been described. These include pleural effusions, atelectasis, and

poor compliance due to raised intra-abdominal pressure (IAP) or reduced thoracic compliance due to chest wall edema.

Conventional protective ventilation maneuvers frequently employed for ALI/ARDS can potentially impact on cerebral perfusion exacerbating ICH. A balanced approach is often required, though low tidal volumes (6–8 mL/kg) can achieve normal partial pressures of  $\text{CO}_2$  ( $\text{pCO}_2$ ) in most cases. Increased IAP and decreased lung compliance due to chest wall edema lead to increases in pleural pressure, rendering the plateau pressure a poor measure of transpulmonary pressure. Therefore, attempts to limit plateau pressure below 30 cm water can be difficult to attain and indeed are often unnecessary. The combination of ALI/ARDS with severely elevated intracranial pressure (ICP) with intact physiological autoregulation necessitates tight control of  $\text{pCO}_2$ . When all conventional measures aimed at increasing  $\text{CO}_2$  clearance have been exhausted extracorporeal  $\text{CO}_2$  clearance devices to facilitate control in  $\text{pCO}_2$  may be used. This should be a strategy of last resort due the significant potential for bleeding complications associated with cannulae insertion and limb ischemia. Such devices have been used successfully in traumatic brain injury cases and ARDS [35] and have also been employed on few occasions in ALF patients with developed ARDS post-OLT, when ICH has remained problematic (unreported).

Patients with fulminant ALF are nursed with the head elevated at  $30^\circ$  and attention to avoiding unnecessary turning and other interventions that will exacerbate ICH. Consequently, high positive end expiratory pressure (PEEP) is necessary to optimise recruitment and prevent atelectasis of basal lung segments. The adverse effect of high PEEP on ICH may be outweighed by the improvement of oxygenation and consequent improvement of cerebral blood flow. Recruitment maneuvers such as prone positioning are contraindicated due to the impact on ICH management. Hypoxemia and high fractions of inspired oxygen ( $\text{FiO}_2$ ) can be reasons remove patients with ALF off the transplant waiting list. However, hypoxemia alone appears to be a nonspecific variable in the diagnosis of ALI. Furthermore, a

low partial pressure of oxygen ( $\text{PaO}_2$ ) to  $\text{FiO}_2$  ratio is common, but transient and not necessarily associated with poor outcomes [36]. Transpulmonary thermodilution cardiac output monitors can calculate an estimated measure of lung permeability, the extravascular lung water index, which has been shown to be a useful variable in guiding management [37].

Weaning patients from the ventilator occurs either once the acute phase of the liver injury has subsided or in the post-transplant period when ICH has settled. An assessment of the recovery of ICP autoregulatory mechanisms can be achieved by evaluating ICP responses to enforced elevations in  $\text{pCO}_2$ , mean arterial pressure and reductions in sedation. The return of ICP autoregulation permits a more sustained withdrawal of sedation and weaning from mandatory modes of ventilation. However, once sedation is decreased or stopped neurological problems may arise such as slow emergence from sedation or intensive care delirium. There is also a risk of both subclinical and clinical seizures likely related to ICH during ALF. Critical illness polymyoneuropathy (CIMPM) is also highly prevalent, due to the significant number of risk factors for this condition encountered in ALF, including sepsis, profound systemic inflammatory response syndrome (SIRS), exposure to steroids, high protein catabolism and MOF [38]. A (percutaneous) tracheostomy is often necessary to facilitate weaning from the ventilator and sedating medication. Despite the coagulopathy and thrombocytopenia in ALF it has been demonstrated that a percutaneous tracheostomy can be performed safely [39].

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## Gastroenterology

### Nutrition

Numerous metabolic abnormalities and their associated complications are encountered in ALF but only few studies have been undertaken to assess and identify best practice. Hypoglycemia is a significant metabolic abnormality encountered in ALF. It is due to the loss of hepatic glycogen stores, impaired gluconeogenesis and

hyperinsulinemia and a poor prognostic variable in the initial presentation of ALF. Along with other parameters of hepatic necrosis hypoglycemia may help determine which patients require referral to specialist centres (Table 2.2). ALF is also associated with impaired peripheral uptake of glucose and decreased peripheral insulin sensitivity, which is usually restored within 2 weeks in those patients that survive [40].

It is important to establish and then maintain normoglycemia early with infusions of 20–50% dextrose, which will continue until enteral nutrition is commenced. The control of blood glucose has attracted great attention since the landmark study by Van Den Berghe in 2001 that favoured tight glycemic control—glucose 4.4–6.1 mmol/L—being championed now included in the Surviving Sepsis Guidelines. Other studies have also demonstrated more adverse effects and worse outcome with hyperglycemia—glucose >12 mmol/L—in patients with neurovascular brain injury and indeed in ALF where it contributes particularly to poor ICH control [41]. However, meta-analyses assessing tight glycemic control studies since 2001 have not confirmed the impressive mortality benefit demonstrated in the original study population but an increased rate of hypoglycemic episodes intensive insulin regimens. Ultimately, a balanced approach is required with the goal of achieving blood glucose levels closer to the lower limit of 6 mmol/L (108 mg/dL) avoiding hypoglycemia and elevated levels greater than 12 mmol/L (216 mg/dL).

An early nutritional goal to start enteral feeding within 24 h of admission aiming to achieve 25–30 kcal/kg/day is recommended. The use of opioid-based sedation, aggressive fluid regimens causing bowel wall edema, raised IAP, and constipation all contribute to abnormalities of gut motility resulting in decreased absorption. If gut failure and poor absorption persist despite attention to constipation therapy and the use of prokinetics early intervention with total parenteral nutrition (TPN) may be warranted. Previous concerns about TPN-induced liver toxicity are not encountered with newer hypocaloric regimens [42]. Furthermore, there is currently no evidence



**Table 2.2** Criteria for referral/discussion to specialist centre [3]

Paracetamol overdose (time from ingestion, days)			Non-paracetamol overdose (ALF classification, time from jaundice to encephalopathy)		
Organ system	Day 2	Day 3	Day 4	Hyperacute	Subacute
Liver	INR > 3.0	INR > 4.5	INR > 6	INR > 2.0	INR > 1.5
	Or	Or	Or	Or	Or
	PT > 50 s	PT > 75 s	PT > 100 s	PT > 30 s	PT > 20 s
				Or	Or
				Shrinking liver volume	
Metabolic	pH < 7.3 or HCO <sub>3</sub> < 18	pH < 7.3 or HCO <sub>3</sub> < 18	pH < 7.3 or HCO <sub>3</sub> < 18	Hypoglycemia	Hypoglycemia
	Or	Or	Or	Or	Or
	Lactate > 3.0	Lactate > 3.0	Lactate > 3.0	Hyperpyrexia	Hyponatremia < 130 µmol/L
	Or	Or	Or	Or	
	Hypoglycemia	Hypoglycemia	Hypoglycemia	Hypoglycemia < 130 µmol/L	
Kidney	Oliguria (< 0.5 mL/kg/h for > 12 h)	Oliguria (< 0.5 mL/kg/h for > 12 h)	Oliguria (< 0.3 mL/kg/h for > 24 h or anuria for 12 h)	AKI Stage 1–3	AKI Stage 1–3
	Or	Or	Or		
	SCr > 200 µmol/L	SCr > 200 µmol/L	SCr > 300 µmol/L		
Brain	HE	HE	HE	Any degree of HE	Any degree of HE
Hematology		Severe thrombocytopenia	Severe thrombocytopenia	Pancytopenia	Pancytopenia

HE hepatic encephalopathy; AKI acute kidney injury; SCr serum creatinine; INR international normalised ratio; PT prothrombin time

suggesting that normal protein intake of approximately 1 g/kg/day worsens hyperammonemia and hepatic encephalopathy. This is important, because ALF patients are often catabolic with supranormal energy expenditure, despite significant hepatocyte loss. Furthermore there is significant protein catabolism with muscle wasting, amino acid losses, and vitamin deficiency, which all impact on immune function. This necessitates the supplementation of multiple vitamins and trace elements in patients with ALF, especially in those on continuous renal replacement therapy (CRRT) regimen where losses are exacerbated [43, 44]. Hypophosphatemia is frequently encountered with CRRT, especially high volume regimens and requires prompt replacement. However, hypophosphatemia may also herald liver regeneration with increased hepatic ATP production and serve as a good prognostic marker [45].

### Immunity and Bacteremia

The degree of SIRS is associated with an increase in mortality and macrophage-related cytokine release. In ALF the incidence of clinical bacteremia is high (approximately 35%) [34] evidence of the complex changes in the innate immunity that are predominantly balanced toward an anti-inflammatory environment. The deactivation of monocytes is thought to be the leading cause of increased susceptibility to infection. Approximately 30% of bacteremias manifest without pyrexia and elevation of white cell count reflecting hypo-responsiveness to infection though this is associated with a mortality benefit [46]. Bacteremia and SIRS both appear to influence the degree of hepatic encephalopathy (HE) [47].

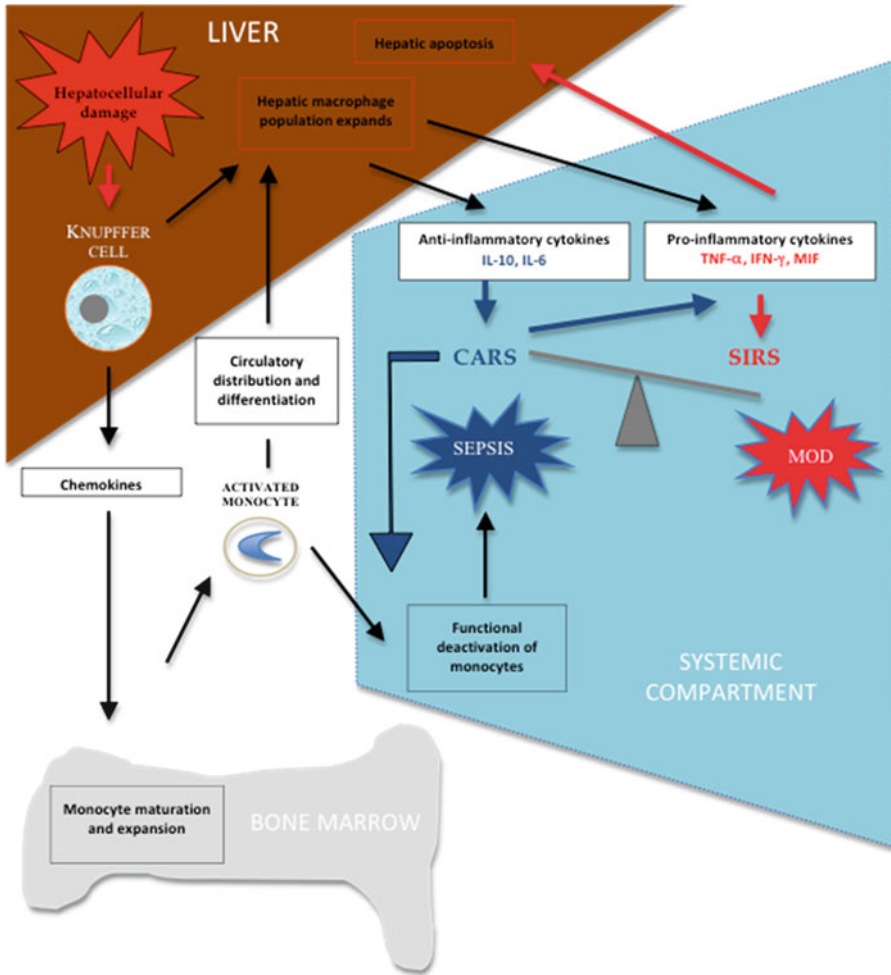
The use of empirical broad-spectrum antibiotics, attention to appropriate nutrition, gut decontamination, oral hygiene, ventilator care bundles, intense daily scrutiny of the indwelling intravenous catheters, and vigilant infection control measures are important in limiting the occurrence of bacteremia. Such interventions have affected the epidemiology of bacteremia in ALF with longer median times to evolution of bacteremia and a shift toward greater incidence of gram-negative

organisms [34]. The grade of encephalopathy appears to be independently associated with bacteremia and Acute Physiology and Chronic Health Evaluation II scores (APACHE-II) independently predictive of mortality [34]. The significant incidence of fungal sepsis, around 32% with cases predominantly due to *Candida* species necessitates the early empirical use of antifungal therapy, usually fluconazole [48].

There are marked changes in the pharmacokinetics and pharmacodynamics of drugs during critical illness that requires close drug monitoring when possible. In the absence of drug monitoring, antibiotic prescriptions should aim to “overdose” treatments with a low toxicity. The immunoparesis associated with ALF makes avoidance of antibiotic under-dosing important. Furthermore, changes in renal replacement therapy (RRT) dose to higher volume exchanges often warrant the adjustment of antibiotic doses to compensate for potential increases in drug clearance.

The innate immunity undergoes significant changes in response to acute liver injury and has a central role in the subsequent development of the clinical manifestations of ALF. Many of these closely resemble the clinical features of systemic sepsis with a SIRS that often culminates with the development of a vasoplegic circulation and MOF. These complex immune responses have been integrally related to some of the clinical complications of ALF, particularly, the increased incidence of bacteremia and the degree of encephalopathy.

The innate immune system appears to be overwhelmingly activated initially with the mobilisation of immune cellular components, including neutrophils, monocytes, and macrophages. They are involved in the profound release of cytokines orchestrating the pro- and anti-inflammatory response to sustained liver injury and subsequent facilitation of cellular repair. There are also significant reductions in the production of complement factors impairing opsonisation of bacteria [49]. There is evidence of impaired neutrophil function with reduced chemotaxis, bacteriocidal activity, and impaired production of superoxide and hydrogen peroxide



**Fig. 2.3** A schematic of the inflammatory responses to hepatocellular damage. Adapted from ref. [47]

with defective phagocytosis. Additionally, both monocytes and macrophage have been implicated in the initiation, propagation, and resolution of acute liver injury. It appears that shortly after acute liver injury macrophages enthusiastically release chemokines and pro-inflammatory cytokines. This response is balanced by the initiation of anti-inflammatory responses accompanying the recruitment of monocytes to the site of the liver injury to initiate repair processes. Activated macrophages release TNF- $\alpha$ , interleukin (IL)-1, IL-6, proteolytic enzymes, reactive oxygen intermediates, and lysosomal enzymes. Bacterial products can also induce TNF- $\alpha$  affect-

ing microvascular permeability and further releases of IL-6. The elevation of TNF levels appears to correlate with the development of sepsis and IL-6 with MOF and mortality (Fig. 2.3).

### Acute Kidney Injury

The incidence of AKI, defined using either the acute kidney injury network (AKIN) or the RIFLE criteria developed by the acute dialysis quality initiative (ADQI) in one study of 16,784 critically ill patients in non-specialised intensive care units was shown to be 28.5 and 35.5%,

**Table 2.3** Criteria for super-urgent listing for orthotopic liver transplantation [3]

Organ system	Paracetamol overdose	Sero-negative hepatitis (SNH), hepatitis A, hepatitis B, or an idiosyncratic drug reaction (IDR)
Liver	<i>INR &gt;6.5 or PT &gt;100 s</i> WITH BOTH AKI Stage 3 and Grade 3/4 HE <sup>a</sup>	<i>INR &gt;6.5 or PT &gt;100 s or pH &lt;7.3</i> WITH any grade of HE OR <i>Three of the following:</i> ( <i>INR &gt;3.5 or PT &gt;50 s, bilirubin &gt;300 μmol/L, jaundice to HE &gt;7 days, unfavourable etiology SNH or IDR, age &gt;40</i> )
Metabolic	<i>pH &lt;7.25</i> OR <i>Lactate &gt;3.0 mmol/L<sup>a</sup></i>	
Kidney	<i>AKI Stage 3 (SCr &gt;300 μmol/L or anuria)</i> WITH BOTH ( <i>INR &gt;6.5 or PT &gt;100 s AND Grade 3/4 HE</i> ) <sup>a</sup>	
Brain	<i>Grade 3/4 HE</i> WITH BOTH ( <i>INR &gt;6.5 or PT &gt;100 s AND AKI stage 3</i> ) <sup>a</sup>	<i>Any grade of HE</i> WITH <i>INR &gt;6.5 or PT &gt;100 s</i>
Cardiac	<i>In the UK increased inotrope or vasopressor requirement in the absence of sepsis</i> WITH 2 out of 3 ( <i>INR &gt;6.5 or PT &gt;100 s, AKI Stage 3, Grade 3/4 HE</i> ) <sup>a</sup>	

HE hepatic encephalopathy; AKI acute kidney injury; SCr serum creatinine; INR international normalised ratio; PT prothrombin time

<sup>a</sup>Assessment at >24 h post-ingestion and should occur within a 24 h window, despite aggressive fluid resuscitation

respectively. This is associated with an increase in hospital mortality of 36.4% [50]. In ALF the incidence of AKI is significantly higher than that of the general critically ill population ranging from 40 to 85% depending on etiology, with POD associated with a higher incidence of around 75% [51]. The AKI staging utilizing the serum creatinine (SCr) criteria classifies increases greater than 300% from baseline as stage 3; in patients with previously normal kidney function (SCr 80–120 μmol/L) this equates closely to the SCr of 300 μmol/L that is associated with poor prognosis in ALF. This is an important clinical criteria for referring to a specialist centre and listing patients for OLT (Tables 2.2 and 2.3).

The mechanisms involved in the development of AKI in ALF are similar to the pathophysiological models of hepatorenal syndrome and septic AKI. The release of vasoactive mediators, like

nitric oxide and other free radicals, leads to a hyperdynamic circulation with circulatory vasoplegia “vascular failure” and functional hypovolemia. These vasoactive mediator-induced changes to the circulation cause heightened homeostatic responses involving the sympathetic nervous system and renin angiotensin system (RAS) culminating in arterial vasoconstriction in the kidney. The intraglomerular arteriolar vasoconstriction results in ischemic acute tubular necrosis that is now increasingly recognised as a complex interplay between endothelial dysfunction and leukocyte activation and release of cytokines causing profound intracellular oxidative stress. Furthermore, recent studies of hemodynamic changes in septic AKI suggest other microcirculatory changes, particularly renal venous congestion associated with disturbed cellular energy mechanisms independent of tissue oxygen availability [52].

### AKI in Acute Liver failure

<b>Glomerular disease</b>	<b>Factors associated with greater AKI susceptibility</b>
<p><b>Rapidly progressive glomerulonephritis</b></p> <p>(A pathological classification based on immunofluorescence patterns [55])</p> <p><b>Type I (3%) – anti glomerular basement membrane disease</b></p> <p style="padding-left: 40px;">Goodpasture's</p> <p><b>Type II (45%) - Immune complex mediated</b></p> <p style="padding-left: 40px;">Postinfectious (staphylococci/streptococci) Collagen-vascular disease Lupus nephritis Henoch-Schönlein purpura (immunoglobulin A and systemic vasculitis) Immunoglobulin A nephropathy (no vasculitis) Mixed cryoglobulinemia Primary renal disease Membranoproliferative glomerulonephritis Idiopathic</p> <p><b>Type III (50%) Pauci immune - Antinuclear cytoplasmic antibody mediated</b></p> <p style="padding-left: 40px;">Wegener granulomatosis (WG) Microscopic polyangiitis (MPA) Renal-limited necrotizing crescentic glomerulonephritis (NCGN) Churg-Strauss syndrome</p> <p style="padding-left: 40px;"><b>Other</b> Glomeruloendotheliosis – pre-eclampsia Thrombotic microangiopathy – TTP, HUS</p>	<p><b>Reactive increases in afferent arteriolar tone</b></p> <p style="padding-left: 40px;">'Vascular failure' – acute liver failure Sepsis including rarely leptospirosis Hepatorenal syndrome – Type 1 Contrast</p> <p><b>Structural failure to decrease afferent arteriolar resistance</b></p> <p style="padding-left: 40px;">Age Atherosclerosis – includes micro and macro vascular renovascular disease Chronic kidney disease Chronic hypertension Malignant hypertension Severe pre-eclampsia</p> <p><b>Nephrotoxic Drugs</b></p> <p style="padding-left: 40px;">(Direct toxicity or tubulo-interstitial nephritis)</p> <p style="padding-left: 80px;">Paracetamol Aminoglycosides Contrast Penicillin Non-steroidal anti-inflammatory drugs Herbal remedies</p>

**Fig. 2.4** Acute kidney injury (AKI) in acute liver failure

Patients who are critically ill with ALF can display a wide spectrum of susceptibilities for AKI beyond those associated with the “vascular failure” and hemodynamic changes encountered. These are related to failure to increase or decrease afferent arteriolar vascular tone leading to reduced glomerular perfusion and ischemia in hypotensive states. Additional insult can be caused by the numerous drugs that patients are exposed to, which can be directly nephrotoxic or sometimes implicated in tubulointerstitial nephritis. Furthermore, specific glomerular pathologies, that result in rapidly progressive glomerulonephritides, should be considered and excluded by including urine dipstick and microscopy for red cell casts in conjunction with testing for autoantibodies to exclude small vessel vasculitides and serological testing for leptospirosis (Weil’s disease), if the history and examination suggest such diagnoses (Fig. 2.4) [53].

The mode and mechanism of renal cell death in paracetamol nephrotoxicity remains obscure and yet it is clear that it differs from the mechanisms involved in hepatotoxicity. Evidence in support of this theory originates from rat models

that demonstrate that NAC does not protect tubular cells [54]. Paracetamol is a phenacetin metabolite that has been implicated in proximal tubule cell apoptosis in AKI and chronic kidney disease (CKD). Consequently, cellular mechanisms and the induction of apoptosis in renal tubular cells has been the focus of studies into paracetamol-induced nephrotoxicity. It seems likely that the mechanism for nephrotoxicity lies with endoplasmic reticulum stress and caspase-mediated mechanisms that cause apoptosis [55]. Other speculated mechanisms include induction of oxidative enzymes such as cytochrome P-450 mixed function oxidase isoenzymes in the proximal tubule of the kidney. Additionally, the role of prostaglandin synthetase and *N*-deacetylase enzymes have also been postulated to be involved [56]. Finally, it appears that glutathione, an important element in the detoxification of acetaminophen and its metabolites has paradoxically also been implicated in the formation of glutathione conjugates that are thought to be nephrotoxic.

The high incidence of AKI frequently requires the use of CRRT often for both renal-specific and

non-renal-related reasons. Numerous issues are associated with CRRT in patients with ALF, including the need for anticoagulation to extend filter life span. Despite the coagulopathy and thrombocytopenia seen in ALF it has been demonstrated that CRRT circuits continue to clot as a result of losses of both pro- and anticoagulation factors [57]. Good vascular access, as well as an expanded intravascular compartment, is essential to extend filter life. Specific, yet standard maneuvers to extended filter life include the use of pre-dilution fluid replacement; high blood flows to reduce the ultrafiltration fraction, prompt attention to machine alarms, and use of prostacyclin anticoagulation. Prostacyclin has a half-life measured in seconds and represents a safe anticoagulant in ALF in the absence of hemorrhage. The use of heparin is not recommended during the initial presentation of ALF with evolving coagulopathy and citrate anticoagulation is complicated by the risk of citrate toxicity, due to the integral role of the liver in citrate metabolism. However, a case report of the safe use of a citrate-based dialysate, where heparin and regional citrate were contraindicated, demonstrating no signs of citrate toxicity intra-operatively during liver transplantation for a patient with paracetamol-induced ALF patient and AKI [58]. It is likely this was possible due to the low doses of citrate used (0.8 mmol/L; only about one-fifth of the concentration necessary to achieve anticoagulation) and the likely predominant role of muscle metabolising citrate. The role of citrate dialysate for RRT in ALF is, however, likely to be limited to short treatment periods and the intra-operative period and is not a common practice in the UK.

The use of RRT in the ICU continues to be the focus of much debate. The issues range from the mode, timing of initiation, indications for initiation; dose, anticoagulation use, and the perception that continuous replacement regimens are superior to intermittent regimens. There is, however, little compounding evidence available to clearly delineate any of these issues. Only the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study to date has endeavoured to answer and also establish some conclusions regarding the dose of ultrafiltration in AKI. No associated benefit was

demonstrated with higher ultrafiltration doses of 40 mL/kg/h vs. lower rates of 25 mL/kg/h [59]. However, RRT often needs to be tailored to address the clinical fluctuations affecting fluid management and the profound metabolic disarray encountered. In ALF mortality is inextricably linked to the severity of the underlying liver insult. However, profound catabolism, hyperlactemia, SIRS, vasoplegia, and high vasopressor requirements often necessitate the use of pulse high volume hemofiltration (PHVH) at 60–90 mL/kg/h. PHVH has been shown in animal and clinical studies to effectively reduce vasopressor requirements, which in ALF patients can be valuable to prevent vasopressor-induced ischemic insults [60]. Although there is no proven mortality benefit, it does allow the effective management of episodes of deterioration often associated with sepsis limiting further hepatic damage.

## Coagulation

The integral relationship between clotting factor production and acute hepatocyte necrosis is key to understanding the significant role coagulation tests have in determining both bleeding risk and prognosis. The measurement of prothrombin time (PT) is a measure of the extrinsic pathway of the classically conceptualised Y-shaped clotting pathway and reflects activity of clotting factors V, VII, and X. The half-life of factor VII is around 2 h, which implicates it as a good marker of synthetic liver function and the extent of hepatic necrosis. Factor V has itself too has been shown to be good prognostic indicator in Hepatitis B induced ALF [61]. However the assay of individual clotting factors is not routinely available. Consequently, there is continued reliance on the PT for prognostic assessment. In POD a PT of 36 s at 36 h after ingestion predicts 50% of patients will go on to develop ALF. Furthermore, a PT increasing on day 4 after ingestion and a peak PT of greater than 180 s is predictive of a 65% mortality [62].

However, it should be highlighted that the role of PT in assessing bleeding risk needs to be cautioned in the context of ALF. Numerous disruptions have been observed to occur across the



range of the more accepted yet complex primary cell-based processes thought to be integral to normal hemostasis. Both thrombocytopenia and platelet function seem to correlate better with bleeding risk. Importantly, the use of blood products containing clotting factors can have a significant impact on the interpretation of the PT and the assessment of prognosis, impending ALF and mortality. Blood products to correct coagulopathy should only be used when there is active bleeding or an invasive procedure beyond central and arterial line insertion, such as ICP bolt insertion or if transplantation is to be undertaken. Furthermore, it is often advisable to establish central access early in the course of the clinical presentation of impending ALF.

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## Prognosis of ALF

Spontaneous recovery in ALF is largely determined by the underlying pathology; therefore, establishing a diagnosis is important for determining prognosis and subsequent management, including the decision to undergo transplantation. Several prognostic variables have been identified and have been incorporated into different transplantation criteria for ALF.

### King's College Criteria (INR, Hepatic Encephalopathy, Acidosis, Serum Creatinine, Lactate)

Clinical criteria predicting prognosis in patients with ALF were first described at King's College Hospital, London. A retrospective analysis of patients with ALF who were medically managed between 1973 and 1985 was performed with the aim of identifying prognostically significant clinical parameters. The value of these parameters was then assessed, with the subsequent development of the King's College criteria (KCC), which have become the most widely used criteria for assessing prognosis in ALF. However, despite demonstrating high specificity for mortality without transplantation it has been widely accepted that the sensitivity and negative predictive value

(NPV) of the KCC are low. These criteria tend to fail to identify patients early enough in the clinical course of ALF or to predict those that will die without OLT. Furthermore, it has been reported that up to 25% of ALF cases survive without transplantation with a life expectancy of 13.4 years, which compares to 13.5 years with transplantation, though this falls to 8.1 years when adjusted for quality of life [63]. The impact of transplantation on quality of life is an important aspect of the decision-making process especially for those patients with POD, who may also have chronic psychiatric conditions predominate their lives. Ultimately, the combination of all these factors and the scarcity of donor organs have mandated an ongoing search for additional parameters that can predict prognosis earlier. Persistently elevated blood lactate has been closely associated with mortality and consequently incorporated into the KCC for paracetamol-related ALF. The variability of blood lactate level in response to aggressive circulatory, fluid, resuscitation extends the importance of this aspect of care in determining the predictive strength of this parameter [26]. The KCC have been developed for both paracetamol- and non-paracetamol-related ALF to assist decisions regarding referral to specialist centres that perform OLT and to decide whom to priority list for transplantation as outlined in Tables 2.2 and 2.3.

### Clichy Criteria (Hepatic Encephalopathy and Factor V Levels)

The Clichy criteria were developed from a group of 115 patients with acute hepatitis B causing ALF utilising the two variables, hepatic encephalopathy and clotting factor V levels. Factor V levels were found to be prognostically important if these were less than 20% for patients under 30-year-old and less than 30% for those greater than 30 year. A comparison study assessing this group of adult patients with ALF due to hepatitis B yielded a positive predictive value (PPV) of 75% and a NPV of 58% for the Clichy criteria compared to the KCC, which had a PPV 80% and NPV 77% [64].

## **BiLE Score (Lactate, Bilirubin, and Etiology)**

This simple score has been evaluated in a number of studies as a tool for assessing prognosis in ALF. One study of ALF patients in Germany assessed the BiLE score and demonstrated a prognostic sensitivity of 79% and specificity of 83% [65]. A direct comparison of BiLE scoring against the KCC was assessed at King's College Hospital confirming a statistically significant difference between survivors and non-survivors using BiLE scores. However, patients that underwent liver transplantation with a BiLE score above a threshold set at 6.9 were compared to KCC criteria. In our institution, a BiLE score at this threshold performed with limited sensitivity and accuracy [66].

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## **Contraindications to Liver Transplantation**

The assessment and comparison of prognostic criteria has always been open to bias with selected criteria performing best in the study centre where they were originally validated. Consequently, there will be an ongoing endeavour to develop improved criteria that identify patients with a high mortality earlier and with greater accuracy. All the current criteria are associated with problems of accurate selection of patients for transplantation, which can greatly affect patient survival, graft use from the limited donor pool and the physical and psychological consequences associated with long-term immunosuppression. Consequently, all patients with ALF require an early assessment of prognosis that must be individualized in the context of existing validated criteria. Thereafter, a process of continuous review of any such decision to list for transplantation is essential, due to the large potential for significant clinical deterioration that may nullify any mortality benefit from transplantation. The development of ongoing specific organ failure, despite maximal supportive therapies should prompt re-evaluation of any listing decision by the multidisciplinary team.

Age is one of the prognostic factors, that has been studied to some extent in terms of prognosis and extremes have been shown to affect mortal-

ity. Consequently, it has been incorporated into the non-paracetamol classification of ALF transplantation criteria and confirmed as poor prognostic variable in a number of studies. However the cut-off age associated with poor prognosis ranges from as low as 40 to as high as 60 years. Interestingly, older age does seem to be correlated with overall poor survival, however, there is no statistical difference between young and old in spontaneous survival. Ultimately, older patients require greater attention to co-morbidities and whole body biology than age per se (Fig. 2.5).

We have found anecdotally and without supportive evidence that transplantation is unlikely to alter outcome if there is circulatory failure with any of the following: a low cardiac index, right heart failure, or pulmonary hypertension with a pulmonary artery pressure >50 mmHg associated with escalating vasopressor requirements in association with ischemic extremities. In addition, severe lung injury with high PEEPs (10–15 cm of water) and fractional inspired oxygen >0.8 with oxygen saturations <92% represent an extreme in the setting of ALF. However toxic liver syndrome as a cause of lung injury, needs to be considered and there is possibly a benefit associated with transplantation in this setting.

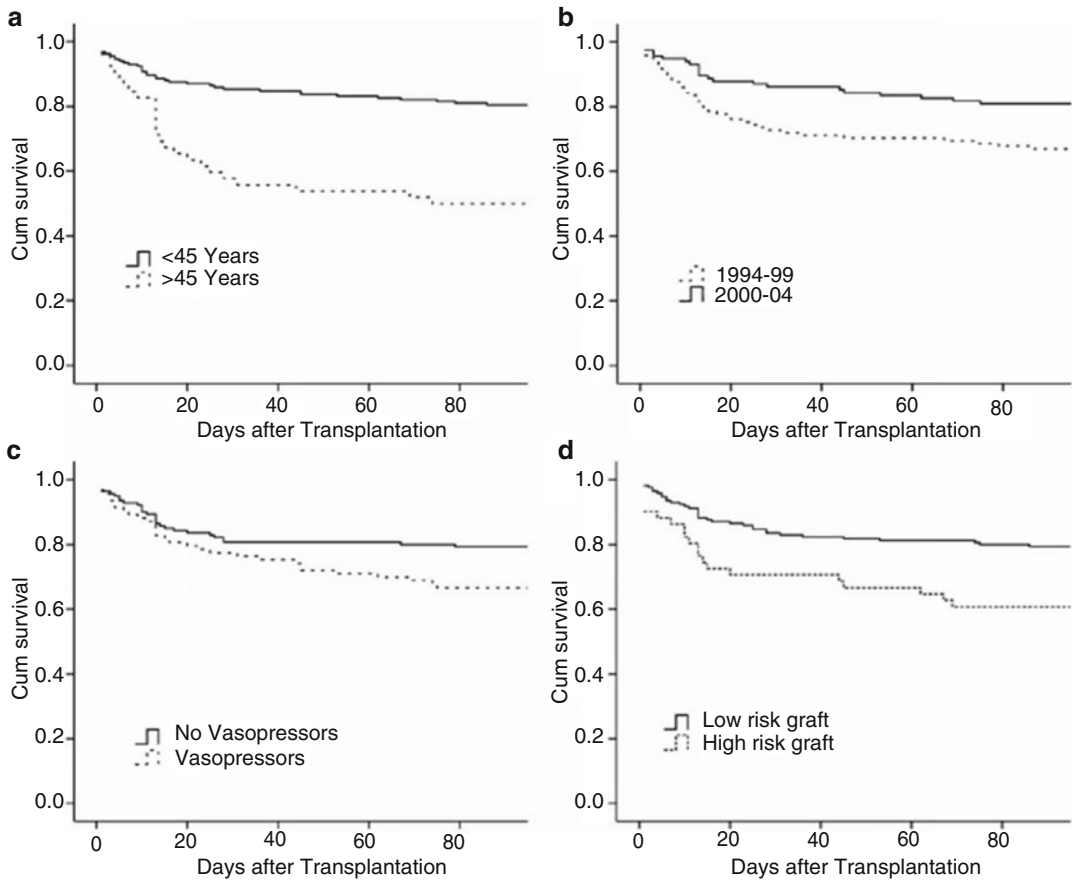
Bacteremia is also an important potential contraindication for transplantation that should delay the listing for transplantation until exposure to targeted antibiotics for a minimum of 24 h has elapsed. Both fungal sepsis and necrotising pancreatitis are similarly associated with an extremely poor outcome in transplanted ALF patients. Finally, fixed dilated pupils for greater than 2 h and a cerebral perfusion pressure <45 mmHg for prolonged lengths of time in the context of other related physiological variables such as a low cardiac index and hypoxemia are associated with a very poor prognosis.

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## **Summary**

ALF is a multisystem disorder requiring both predictive and reactive management strategies to support and protect organs from both the initial and subsequent insults. Early referral to a specialist





**Fig. 2.5** Survival of patients transplanted (a) aged >45 and <45 years. (b) between 1994-1999 and 2000-2004. (c) requiring vasopressor or no vasopressor following transplantation (d) with liver grafts with a calculated donor risk score either high or low

liver centre with the option of liver transplantation and an experienced multidisciplinary team is recommended. Such teams include liver intensivists, transplant surgeons, hepatologists, pharmacist, and physiotherapists all working to ensure a high standard of care is delivered. Furthermore, a good understanding of the poor prognostic variables is necessary to determine those most at risk of developing ALF to facilitate timely and safe transfer.

The initial primary goal of management is to establish a diagnosis to facilitate the initiation of therapies that can prevent further liver injury. Additionally, particular attention to the optimization of the circulation with both appropriate early invasive monitoring directing aggressive fluid resuscitation and vasopressor support is the key. The early use of empirical antibiotics and antifungal agents along with strict infection control mea-

asures are necessary. Furthermore, due to the high frequency of sepsis in the absence of SIRS symptoms a low threshold for obtaining cultures and broadening antibiotic cover deteriorates is required when the clinical condition. A keen awareness of the potential for raised ICH, particularly in the young, necessitates appropriate monitoring and management, which will be discussed in detail in a separate chapter. Furthermore, in parallel with supportive measures an assessment of the clinical history and prognostic variables must be undertaken to determine, which patients fulfil national transplantation criteria. The decision to list a patient for super-urgent liver transplantation is often difficult and can be affected by age, co-morbidities, the dynamics of the clinical condition, and psychosocial factors. The clinical course for those that are not transplanted is often

precarious and associated with a high mortality. It is affected by the speed and degree of hepatic regeneration and the impact of the cumulative insults that include recurrent sepsis, persistent AKI requiring prolonged RRT, and critical illness neuropathy/myopathy resulting in extended periods of rehabilitation in those that survive. On the contrary, patients who proceed to transplantation and receive a good functioning graft often experience swift resolution of the circulatory and neurovascular disarray and have significantly improved outcomes albeit offset by the long-term impact of lifelong immunosuppression.

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## Introduction

Any medication entering the body must be eventually metabolized and/or excreted. The liver is the organ positioned between the upper gastrointestinal tract and the general circulation, which is responsible for elimination and metabolism. It participates in drug elimination via hepatocellular uptake, metabolism, and biliary excretion. As blood travels through the liver, low-molecular weight substances can enter the hepatocytes by passive diffusion or active transport. Clearance of drugs is then facilitated by metabolizing enzymes and transport proteins [1].

Metabolism in the liver is a major route of elimination for a wide variety of drugs and the hepatic clearance of medications can be affected by patient factors and drug properties. Intrinsic patient factors include volume status, perfusion, gut motility, and organ function. The major drug properties that affect the quantity of drug elimination by the liver include hydrophilicity/lipophilicity, extraction ratio, and protein binding [1]. To fully understand the impact of hepatic dysfunction on the pharmacokinetic (PK) and pharmacodynamic (PD) properties of a medication,

an appreciation of the underlying determinants of hepatic clearance is necessary.

Hepatic clearance ( $Cl_h$ ) of a medication is a function of the hepatic blood flow ( $Q$ ) and the extraction efficiency of the liver for the particular drug ( $E_h$ ) [2] and it can be represented by the formula:

$$Cl_h = Q \times E_h$$

The extraction efficiency of a particular drug is dependent on liver blood flow, intrinsic clearance ( $Cl_{int}$ ) of unbound drug, and the fraction of unbound ( $f_u$ ) drug in the blood [2] and can be represented by the formula:

$$E_h = [(f_u \times Cl_{int}) / (Q + f_u \times Cl_{int})]$$

Taken together the equation for hepatic clearance is:

$$Cl_h = [(Q \times f_u \times Cl_{int}) / (Q + f_u \times Cl_{int})]$$

This equation contains the three primary components of hepatic drug elimination: blood flow, drug protein binding, and  $Cl_{int}$ .  $Cl_{int}$  can be defined as the sum of all enzyme and transported protein activity involved in hepatic metabolism.

Medications can be categorized according to the extraction efficiency: high ( $E_h < 0.7$ ), low ( $E_h < 0.3$ ), or intermediate ( $0.3 < E_h < 0.7$ ). Drugs with a high extraction ratio are dependent on blood flow and usually relatively insensitive to changes in protein binding or enzyme activity ( $Cl_h \approx Q$ ). On the other hand, drugs with low

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**Table 3.1** Classifications of relevant medication pharmacokinetic characteristics[4]

PK Profile	Hepatic Extraction	Effect of portosystemic shunts	Examples
Low extraction/Low protein binding (<90%)	<0.3	None	Alprazolam, amoxicillin, doxycycline, fluconazole, isoniazid, lamivudine, methyl-prednisolone metronidazole, phenobarbital, prednisone, primidone, theophylline
Low extraction/High protein binding (>90%)	<0.3	None	Ceftriaxone, chlordiazepoxide, clarithromycin, clindamycin, diazepam, lansoprazole, lorazepam, oxazepam, methadone, mycophenolate, phenytoin, prednisolone, rifampin, valproic acid
Intermediate extraction	0.3-0.6	Usually not clinically relevant	Alfentanil, amiodarone, azathioprine, atorvastatin, carvedilol, codeine, diltiazem, erythromycin, itraconazole, lidocaine, meperidine, nifedipine, omeprazole, ranitidine
High extraction	>0.6	Clinically significant	Fentanyl, isosorbide dintrate, morphine, nitroglycerin, sufentanil

extraction efficiency are affected by changes in protein binding and intrinsic hepatic clearance ( $Cl_h \approx f_u \times Cl_{int}$ ) [2]. See Table 3.1 for a list of relevant medications and their corresponding PK profiles and expected effect of liver dysfunction.

### Effect of Liver Failure on Medication Pharmacokinetics (PK) and Pharmacodynamics (PD)

Hepatic disease may result in many physiologic changes in the liver leading to alterations in medication PK and PD.

### Absorption

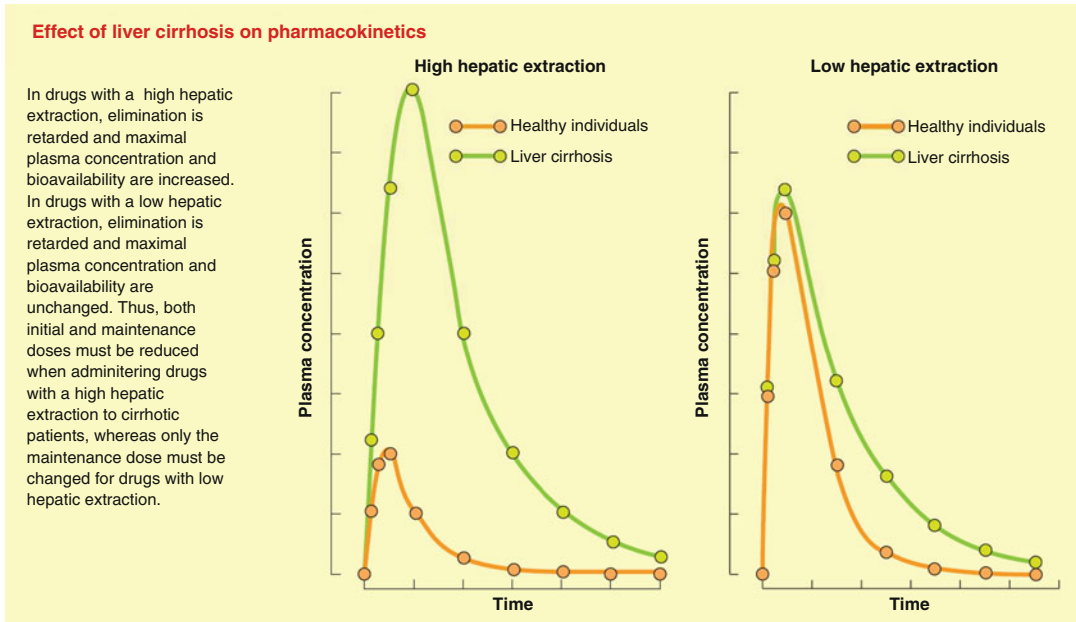
Drugs administered orally with a high extraction ratio would normally have a low bioavailability given the significant first pass effect. Cirrhosis may lead to endogenous or therapeutic portosystemic shunts (transjugular intrahepatic portosystemic shunt), which may significantly decrease liver blood flow [3]. Since high extraction drugs are mostly affected by hepatic blood flow, cirrhosis may lead to a considerable decrease in

extraction of these medications, and therefore an increase in bioavailability. In fact, studies that evaluate medications with intermediate to high extraction ratios have found an increase (ranging from 2 to 12 fold) in bioavailability after enteral administration (Fig. 3.1) [4].

For high extraction drugs that are administered intravenously, a normal initial dose can be administered and the maintenance dose should be reduced according to hepatic blood flow. Theoretically, assessment of hepatic blood flow with sonograph might be helpful to guide drug dosing for high extraction drugs in patients with significant shunt fraction; however, there is little clinical evidence to support this approach [4]. The serum bile acid level has shown good correlation with the shunt index ( $r=0.82$ ) and may serve as a surrogate for hepatic blood flow [5].

### Protein Binding and Distribution

Only a free drug, which is unbound by protein, can diffuse across tissue. The distribution of a drug is largely dependent on its binding to proteins and other macromolecules. Many drugs are highly bound to either albumin or  $\alpha_1$ -acid glycoprotein. Decreased protein binding would result



**Fig. 3.1** Effect of liver cirrhosis on concentrations of low and high extraction medications

in increased free fraction of a drug and decreased total plasma concentration (Fig. 3.2). Hepatic disease may decrease protein binding via reduced synthetic protein production, accumulation of endogenous compounds that inhibit plasma protein binding, and conformational changes in proteins that may qualitatively alter binding. Decreased protein binding is particularly important for drugs with a low extraction ratio, where hepatic clearance is largely dependent on fraction unbound and intrinsic clearance ( $Cl_h \approx f_u \times Cl_{int}$ ). Medications with a low extraction ratio can be further broken down to those with high protein binding ( $\geq 90\%$ ) and those with low protein binding ( $< 90\%$ ) (Table 3.1). The drugs with low extraction ratio and low protein binding are most affected by hepatic enzymatic activity or  $Cl_{int}$ . Please refer to the metabolism section below for a further review on the effects of hepatic disease on intrinsic hepatic clearance activity. Drugs with low extraction and high protein binding are equally affected by  $Cl_{int}$  and fraction unbound. An important distinction to realize in these drugs is that the total plasma concentration may be

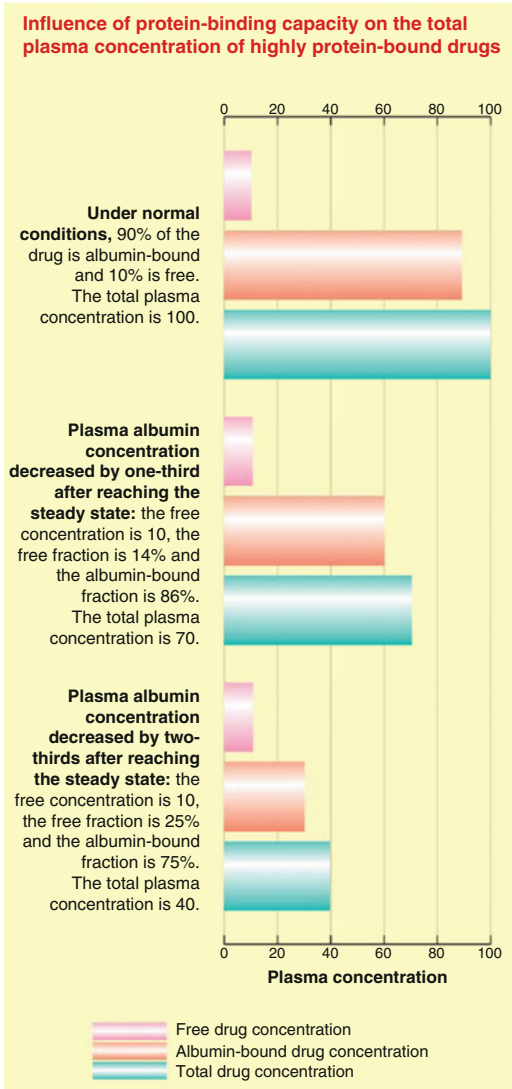
decreased while their free concentrations are either normal or even increased [6].

Aside from protein binding, end-stage hepatic disease may also lead to changes in drug volume of distribution ( $V_d$ ). Water-soluble drugs particularly may have a significant increase in the  $V_d$  because of the presence of peripheral edema and ascites. As a result, the initial dose of a hydrophilic medication should be increased in order to obtain a similar anticipated effect. Since many hydrophilic medications are excreted by the kidneys, renal function should also be considered when choosing an appropriate dose [1].

## Metabolism

Numerous pathophysiologic changes during chronic liver failure may affect drug metabolism and reduce intrinsic hepatic clearance. A reduction in liver cell mass may lead to decrease in enzymatic activity. Furthermore, sinusoidal capillarization may impair oxygen and compound uptake, which further limits drug metabolism. Two different





**Fig. 3.2** Influence of protein-binding capacity on the total plasma concentration of highly protein-bound drugs

types of reactions are primarily responsible for the liver's metabolizing capabilities: phase I oxidative metabolism and phase II glycosylation and glucuronidation. Phase I reactions, which are usually mediated by the cytochrome P450 isoenzymes (CYP), require the presence of oxygen molecules, and therefore, are more susceptible to functional deficiencies due to lack of oxygenation from decreased hepatic perfusion. Conjugation phase II reactions such as glucuronidation are less susceptible to the effects of liver cirrhosis [7].

## Liver Failure and Other Organ Systems

Pathophysiologic processes, such as primary sclerosing cholangitis, cholangiocarcinoma, and primary biliary cirrhosis, may lead to both liver failure and extrahepatic cholestasis. Furthermore, hepatocyte dysfunction and slowing of bile flow from the liver may lead to intrahepatic cholestasis. Reduced formation and secretion of bile into the duodenum may lead to decreased clearance of both endogenous and exogenous substances that are primarily eliminated via biliary excretion. Drugs and metabolites that are normally excreted by the bile may accumulate in liver failure patients with biliary obstruction [2].

Advanced liver disease is frequently complicated by impaired kidney function due to hepatorenal syndrome. To further complicate matters, patients with liver failure often have reduced muscle mass and impaired metabolism of creatine to creatinine. Therefore, equations such as the Cockcroft-Gault method may overestimate true glomerular function. Hence, clinicians must be cautious even when prescribing a renally eliminated medication [2].

## Pharmacodynamic (PD) Changes in Liver Failure

Many studies have alluded to PD changes in patients with liver disease. However, it should be pointed out that few of these studies have taken into account the pharmacokinetic (PK) alterations of hepatic dysfunction as discussed above. It is inherently difficult to demonstrate an altered therapeutic response that is independent of the PK effects. The discussion on PD changes will focus on instances where changes in drug receptor binding or intrinsic activity of the receptor has been demonstrated

Studies have indicated a decrease in the number of beta adrenoreceptor sites in patients that may correspond with the degree of liver abnormality [8–10]. This translates to both a decrease in isoproterenol chronotropic effects [9] and a decrease therapeutic effect with B-adrenoreceptor antagonist [8,10].

A decreased PD effect has been observed with various diuretic therapies, including furosemide, triamterene, torsemide, and bumetanide [11–14]. In general, all of those studies found a decreased PD response to diuretics in cirrhotic patients and a higher tubular concentration required to produce the desired sodium excretion effect. One author suggested that the decreased PD response may be due to reductions in number of nephrons or due to decreased maximum response per nephron [14].

An increased PD effect of opioids and benzodiazepines may be observed in cirrhotics. Studies have shown that these medications may cause disproportional sedation effects beyond PK changes [15–17]. Hypotheses for the physiological explanation for this phenomenon include increase blood–brain barrier permeability, increase in gamma-aminobutyric acid (GABA) receptors, and increase GABA baseline activity via accumulation of endogenous non-benzodiazepine receptor compounds.

### Liver Function Assessment

There are no physiologic or laboratory measurements to adequately estimate the hepatic clearance of medications unlike the assessment of renal function by creatinine clearance that allows a more precise estimation of organ performance. Furthermore, given the complex interaction between drug properties and both physiologic changes and altered  $Cl_{int}$  activity in liver failure, it is unlikely that a single dynamic marker of liver function would accurately predict PK changes for the majority of medications. The Child-Pugh classification of severity of liver disease has been used extensively to categorize patients according to the severity of liver function impairment (Table 3.2) [18]. Although the Child-Pugh score is widely used for the assessment of prognosis in patients with liver cirrhosis, it does not reflect the hepatic clearance or PD of medications in those patients. As previously described, reduced liver function is the result of a combination of hepatocellular dysfunction and decrease blood supply with portal-systemic shunts. The Child-Pugh

Score does not provide objective data for either of those functions. Furthermore, two of the five components of the Child-Pugh Score (encephalopathy and ascites) are subjective and may alter with treatment. Despite these deficiencies, the Child-Pugh score is endorsed by both the Food and Drug Administration and the European Medicines Agency to categorize patients according to their degree of hepatic impairment for pharmacokinetic studies.

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## Specific Classes of Medication

### Sedatives

Patients with liver failure usually have more exaggerated effects to sedatives, which may partially be explained by PD alterations as discussed above. However, many of the sedatives commonly used in the management of critically ill liver failure patients also have significant PK changes.

Midazolam is almost solely transformed by CYP 3A4. Patients with moderate liver impairment will experience changes in midazolam PK. After a single intravenous dose of 0.2 mg/kg of midazolam in ten patients with moderate alcoholic liver disease, the area-under-curve (AUC) increased by 57% and the half-life ( $t_{1/2}$ ) was prolonged by 25%, when compared to controls [19]. In patients with severe liver cirrhosis, the AUC and  $t_{1/2}$  could potentially double [17]. Similarly, investigations of diazepam, which is also metabolized by CYP 450 enzymes, have also demonstrated doubling of elimination  $t_{1/2}$  in cirrhotic patients. Diazepam and midazolam should be used with caution in patients with liver disease and an empiric dose reduction of 50% should be employed. Clinicians should also be cognizant of possible prolonged sedative effects. The PK discoveries of midazolam and diazepam in patients with liver disease are in contrast to the findings involving lorazepam. Studies of lorazepam, which is metabolized by glucuronidation, in liver disease have demonstrated little to no PK changes [20].

Propofol is a rapidly acting anesthetic agent with multi-compartmental kinetics. It has an



**Table 3.2** Child-Pugh Classification of Liver Disease[18]

Clinical criteria	1 point	2 points	3 points
Serum bilirubin (mg/dL)	<2	2–3	>3
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (s>control)	<4	4–6	>6
Encephalopathy (grade)	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate

Points are aggregated and the total score is classified according to severity as follows: 5–6 points: group A (mild), 7–9 points: group B (moderate), 10–15 points: group C (severe)

extremely large  $V_d$  and an elimination half-life of 13–44 h [21]. In a controlled study of ten patients with cirrhosis, anesthesia was induced with a propofol infusion and PK parameters were measured and compared with ten control patients.[22] The investigators found that the termination  $t_{1/2}$  and total body clearance of propofol were similar between the two groups. Although the mean recovery time was significantly longer in the cirrhotic group, it did not translate to a clinically significant difference. The authors concluded that the PK parameters of propofol were not significantly affected by cirrhosis.

### Neuromuscular Blocking Agents

Hepatic failure may contribute to alterations in neuromuscular blocking medications PK and PD. Factors leading to these alterations include decrease elimination, altered  $V_d$ , acid base disturbances, and reduced plasma cholinesterase activity. Prolonged neuromuscular blockade following succinylcholine administration has been reported in patients with liver dysfunction [23]. Furthermore, a delayed onset of action has been observed possibly due to an increased  $V_d$  in cirrhotics [24,25].

Of the neuromuscular blocking agents, pancuronium, vecuronium, and rocuronium are most likely to be affected by end-stage liver disease. Pancuronium is primarily renally eliminated; however, 35% of it undergoes hepatic metabolism with biliary excretion. The  $V_d$  of pancuronium is increased by 50% in cirrhotics and its clearance is reduced resulting in a prolonged  $t_{1/2}$  (114–208 min). Patients may require a larger ini-

tial dose for desired effect, but slower elimination may lead to prolonged blockage [26]. Vecuronium is predominantly eliminated via biliary excretion, and only a small portion undergoes hepatic metabolism to an active metabolite. The effect of liver dysfunction on the PK of vecuronium depends on the dose administered. Smaller doses of vecuronium are primarily dependent on redistribution termination; however, larger doses depend on hepatic function. A dose of <0.1 mg/kg has a slower onset and shorter duration of action in cirrhotics, which is most likely attributable to increase  $V_d$ . A dose of >0.2 mg/kg has a similar onset time in cirrhotic patients, but a significant increase in duration of action (91 vs. 65 min).[27] Rocuronium elimination is dependent on biliary excretion as an unchanged drug. A small proportion of rocuronium is also renally excreted. Studies in liver failure patients have demonstrated a larger  $V_d$  and a prolonged duration of action.

Atracurium and cisatracurium both undergo Hoffmann degradation and ester hydrolysis. Studies have demonstrated that the presence of end-stage liver disease does not alter the elimination  $t_{1/2}$  of either medications [28]. In patients with liver disease where a prolonged action of neuromuscular blockade may not be desirable, preference should be given to these two agents.

### Opioids

Morphine is an opioid with partial  $\mu$  receptor agonist activity. It is metabolized to intermediate metabolites, including morphine-6-glucuronide and morphine-3-glucuronide via phase II reactions,

which are mostly spared in liver disease. It is usually 30–40% protein bound to albumin and extrahepatic clearance accounts for about 40% of its elimination [29]. For the most part, morphine PK is unaltered in early liver disease. However, in severe liver disease, the  $t_{1/2}$  is doubled, and correlates with prolonged prothrombin time, hypoalbuminemia, encephalopathy, ascites, and jaundice [16]. The intermediate metabolites of morphine are renally eliminated and the presence of hepatorenal syndrome may drastically prolong their elimination. In general, the initial intravenous dose of morphine does not need to be adjusted to obtain the desired effect. However, clinicians should be cognizant of the potential for prolonged duration of action and possible increases in neuroexcitation toxicity, particularly in the presence of hepatorenal syndrome.

Hydromorphone is metabolized via glucuronidation to hydromorphone-3-glucuronide, which is inactive, but may be neurotoxic. Little is known about the PK of intravenous hydromorphone in patients with liver dysfunction. However, the PK of orally administered hydromorphone is moderately affected by liver disease. In patients with advanced cirrhosis, the max concentration ( $C_{max}$ ) and AUC of hydromorphone was 4-fold higher than normal and the  $t_{1/2}$  remains unchanged. It is unclear whether these PK changes are solely due to increases in the bioavailability from oral administration as a result of decreased extraction and are not applicable when hydromorphone is given parenterally.

The piperidine opioids (remifentanyl, alfentanil, sufentanil, fentanyl) exhibit multiple-compartment PK, where the onset and magnitude of action is dependent on distribution half-life ( $t_{1/2\alpha}$ ), while the duration of action is dependent on both  $t_{1/2\alpha}$  and elimination half-life ( $t_{1/2\beta}$ ). Alfentanil, sufentanil, and fentanyl are all highly protein bound (85–96%) and rapidly distribute to tissue. All of them are metabolized by CYP 3A4; however, the redistribution from the peripheral to central compartment is usually the rate limiting step. In cirrhosis, hepatic elimination becomes slower than redistribution and turns into the rate limiting step. In general, their PK parameters are spared in mild liver disease, but in severe disease the free fractions are higher given decreased

protein binding and the  $t_{1/2\beta}$  is prolonged. The PK of sufentanil and fentanyl are more likely to be significantly altered by liver disease since their extraction ratios are higher than that of alfentanil (0.8 vs. 0.4) [29,30]. Remifentanyl is rapidly acting and metabolized by plasma esterases. Studies have shown that remifentanyl PK are not affected by liver dysfunction.

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## Laboratory Tests of Liver Status

The liver is the most complex internal organ in terms of its functions. In addition to its roles in metabolism of carbohydrates, lipids, and proteins, it is the major site of drug metabolism, an important issue in critical care medicine and anesthesiology. Like many other organs, the liver has an extensive reserve capacity, so that many patients with liver disease may have normal or near-normal liver function.

Laboratory tests are available to evaluate a few of the many functions of the liver. While a number of commonly performed tests are affected by severe liver dysfunction (glucose, urea or BUN, albumin, cholesterol, and triglycerides), most abnormalities of these tests are not due to liver disease and they are therefore poor tests for the evaluation of the liver.

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## Serum Bilirubin

Bilirubin, produced from degradation of heme (mainly during clearance of senescent red blood cells in the spleen) is transformed in the liver to water soluble conjugates that are excreted in the bile in an energy-dependent fashion. In normal serum only unconjugated bilirubin is found and with liver damage increased levels of conjugated bilirubin are a sensitive test of hepatic dysfunction. Conjugated bilirubin can become covalently bound to albumin (termed biliprotein), markedly prolonging its half-life. Laboratory tests measure total bilirubin and a parameter termed direct-reacting bilirubin, an estimate of the sum of conjugated bilirubin and biliprotein. The difference between total and direct-reacting bilirubin is termed indirect bilirubin, an estimate of unconjugated bilirubin.

Increases in bilirubin levels are best interpreted based on whether the increase is primarily of direct or indirect bilirubin. Increases of indirect bilirubin are most commonly due to increased turnover of heme (hemolytic anemia, resolution of large hematomas, rarely rhabdomyolysis), inborn errors of bilirubin conjugation (Gilbert's syndrome, Crigler-Najjar syndrome), or portal hypertension (usually due to hepatic cirrhosis). Increases in direct bilirubin are most commonly due to hepatic injury, bile duct obstruction, and impaired hepatic bilirubin excretion in acute illness, particularly sepsis [1, 2]. Although not often considered as a reason for jaundice, sepsis was the cause of about 30% of cases of hyperbilirubinemia in one series

[3] and associated with a high mortality of 51%. Usually, bilirubin does not exceed 10 mg/dL in such cases unless sepsis is severe.

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## Serum Proteins

Most serum proteins are produced by the liver (with the major exception of immunoglobulins). Albumin is the protein most widely used for the evaluation of liver synthetic function and is one of the parameters of the Child-Pugh scoring system for cirrhosis. Other factors besides liver disease are important causes of low albumin. Albumin levels fall rapidly, often markedly, in acute illness and are an important determinant of prognosis in hospitalized patients [4]. Mechanisms involved in this decrease include increased catabolism of albumin, increased capillary permeability to proteins, and decreased albumin synthesis; inflammatory cytokines are believed to be involved in all of these processes.

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## Prothrombin Time and International Normalized Ratio

Prothrombin time measures the function (and levels) of a number of clotting factors (I, II, V, VII, X) synthesized in the liver. As such it is a test of liver function. Prothrombin time is often reported along with (or replaced by) its international normalized ratio (INR). INR was developed to standardize results between laboratories for patients taking warfarin, however it actually created greater differences in results in patients with liver disease [5]. Attempts have been made to develop a liver-specific INR [6, 7] but these have not been widely adopted. Prothrombin time and INR are also affected by vitamin K deficiency, as can occur with ongoing cholestatic disease; in this case, normalization typically occurs when vitamin K is given.

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## Quantitative Liver Function Tests

Because of the key role of the liver in metabolism of drugs, there has been keen interest in monitoring the rate of metabolism of drugs or other chemicals as tests of liver function. Indocyanine

green clearance is one of the first tests that has been developed for this purpose. It is affected both by liver blood flow and hepatic extraction. Other tests that have been proposed include caffeine, lidocaine, and aminopyrine metabolism. While such tests are more sensitive markers of liver function than traditional tests [8], they seem to provide only modest incremental benefit in predicting surgical survival or prognosis in critically ill patients [9].

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## Ammonia

Ammonia is effectively removed from the circulation by the liver through the urea cycle. Increased ammonia levels are thus evidence of poor hepatic function. In acute hepatitis, ammonia levels  $>200 \mu\text{mol/L}$  are specific markers of liver failure, but detect only a minority of patients with intracranial hypertension due to hepatic encephalopathy [10].

In hepatic cirrhosis, ammonia levels are often measured to evaluate the patient for hepatic encephalopathy. While increased brain ammonia is related to severity of encephalopathy, blood ammonia levels correlate very poorly with brain ammonia and therefore with hepatic encephalopathy. Ammonia levels are not recommended to monitor patients with cirrhosis or hepatic encephalopathy, but may be helpful in evaluating patients with encephalopathy of unclear etiology, and normal levels rule out a hepatic cause [11, 12].

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## Liver Enzymes

Most individuals with chronic liver disease and many with acute liver disease have normal bilirubin and normal liver produced proteins. More sensitive tests of liver injury are needed to detect liver injury in these patients. Liver enzymes are the most sensitive indicators of liver injury. The pattern of enzyme results provides clues to the type of injury.

Aspartate (AST) and alanine (ALT) aminotransferase are enzymes that are found primarily in hepatocyte cytoplasm and released into the serum with cell injury. There is more AST

than ALT within the hepatocytes and the intracellular AST to ALT ratio increases with alcohol abuse, malnutrition, and in cirrhosis. Once released AST has a much shorter half-life than ALT (16–18 h vs. 42–48 h respectively). Therefore ALT increases more than AST soon after liver injury in most patients with liver injury. However if injury is detected very early or injury occurs in conditions with a higher than normal AST to ALT ratio, AST may consistently remain higher than ALT. AST and ALT are also found in skeletal and cardiac muscle with a much higher ratio of AST:ALT within muscle cells. With acute injury to cardiac or skeletal muscle the ratio of AST to ALT is often greater than 3 to 1. Muscle injury can be confirmed by measuring creatine kinase (CK) for skeletal muscle injury or troponin I for cardiac injury.

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### Alkaline Phosphatase

Alkaline phosphatase (ALK) is a membrane-bound enzyme found mainly in liver and bone but also within the intestines and the placenta. Except during pregnancy increased levels of ALK are usually due to either liver or bone disease. In the liver, ALK is found attached to the inner membrane of hepatocytes on the canalicular surface. It is attached by a lipid linkage that can break in cholestatic disorders. Increases of ALK generally occur gradually with cholestatic processes and in the early stages of obstruction ALK may be normal. In a small number of cholestatic cases with prolonged obstruction ALK is not increased, the precise mechanism of this remains to be determined. Decreases in ALK can occur after blood transfusion due to chelation of metal (zinc, magnesium) ions that are required for the measurement of ALK. High copper levels in blood (as occur with acute hepatitis in Wilson's disease) also prevent attachment of these ions and a very low ALK can provide a diagnostic clue to Wilson's disease as a cause of acute liver injury. If the origin of elevated ALK is not obvious measurement of ALK isoenzymes may help although heat fractionation measurements are not reliable.

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### Gamma-Glutamyl Transferase

Gamma-glutamyl transferase (GGT) is an enzyme found in a variety of organs but blood levels typically reflect liver sources. Like ALK, GGT is a canalicular enzyme and is released from hepatocytes with cholestasis. Production of GGT is also induced by drugs that stimulate production of microsomal enzymes, most prominently ethanol, phenytoin (and many other anti-epileptic drugs), and many calcium channel blockers. GGT levels decrease after meals and are increased by smoking. GGT is most helpful in confirming that liver is the source of elevations of AST, ALT, or ALK. Isolated elevations in GGT are often not necessarily the result of liver disease but due to other (extrahepatic) factors.

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### Patterns of Liver Disease

The liver has a limited number of ways of responding to injury. Two major patterns are observed: those in which the major injury is to hepatocytes (termed hepatitis) and those in which obstruction of biliary drainage is present (termed cholestasis). When either type of injury is ongoing, stellate cells in the liver may be activated and transform to a collagen-synthesizing phenotype, leading to hepatic fibrosis and, ultimately, cirrhosis.

Acute hepatitis is the most dramatic form of liver disease reflecting injury to hepatocytes that occurs over a short period of time. Most patients with acute hepatitis recover completely, but a small minority progress to such severe damage that acute liver failure develops. Depending on the cause for hepatitis some patients will develop chronic hepatitis. Clinically acute hepatitis is often recognized by the presence of jaundice but only a minority of affected patients develop this feature. Acute hepatitis is most reliably detected by elevated levels of AST and ALT. Table 4.1 summarizes the laboratory patterns observed with varying causes of acute elevations in AST and ALT, and additional tests that may help in determining the exact etiology.

**Table 4.1** Approach to causes of elevated AST and ALT

Feature	Viral hepatitis	Alcoholic hepatitis	Ischemic or toxic hepatitis	Drug-induced hepatitis	Acute biliary obstruction	Rhabdomyolysis
Peak ALT (xnormal)	10–100	2–10	50–500	5–100	5–30	5–100
AST/ALT ratio	<1	>1, often >2	>1 for 1–2 days	<1	>1 for 1–2 days	>3, >1 for several days
ALK (% >3 x normal)	5–10% (HBV, HCV), 10–20% (HAV)	15–25%	0	Up to 50%	80–90% late, <10% early	0
Peak bilirubin (mg/dL)	5–15	5–20	<5	5–15	5–20	<5
Bilirubin >5 mg/dL (%)	Rare in children, 50–70% HAV, 30–50% HBV, 10% HCV	70%	<10%	Probably <10%	70–80% if persistent	0
INR >1.3 (%)	<5%	<5%	95%	<5%	<5%	0
Other tests/features helpful in diagnosis	IgM anti-HAV, HBsAg, IgM anti-HBc, anti-HCV, HCV RNA	History	Acetaminophen levels, history	History	History, ultrasound	CK

AST Aspartate aminotransferase; ALT alanine aminotransferase; ALK alkaline phosphatase; INR international normalized ratio; HAV hepatitis A virus; HBV hepatitis B virus; HCV hepatitis C virus; HBsAg hepatitis B surface antigen; anti-HBc antibody to hepatitis B core antigen; CK creatine kinase



The most common causes of acute hepatitis in hospitalized patients are ischemic hepatitis, drug-induced liver injury (DILI), and alcoholic hepatitis. Ischemic liver injury is common in critically ill patients; one study reported an incidence of 1% of all admissions [13]. It usually occurs in patients with shock and is associated with marked elevations in AST, ALT, and INR that develop very quickly and then rapidly return to normal if shock is controlled. The diagnosis is usually obvious. DILI cannot be diagnosed definitively by laboratory tests and is often associated with concomitant elevations of AST, ALT, and ALK. DILI often develops soon (within a few weeks) after starting a medication and is not due to direct toxicity but an idiosyncratic reaction to drugs. However DILI can sometimes develop in patients who have been taking a medication for many months. A large variety of drugs have been linked to DILI but antibiotics are a common cause of DILI. Biopsy may be helpful if the cause of acute liver injury is not obvious.

Although rare as a cause of acute hepatitis acetaminophen toxicity is the most common cause of acute liver failure [14]. Its clinical presentation is similar to ischemic hepatitis with marked increases in AST, ALT, and INR but minimal increases of bilirubin. In the United States it is more common to see toxicity from accidental overdose than intentional overdose and a high index of clinical suspicion is needed for the correct diagnosis [15]. Acetaminophen levels are helpful in determining exposure to acetaminophen.

Testing for acute viral hepatitis is usually indicated in patients with acute hepatitis unless another obvious cause is present. An acute hepatitis panel should include IgM anti-HAV and IgM anti-HBc (both typically positive for only 3–6 months after disease onset), HBsAg, anti-HCV, and HCV RNA (since only about 60% of patients with acute HCV infection have detectable antibody at the time of presentation). Patients with acute HBV usually have both HBsAg and IgM anti-HBc at presentation. Acute HCV may be difficult to distinguish from chronic HCV by serologic findings. Acute HCV should be suspected if anti-HCV is negative but HCV RNA is positive, if both are positive but HCV RNA level

falls or rises on repeat testing after 1–2 months or if anti-HCV titer rises on repeat testing after 1–2 months.

Although Wilson's disease is a rare cause of acute hepatitis, acute presentations of Wilson's disease are often associated with acute liver failure and frequently fatal without transplantation. Traditional tests for chronic Wilson's disease, including ceruloplasmin, urine copper, and serum copper can be normal or misleading with acute presentations. The clinical picture of acute hepatitis with mildly elevated AST, usually higher than ALT, hemolytic anemia, increases in unconjugated bilirubin, and acute renal failure is highly suggestive of acute Wilson's disease; low ALK (well below the lower limit of normal) is a highly suggestive finding as well [16].

Prognosis in acute hepatitis is usually good, and levels of AST and ALT are not helpful in predicting outcome. The most reliable clinical feature in predicting outcome is hepatic encephalopathy. The most reliable routine tests for predicting prognosis are prothrombin time/INR and in some causes of liver injury bilirubin levels. Table 4.2 summarizes data on prognostic tests in various causes of acute hepatitis. In a recent study, clinical and laboratory features were found to be more reliable than scoring systems but the study was limited to patients with viral hepatitis [17].

Acute bile duct obstruction (usually due to choledocholithiasis) can produce a clinical picture that initially resembles acute hepatitis (Table 4.1). In the first day or two, AST and ALT are often significantly increased while ALK is normal or only slightly increased. As obstruction persists, AST and ALT gradually decrease, while ALK and bilirubin gradually increase consistent with the more typical pattern of obstruction. In the early stages history (abrupt onset of right upper quadrant pain) and imaging studies showing dilated ducts may be diagnostic although in very early obstruction ductal dilatation may not be present.

Chronic hepatitis is usually not a major concern in anesthesia or critical care medicine although mild impairment in drug metabolism may be present [8]. Chronic hepatitis is usually recognized by mild (typically 1–5 times the upper



**Table 4.2** Features suggesting poorer prognosis in acute hepatitis

	Total bilirubin	PT/INR	NH <sub>3</sub>	MELD score	Encephalopathy
Viral hepatitis	No	>1.3	>200	No	Yes
Alcoholic hepatitis	Yes <sup>a</sup>	Yes <sup>a</sup>	No	>11	Yes
Acetaminophen	No	If >1.3 at 4 days	>200	?	Yes
Drug-induced liver injury	>5	No	?	No	Yes
Ischemic hepatitis	No	No	No	No	No

<sup>a</sup>Included in Discriminant Function: DF=4.6 (PT—normal PT)+bilirubin (mg/dL)

MELD—model of end stage liver disease. MELD score is calculated as  $[3.8 \times \ln \text{bilirubin (mg/dL)}] + [11.2 \times \ln \text{INR}] + [9.6 \times \ln \text{creatinine (mg/dL)}]$

Values of 32 or above indicate possible benefit from glucocorticosteroids

limit of normal) increases in ALT, with lesser increases in AST. Other liver-related tests are usually normal. The vast majority of cases are due to chronic infection with HBV or HCV, or to nonalcoholic fatty liver disease. The major concern in patients with chronic hepatitis is progression to cirrhosis which is estimated to occur in almost half of the patients with chronic HCV after 20–30 years of chronic infection [18].

Chronic obstruction if not accompanied by jaundice does not have a significant effect on liver function. Chronic cholestasis is often recognized by the presence of persistent increases in ALK and GGT. If obstruction does not block drainage from most of the liver jaundice is typically not present. In some cases mild increases in AST and ALT (usually <2 times the upper reference limits) are also present. Common causes for chronic obstruction without jaundice include stable narrowing of extrahepatic bile ducts (strictures, primary sclerosing cholangitis) or intrahepatic bile passages (primary biliary cirrhosis). Primary sclerosing cholangitis often causes episodes of acute obstruction and cholangitis, and may necessitate admission to critical care units. It is typically recognized by presence of multiple, irregular constrictions of the bile ducts often associated with ulcerative colitis. Congestive heart failure may produce a picture that resembles chronic cholestasis with normal to mildly increased AST and ALT, increased ALK and GGT along with increased bilirubin (occasionally >10 mg/dL) [19]. Bilirubin is a strong predictor of adverse outcomes in patients with heart failure [20].

Cirrhosis is the end stage of chronic liver injury from any of a large variety of causes. Recognition of cirrhosis is not reliable in its earliest stages unless biopsy or abdominal imaging is performed. In ambulatory patients abnormal liver function (low albumin with normal or increased total protein, increased INR, increased indirect bilirubin) along with other features often seen in cirrhosis (AST increased more than ALT, thrombocytopenia) may raise the suspicion for hepatic cirrhosis. Such findings are helpful in evaluating patients before elective non-hepatic surgery and anesthesia but are not reliable in critically ill patients since nonspecific changes may affect these tests in the setting of acute illness.

In both critical care and anesthesiology the likelihood of adverse outcomes is related to the severity of liver dysfunction. Patients with esophageal varices or ascites have significant portal hypertension and therefore are likely to have substantial functional hepatic impairment. Although a poor marker of hepatic encephalopathy ammonia levels do correlate with degree of portal hypertension; one recent study found that elevated ammonia levels predicted the presence of ascites and varices [21]. Two different scoring systems have been developed to assess risk of mortality in hepatic cirrhosis. The Child-Pugh classification system of cirrhosis has been used for many years to classify patients with cirrhosis (Table 4.3). Patients with class A cirrhosis have near-normal operative mortality while those with class B or C cirrhosis have progressively higher mortality rates. The MELD score, developed to predict outcome after transvenous intrahepatic

**Table 4.3** Calculation of Child-Pugh score and class

Feature	One point	Two points	Three points
Bilirubin (mg/dL)	<2	2–3	>3
Albumin	>3.5	2.8–3.5	<2.8
INR	<1.7	1.8–2.2	>2.2
Ascites	None	Controlled or mild-moderate	Poorly controlled
Encephalopathy	None	Controlled or mild (grade 1–2)	Poorly controlled or severe (grade 3–4)

Class A—score 5–6; Class B—score 7–9; Class C—score >9

shunt procedures and used to predict survival of patients awaiting liver transplantation is also a good predictor of perioperative mortality. A large retrospective study found a low operative mortality in cirrhotic patients with a MELD score <8, while >50% of patients died with a MELD score >20 [22]. In a smaller study, MELD score and Child-Pugh score performed comparable in predicting operative mortality [23]. Only few small studies have directly compared the two classification systems and it is therefore difficult to draw reliable conclusions as to whether one is superior to the other.

## Liver Transplant Monitoring

Orthotopic liver transplantation has become an increasingly used procedure for treatment of patients with liver failure. While the liver is considered an immunologically privileged site transplant rejection is a common complication. Following transplantation, there is typically a rapid improvement in tests of liver function (bilirubin, INR) and injury (AST, ALT). Acute cellular rejection, the most common form of rejection occurs in about half of all transplanted livers, often within the first several weeks after the procedure. The earliest signs of rejection are increases in liver-associated enzymes, particularly GGT and ALK, ALK typically rises first, likely due to injury of the bile ducts that is a histologic feature of acute rejection [24]. Although increases in bilirubin, AST, and ALT tend to occur later, a study using neural networking found that the rate of change of these two markers and time since transplantation was a fairly

sensitive and specific predictor of rejection [25]. This may be because serum bilirubin, AST, and ALT correlate well with the severity of rejection while GGT and ALK only correlate with presence of bile duct injury on biopsy [26].

Laboratory tests alone are not considered reliable indicators of rejection, since a number of other factors can cause liver damage in the postoperative period. These include ischemic injury to the liver during pre-transplant handling (cold and warm ischemia), surgical complications such as bile duct strictures and vascular damage and recurrence of the underlying cause of liver disease. Recurrence seldom is an issue in the first several weeks after transplantation however ischemic injury and surgical complications often become apparent early after transplantation. Liver biopsy is therefore usually performed in recipients with unexplained increases in liver-related tests.

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## **Part II**

# **Anesthesiology for Liver Transplantation**

J.R. Klinck

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## Introduction and Early Development

Clinical liver transplantation began in the 1960s, but depended on key advances in immunology and experimental kidney transplantation over several preceding decades. Carrel described organ transplantation in animals in 1908, and was awarded the Nobel Prize in 1912 for pioneering the techniques of vascular anastomosis. In the 1930s, he worked on the extracorporeal perfusion of organs, collaborating with the famous aviator and inventor Charles Lindbergh to develop an apparatus that preempted the modern heart-lung machine. However, Carrel's laboratory transplants and Voronoy's attempts to transplant human kidneys in the late 1930s failed consistently from ischemic injury or the abrupt onset of rejection. Rejection was thought to be a nonspecific inflammatory process until Medawar's groundbreaking work in the 1940s showed that it was an acquired and donor-specific response generated by the host's immune system, possibly amenable to therapeutic manipulation. Medawar and others also established that rejection was predominantly lymphocyte-mediated, leading to experiments with whole-body radiation and donor bone marrow infusion, known to induce

tolerance in animals, in the 1950s. These included human kidney transplants, which were aided by the introduction of hemodialysis, but results remained poor. By 1960, however, azathioprine and steroids had also been found to suppress cell-mediated immunity and several groups had established animal models of kidney and liver transplants to study immunosuppression [1].

Welch described the first experimental liver transplant in 1955, placing a canine liver graft in the abdomen heterotopically, without removal of the native organ. The liver was found to be less vulnerable to rejection than the kidney, but without portal inflow it rapidly atrophied and was thus unsuitable for studies of immunosuppression. However, the belief at the time that the liver mediated rejection and might therefore be tolerated if removed from the recipient, led to the development of the replacement (orthotopic) technique. Rejection was not prevented, but the orthotopic technique created an enduring model for experimental immunosuppression and a method of implantation that remains the standard today. With confidence in the surgical technique and useful experimental data on azathioprine and steroid-based immunosuppression, Starzl performed the first human liver transplant in a 3-year-old child with biliary atresia in Denver in 1963 [2].

Calne refined a pig model and began clinical liver transplantation in Cambridge in 1967. Starzl and Calne continued experimental work on surgical technique, preservation, and immunosuppression, and performed a number of human liver

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transplants throughout the 1970s. However, survival at 1 year remained less than 25%, and it was not until the discovery of cyclosporin and its introduction into clinical practice in the late 1970s that rejection could be controlled. This provided the breakthrough needed to move the procedure beyond its 20-year experimental phase into mainstream care [3].

The US National Institute of Health (NIH) Consensus Conference on Liver Transplantation in 1983 signaled recognition of the operation as worthy of broader introduction [4]. At that time four pioneering liver transplant centers (Denver, Cambridge, Hannover, and Groningen) presented results of 540 grafts, and demonstrated much better outcomes compared with matched controls which were not transplanted. In cyclosporine-treated recipients 1-year survival was 60%, vs. 25–35% in the pre-cyclosporine era. Organ donation legislation, using the Harvard Criteria to define brain death, and important advances in liver procurement and preservation also made vital contributions to this success [5].

From 1983 continuing into the 1990s, a positive cycle was created and produced rapid growth in liver transplant numbers. Better results brought more referrals, and more experience yielded better results. Specialists in a range of supporting disciplines were attracted to the challenges presented by transplant patients and brought wider expertise to liver transplant teams, further enhancing care. Today more than 6,000 patients receive liver transplants worldwide each year. One-year survival is >85%, while 5- and 10-year survival and quality of life for the majority of recipients are excellent.

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### **Evolution of Surgical Technique: Caval Replacement Versus Piggyback, Use of Venovenous Bypass**

Although both main techniques of whole-liver grafting, namely caval replacement (classical) and caval preservation (piggyback), date from the first clinical descriptions in the 1960s, the relative simplicity and greater laboratory experience of caval replacement led to its rapid adoption as the

standard method. Also, while in animal models full caval and portal clamping caused fatal splanchnic stasis and hypotension unless an extracorporeal portosystemic shunt was used, it was tolerated in humans without shunting, further reducing the incentive to apply the more demanding piggyback technique.

However, most of the early recipients were children or relatively fit adults with tumors, and with more experience it became clear that some recipients tolerated clamping poorly. Moreover, the deteriorating state of the patient during the anhepatic phase meant that implantation needed to be performed quickly, by a very experienced surgeon, which made teaching difficult. Passive shunts were tried but some clotted or caused fatal thromboembolism. In Cambridge Calne developed a technique of venoarterial (femoral vein to femoral artery) pumped perfusion with heparinization and an oxygenator, which was implemented in five patients intolerant of a trial clamping of the IVC. This was reported to have restored arterial blood pressure, clearly by increasing and redistributing arterial blood volume rather than supporting venous return. All survived the transplant but four of the five patients died within a few weeks of surgery. An intraoperative death in Pittsburgh in 1982 partly attributed to severe splanchnic stasis led to a trial of a roller pump-driven venovenous bypass circuit with systemic heparinization. Although this was successful in several patients, deaths from uncontrolled bleeding soon followed. Late in 1982, a newly developed centrifugal blood pump, causing less turbulence than conventional roller pumps and already in use without heparin in patients on membrane oxygenators, was trialed successfully in animal transplant models. This was used in human liver recipients from January 1983 on, and with the addition of heparin-bonded tubing, became standard care in adult liver transplants in Pittsburgh for the next 20 years [2].

The adoption of venovenous bypass was widespread thereafter, given the preeminence of Pittsburgh in training in liver transplantation and the facilitating role of bypass in the surgical teaching of liver implantation. In Cambridge, although the venoarterial technique was

abandoned after 1983, venovenous bypass as developed by Shaw and Starzl was used only occasionally. A percutaneous technique for outflow and/or return was developed independently in several centers in the mid-1980s, reducing the incidence of wound infection and axillary lymphocele associated with cut-downs. This continues to be used.

However, routine use of venovenous bypass in adult recipients has declined progressively over the past 15 years for several reasons. First, many long-established programs have used it only occasionally, including Cambridge UK, London Ontario, University of Minnesota, and University of California San Francisco, and it has never been used routinely in children. A number of fatalities have been associated with its use mainly due to perforation of central veins when large-bore percutaneous access is used, and observational studies have not shown any clear benefit. Probably most significant is that the piggyback technique has become more widely practiced, providing better hemodynamic stability by preserving some caval flow during the implantation phase.

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## Evolution of Anesthesia and Perioperative Care

Early descriptions of anesthesia for clinical liver transplantation come from Aldrete in Denver [6] and Farman and Lindop in Cambridge [3]. Most of the key problems were identified, including hemodynamic instability, hemorrhage, hypocalcemia, hypothermia, and acidosis. Changes in cardiac output, vascular resistances, and pulmonary artery occlusion pressure were reported by Carmichael in 1985, who placed pulmonary artery catheters in a series of patients in Cambridge [7]. Similar observations were reported by Marquez and colleagues in Pittsburgh [8]. Transient but occasionally severe reperfusion hyperkalemia was also described which remains a cause of intraoperative cardiac arrest and death to this day. Use of the pulmonary artery catheter in the critical care setting declined sharply after a randomized trial in 2005 demonstrated no benefit. However it is still widely used in cardiac surgery

and liver transplantation, where the diagnosis and management of pulmonary hypertension and frequent measurement of cardiac index still provide compelling reasons for its use. Rapid point-of-care measurement of blood gases, available only from the late 1970s, was gradually extended to include sodium, potassium, ionized calcium, hemoglobin, and lactate over the next 20 years and has been a standard of care for many years.

Anesthetic agents used in the earliest descriptions included fluoroxene, trichloroethylene, and nitrous oxide. Halothane was widely used in the 1970s but avoided in liver surgery because of rare but severe hepatotoxicity. Enflurane (from 1975), isoflurane (from 1982 and still widely used), and later desflurane and sevoflurane became the agents of choice, influenced by the work of Gelman and others on the effects of anesthetic agents on splanchnic blood flow [9]. High-dose fentanyl (50–100 ug/kg) as a sole anesthetic agent, then popular in cardiac surgery but associated with reports of awareness, was used in some centers in the 1980s.

Changes in coagulation and the use of coagulation tests, including factor assays and serial thromboelastograms, were well described by Groth in 1969 [10]. He reported both hyperfibrinolysis and unexpected venous thrombosis and pulmonary emboli along with treatments including epsilon-aminocaproic acid, fibrinogen, heparin, and protamine. He also observed that a functioning graft was critical to normalization of clotting. The use of fresh whole blood was described by Aldrete, and also advocated by Farman [6]. Kang reported in detail on the use of thromboelastography and the diagnosis and management of hyperfibrinolysis in liver recipients in 1985, establishing TEG as a valuable point-of-care modality. It is now widely used and refinements continue to be developed [11].

The use of targeted antifibrinolytic therapy as demonstrated by Kang was extended to prophylactic use in many liver transplant units following the publication of a randomized trial of aprotinin in cardiac surgery by Royston in 1987. Significant reduction of blood loss during liver transplants was later demonstrated in double-blind, randomized trials of tranexamic acid and aprotinin.



However, aprotinin was removed from the market in 2008 when studies in cardiac surgery suggested an increased risk of multi-organ failure and death. Tranexamic acid continues to be used prophylactically in selected patients in many centers.

Further early improvements in anesthesia care included adequate fluid warming, warm water mattresses, and forced-air warming from the mid-1980s. Commercial cell salvage systems were developed in the early 1980s, coinciding with the rapid growth of cardiac and major vascular surgery and liver transplantation. Concerns about the safety of donated blood, given the epidemic of HIV at that time, and the rising costs of transfusion were major stimuli to the introduction of this technology. Rapid infusion systems, such as that developed by Sassano in Pittsburgh in 1982 using a fluid reservoir, mechanical pump, counter-current fluid warming, and air detector, became commercially available in the mid-1980s and are now used in most liver transplant units.

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### **Fast Tracking and Early Postoperative Care**

Early reports of clinical liver transplantation describe elective postoperative ventilation for up to 24 h [3, 6]. The rapid growth in surgical and anesthetic experience through the 1980s and 1990s, the introduction of shorter-acting anesthetic agents, muscle relaxants and analgesics, and better prevention of hypothermia and bleeding led to efforts to wean patients from mechanical ventilation earlier. Improved patient selection, cost considerations, and limited availability of critical care beds also contributed. Several units reported safe extubation of selected patients in the operating room from the mid-1990s, and a multicenter trial published in 2006 demonstrated cost-effectiveness [12]. “Fast tracking”, or extubation in the operating room with subsequent admission to a high-dependency area, is now well-established, although in most units a policy of ICU admission and extubation within a few hours is usual. Early extubation after liver transplant depends on good graft function, minimal comorbidity, and low operative blood loss.

The use of epidural analgesia was described in the early Cambridge series by Lindop [3], although it was stopped owing to concerns about the perioperative evolution of coagulation. Although this and other series have been described, including one from King’s College Hospital in London of over 140 patients, the rapid onset of coagulopathy from poor graft function cannot be predicted and careful assessment of risk-benefit has been advocated.

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### **Trends in Liver Disease, Donation, and Organ Allocation**

Over the past 25 years, the success of liver transplantation has led to a huge increase in referrals for treatment. Epidemics of hepatitis C, alcohol-related disease, non-alcoholic fatty liver disease, and hepatocellular carcinoma in aging populations have compounded this effect. However, the supply of cadaveric, heart-beating donors has been even or declining since the early 1990s, a result of demographic changes and improvements traffic safety and critical care. Waiting list mortality has increased, stimulating the development of alternative sources of organs for transplant. Technical innovations such as split-liver donation to two recipients have helped, but few donor livers are suitable for this. Livers from marginal donors are increasingly used, and research allowing better prediction of graft function in older and otherwise suboptimal donors continues.

Living donor liver transplantation (LDLT) has also developed to meet this need and to allow treatment of patients in countries where the use of heart-beating donors is outside cultural norms. LDLT programs have grown rapidly since the first successful adult-to-child living donor procedure by Strong and Lynch in Brisbane in 1989. Although living donation peaked in the United States in 2001 at over 500 transplants, it has since fallen in North America and Europe after donor deaths. Nonetheless, it is the main source of organs in Japan, Korea, Hong Kong, Taiwan, Turkey, India, and the Middle East. Recipient survival is now as good as that obtained in cadaveric



donation but significant donor morbidity and mortality remain a striking negative feature.

Donation after cardiac death has been a source of donor organs for many years in some centers, particularly in Spain, but has recently gained wider acceptance in North American and other European countries. This has the potential to make a significant difference to donation rates, although outcomes, especially in terms of biliary complications, remain poorer than those seen in cadaveric donation. Research into improved preservation techniques in this setting, including normothermic machine perfusion, continues.

The management of waiting lists and organ allocation has evolved significantly in the past 30 years. The choice of recipient from among size and blood group-matched peers was typically carried out by transplant center physicians, based on geography, subjective judgments of need or benefit, poorly validated prognostic scoring, or even length of time on the waiting list. A move to a “sickest first” model based on MELD (Model for End-stage Liver Disease) was implemented in the United States in 2002, and has now been adopted in varying forms in most other countries. The MELD score is derived from three simple laboratory assays (International Normalized Ratio of the prothrombin time, creatinine, and bilirubin) and was developed at the Mayo Clinic to predict survival in end-stage liver patients after transjugular intrahepatic portosystemic shunting. It has been shown to predict transplant waiting list mortality and to improve overall survival when used to prioritize listed patients, although exception rules are needed in conditions such as hepatocellular carcinoma. This allocation system has been criticized, however, since it does not maximize “transplant benefit”, or life-years gained after transplantation.

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### **Worldwide Growth, Regulation, and Academic Organizations**

The number of liver transplant programs in North America and Europe increased rapidly after NIH endorsement in 1983, slowing only in the

mid-1990s when the donor supply reached a plateau. From about 2000 on economic development initiated a second phase of rapid expansion, mainly in China, Eurasia, the Middle East, India, and South America. Living donation has accounted for much of this growth. Established in Japan, Korea, and China since the mid-1990s, living donor programs have grown rapidly in Turkey, Egypt, and India in the past 10 years and continued expansion is likely. There are now more than 500 liver transplant centers in 81 countries across the world [13].

Organizations to promote and coordinate organ procurement and distribution, and to monitor and maintain standards in liver transplantation have been created in all countries in which national legislation addressing transplantation has been passed. In the United States the United Network for Organ Sharing also funds the Scientific Registry of Transplant Recipients. There are comparable bodies in European, Australasian, Asian, and South American countries, although data quality, transparency of outcomes, and overall effectiveness are reported to vary between organizations.

National and international academic societies contribute enormously to progress in the field by supporting education, mentorship, and research, and by advising on standards. These include the following:

- International Liver Transplantation Society (ILTS)
- The Transplantation Society (TTS)
- American Association for the Study of Liver Diseases (AASLD)
- European Association for the Study of the Liver (EASL)
- American Society of Transplantation (AST)
- European Society of Organ Transplantation (ESOT)
- American Society of Transplant Surgeons (ASTS)
- Liver Intensive Care Group of Europe (LICAGE)
- European Liver and Intestinal Transplant Association (ELITA)

Many smaller national specialist societies are also very active in this field.

## Conclusion

The history of liver transplantation, spanning only a few decades, provides one of the most compelling and multifaceted accounts of scientific progress in the history of medicine. The procedure has yielded dramatic improvement in survival and quality of life for tens of thousands of patients and has engaged the talents and imaginations of an ever-increasing community of physicians and scientists around the world. However, important challenges remain, many of which could be effectively addressed by anesthesiologists and intensivists in the perioperative period. Important goals include increasing the supply of donor organs, improving the preservation of those from non-heart-beating and marginal donors, optimizing the function of those transplanted and preserving function in other organs. All of these could be pursued in interventional studies led by perioperative and critical care physicians.

Well-designed observational studies relating to the care of liver donors and recipients in the perioperative period would also greatly enhance progress in this field. Initiatives to collect standardized data on comorbidity, perioperative techniques, and outcomes should be supported. Krowka and Mandell's multicenter report on portopulmonary hypertension [14], which answered many key questions on this condition and altered management significantly, provides an excellent example of the value of such an effort. Survey data on perioperative management published by Walia and Schumann [15] showed that voluntary data collection is achievable with a well-designed user interface. Although obstacles to this ideal remain, they should not be insurmountable, and web-based data collection is now relatively simple and inexpensive. Efforts in this direction are underway, supported by many of the authors in this volume.

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# Recipient and Donor Selection and Transplant Logistics—The European Perspective

# 6

Gabriela A. Berlakovich and Gerd R. Silberhumer

The intermediate and long-term outcome following orthotopic liver transplantation (OLT) has improved significantly over the years, with 1- and 5-year patient survival rates of 90% and 75%, respectively. This success resulted in growing numbers of potential transplant recipients on waiting lists. The unchanged number of liver grafts during the last decades cannot meet the increasing demand for available organs (Fig. 6.1). Therefore regardless of various organ allocation policies adopted by transplant programs, waiting list mortality remains a major problem. This chapter will describe the current situation in Europe with special emphasis on efforts to increase the availability of liver grafts.

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## Recipient Prioritizing

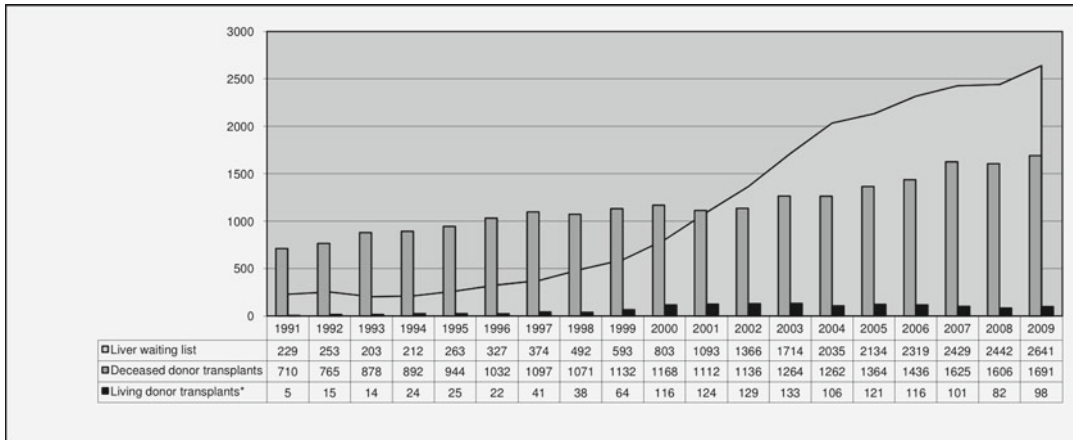
In most transplant centers all over the world liver allocation is performed on the basis of the MELD score [1], which predicts waiting list survival at 3 months. For some underlying diseases severity of chronic liver failure is not reflected by laboratory MELD (lab MELD) score, such as hepatocellular carcinoma in mild cirrhosis, some metabolic diseases, and others. Therefore, standard exceptions were defined that receive usually

22 MELD points (15% 3-month mortality equivalent). Patients can be requested for a standard exception (SE) at any time after registration in the Eurotransplant area. Recipients must fulfill country- and disease-specific criteria before the exceptional MELD (match MELD) can be approved. If the exceptional MELD was approved, this status is granted for the duration of 90 days. Before the expiry of this 90-day period the SE status must be reconfirmed.

In Eurotransplant MELD allocation was introduced in 2006, but typically for the heterogeneity in Europe modalities are somewhat different between the countries. Germany, Belgium, and the Netherlands pursue a patient-based allocation system according to match MELD. In contrast, Austria, Croatia, and Slovenia use a center-oriented allocation system. The advantages of allocation based on the MELD score is the transparency and objectivity. Nevertheless, medical urgency is not always appropriately expressed by the MELD system and for several disease patterns standard exceptions have been defined to overcome this problem. Another significant disadvantage under strict patient-oriented allocation system (according to MELD) is the impossibility for donor and recipient matching. For example ECD organs may have a higher risk for initial dysfunction, fair even worse with prolonged cold ischemia time and may therefore not be suited for every candidate. Despite a number of models predicting outcome based on donor and recipient factors [2–4] the clinical judgment of the transplant team has the final decision.

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**Fig. 6.1** Dynamics of the Eurotransplant liver waiting list and liver transplants between 1991 and 2009 [1]

## Organ Distribution

Objectives of Organ Procurement Organizations (OPOs) are almost comparable all over the world and aim to achieve an optimal use of available donor organs and secure a transparent and objective allocation system. Furthermore, they assess the importance of factors that have the greatest influence on waiting list mortality and transplant results. OPOs also promote, support, and coordinate organ donation and transplantation. In Europe many different OPOs exist: national structured agencies like in Spain, France, or Italy as well as multinationally structured agencies. Within a multinational OPO legislation the national legislation is prioritized over international interests of the organization, for example, when it comes to issues such as presumed or informed consent for organ donation. The most important multinational OPOs in Europe are the following:

- Scandiatransplant [5] is the Scandinavian organ exchange organization and covers a population of 24.5 million in five countries (Denmark, Finland, Iceland, Norway, and Sweden). The most frequent exchanged organ between centers within Scandiatransplant is the liver followed by heart. The overall exchange rate of kidneys has stabilized around 12% during the last years. One third of kidney transplants are performed from living donors.
- NHS Blood and Transplant [6] combines the United Kingdom and the Republic of Ireland

with a total population of 65.4 million. Donor livers are not allocated to patients but are center-specific according to the “Donor Organ Sharing Scheme” prepared by the Liver Advisory Group. Following these general principles donor/recipient matching should be provided, especially for livers derived from donors with extended criteria.

- Eurotransplant [7] is the central European OPO and covers a population of 124.6 million inhabitants in seven countries (Austria, Belgium, Croatia, Germany, Luxemburg, the Netherlands, Slovenia). The most frequently exchanged organs between centers are kidneys. In the setting of acute liver failure the next available appropriate organ within the ET area is offered to the requisitioning transplant center. Liver exchange thereafter follows a payback system, which means that the recipient center has to offer the next available donor liver of equal blood group to the previously donating center. Allocation priority is ranked from “high urgency” to “accepted combined transplantation” to “center” to “ET pool.”
- The Spanish transplant system [8] is well known all over the world as (one of) the most successful in the world with more than 35 donors per one million inhabitants. The main principles of the Spanish Model of Organ Donation are an unrivaled transplant coordination network. In-house coordinators perform a continuous audit on brain deaths and

outcome after donation at intensive care units in transplant procurement hospitals. They are specially trained in communication with hospital staff as well as relatives. A central office as an agency in support of the process of organ donation has a great influence on medical training and maintains close relationships with the media and intensive care units.

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## Donor Selection

The disparity between organ demand and available grafts has increased over the past years. Since outcome of liver transplantation has improved transplant centers now face the problem of increasing numbers of patients listed for liver transplantation. On the other hand the number of available donors remained stable [7, 9, 10]. Therefore, several strategies have been developed to increase the donor pool (Fig. 6.2a). Most popular strategies are the use of extended criteria donors (ECDs), donation after cardiac death (DCD), and living donation (LD) (Fig. 6.2b).

### Extended Criteria Donor

Several publications convincingly showed that donor factors such as age, gender, race, graft type, and ischemia time affect post-transplant survival [2]. Despite the definition of risk factors, their relative risk for post-transplant primary non-function or poor function is weighted differentially [3, 11] and an accepted definition of ECD livers with cut-off values has not been established yet. Age is one of the best-described extended donor factors. Several studies investigated a donor age older than 55 as significant factor for poorer graft survival [2, 3, 12]. Nevertheless due to changes of the donor demographics in the last decades donor age and age-related comorbidities have increased. Donor death from cardiovascular reason is now more common than trauma as the cause of death [13] and more than 60% of organs are harvested from donors who died due to cardiovascular disease.

Cold ischemic time is another very well-documented donor risk factor and an imprecise cutoff between 10 and 13 h has been investigated [2, 3, 14]. In an era of MELD-based allocation this is a very important aspect. Increased local donor utilization would therefore result in decreased transportation times and reduced cold ischemic times.

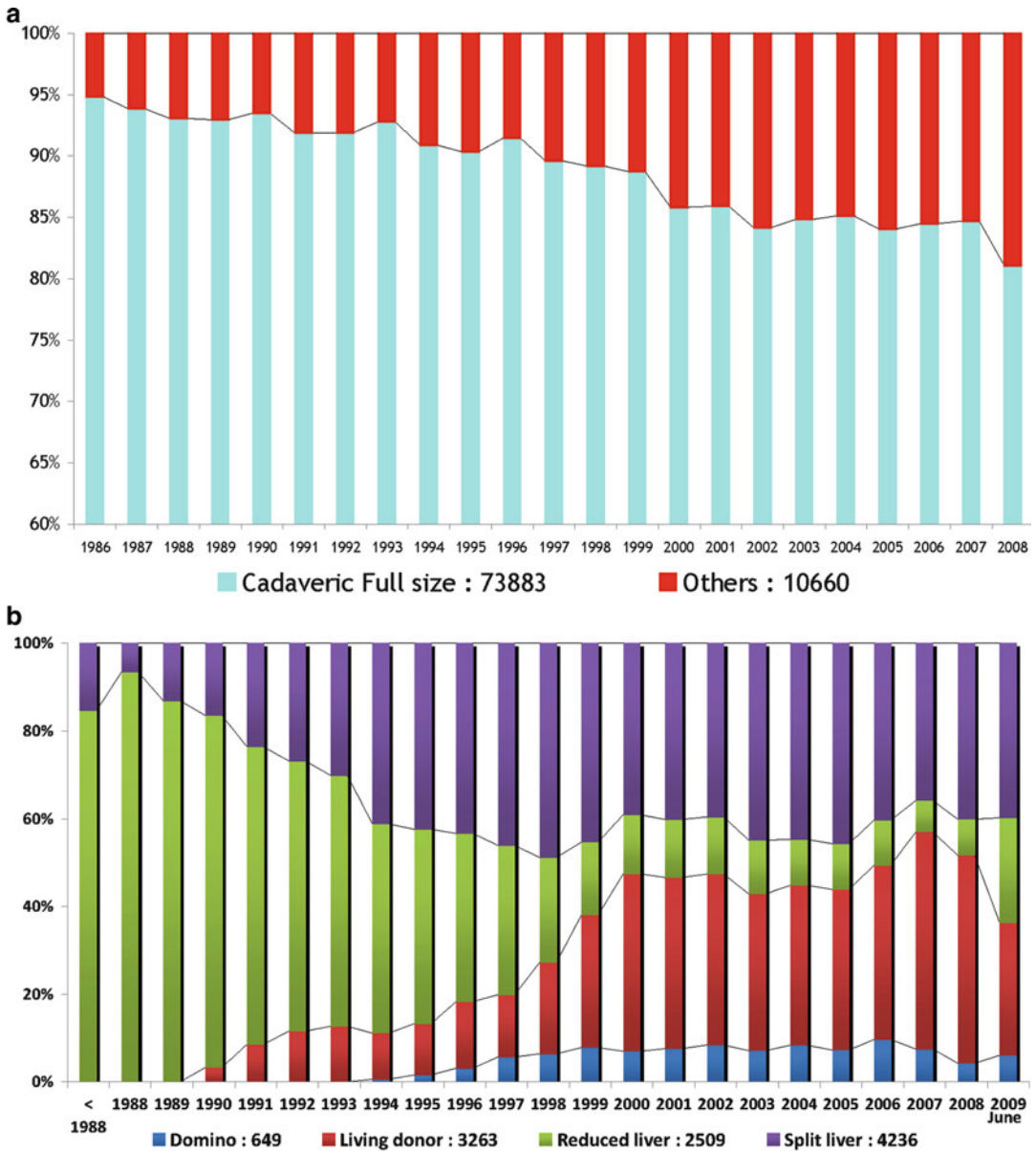
Donor graft quality is one of the main determinants of outcome in liver transplantation. It is difficult to classify the quality of organs based solely on laboratory values however some authors consider donor transaminases levels >150 U/l as risk factors [15, 16]. Increased donor gamma-glutamyl transpeptidase has also been identified as a risk factor for increased 3 months graft failure but not 1-year survival [17]. Biopsy-proven steatosis was responsible for primary non-function rates up to 25% and was highly correlated with increased donor age and obesity [18].

Direct osmolar damage caused by increased plasma sodium levels is responsible for hepatocellular swelling and dysfunction. Totsuka et al. [19] reported comparable outcomes between normonatremic and hypernatremic donors after correction of sodium levels below 155 mEq/ml. However we found that the peak sodium values during the intensive care unit stay was a significant factor for post-transplant outcome [17]. This supports the theory that a short duration of plasma sodium value deviations may cause long-lasting damage in hepatocytes due to changes of intracellular osmolarity even when sodium levels are rapidly and aggressively corrected.

### Donation After Cardiac Death

DCD is the donation of organs shortly after cardiorespiratory support has been terminated and cardiac death ensued. Most DCD donors are patients who suffered severe irreversible cerebral injury but not brain death and the family/health care proxies wish to withdraw support. Minutes after death occurred the organs are harvested for transplantation.

The recent increase of DCD in some European countries has contributed to an increase in the number of transplants with outcomes comparable



**Fig. 6.2** (a) Type of liver graft in Europe according to the date of transplantation. (b) Alternatives to the use of full-size cadaveric liver grafts in Europe [3]

to grafts from brain death donors (DBD). However DCD donation may not be necessarily a new and additional source of grafts, as data from the Netherlands [20] indicate because the use of DCD organs may have caused a shift from potential heart-beating donors to DCD. Intensive care providers may be encouraging DCD donation rather than awaiting brain death and subsequent

heart-beating donation. This development could be reversed during the last years, resulting in an effective increase in organ availability.

In DCD organs, the effects of cold ischemia are superimposed by the injury occurring during warm ischemia. Biliary epithelium is particularly vulnerable to ischemia/reperfusion injury and a high incidence of biliary strictures and/or bile



cast syndrome [21, 22] has become of concern. Ischemic cholangiopathy has been reported in 9–50% of DCD recipients. This complication tends to present within the first few months after OLT and may resolve with biliary drainage, require repeated interventions, or lead to graft loss and retransplantation.

In the future extracorporeal machine perfusion of liver grafts may be a potential feature to overcome ischemic cholangiopathy. Various techniques have been investigated in animal studies including normothermic or subnormothermic perfusion [23, 24]. Extracorporeal perfusion may have the ability to “recondition” the damaged liver graft that has undergone warm ischemic injury during DCD procurement [25, 26].

Patient and graft survival rates similar to those of DBD OLT can be achieved by using controlled DCD grafts and very restrictive criteria, despite a higher risk of biliary stricture [27]. Recommended Practice Guidelines have been published recently by ASTS [28] and are similar to selection criteria recommended by European centers [22, 27, 29]. Considering organ shortage and death on the waiting list DCD grafts remain a small but valuable resource.

## Living Donor Liver Transplantation

Unlike kidney transplantation, there has not been clear-cut evidence for a significant advantage in post-transplant survival after living donation yet. The overall results with good patient and graft survival combined with acceptable donor morbidity and mortality has led to the acceptance of LDLT in the transplant community.

Left-lateral LDLT in children has become a standard procedure with excellent results, whereas LDLT in adults has still some conflicting issues. The number of LDLT procedures peaked in 2001 in Europe and the US, thereafter showing a significant decrease of cases in the US and no further increase in Europe. In the assessment of the reason for this development LDLT grafts were most likely to fail because of graft-related issues [10]. Recipients have a higher risk for primary non-function or dysfunction due to small

for size and a significantly higher risk for technical failures, especially biliary and vascular complications. Additionally the mortality risk of approximately 0.2% and morbidity risk of 11–28% for donors represent non-negligible limitations for the use of LDLT grafts.

LDLT accounts for less than 5% of all liver transplants in Europe and US, respectively [9, 10]. The number of LDLT in Asia has continued to increase due to the limitations in DBD caused by legal and cultural restrictions on deceased organ donation. Ninety-five percent of all OLTs in Asia excluding mainland China are LDLT [30].

One of the main advantages of LDLT is the precise scheduling of the procedure due to independence of waiting time and available liver grafts. Therefore OLT can take place according to disease severity and recipient conditions. Especially for patients suffering from hepatocellular carcinoma, LDLT represents a useful treatment option to reduce waiting time and consecutive disease progression.

A potential survival benefit due to decreased death on the waiting list and reduced disease progression has to be balanced with higher morbidity and mortality following transplantation. Future application of LDLT will be based on the accurate definition of risks imposed on donors compared with potential benefits realized by recipients.

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## Conclusion

The progress of transplantation is limited by organ shortage. Several strategies have been developed to overcome this problem during the last few decades. Most important for increasing the pool of deceased donor seems to be education of the public and physicians. It is important to increase the awareness for organ donation and transplantation. ICU staff must be continuously contacted and informed about the benefits of transplantation, and guidelines should be established to support them with donor management. With the current organ shortage a number of patients are rejected as recipients although they may derive a significant benefit from this OLT.

It remains a formidable challenge to balance the demands of individual autonomy of the recipient and the utility of the donor organ on a background of justice and equity.

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# Recipient and Donor Selection and Transplant Logistics: The US Perspective

# 7

Ingo Klein and Claus U. Niemann

Liver transplantation is the therapy of choice for acute liver failure and many forms of chronic liver disease including hepatocellular carcinoma (HCC) in cirrhotic patients. Significant advances in surgical technique as well as the perioperative management have decreased the perioperative (3 month) mortality to about 5% in the USA and Canada. This caused a wide acceptance of the procedure and many liver transplant programs have been emerging throughout the country. As a result, the number of liver transplants in North America has increased more than threefold from about 2,000 transplants per year in 1989 to more than 6,000 liver transplants in 2005 with currently about 120 liver transplantation programs in the United States [1]. Since 2005 the number of transplanted livers has remained stable above 6,000 transplants per year (Fig. 7.1). In addition to liver transplantation for established indications, new developments in the (pre- and post-transplant) medical management of the underlying

liver diseases and the careful evaluation of preexisting conditions and comorbidities (i.e., coronary artery disease) of liver transplant candidates have broadened the indications for liver transplantation even further. This resulted in a tremendous discrepancy of patients listed for liver transplantation and available organs. In 2009 more than 16,000 patients were actively listed on the United Network for Organ Sharing (UNOS) waiting list for liver transplantation compared to 6,651 liver transplants performed in 2009 by the USA and Canadian transplant centers. The number of patients who died waiting for a liver transplant remained relatively stable around 2,000 listed patients per year over the last several years, however, this number does not account for the substantial number of patients who were removed from the waiting list for example secondary to tumor progression [1].

Liver cirrhosis secondary to Hepatitis C virus infection is the leading indication for liver transplantation in the United States with around 2,400 performed liver transplants annually comprising about 35% of the total number of liver transplants [2]. The number of transplant recipients with malignant neoplasms has increased from 100 cases in 1999 to 1,061 cases (17.5%) in 2008, which is the largest increase for any indication over the past decade. The absolute numbers for cholestatic liver disease/cirrhosis and acute hepatocellular necrosis have remained relatively stable since 1999; however, the relative percentage of these two indications has decreased with the overall increase in transplant numbers (Table 7.1).

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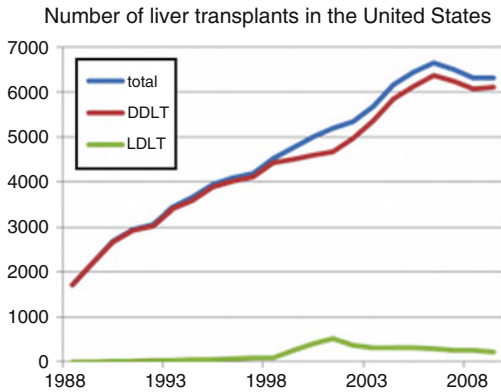
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**Fig. 7.1** Number of liver transplants in the United States from 1988 to 2008. *DDLTL* deceased donor liver transplant; *LDLTL* living donor liver transplant

It is expected that nonalcoholic steatotic hepatitis (NASH) will become one of the most frequent indications for liver transplantation in the United States within the next decade.

While the absolute number of deceased liver donors in the United States has increased from 1,833 in 1988 to 6,740 donors in 2009, the proportion of young donors aged 11–34 years has decreased in half from 61% in 1988 to 32% in 2009, whereas the proportion of older donors has increased substantially following critical evaluation of older donors for certain transplant indications [3, 4]. In 2009, donors 50 years and older comprised more than one third (35%) of the entire deceased donor population (Fig. 7.2). During the same time period, the proportion of donors dying from anoxia has almost doubled from about 10% in 1988 to 18% in 2007, while the proportion of head trauma decreased from 43 to 37%.

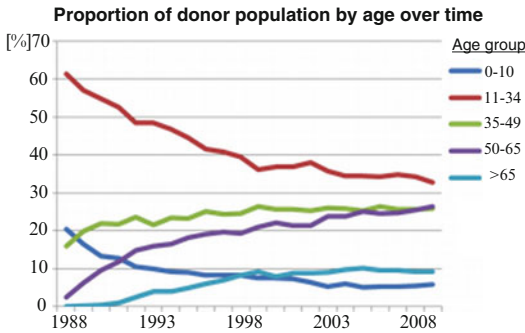
### Liver Allocation in the USA: From Waiting Time to Medical Criteria

The allocation of deceased donor livers in the United States before 1996 prioritized the patient's level of care with the first priority given to patients continuously requiring treatment in Intensive Care Units (ICUs) for medical complications such as exacerbation of hepatic encephalopathy, variceal bleeding not manageable by endoscopic therapy or hepatorenal syndrome. The second

priority was given to patients who required continuous hospitalization and the third priority was given to patients with compensated end stage liver disease who were managed on an outpatient basis. With an increasing number of patients awaiting liver transplantation, waiting time was used to prioritize within these groups. Since ranking into one of the three categories was primarily based on center-specific criteria and subjective interpretation of the patients' condition, the Child-Turcotte-Pugh scoring system was introduced in 1996 to categorize patients for chronic liver failure in the spirit of the existing categories: Status 2a with a CTP score  $\geq 10$  or admission to the ICU; status 2b with a CTP  $\geq 10$  or CTP  $\geq 7$  in conjunction with at least one major complication of portal hypertension or stage 1 HCC. Status 3 was attributed to patients with CTP  $\leq 7$ . The highest priority (status 1) was reserved for patients with fulminant hepatic failure, primary graft non-function, hepatic artery thrombosis within 7 days after transplantation, and decompensated Wilson's Disease (which remained essentially unchanged in the present allocation system). This allocation system created three large categories for chronic liver patients and the amount of waiting time on the list was used to prioritize liver allocation within these groups. Subjectivity in grading hepatic encephalopathy and ascites, important components of the score, posed another inherent problem of the Child-Turcotte-Pugh scoring system. Furthermore patients were listed long before their actual need for liver transplantation in order to be on top of the waiting list by the time they actually needed a liver transplant. This allocation system resulted in a dramatic increase of patients listed for transplantation and on the other hand a large number of patients who died waiting for a liver transplant because they were not listed early enough to accumulate enough waiting time. Evaluation of the allocation system revealed that apart from its subjective components, time spent on the waiting list was not associated with an increased death rate (higher mortality risk) [5] and did not reflect any medical need for liver transplantation [6, 7]. In 1998 the Department of Health and Human Services Final Rule determined that objective

**Table 7.1** Percentages of cholestatic liver disease/cirrhosis and acute hepatocellular necrosis

	1999	2008
Non-cholestatic cirrhosis	64.4% (2,895)	55.9% (3,391)
Cholestatic liver disease/cirrhosis	11.1% (498)	7.8% (475)
Acute hepatic necrosis	9% (405)	5.3% (324)
Biliary atresia	4.2% (188)	3% (180)
Metabolic disease	3.3% (150)	3% (180)
Malignant neoplasms	2.2% (97)	17.5% (1,061)
Other	5.9% (265)	7.5% (458)



**Fig. 7.2** Proportion of donor population by age over time from 1998 to 2009

medical criteria should determine the priority for liver allocation [8]. A report of the Institute of Medicine [9] recommended that short-term mortality risk would be a more appropriate measure to prioritize liver transplant candidates and the model for end stage liver disease (MELD score) was chosen to rank chronic end-stage liver disease patients for liver transplantation with waiting time being only a subordinate component of liver transplant allocation. The MELD score was originally developed to assess the short-term prognosis of patients evaluated for transjugular intrahepatic porto-systemic shunt (TIPS) procedures and utilizes three objective, reproducible, and patient-specific standard lab values (INR, bilirubin, and creatinine) to calculate a score that can be used to predict 3-month mortality (Table 7.2). Several modifications were made by UNOS before utilizing it as part of the liver transplant allocation algorithm: The score is capped at a maximum of 40 points, ranging from 6 to 40. The serum creatinine value is capped at 4 mg/dL and is set to its maximum if the patient underwent hemodialysis twice or had continuous renal

**Table 7.2** 3-Month mortality

MELD score	3-Month mortality (%)
6–9	1.9
10–19	6
21–29	19.6
30–39	52.6
≥40	71.3

$$MELD = (0.957 \times \log[\text{creatinine mg/dL}]) + (0.378 \times \log[\text{bilirubin mg/dL}]) + (1.12 \times \log[\text{INR}]) + 0.643 \times 10$$

$$PELD = (0.43 \times \text{age}) - (0.687 \times \log[\text{albumin g/dL}]) + (0.480 \times \log[\text{bilirubin mg/dL}]) + (1.857 \times \log[\text{INR}]) + (\times \text{growth failure } 0 \times 10)$$

replacement therapy for more than 24 h within the last 7 days. Any value under one for creatinine, bilirubin, or INR was fixed at one to prevent the occurrence of negative scores.

For pediatric use, creatinine was removed since it was not found to predict short-term mortality. Serum albumin, growth failure (yes/no), and age (<1 year/>1 year) proved to be important prognostic factors in infants and children and were included in the pediatric end-stage liver disease model (PELD) [10] (Table 7.2).

The MELD score system was validated to accurately estimate the disease severity and predict the 3-month survival of patients with chronic liver disease at the time of listing and was therefore considered suitable to allocate liver grafts on the basis of disease severity and medical urgency [11]. However, the overall prognosis of several patient populations was not well characterized by the mortality risk of intrinsic liver disease [12]. Most notably, patients with stage II HCC face a much greater risk of tumor progression beyond the accepted Milan criteria which would result in their removal from the waiting list and essentially exempt these patients from curative therapy. To compensate for

this mortality risk that is unappreciated by the laboratory MELD score, stage II HCC patients are assigned an arbitrarily higher MELD score starting at 22 irrespective of their “true MELD score” (“laboratory-MELD”). Since the risk of tumor progression increases over time, the MELD score of these patients can be increased by three exception MELD points every 3 months. Regional review boards in each of the 11 UNOS regions were appointed to oversee the HCC MELD exception point process and also decide about individual cases of transplant candidates who may be disadvantaged by the current MELD system. Common examples are patients with severe hepatopulmonary syndrome, familial amyloidosis, polycystic liver disease, metabolic disorders, and other liver tumors.

As mentioned earlier, exception points for HCC has led to a significant increase in the number of liver transplants for HCC (Table 7.1) as well as a significant reduction in “time on the waiting list” for HCC patients. In addition new therapeutic options, such as highly selective transarterial chemoembolization (TACE), transcatheter and laparoscopic radio frequency ablation (RFA) have decreased the mortality of patients with HCC awaiting liver transplantation. This has resulted in a decrease of the extra points awarded to HCC patients. The entry-level of 22 MELD points for HCC stage II patients is currently debated and may be reduced in the future. The MELD allocation system is under constant review as factors other than the three laboratory values are known to affect waiting time significantly. The three most important additional factors are serum albumin, ascites, and encephalopathy [13]. Since ascites and encephalopathy are not easily quantified, serum sodium has emerged as a potential substitute for ascites particularly in the low-MELD patient population [14].

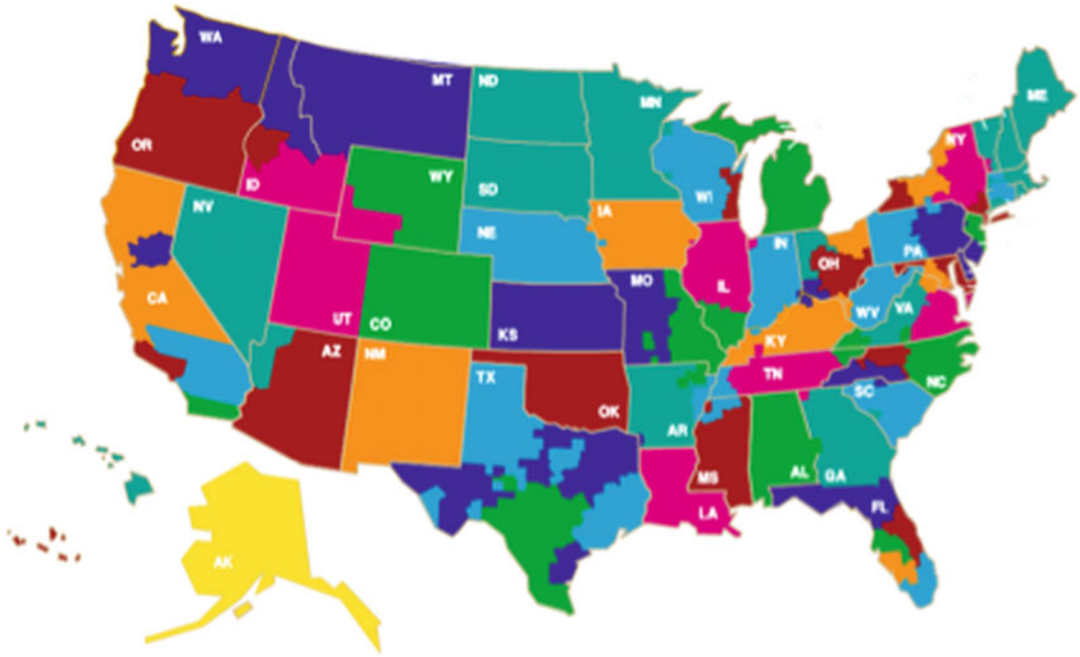
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### **Current Donor Liver Distribution Resulting in Regional Disparities in Liver Allocation**

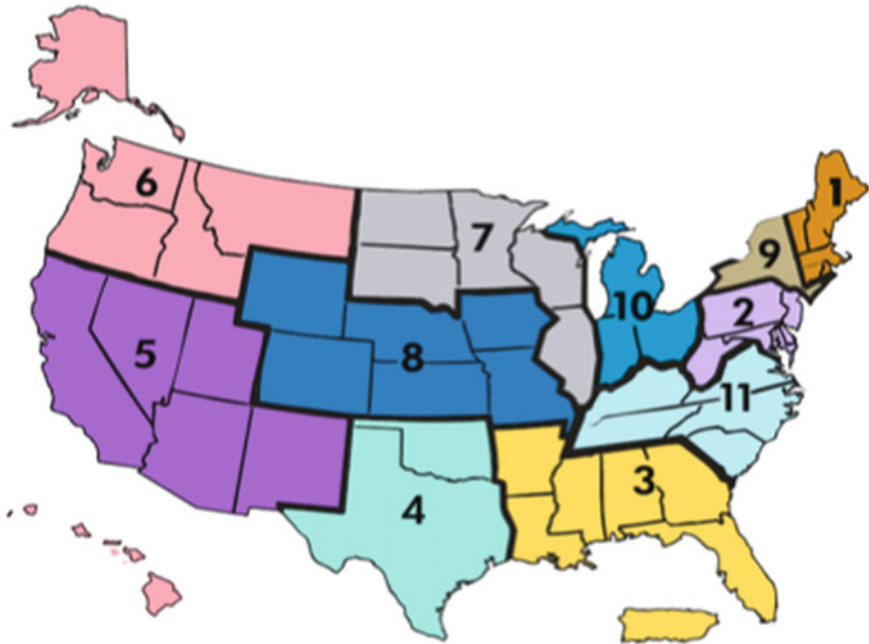
As a result of the introduction of the MELD score to allocate donor livers the mean MELD score at the time of transplantation increased from 18.5 to 24.1

and the mean PELD score from 10.7 to 17.7. The number of patients that had to be removed from the waiting list because they were too sick to be transplanted or had died on the waiting list decreased for the first time since introduction of the UNOS waiting list, indicating that the goal to reduce death on the waiting list and to prioritize the sickest patients for liver transplantation had been achieved [15].

The US distribution system is traditionally based on local, regional, and national distribution units, with 63 Donor Service Areas (DSA) for the local Organ Procurement Organizations (OPO, Fig. 7.3) and 11 Organ Procurement Transplant Network (OPTN) regions within the United States (Fig. 7.4). Since its commission in 1986, the OPTN is operated by the UNOS, a private nonprofit organization under federal contract. The OPTN regions are therefore usually referred to as OPTN/UNOS or UNOS regions. For non-emergent adult patients listed for liver transplantation, deceased donor livers are first offered to candidates within the local DSA in which the organ was procured, then within the UNOS region, and last to the national list. This system resulted in a significant difference in the mean MELD score at the time of transplant between the 11 UNOS regions (Fig. 7.5). Outcome studies focusing on post-transplant survival vs. patients remaining on the waiting list demonstrated that particularly patients with high MELD scores benefited from liver transplantation. In contrast, adult liver transplant candidates who were transplanted with a low MELD score (<15) had a significantly higher probability of dying after liver transplantation compared to matched patients who remained on the waiting list [16]. As a result of these studies the so-called Share 15 Rule was implemented in January 2005 which required donor offers to be made first to patients with a MELD score  $\geq 15$  within a UNOS region, before the organ could be allocated to a local recipient with a MELD score <15. The Share 15 policy change resulted in a significant reduction in the number of low-MELD score (<15) liver transplants throughout the country, with a minimal amount of organs being shared outside the local DSAs. This could indicate that the Share 15 policy induced to some degree behavioral changes

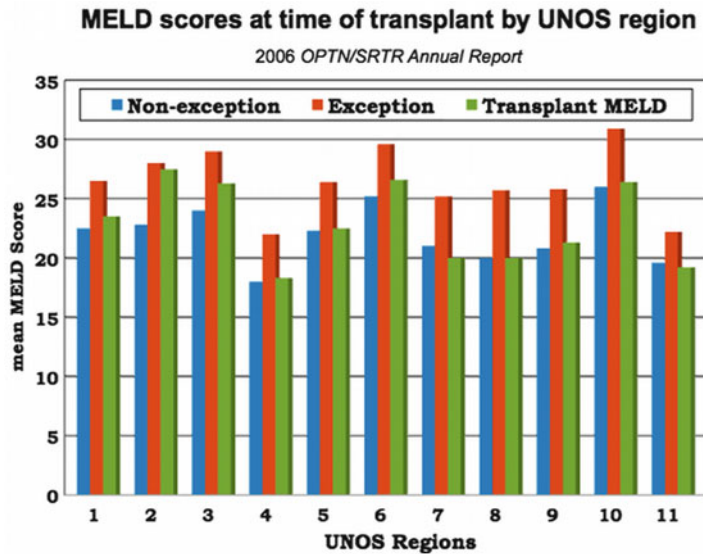


**Fig. 7.3** Map of the 63 Donor Service Areas (DSA) for the local Organ Procurement Organizations (OPO) in the United States



**Fig. 7.4** Map of the 11 regions of the Organ Procurement Transplant Network (OPTN) in the United States

**Fig. 7.5** Model of End-stage Liver disease (MELD) score at the time of transplant by United Network for Organ Sharing (UNOS) regions



on a local DSA basis and more organs are now accepted for high-MELD patients instead of utilizing them for low MELD patients [17].

The Share 15 Rule illustrates how geographical differences in donor organ distribution can influence allocation justice. Regional differences are considered one of the most significant factors of inequity in the liver allocation system to date [18]. Several geographic models to share donor livers in favor of recipients with higher MELD scores are currently being evaluated and weighted against inevitably longer cold ischemia times and higher transportation cost [19].

The variance in waiting time in different UNOS regions also results in significantly earlier transplantation of patients with HCC-exception points in some UNOS regions. Shorter waiting time in HCC patients has been associated with higher recurrence rates in some studies with the argument that biologically aggressive tumors are not negatively selected by drop out from the waiting list during prolonged waiting time [20, 21].

### Expanding the Donor Pool/Amount of Transplantable Organs

The shortage of donor organs remains the principal limitation of liver transplantation and has led to the re-evaluation of donor selection criteria

and donors that were previously considered unsuitable for transplantation. These so-called expanded criteria organs that bear a higher risk for the recipient can be categorized as increasing either the disease transmission risk (infection, neoplasm, etc.) or the risk organ dysfunction (primary non-function, delayed graft function, chronic transplant failure, etc.). The utilization of grafts from infectious donors has to be carefully evaluated in light of the recipient's immunosuppression. The risk of transmitting a bacterial infection in case of donor bacteremia is low and can be reduced even further by prophylactic use of antibiotics in the recipient. Donors with documented bacterial meningitis can be safely utilized using prophylactic antibiotics in the post-transplant period [22]. Donors with unspecified potential central nervous infections should not be considered without extensive virological workup using nuclear acid testing. The general risk of transmitting infections like rabies, West Nile fever, and others is considered low, however possibly fatal in case of transmission [23]. The incidence of malignancy in organ donors is estimated to be 3% and the risk of transmitting malignancy by transplantation of a solid organ is approximately 0.01% [24].

In terms of decreased organ function, Cox regression studies identified seven donor characteristics which independently predicted



substantially increased risk of graft failure: Donor age >40 years, donation after cardiac death (DCD) and split/partial liver graft were strongly associated with graft failure. Cerebrovascular accident and “other causes” of brain death, reduced height, and African-American race were modestly associated with graft failure. All seven factors were quantitatively combined to the donor risk index (DRI) to objectively assess the risk of post-transplant graft dysfunction [25]. Older donors were found to have an increased risk of graft failure starting at the age of 40, but particularly >60 years. Advanced age also significantly increases the severity of hepatitis C viral recurrence [26]. In adult transplant recipients, the rate of graft failure and post-transplant morbidity is significantly higher in split-liver recipients with a reduced graft volume compared to the recipient’s standard liver volume and secondary to technical challenges. Even when the organ donor is young, with preferential parenchyma and a short cold ischemia time the organ should be considered an expanded criteria organ. In pediatric recipients, the utilization of a split-liver transplant yielded significantly better results [27]. During DCD, the donor liver is subjected to a variable period of warm ischemia time. The number of DCD liver procurements was about 450 organs per year or 6.4% of all recovered livers in 2007 [28]. Livers from DCD procurements have an increased rate of primary non-function, delayed graft function, and a well-described increased rate of late ischemic-type biliary complications, resulting in a significant reduction of quality of life and graft survival [29, 30]. African-American race vs. white race in the donor, reduced height (in 10 cm decrements from 170 cm), and cerebrovascular accident or “other” cause of death (not trauma, anoxia, or stroke) as well as cold ischemia time (indicated by regional or national share) are other general factors associated with liver graft failure [25].

Steatosis of the donor liver, especially in the form of large droplet fat (fat vacuoles >50% of the hepatocyte size) potentiates ischemia reperfusion injury and has been demonstrated to increase complications after liver transplantation. The rate

of primary graft dysfunction correlates with the extent of steatosis with particular poor results if the large droplet steatosis is greater than 60% of the liver parenchyma resulting in a high rate of primary non-function, prolonged ICU stay, and hospitalization [31].

In most cases a frozen section liver biopsy can clarify the suitability of a donor organ by determining the amount and type of steatosis, potential fibrosis, inflammatory infiltration, or hepatocyte necrosis. These criteria cannot be quantified macroscopically and may present contraindication for organ donation and transplantation. However processing and evaluation of a biopsy can prolong cold ischemia time which is preferably kept as short as possible when using of expanded criteria organs. A pre-procurement biopsy is preferable, but if not feasible, the gain of additional information obtained through back-table biopsy has to be weighed against the risk of prolonging cold ischemic time.

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### Donor Management Prior to Procurement

Brain death is associated with multiple pathophysiologic changes that may progress to hemodynamic instability, hypoperfusion, metabolic and endocrine decompensation, and may ultimately result in multi-organ system failure and pre-procurement demise [32, 33]. Impaired oxygen use and a subsequent shift from aerobic to anaerobic metabolism with consecutive lactic acidosis has been observed following brain death and was associated with decreased levels of triiodothyronine (T3), thyroxine (T4), cortisol, and insulin. The administration of T4 in donors awaiting organ procurement almost completely reverses the anaerobic metabolism, restores cardiovascular function, and is associated with a significantly higher number of procured organs per donor when compared to donors managed without thyroxine [34]. Standard donor specific therapy therefore includes the administration of T4, methylprednisolone, and insulin as soon as the potential donor requires extensive fluid resuscitation and vasoconstrictors. Early identification



and management of disseminated intravascular coagulation (DIC), diabetes insipidus (DI), and neurogenic pulmonary edema, hypothermia, and cardiac arrhythmias is essential [35]. A mean arterial blood pressure between 65 and 100 mmHg, urine output of 1–1½ cc/kg/h, hemoglobin of 7–9 g/dL, arterial oxygen partial pressure of ≥80 mmHg, and a core body temperature of 35.5–38 °C were demonstrated to be ideal for hemodynamic and metabolic stability prior to organ recovery and should be the clinical goal parameters. Donor management goals (DMGs) are increasingly used to standardize donor management and optimize end-organ function [36].

### Living Donor Liver Transplantation

Living donor liver transplantation in the USA has emerged as a consequence of the organ shortage and long waiting time. The first recipients were primarily children and in 1989 almost 65% of the donors were their parents. However, right lobe and later left lobe living donor liver transplantation for adult recipients outnumbered the pediatric liver transplants very quickly and now represent the majority of living donor liver transplantation (67% vs. 23% in 2007). A total of more than 3,000 living donor liver transplants in more than 100 centers have been performed in the USA between 1998 and 2007 with about one-third pediatric recipients. Over all the enthusiasm of the procedure has declined steadily from a peak of 522 living donor liver transplants in 2001 (111 children, 411 adult recipients) to 219 cases in 2009. Six fatal outcomes in living liver donors have been reported in the USA, two of them in 2010 (personal communication). Apart from the calculated mortality risk of 0.2–0.5%, there is a significant incidence of postoperative morbidity (up to 30%) which emphasizes the risk of this major operation for the organ donor [37]. So far, this has affected the wide application of this procedure and will therefore not significantly increase the number of available organs for transplantation in the near future. However, it has been demonstrated that for children under 2 years living donor liver transplant is preferable over

split-liver or pediatric whole organ transplantation [38]. In adult recipients, the procedure has evolved into a treatment option for patients with a significant reduction in quality of life and relatively preserved hepatic function who are unable to receive MELD exception points in the current allocation system such as patients with cholestatic cirrhosis.

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Abdulelah M. Alhawsawi and Juan del Rio Martin

## Introduction

Liver transplantation is the standard of care for end-stage liver disease, fulminant liver failure, unresectable primary tumors of the liver, and some metabolic diseases whose enzymatic defect occurs primarily in the liver. The evolution of liver transplantation has involved surgical technique, the development of more effective and less toxic antirejection medications and patient selection to achieve outcomes unthinkable only few years ago [1, 2].

The surgical technique of liver transplantation has evolved since the pioneering times with improvements related to the better knowledge of liver hemodynamic physiology [3]. The success of the liver transplantation will depend on the creation of adequate inflow, both portal and arterial, and adequate outflow into the inferior vena cava (IVC). Reaching the reperfusion phase in the best hemodynamic condition is paramount for reducing the reperfusion syndrome with important consequences for short- and long-term outcomes [4].

The liver embraces the retrohepatic vena cava. Initially, without the ability to dissect the liver off

the vena cava, it was considered excessively complex to perform the hepatectomy while preserving the vena cava. The surgical technique more widely used is the orthotopic liver transplantation (OLT) without preservation of the vena cava that was described initially by Starzl et al. [5] (Fig. 8.1a). It consisted of the removal of the diseased liver during temporary cross-clamping of portal vein and the vena cava, above and below the liver. Clamping of the vena cava and portal vein affected the hemodynamic equilibrium of the recipient with a drastic reduction of the blood return and caval and splanchnic bed congestion. To overcome the deleterious effects of this reduction of the preload, Shaw et al. [6] described the use of the venovenous bypass (VVB). It consisted of the cannulation of the femoral or saphenous vein, usually by cut-down technique, cannulation of the portal vein and, with the help of a centripetal force pump, deviate the flow from the splanchnic and systemic circulation extracorporeally returning it through a cannula placed in the axillary vein, also by means of a cut-down technique. The benefits of the bypass were clearly defined with reduction of the hemodynamic instability during the anhepatic phase, preservation of the renal function, reduction of blood loss, and prevention of portal and systemic congestion. Nevertheless overall incidence of complications due to the use of VVB is reported to be between 10 and 30%. VVB can lead to fatal complications, such as decannulation of the bypass circuit and air or thrombotic pulmonary emboli. Other reported complications include hypothermia, blood clotting

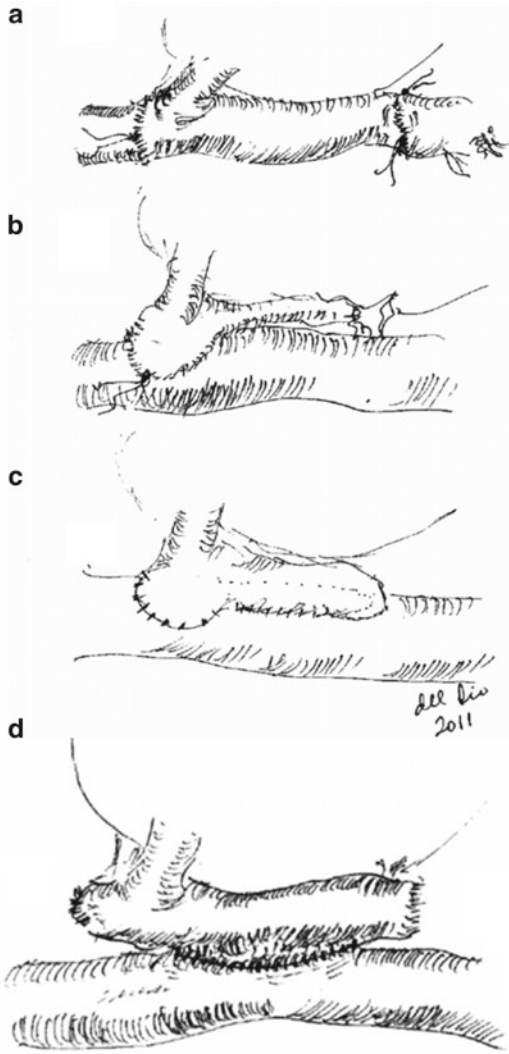
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**Fig. 8.1** Different surgical techniques of liver transplantation. (a) Caval removal with end-to-end anastomosis (standard technique). (b) Vena cava preservation and end-to-side anastomosis (Piggyback technique). (c) Modification of the end-to-side anastomosis with extension of the anastomosis into a side-to-side caval anastomosis. (d) Vena cava preservation with cavocavostomy and closure of both ends of the donor vena cava (Belghiti modification)

in the bypass system and vessel thrombosis, lymphocele formation, hematoma, vascular and nerve injury as a complication of catheter placement, wound infection or dehiscence, infected vascular suture lines, hemothorax after insertion of a large

bore cannula percutaneously, and prolonged operative and warm ischemia time [6, 7]. These complications and the higher cost, unacceptable for developing health systems entering the liver transplant endeavor stimulated the investigation of new surgical techniques.

Sir Roy Calne described the caval preservation technique with the use of a pediatric donor liver into an adult in his initial paper in 1968 [8] (Fig. 8.1b–d). Others also published the use of the caval preservation technique [9]. In 1989 Tzakis published the first detailed description of liver transplantation with vena cava preservation or “piggyback” technique [10]. The first large series of liver transplantats using this technique showed better hemodynamic stability, lower blood transfusion requirements, and shorter operative time. The initial description of the piggyback technique used the junction of the middle and left hepatic veins as outflow which produced the unintended consequence of outflow dysfunction [11]. Belghiti et al. approached the outflow problem by developing a new technique of side-to-side caval anastomosis [12] (Fig. 8.1d). Although the piggyback technique made the VVB unnecessary, it did not solve the problem of splanchnic congestion which may induce renal dysfunction and complicates the dissection. Again Tzakis, in 1993 published the addition of the temporary portocaval shunt (TPCS) resolving this question and allowing the hepatectomy to be performed without portal hypertension, reducing blood loss and obtaining outstanding hemodynamic stability [13] (Fig. 8.2). Cherqui and Belghiti in France during the mid 1990s published the initial long series of TPCS during liver transplantation [14, 15] but it was the Barcelona Group that proved, in a randomized controlled trial, the definitive benefits of this technique. The use of the TPCS allowed better hemodynamic stability during the anhepatic phase with lower transfusion needs and better renal function in patients with higher portal flow or portocaval gradient [16]. Recently the early experience with TPCS by the Mount Sinai Group proved its benefit in high risk donors [17]. It should be noted that in cases of fulminant hepatic failure, where



**Fig. 8.2** Creation of a temporary portocaval shunt (TPCS) during the hilar dissection

no hepatofugal circulation has developed and brain swelling limits the fluid infused during the anhepatic phase, this technique is particularly useful [18]. The piggyback technique demands finesse to dissect the liver from the vena cava by suture ligating all retrohepatic short vessels and finally dissecting the right, middle, and left hepatic veins.

With the definitive anatomical definition of vascular and biliary segmentation of the liver by Couinaud partial hepatectomies were introduced for benign and malignant diseases of the liver and opened a new front to introduce splitting techniques to obtain two grafts from a single diseased donor and to develop living donor liver transplantation [19, 20].

## The Liver Transplant Procedure

Before starting a liver transplant it is convenient to review the unique characteristics of the case (anatomical variations, presence of arterial variants, portal vein thrombosis (PVT), inflammatory reactions post TACE or RFA of tumors located close to vascular structures), to determine the most

beneficial technique. For example, if a hypertrophied caudate lobe wraps around the vena cava a piggyback technique could be extremely difficult and the caval removal technique might be the adequate choice. If a hypertrophied left lateral segment is intimately attached to an enlarged and congested spleen, it will make sense to create a portocaval shunt to decompress the splanchnic territory and then perform a hepatectomy as piggyback from right to left leaving the attachments to be dealt with once the hepatectomy is finalized and the spleen congestion has subsided.

It is also fundamental to remain in continuous communication with the procurement team in order to time the initiation of the recipient operation to reduce ischemia time as well as alert of possible deviations from normality in the characteristics of the donor. It is important to make sure that general conditions of the recipient have not deteriorated since last time examined by a thorough physical exam and laboratory and radiology testing prior to surgery.

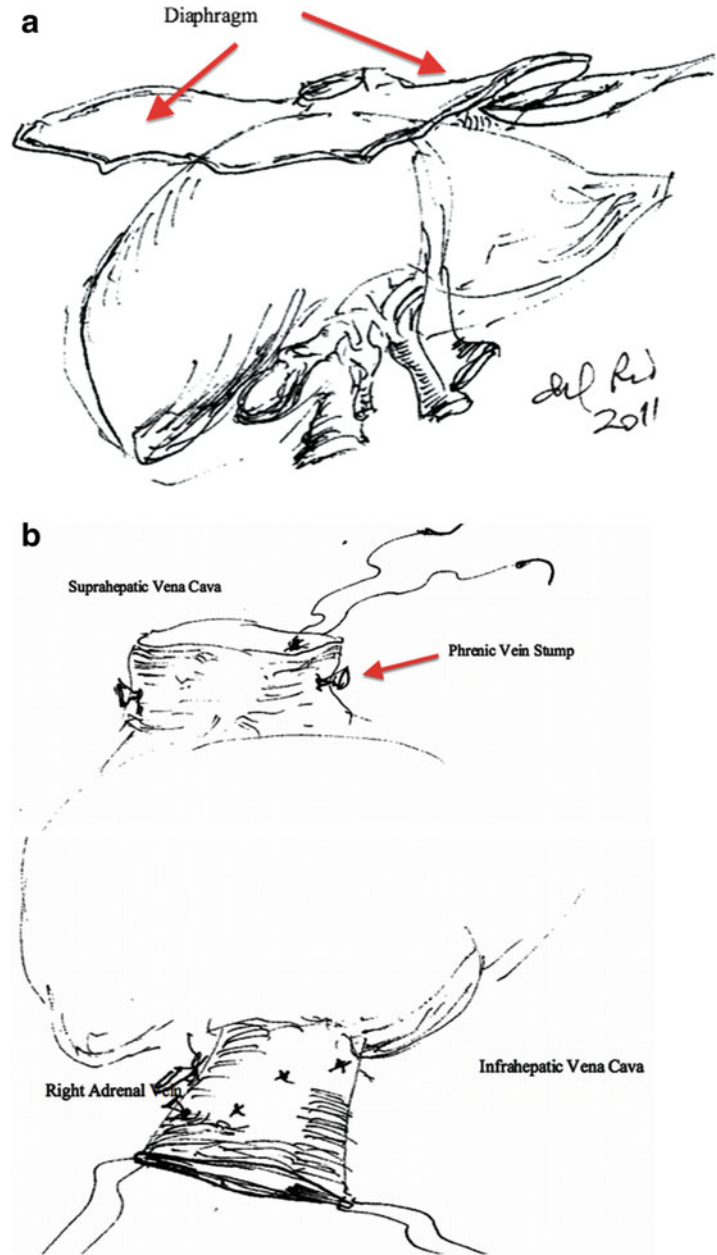
## Back Table Preparation

Organ preservation and cold ischemia time (CIT) are very important donor factors. A short CIT correlates with improved function of the allograft [21]. This should involve a good coordination between the surgical (Donor–Recipient) and the anesthesia team. The goal should be to finalizing the back table by the time the recipient team is ready to make the patient anhepatic.

Back table preparation involves dissection of the diaphragm off the donor liver (Fig. 8.3a). Next, both ends of the IVC are prepared for anastomosis (Fig. 8.3b), avoiding leaks at reperfusion by stitching up all branches off the vena cava. The focus is then shifted towards cleaning the portal vein by dissecting it from its origin at the junction of Splenic and Superior Mesenteric Veins to its bifurcation. Finally, the hepatic arterial supply is delineated and dissected all the way up to the celiac trunk origin along with an aortic patch. Care should be taken not to extend the dissection proximally beyond the gastro-duodenal



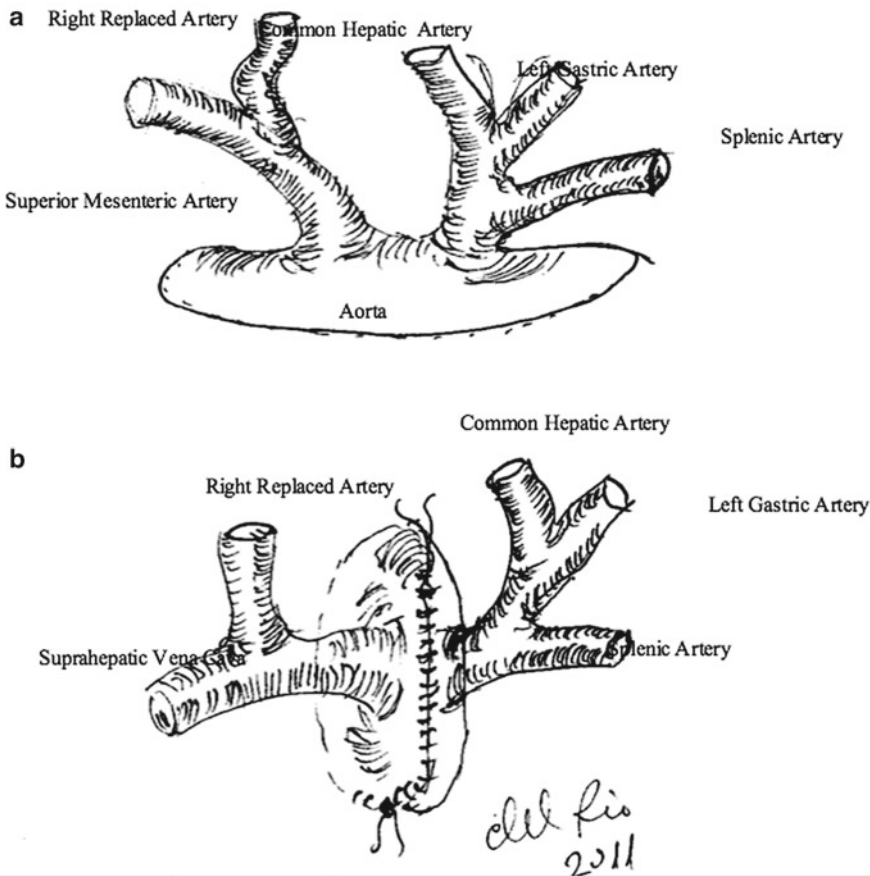
**Fig. 8.3** Back table preparation. (a) Dissection of the donor liver of the diaphragm. (b) Preparation of the inferior vena cava. 1 Suprahepatic ligation of the phrenic vein stump. 2 Infrahepatic ligation of the right adrenal vein



artery. It is at this stage where arterial reconstruction is performed in case of an aberrant arterial anatomy. Surgeon's preference will decide about leaving a short RHA by anastomosing it to the stump of the GDA (Fig. 8.4), or a long RHA, while bending the aortic flap and leaving the SMA or the splenic artery to anastomose to the native arterial inflow (Fig. 8.5a, b).

### Abdominal Incision and Exposure

Adequate exposure is fundamental to allow the appropriate dissection and access for the native liver hepatectomy. The incision most commonly used consists of the subxiphoid extension of the bilateral subcostal incision (Fig. 8.6a). This incision allows excellent exposure of the supra-



**Fig. 8.4** Preparation of the arterial reconstruction with aortic flap. (a) With native aorta. (b) With bending the aortic flap

hepatic IVC but increases the risk of incisional hernia due to the poor vascularity at the junction. Another commonly used incision is the “J” shaped (also known as Hockey Stick or Makuuchi’s incision) which has been used alternatively as it allows adequate blood supply to the wound edges [22] (Fig. 8.6b).

### Native Liver Hepatectomy

The hepatectomy can be divided in three general steps: (1) Mobilization of the liver. (2) Dissection and Division of the hilar structures (hepatic artery, portal vein, and common bile duct). (3) IVC management. The order of the steps may change according to technique and surgeon preference.

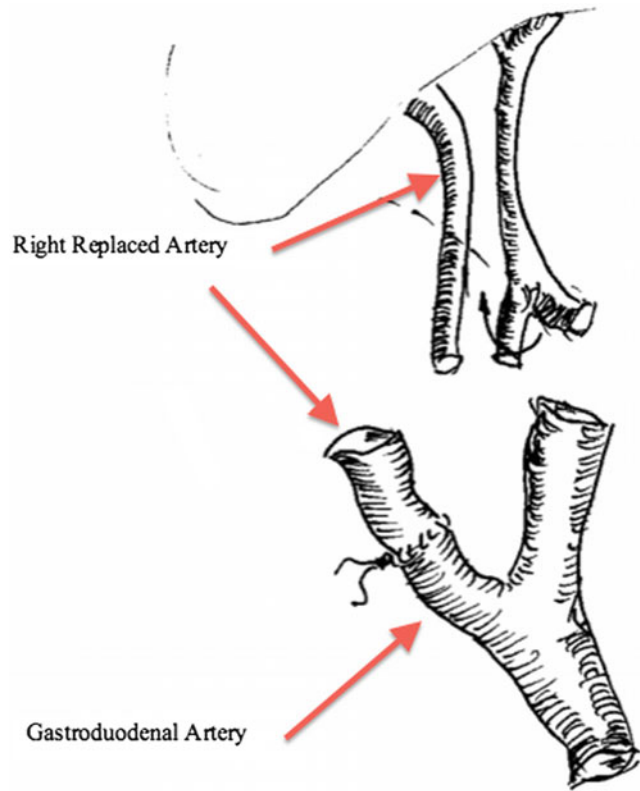
Once inside the abdomen, the surgeon should explore the peritoneal cavity for any signs of transplant contraindication, e.g., active infection and advanced tumor disease. Any ascites will be suctioned out and a sample sent for cell count and culture.

The falciform ligament is divided cephalad using electrocautery until the anterior surface of the suprahepatic IVC is identified. A self-retaining retractor will be used based on the surgeon’s preference. We prefer to use the Thompson retractor. Mobilization of the left lobe of the liver is begun by dividing the left triangular ligament and coronary ligament.

Hilar dissection starts by dividing the hepatoduodenal ligament and encircling the porta hepatis searching for arterial variants. The most



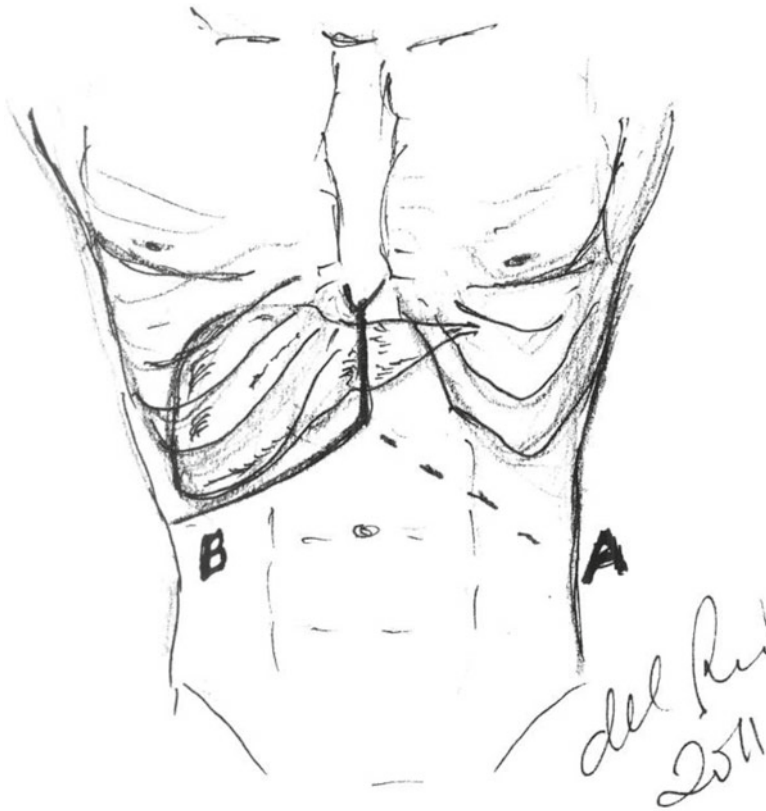
**Fig. 8.5** Short right hepatic artery anastomosis with the stump of gastro-duodenal artery (GDA)



common are the replaced right hepatic artery from the SMA behind the portal vein and left hepatic artery from the left gastric artery in the gastrohepatic ligament [23]. The porta hepatis is put under tension by retracting the liver cephalad, the stomach, duodenum, and transverse colon caudad. Both the left and right hepatic arteries are identified and divided close to the liver. The common hepatic artery is dissected proximally towards the GDA junction. The common bile duct is isolated and divided close to the liver. Care must be taken to preserve the blood supply of the common bile duct by preserving as much periductal tissue as possible. The portal vein is dissected next. The dissection is carried out all the way up to the bifurcation proximally and to the superior aspect of pancreas distally. In cases with PVT the dissection will continue up to the junction of the splenic vein and the superior mesenteric vein and the thrombus removed by thrombectomy while the surgeon controls the flow proximally [24] (Fig. 8.7a).

Management of the portal vein at this point will depend on the technique chosen, preserving vs. not preserving the vena cava. If preservation of the vena cava technique is chosen without TPCS, the portal vein will be left untouched until the final steps of the hepatectomy in order to preserve some portal decompression and it will be clamped right before explantation.

If a TPCS is performed, it is constructed by exposing the infrahepatic IVC and performing an end-to-side portocaval anastomosis with a running suture with 5/0 polypropylene (Prolene 5/0; Ethicon, Somerville, NJ, USA). The rest of the hepatectomy will be facilitated by the complete devascularization and reduction of the portal pressure. The caudate lobe is dissected off the anterior portion of the vena cava by suture ligation of the short retrohepatic veins. When the portal vein is not sectioned, this dissection is more difficult and demands to alternate the hepatic sides to advance cephalad. Care should be taken due to the anatomical diversity of the

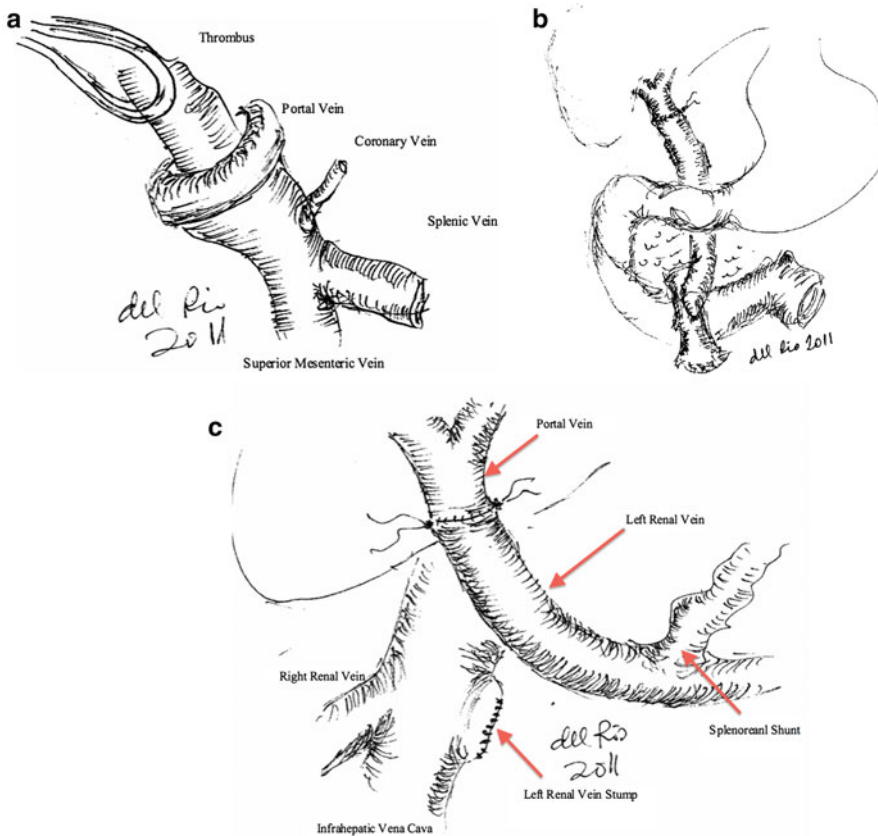


**Fig. 8.6** Abdominal incision and exposure with either subxiphoid extension of the bilateral subcostal incision (A) or right “J” shaped “Hockey Stick” incision

retrohepatic veins and we recommend using small clamps and suture ligation when those veins are larger than 3 mm. Once the hepatocaval ligament is divided and suture ligated we recommend to clamp and section the right hepatic vein independently of the middle and left hepatic veins that will be clamped together. We usually extend the dissection of the vena cava above the hepatic veins, severing the attachments in the left side and dissecting, ligating, and sectioning the phrenic veins. The shape of the vena cava will round up improving continuous flow return while side clamped.

In the standard technique, the vena porta is dissected in the same way and prepared for clamping and section as proximal to the liver as possible. When a VVB is used, the portal vein is cannulated to decompress the splanchnic territory

and connected to a Y shaped tubing system that also decompresses the subhepatic caval system through a cannula placed in the left femoral or saphenous vein. Both portal and systemic flow will then be directed towards the superior vena cava through a cannula placed either in the left axillary vein, approached through cut-down technique, or a percutaneous left internal jugular approach. The extracorporeal circuit is completed with the use of a centripetal force pump. The complexity of this process with multiple weak links, cannula placement, collapsing vessels, thrombosis, or gas emboli through the multiple connectors needed stimulated the investigation of simplified systems. In fact a high percentage of cases performed with the standard technique is now done without the use of the VVB [25]. A hemodynamic test is performed clamping the



**Fig. 8.7** Treatment of portal vein thrombus. (a) Eversion thrombectomy. (b) Jump graft from patent superior mesenteric vein to donor portal vein using a donor iliac vein segment. (c) Renoportal anastomosis

portal inflow and the supra and infrahepatic vena cava during a 5 min span. If the patient tolerates the test, the standard technique will continue without the VVB [26].

Once the VVB is set, minimal dissection of the infrahepatic vena cava is needed. It is encircled cephalad to the left renal vein with a vessel loop. The right adrenal vein is suture ligated. After mobilizing the liver bilaterally the suprahepatic vena cava is also encircled with blunt digital dissection and prepared for clamping. The vena cava is sectioned leaving adequate cuff at both ends for anastomosis and the native liver is removed from the field.

Before initiating the vascular anastomosis adequate hemostasis is mandatory, especially in

the retrohepatic retroperitoneal area, closing the bare area with a 3/0 running suture of Prolene.

### Implantation of the Donor Liver

The donor liver has been prepared in the back table for implantation. Once the upper cava anastomosis has been performed with a 3/0 Prolene running suture, hypothermic or normothermic [27] solution is flushed through the donor portal vein to clear the high potassium content of the UW preservation solution. The solutions used differ according to centers and include albumin or Ringer Lactate. The lower cava anastomosis is left open for drainage. Once the effluent is clear

the lower cava anastomosis is finalized. The flushing can also be performed by the passage of blood antegrade after the portal anastomosis is performed and its clamp removed or retrograde after removing the caval clamps and draining the blood through a loose portal vein anastomosis before tightening it up.

The piggyback technique entails preserving the recipient's entire IVC along with the orifices of the hepatic veins. The orifices of the left and middle hepatic veins are joined together whereas the right hepatic vein is over sewn. A common ostium is then created by joining the left and middle hepatic veins with a portion of the anterior IVC (between the middle and right hepatic veins) and then anastomosing the donor's suprahepatic IVC to that common opening on the anterior aspect of the recipient's IVC in an end-to-side fashion. The lower cava is closed once the flushing is finalized by means of a silk tie or the use of vascular stapling [28]. In the cases with TPCS, this is taken down easily by using a vascular stapling device. The native portal vein will then be anastomosed to the donor portal vein in an end-to-end fashion.

In the modified piggyback technique by Belghiti (Cavocavoplasty), both the supra- and the infrahepatic IVC of the donor are over sewn, and the cavocaval anastomosis is created between the donor and recipient IVCs in a side-to-side fashion [12].

Figure 8.8a–f depict the sequence of piggyback technique with TPCS.

Once the caval anastomosis is finished, the portal vein anastomosis is created in an end-to-end fashion. A growth factor is left while tying the suture to avoid narrowing the anastomosis.

Reperfusion is done after the portal vein anastomosis is finished. Considerable coordination must take place between the surgical and anesthesia teams to assure that the patient's hemodynamics are optimal at this critical stage [4].

After assuring an uneventful reperfusion, hepatic arterial anastomosis follows. The anastomosis is performed in an end-to-end fashion between the donor and recipient common hepatic artery. The goal should be to make the anastomosis

as wide and straight as possible to avoid hepatic artery stenosis or kink. Dissecting the common hepatic artery off lymphatic tissue and ligating and excising the gastroduodenal artery will facilitate such intention. Others prefer to use the aortic patch for anastomosis to the recipient arterial inflow.

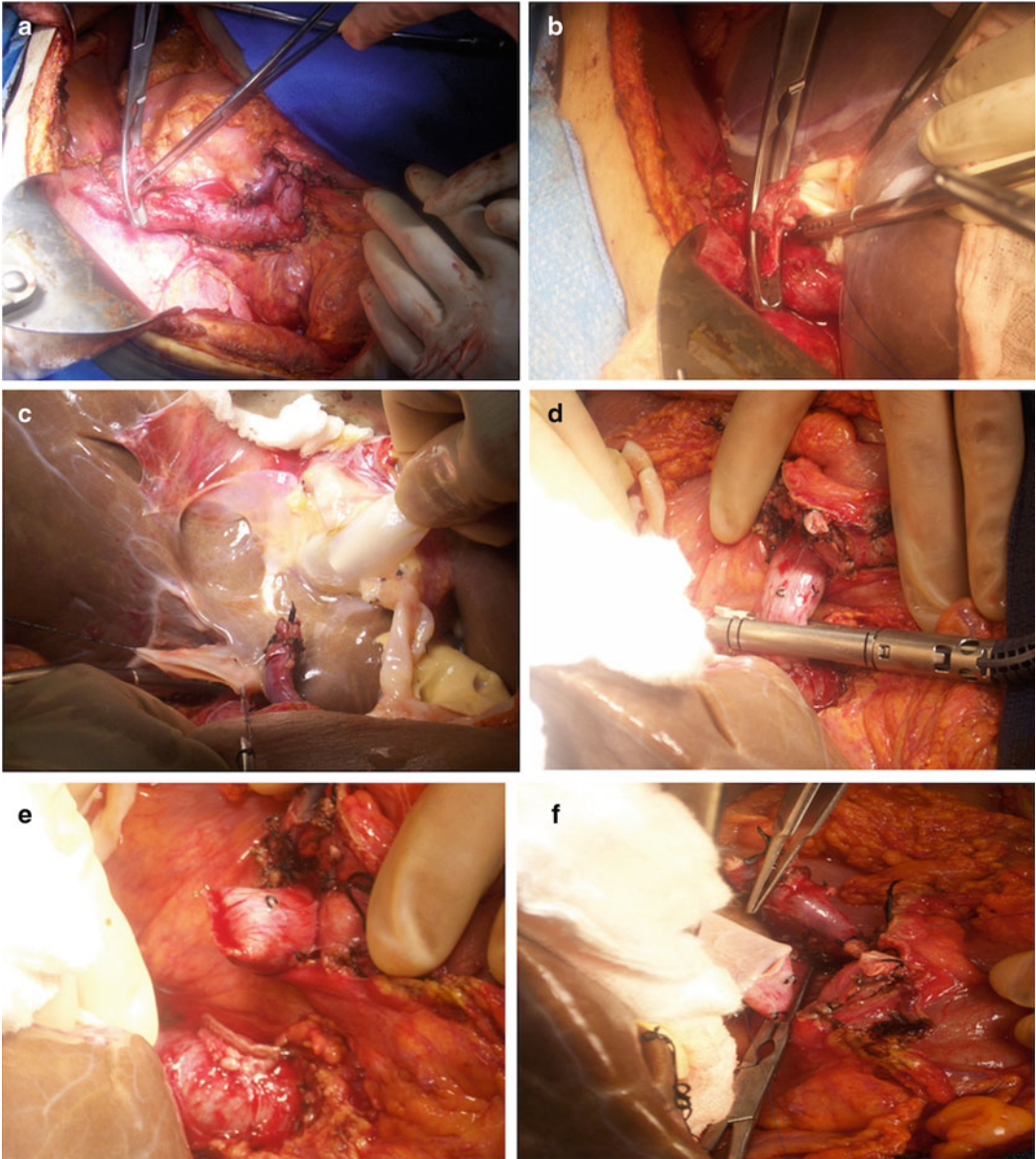
In cases of inadequate arterial inflow due to trauma during TACE, or retransplantation, we may be forced to use a donor arterial conduit either from the infrarenal or supraceliac aorta according to judgement.

Liver transplantation is finished by performing the biliary reconstruction. A cholecystectomy is performed in the donor liver. This is a modification from the early days in which the donor gallbladder was used as part of the biliary reconstruction. The demonstration of high risk for ischemic cholecystitis in the posttransplant period directed the modification. After the cholecystectomy we should avoid redundancy of the donor bile duct by excising the distal end and limiting ischemic cholangiopathy at the bile duct anastomosis. The donor's bile duct is divided proximal to the cystic duct to assure adequate blood supply. The bile duct anastomosis is constructed in an end-to-end fashion. This can be done either interrupted or continuous using a 5-0 or 6-0 PDS suture. The use of t-tube drain to protect the biliary anastomosis is in decline after several studies demonstrated it to be the source of severe complications [29].

There are certain situations where end-to-end biliary anastomosis is contraindicated either for disease-related reasons, e.g., some cases of primary sclerosing cholangitis (PSC), or technical reasons, e.g., living-related liver transplants or split livers. In these circumstances, the biliary reconstruction is done by a Roux-en-Y hepatico—jejunostomy.

Biliary reconstruction with the technique of hepatico-jejunostomy is done by first, dividing the donor's bile duct proximal to the cystic duct junction to guarantee a well-vascularized end for anastomosis. A Roux-en-Y jejunal limb is then created by mobilizing a suitable loop of proximal jejunum of approximately 50 cm in length. The anastomosis is then constructed with a standard end-to-side





**Fig. 8.8** Sequence of steps from top to bottom: (a) Anhepatic phase with side clamp of the hepatic veins and the temporary portocaval shunt. (b) End to Side cavocaval anastomosis. With the inclusion of the right hepatic vein of the recipient the diameter of both ends is similar reducing the risk for outflow dysfunction.

(c) Flushing of the donor liver to remove high potassium content University of Wisconsin solution. (d) Portocaval shunt takedown with the use of the vascular stapler. (e) Stapled stumps of the caval end and main portal vein preparing for anastomosis. (f) End to end portal vein anastomosis

Roux-en-Y hepatico-jejunostomy, typically using a single layer of 6-0 PDS. We strongly recommend the retrocolic and retrogastric technique in order to avoid the tension created by gastric or colonic distension on the anastomosis.

### Portal Vein Thrombosis

The incidence of PVT at the time of liver transplantation varies from 2.1 to 26% [30, 31]. PVT used to be an absolute contraindication to

liver transplantation. Recently, due to technical advances in vascular anastomoses, PVT has become a challenge but not a contraindication.

According to the extent of the thrombosis, PVT can be classified into four grades: Grade 1 Partially thrombosed PV, in which the thrombus is confined to <50% of the vessel lumen, with or without minimal extension to the SMV. Grade 2 >50% occlusion of the PV, including total occlusions, with or without minimal extension to the SMV. Grade 3 Complete thrombosis of both PV and proximal SMV. Distal SMV is open. Grade 4 Complete thrombosis of both PV and proximal as well as distal SMV [30].

For grades 1, 2, and 3 PVT, eversion thromboendovenectomy (ETEV) has been suggested as the surgical technique of choice by many authors (Fig. 8.7a) [24, 30, 32].

In grade 4 PVT, where the thrombus extends beyond the junction of superior mesenteric and splenic veins, ETEV is often not feasible and vein grafts have to be taken into account [33].

A good option in this situation is a jump graft from a patent segment of the proximal SMV to the donor portal vein using an iliac vein segment of the donor. The graft is tunneled through the transverse mesocolon (Fig. 8.7b).

If the portal flow continued to be suboptimal, some authors suggested other options including: arterialization of the portal vein, cavoportal hemitransposition (CPHT), or renoportal anastomoses (RPA).

Arterialization of the portal vein involves augmenting the portal inflow by anastomosing the portal vein to the splenic artery, common hepatic artery, or directly to the aorta using a jump graft [34, 35]. Long-term patient survival posttransplantation with normal liver function and lack of portal hypertension with the use of a calibrated portal vein arterialization has been recently reported [36]. When a pretransplant portosystemic shunt is created, distal splenorenal and mesocaval shunts are safer shunts if subsequent transplantation is planned [37].

CPHT involves using the IVC as a source of portal vein inflow. There are a variety of ways to performing CPHT: an end-to-end anastomosis

between the native IVC and the portal vein of the liver graft (Fig. 8.1a), side-to-end fashion with deliberate luminal constriction (Fig. 8.1b), or calibration of the vascular diameter by placing clips (Fig. 8.1c) on the retrohepatic IVC [38, 39].

A new variant of portal inflow in PVT Grade 4 is the creation of anRPA, an end-to-end anastomosis is created between the native left renal vein and the donor portal vein in those cases in which a large spontaneous or constructed splenorenal shunt is present that will derive most of the splanchnic flow into the left renal vein [40, 41] (Fig. 8.7).

## Domino Liver Transplantation

There are systemic diseases based on a single enzymatic dysfunction located in the liver parenchyma in whom the liver function is otherwise normal. Familial amyloidotic polyneuropathy (FAP) is a genetic condition residing in the hepatocyte that produces a mutation of transthyretin; this abnormal protein is deposited in peripheral nerves, gastrointestinal tract, heart, and kidneys. The liver of these patients, apart from producing this abnormal protein, is otherwise normal, and has been used as an organ for recipients with desperate need of a liver transplant [42]. No added risk to either the FAP patient or their recipients has been found in a recent review [43].

In these cases the hepatectomy demands the removal of a long portion of the retrohepatic vena cava as a standard technique, with or without the need for VVB. Long arterial and portal segments are necessary for the graft and the patient. The hepatic artery is clamped and divided proximal to the take-off of the gastroduodenal artery. The portal vein should be clamped and divided just 1 cm below portal bifurcation. Finally the vena cava is divided above and below the liver.

On the back table the liver is perfused through the portal vein and the hepatic artery. The biliary tree is also washed. The recipient of the domino liver will be transplanted with the piggyback technique, while the patient with FAP will have a standard procedure (see above) [27, 44].

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## Introduction

Liver transplantation has made great strides over the last decades towards a standardized procedure but still remains costly and resource-intensive [1, 2]. Given the fact that underlying acute liver failure (ALF) and end-stage liver disease affect all physiologic systems and may cause hemodynamic, hematological, metabolic, and other homeostatic abnormalities, monitoring remains a key issue and prerequisite for success of liver transplantation [3].

With few if any contraindications to liver transplantation, the implementation of scoring systems allocating grafts to the sickest patients and the use of marginal liver grafts, the importance of a system to optimally monitor perioperative therapy becomes more important [4]. Early recognition of homeostatic disturbances and subsequent treatment as well as continuous assessment of graft function improves outcome and decreases perioperative mortality.

Only few consistent monitoring recommendations are found in the current literature and monitoring during liver transplantation is center specific and far from being standardized. Procedures and practice patterns are poorly

defined and seem to depend on personal experience and preferences [4–6]. Additionally management is probably modified for specific patient subpopulations.

This chapter aims to describe the basic pathophysiological characteristics of monitoring procedure and a judicious approach to intraoperative (step-wise) monitoring based on recent developments in clinical as well as translational research. It is divided into three parts: conventional monitoring, hemodynamic monitoring, and monitoring of graft function.

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## Conventional Monitoring

Profound disturbances of homeostasis typical for liver dysfunction and failure irrespective of origin are common findings during OLT. These abnormalities can severely compromise other organ functions, organ interaction, and overall metabolic function. Detection and monitoring of rapidly changing metabolic disturbances are an essential part of rational intraoperative management in OLT [5]. Although monitoring of these parameters in general anesthesiology is common knowledge, their specific relevance in the context of OLT is evaluated and the importance and necessity of regular intra-operative assessment for OLT is emphasized. The individual course of some of these parameters may also serve as an estimate of the future function of the transplanted graft. Due to the lack of stringent recommendations, monitoring conventional parameters should

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be adapted to the patient's actual situation and the choice of method as well the frequency of measurements should be at the discretion of the anesthesiologist.

## Metabolism

End-stage liver dysfunction is associated with various alterations in metabolism. Glucose metabolism is frequently affected. The peripheral insulin resistance in ESLD patients is characterized by a decrease in nonoxidative glucose disposal, which improves, but does not normalize after OLT. Correspondingly metabolic syndrome has a higher prevalence in liver transplant recipients than in the general population and is associated with an increased risk of vascular events [7].

Not surprisingly, tight blood glucose control, based on a simple monitoring and intervention algorithm performed intra-operatively, contributes significantly to a decreased infection rate and 1-year mortality [8]. In experimental settings cold storage time was closely correlated with the extent of altered glucose metabolism [9]. The most precise descriptions of metabolic changes were derived from microdialysis studies in rodents and pigs but these have rarely been transferred into human settings or adopted as routine monitoring during OLT: Intrahepatic glucose levels may result from glycogen degradation in ischemia-injured hepatocytes [10, 11] and these alterations may be associated with increases in lactate is easily measured [12, 13]. Two major mechanisms are considered responsible for hyperlactatemia in OLT patients: The shift to anaerobic glycolysis when oxygen demands exceed oxygen supply and cells attempt to maintain function despite tissue hypoperfusion with consecutive accumulation of lactic acid. Secondly a decrease of whole body lactate clearance by the insufficient liver [9, 14] will cause hyperlactatemia. Routine lactate monitoring might not be able to discriminate between either variant but continuous hyperlactatemia should trigger further investigations whereas normal lactate clearance is a good indicator of stable graft function. Furthermore interstitial lactic acidosis in the

donor allograft has been observed during reperfusion injury whereas isolated acid base disturbances were attributed to cardiovascular disturbances after reperfusion. These were only associated with advanced ASA status but not with ischemia times [11, 15, 16].

Another important substrate of reduced metabolism in liver disease is serum ammonia resulting from urea cycle and interorgan trafficking [17]. Hepatic encephalopathy may develop due to uptake of ammonia by cortical astrocytes and its detoxification to osmotically active glutamine, followed by passive influx of water. This results in osmotic cerebral edema and subsequently intracranial hypertension (ICH) of varying severity [18–20]. The association between ammonia neurotoxicity and hepatic encephalopathy (HE)—despite the lack of a good correlation between blood levels and the severity of HE—has been the basis for the treatment of HE by decreasing plasma ammonia or modulating its intestinal generation [21, 22]. However there are few therapeutic options with sufficient evidence and only routine preoperative measurement is recommended. For instance, it has been questioned whether small changes in pH might affect the equilibrium and the amount of un-ionized ammonia (NH<sub>3</sub>) the form that passes the blood–brain barrier by diffusion.

While monitoring the course of single substrates during OLT is established, in the near future particular emphasis will be placed on detecting specific metabolic changes and their interdependencies to correlate specific metabolic profiles or metabolic outliers with complications or worse outcome. Considering the potential metabolic heterogeneity of this patient population, first results of microdialysis retrieved metabolomics are encouraging [23, 24]. The transfer of these technologies into clinical practice and the standardization into routine application are tasks for the upcoming decade.

## Electrolytes

Electrolyte imbalances might also pose serious hazards to patients undergoing OLT and

monitoring is therefore of utmost importance. A recent investigation in more than 1,100 patients identified independent predictors of hyperkalemia in the pre-, early, and late post-reperfusion period [25]. Red blood cell transfusion and higher baseline values were determined as predictors for the pre-reperfusion period, whereas post-reperfusion  $K^+$  increases were associated with warm ischemia time, donor hospital stay and the use of venovenous bypass. The effect of serum sodium levels on outcome has recently been emphasized in several publications [26]. Low serum sodium was found to be an independent predictor for waiting list death and its addition to model for end-stage liver disease (MELD) score improved its accuracy in American and European investigations [3, 27–29]. Low serum sodium values were also found to be a risk factor for poor outcome after OLT likely due to associated increases in infectious complications, renal failure, and neurological disorders. Osmotic demyelination resulting in OLT-associated central pontine myelinolysis is more frequently observed in hyponatremic patients but can develop in patients with low, normal, or elevated sodium plasma levels, which makes the contribution of other trigger factors likely. Frequent assessment and slow correction of sodium plasma levels may be critical in prevention of this devastating complication [30–34].

Other electrolyte abnormalities except for postoperative hypophosphatemia are rare findings or without major impact on anesthetic [35, 36]. There are currently no recommendations about postoperative phosphate supplementation; however, a relatively small study found that preoperative magnesium administration might improve coagulation measured by thrombelastography from a generally hypocoagulable state towards normal [37].

## Temperature

Hypothermia is one of the key symptoms of ALF but there is surprisingly little research about temperature control during OLT. Negative effects of hypothermia on wound healing and the coagulation system are evident even when

plasmatic clotting factor concentrations are normal [38, 39]. Conversely, mild therapeutic hypothermia has been suggested as adjunct therapy for the treatment of raised intracranial pressure (ICP) and decreases brain metabolism and markers of oxidative stress in ALF [19]. Although randomized controlled trials are still needed, an increase in temperature towards normal after reperfusion may be an indicator of a well-functioning graft. Thus continuous temperature control and adaptation should be part of standard management.

## Hemostasis and Coagulation

Recent studies demonstrated a significant reduction of blood product requirements in the last years although hemorrhage during liver transplantation still is a significant risk [40, 41]. Hemorrhage commonly occurs in the preparation phase of the dissection of the native liver, after graft reperfusion and during the completion of the vascular anastomoses; diffuse bleeding however may occur at any time. Bleeding complications are related to the procedure itself as well as to liver disease associated coagulopathy.

Coagulopathy results from various factors such as qualitative and quantitative defects of coagulation factors, both pro- and anticoagulant proteins, diminished clearance of activated factors, hyperfibrinolysis, and disturbances in platelet function and count [42].

Preoperative standard laboratory monitoring of coagulation status has shown to be of little value in the prediction of *intra-operative* requirements, and while waiting for results of conventional coagulation tests sent during OLT, the clinical situation can worsen without real-time information of the recipient's actual coagulation disorders. Adequate guidance of the rational use of pharmacological agents or blood components is hindered if results are delayed. It is therefore not surprising that the transfusion practice during OLT depends on the method of coagulation monitoring that is used [43].

Optimal therapy should ideally be guided by point-of-care testing, such as thrombelastography or ROTEM use. The maximum clot firmness as

well as the shape of the curve that can be assessed within minutes provides information about coagulation in general, fibrinogen levels, as well as platelet count and function in particular [43–45]. This information facilitates decision making on the use of factor concentrates, platelet substitution or use of costly agents such as recombinant factor VIIa and may reduce potential adverse effects of these therapies [46, 47]. Point of care coagulation monitoring might thus help to further reduce the administration of packed red blood cells and other blood products, which has already significantly dropped with the refinement of surgical technique, the acceptance of lower transfusion triggers, and the prevention of intraoperative hypothermia. In experienced centers many OLT are can often be performed without any transfusions [40].

## Neurologic Monitoring

Worsening liver failure is ultimately accompanied by deteriorating neurological function based on mechanisms not yet fully understood, including the synergistic effects of hyperammonemia, proinflammatory cytokines, and oxidative stress [22]. This ultimately results in cerebral edema, subsequent ICH of varying severity or fatal herniation, one of the leading causes of morbidity and mortality in ALF [20, 48, 49]. The clinical correlates are increasing stages of hepatic encephalopathy from mild neurological disturbance to coma if there is no time for compensation.

The best monitoring modality to detect the progression of hepatic encephalopathy is close observation and frequent neurological exams while avoiding any circumstances that may increase ICH such as pain or agitation. Once coma ensues the role of physical examination is limited and should be amended by monitoring EEG, cerebral blood flow, or intracranial (perfusion) pressure (ICP) to diagnose ICH and determine the best time-point for OLT [50, 51].

Quantitative EEG analysis and somatosensory evoked and acoustic potentials are well-established and sensitive monitors in liver transplant candidates [52, 53]. Bispectral (BIS) index mea-

surements derived from electroencephalography parameters, primarily to monitor the depth of unconsciousness, have been also used to monitor peritransplant hepatic encephalopathy and are used in some centers to guide the depth of anesthesia and anesthetic requirements in patients undergoing OLT [54–56]. A correlation was seen with MELD score as a measure of the severity of liver disease [57] and with pharmaceutical requirements to maintain anesthesia.

Transcranial Doppler sonography allows a repeatable—yet not continuous—and reliable noninvasive assessment of cerebral blood flow at the bedside [58]. By calculating resistance, pulsatility indices and evaluating specific wave patterns related to impaired cerebral autoregulation, the development of cerebral edema and concomitant ICH can be assessed and included in the clinical management and decision processes even intraoperatively [59]. Xenon clearance, which is a more precise method to determine cerebral blood flow is clinically difficult to use and is thus solely of scientific interest [60].

Direct measurement of ICP is the most precise method to detect ICH. However when and where to place intracranial probes to monitor ICP in patients with fulminant hepatic failure remains controversial because of uncertain benefits and substantial risks associated with the procedure [61, 62]. Epidural devices have the lowest rate of complications but are considered unreliable and their use has ceased [63]. Subdural devices are the most commonly used and their precision is acceptable. Only few centers use intraparenchymal devices [64, 65].

Cranial computed tomography is insensitive to detect ICH; however, it may be useful to rule out other uncommon intracranial pathology associated with ALF such as bleeding or fatal herniation. Thus CT scans are recommended in cases of severe prolonged coma before proceeding with OLT, but are not a monitoring option to be used on a regular basis to replace ICP monitors.

The benefit and reliability of newer or less invasive monitoring devices such as automated pupillometer, based on the variation of pupil response and recovery pattern remains to be determined [66].

Invasive neurological monitoring should be commenced stepwise with the onset of neurological deterioration and maintained throughout the transplant. The benefit of precise invasive neurological monitoring before undergoing OLT often does not outweigh the risks associated with these invasive monitors considering the limited options of interventions. It thus remains questionable if invasive monitoring can improve outcome.

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## Hemodynamic Monitoring

Abnormal cardiac function is common in many patients with end-stage liver failure and liver transplantation is one of the most stressful cardiovascular situations these patients may experience [67]. Marked circulatory abnormalities such as hyperdynamic circulation due to low peripheral resistance, often in combination with altered intravascular volume status and abnormal response to exercise are frequent [68–70]. The underlying cause of these perturbations may be inherent to the disease process but undoubtedly an increasing rising number of patients also present with cardiac abnormalities such as coronary artery disease and cardiomyopathy unrelated to liver diseases [71–73].

The choice of invasive intra-operative monitoring—a key feature of anesthetic practice—has thus to meet these concerns and often exceeds standard monitors to assess cardiac output, pre- and afterload as well as oxygen supply and demand. Monitoring has to be adapted according to actual needs and ideally should meet the current trend that entails continuous display of information with less invasiveness.

With the evolvement of monitoring modalities during the last decade tailored solutions can be offered for specific patients. The degree of invasiveness and its hazards must be matched with the potential to adequately obtain the necessary information and to manage patients optimally even under extreme situations. All monitoring devices have limitations, which is particularly true during the different phases of OLT [74]. Thorough and cautious interpretation is therefore mandatory.

## Standard Hemodynamic Monitoring

Standard hemodynamic monitoring during OLT comprises at least a pulse oxymetry finger tip, multi-lead electrocardiography as well as arterial pressure monitoring [75].

Arterial pressure monitoring is most frequently accomplished by placing a catheter in one of the radial arteries. Because of the need for blood sampling at times of extreme hemodynamic instability, placing bilateral radial arterial catheters or radial and femoral arterial catheters is done in many centers. This also provides a back-up in case problems arise with one of the cannulae [76, 77].

However, inaccurate invasive pressure monitoring may occur as a result of compression (usually partial, sometimes complete) of the subclavian artery during rib cage retraction, which is considered to be essential during liver transplantation. During extreme hemodynamic instability, especially in combination with excessive vasodilation radial arterial pressure may also underestimate central aortic blood pressure. Therefore, in order to monitor essential organ perfusion pressure, central aortic pressure monitoring and not just peripheral arterial pressure may be necessary, for example by using a femoral arterial catheter. Alternatively brachial or axillary artery catheters can be considered—although their use and accessibility might be limited by positioning. Central arterial catheters aim to provide better information regarding the central aortic blood pressure as compared to the peripheral radial location [76, 78].

ECG monitoring is necessary to detect intraoperative dysrhythmias and other disturbances such as ST segment changes or QT prolongation. An intraoperatively five lead ECG is recommended for ease of detection given the increasing number of patients with cirrhotic cardiomyopathy or coronary artery disease that undergoes OLT and the potentially profound hemodynamic disturbances during the procedure.

Pulse oximetry is a simple technique, widely available at low cost, and has also been suggested as screening tool for portopulmonary hypertension in OLT candidates [79, 80]. Intraoperatively



it reliably predicts changes in arterial oxygen saturation and the presence and severity of hypoxemia occasionally occurring during OLT. Recently pulse oximetry has been adapted to also assess hemoglobin concentration and pulse pressure variation (PPV) and these new modalities are currently under investigation in liver transplantation.

## Cardiac Output

Maintaining adequate tissue perfusion remains the key hemodynamic goal during all phases of liver transplantation. Since classical pressure monitoring is unable to evaluate organ blood flow measurement of cardiac output has been used to assess global organ perfusion. Originally assessed with pulmonary artery catheters (PAC), cardiac output can be assessed today with adequate accuracy continuously by various other techniques such as transpulmonary dye and lithium dilution, Doppler echocardiography, and pulse contour analysis [81–86]. Considering the hazards for example of ventricular arrhythmias during catheterization during insertion of the PAC in OLT patients [87], it should no longer be regarded the only and best way to assess cardiac output and knowledge of its shortcomings is essential to interpret the data. Continuous cardiac output measurements with the PAC, based on short burst of heat dissipation, become inaccurate when central blood temperature is unstable, for example during graft reperfusion. Also, sudden changes in cardiac output, for example when the inferior vena cava is clamped, are not immediately detected by this equipment [88] as it still takes about 10–15 min to achieve stable measuring conditions. However despite these limitations some experienced users of PACs argue that the published risks are exaggerated and more related to careless placement or inexperience than intrinsic problems with the device.

Alternatives such as continuous tracking of changes in left ventricular stroke volume by arterial pulse contour method (continuously integrating the systolic portion of the arterial wave tracing) may measure systemic blood flow during

OLT [89], but use algorithms that assume a characteristic constant impedance, vascular resistance, and arterial compliance, which cannot be assumed in clinical relevant scenarios [81, 84]. Most of these devices have only been clinically validated during stable conditions and not during extreme changes of cardiac output or vasodilatation; these devices suffer from insufficient precision and thus limited liability without an ability to calibrate. Other noninvasive methods such as electrical impedance have also failed to show the precision required during OLT.

## Other Parameters

Since adequate central venous access is required for transfusion purposes, central venous pressure can easily be monitored. The use of peripheral venous pressure during OLT has also been reported even under adverse hemodynamic circumstances [90]. Ventricular filling pressures are not necessarily accurate in determining preload due to changes of compliance [91] and recent studies demonstrated that preload estimates derived from PAC such as central venous pressure or capillary wedge pressure may often be less reliable than volumetric preload parameters like global enddiastolic (GEDV) and intrathoracic blood volume (ITBV) derived from Pulse Contour Cardiac Output Monitoring (PiCCO) [92–94]. However reliance on pressure-derived data has traditionally been used for OLT and changing this may require thorough training and more studies correlating different techniques of hemodynamic monitoring.

The diagnosis and monitoring of portopulmonary hypertension in patients undergoing OLT remains a strong indication for PAC, although echocardiography (addressed below) may be an acceptable alternative [95–97].

Central venous oxygen saturation ( $ScO_2$ ) measurement by short catheters near the upper caval confluence or mixed venous saturation ( $SvO_2$ ) via PAC allows an estimation of oxygen supply and demand. However the results may be difficult to interpret as changes may be a result of rapid variations in supply or demand commonly seen



during OLT [98]. For example, immediately after graft reperfusion temporary hypotension can occur that is associated with a sudden decrease in  $SvO_2$  (due to centralization of pooled venous blood), but should rapidly recover if cardiac output is well maintained. A prolonged reduction of  $SvO_2$  may be due to low CO and should be assessed by further measures and aggressively treated [78].

Positive pressure ventilation during anesthesia induces cyclic changes in left ventricular stroke volume by altering right ventricular filling and ejection with each ventilatory cycle, which can be observed either centrally (stroke volume variation/SVV) or using peripheral pressure derivatives (PPV) [99]. These variations can be increased by applying higher values of positive end-expiratory pressure [100]. SSV and PPV reflect fluid responsiveness in OLT patients and fluid administration regimes based on algorithms using SSV or PPV may be promising in the future [101].

## Transesophageal Echocardiography

The use of transesophageal echocardiography (TEE) has slowly gained more popularity as a monitoring tool for patients undergoing OLT. Initially introduced as part of the preoperative workup of OLT candidates TEE has made its way into the operating room and the initially feared complication of rupturing esophageal varices is seen very rarely. While the cost has decreased, extensive experience and skill to operate and interpret TEE is still required [102]. TEE used during OLT (either limited-scope or comprehensive examinations) led to significant changes in therapeutic algorithms and may affect outcome [103, 104].

TEE allows direct visualization of the heart, monitoring of volume status, contractility, and overall function. In addition, TEE provides valuable information when less common complications occur, such as large pleural effusion, (tension) pneumothorax, or pulmonary thromboembolism. Unfortunately, short-axis visualization of the left ventricle is very limited because of the posterior retraction of the stomach; instead,

4-chamber views are preferably used. TEE is especially helpful in the management of disorders such as pulmonary hypertension, intracardiac clot formation, and hypertrophic cardiomyopathy [105–107]. Finally, TEE allows the visualization of large vessels. For example, incomplete obstruction of the inferior vena cava as a result of an inadequate venous reconstruction can often be diagnosed with TEE [108].

Transesophageal echocardiographic assessment of cardiac output can be achieved by measuring pulse wave Doppler flow at the aortic valve or in the descending aorta. Alternatively various planimetric or volumetric methods based on the changes of the dimension of cardiac cavities using novel software applications can measure cardiac output on a beat-to-beat basis. Both methods show a good correlation with cardiac output measured by thermodilution technique [85]. The major limitation is that absolute values might be more difficult to quantify than observed changes, but this limitation is easily outweighed by the ability to visualize the underlying pathology.

Hemodynamic monitoring remains a key feature of anesthetic practice and in general moves towards continuous information using less invasive monitors. Technological development has created various clinically used devices that are associated with different degrees of invasiveness, specific advantages, and limitations. It remains one of the main tasks of the anesthesiologist to obtain and interpret the necessary information of different monitoring modalities to enable optimal management of patients even under extreme circumstances.

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## Monitoring of Graft Function

Early and regular assessment of graft function is of crucial importance for the surgical success of OLT as well as for long-term outcome. Assessment of adequate graft blood flow is priority as compromised blood flow due to vascular thrombosis or vascular kinking requires urgent revascularization. Inability or late detection of a perfusion deficit is associated with an exceedingly high rate

of graft loss and increased mortality. However the effect of hemodynamic instability on splanchnic and graft perfusion makes stabilization of cardiac output and blood pressure mandatory prior to assessing regional blood flow and potentially revising an anastomosis. Standard liver function testing plays only a minor part at the present day in the assessment of liver graft viability as these tests are too slow and reflect tissue damage more than the graft function and its capacity for tissue regeneration [109, 110]. Direct assessment of graft function either via indirect measurement of homeostatic or metabolic alterations is most widely used [111].

## Blood Flow

Despite the hyperdynamic circulation associated with ESLD hepatic blood flow may vary from well preserved or even increased for example with ALF to severely reduced. The diversion of portal blood flow due to increased portal pressure and a compromised compensatory mechanism of the hepatic arterial buffer response may cause profound decreases of hepatic perfusion. After transplantation ischemia-reperfusion injury can cause tissue swelling and compromise adequate hepatic inflow. Inadequate patency of the vascular anastomoses or increased central venous pressure may cause outflow obstruction and congestion which is more likely to be seen in partial transplantation. With outflow obstruction the hepatic artery buffer response is preserved but its capability to compensate may be limited [109].

Ultrasound Doppler technique remains the only clinical used method to monitor graft blood flow. Difficulties of noninvasive real-time assessment in the perioperative period (for example, obtaining adequate acoustic windows despite an abdominal dressing) can be overcome with experience [112]. A significant improvement of ultrasound techniques was achieved when contrast agents were used to improve flow signal quality in OLT. Use of ultrasound contrast may also provide additional information about the graft by interpretation of the phase of parenchymal enhancement.

Few invasive devices can determine graft blood flow intraoperatively. Temporary implantable flow probes are sometimes used either to detect graft congestion from outflow obstruction in living-donor-liver transplantation or to observe critical anastomoses, e.g., in pediatric OLT [108, 113, 114]. A recent experimental study tested the feasibility of monitoring hepatic blood flow with TEE but has not been repeated in humans [115].

Various ultrasound or Doppler parameters such as flow velocity, pressure gradient, resistive, and pulsatility indices have been defined; however, change and trends of these values is superior to absolute values. The main limitation of ultrasound technique is the requirement of intense education and knowledge and its clinical usefulness remains unsettled due to the lack of reproducibility and accuracy characterized by intra- and interobserver variation. This may have prevented ultrasound from becoming a routine monitor in OLT patients; however, it is nowadays often incorporated in different management algorithms [110, 116].

## Standard Liver Function Testing

Standard or conventional liver function tests, although routine in many institutions, fail to detect acute changes in graft function quickly enough. They primarily reflect graft damage, i.e., the integrity of hepatocytes and the biliary epithelium.

Measurement of transaminases and bilirubin in the postoperative period, their course and pattern reflect the extent of injury caused by harvesting, cold ischemic period, and reperfusion. Additional biochemical parameters such as albumin or clotting factors reflect the improving synthetic capacity of the new graft but due to their long half-life are slow acting markers of function and lack sensitivity.

Although recent developments have contributed to a better understanding of the mechanisms of adequate or impaired hepatic regeneration the importance of biochemical markers such as cytokines, interleukins, and complement factors as predictors of liver function after OLT is not yet completely understood. However, given the fact

that their measurement is now facilitated by commercially available assays, their general acceptance will rapidly increase in clinical practice and may help identify patients at risk.

### Dynamic Liver Function Testing

The introduction of dynamic liver function tests added a significant step in the interpretation of graft (dys-) function and is well suited to predict graft survival and overall outcome [117, 118]. These tests are based on the ability of the graft to metabolize or eliminate specific substances within a relative short time. They reflect the current functional reserve of the liver parenchyma and allow rapid interventions based on detected changes. The quantitative assessment of graft function by these tests is based either on the measurement of hepatic clearance of an administered substance or the formation or retention of a known compound of such a substrate. These tests are dependant on the hepatocyte mitochondrial adenosine triphosphate synthesis that determines the actual energy charge of the liver and its metabolic reserve and most often reflect the oxidative capacity of the hepatic microsomal cytochrome P450 system.

None of these tests have 100% accuracy, and interpretation depends on additional factors such as hepatic perfusion (discrimination between hepatocellular dysfunction and blood flow disturbances thus remains difficult), the functional hepatocyte mass (also assessable by CT volumetry), and the exchange across the blood–hepatocyte barrier. Recent experimental studies have shown that exchange across the blood–hepatocyte barrier can vary between compounds depending on the transport channels and confounding factors that can up- or down-regulate functionality of these transport mechanisms within hours [119, 120].

Several of these tests have been developed in the last decades and have shown some promise in clinical practice. However they are not widely used as they do not fulfill the criteria of an ideal test: cost effectiveness, reproducibility, and ease of performance. These tests are often time-consuming and cumbersome and may require serial

blood sampling or use of volatile or radionuclide substances.

The monoethylglycinexylidide (MEGX) test is based on the transformation of lidocaine to its major initial metabolite MEGX, and may be more useful when assessed serially in individual patients. This is also true for galactose elimination capacity and aminoacid-based functional tests or derived ketone body ratio [121].

Currently only two dynamic tests are used clinically intra- and postoperatively. Indocyanine green (ICG), a water-soluble dye, is removed from the blood within minutes depending on hepatic graft perfusion, hepatocyte function, and biliary excretion. Its elimination can conveniently be measured noninvasively on a photometric basis at 800 nm. Assessment as early as immediately after reperfusion offers relevant prognostic data and may guide therapy through the immediate postoperative period [122, 123]; however, about 1 h delay is required between each measurement. ICG kinetics are a reliable indicator of initial graft function and allow discrimination of dys- or nonfunction including hepatic artery thrombosis and rejection [122]. More recently an improved  $^{13}\text{C}$ -labeled methacetin breath test has been reported [124, 125]. An intravenous bolus injection of  $^{13}\text{C}$ -labeled methacetin results to the exhalation of  $^{13}\text{C}$ -carbon dioxide collected by a face mask. The integral calculation of the exhaled  $^{13}\text{C}$ -carbon dioxide correlates with graft function and provided an adequate functional parameter for a general classification of the graft as well as a predictor of graft regeneration. Other tests are even more complex but do not improve sensitivity and specificity and are not used clinically.

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Ann Walia and Roman Schumann

Liver transplantation (LT) continues to be one of the most complex and resource-intensive multidisciplinary procedures. Since the first successful human liver transplant in the US in 1967 by Thomas Starzl [1], considerable improvements in surgical and anesthetic techniques, perioperative management, and outcomes have evolved [2]. Driven by the limited number of donor organs and an ever-increasing patient waiting list combined with the need to optimize recipient and donor graft outcomes, transplant clinicians are developing evidence-based practices in their respective specialties. The evidence base for perioperative anesthetic management in liver transplantation is an area of active inquiry and an assessment of current practices may promote understanding and establishment of best practices in this specialty. A report on resource utilization in anesthesia for liver transplantation indicated great variability between liver transplant centers in the US in part depending on transplant volume [3]. Despite this practice report in 2003, there remains an information and knowledge gap regarding outcomes related

to such practices, underscoring the need for evidence-based practice recommendations to guide anesthetic management.

A series of comprehensive sequential surveys was developed to assess specific areas of perioperative anesthetic management in liver transplantation within the US and internationally, to provide insight into current anesthetic practice variation and resource utilization. The methodology and a synopsis of the most salient findings are presented here. This summary is intended to highlight current practice patterns that could serve as a basis for future outcome studies related to specific practices, promoting evidence-based best practice recommendations in anesthesia for liver transplantation.

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## Methods

The executive board of the Liver Transplant Anesthesia Consortium (LTrAC) included liver transplant anesthesia specialists from four academic institutions (Vanderbilt University, University of Colorado, University of California at San Francisco, and Tufts University) with input from the Liver Intensive Care Group of Europe (LICAGE). We developed a series of four systematic web-based surveys on perioperative anesthetic care in liver transplantation (LT). The first survey (101) examined the administrative and organizational structure of liver transplant anesthesia teams within their departments. The practice variations of intraoperative monitoring

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(201) and intraoperative fluid, pharmacologic and coagulation management (202) were assessed in the second and third questionnaires, respectively. A final survey (301) focused on qualification requirements of LT anesthesia program directors (prior to implementation of the American Society of Anesthesiologists (ASA) transplant committee guidelines), LT team continuing medical education (CME) practices, preoperative recipient assessment, and postoperative management.

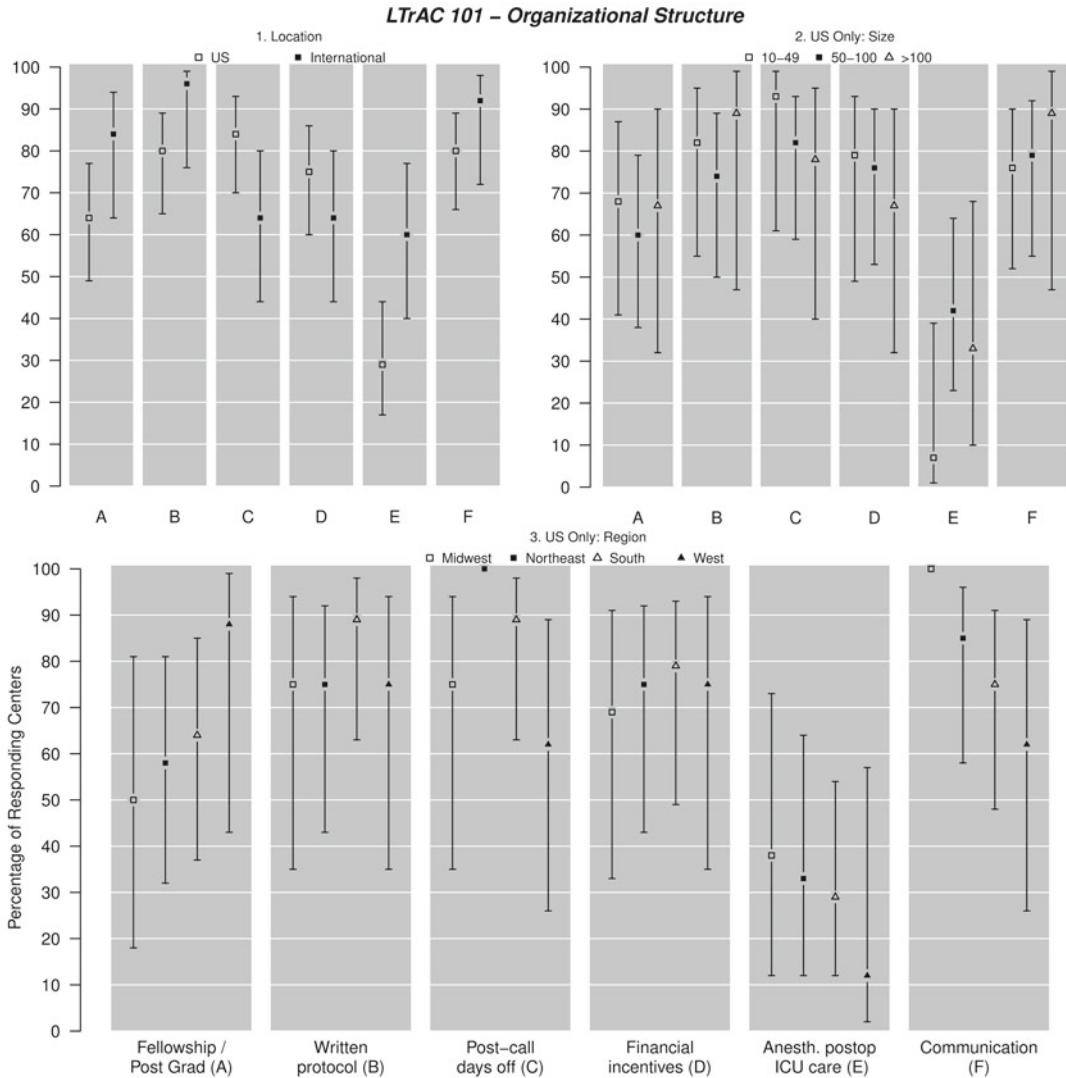
Anesthesiology departments of all US liver transplant centers listed with the United Network for Organ Sharing (UNOS) [4] were contacted electronically or by mail to participate in the survey between 2006 and 2009. Centers performing <10 liver transplants annually, private anesthesia contracting services, pediatric liver transplant centers, and the states of Alaska and Hawaii were excluded. Additional exclusion criteria were ongoing organizational change and UNOS probation status at the time of the survey. Anesthesiologists from international centers participated via a link on the educational website of LICAGE. E-mail reminders were sent every 2 weeks for a total of 3. In the absence of an electronic response, an LTrAC member attempted phone contact with potential participants. Epidemiologic data reported from within the US were confirmed using the UNOS database. US liver transplant programs were categorized according to their annual transplant frequency into large (>100), medium (50–99) and low (10–49) volume centers. US regional practice differences were assessed by geographic program location according to the US census map (West, Midwest, South, and North-East regions of the US). All categorical variables were summarized as weighted percentages. Weights were defined as the proportion of responses from each UNOS center; for example, if two responses came from same center, then the weight associated with each would be 0.5. Weights associated with international responses were generated based on the hospital provided by the respondent. Due to the descriptive nature of this study, inferential comparisons were not performed when stratified by location, US size, and US region, but 95% confidence intervals

were provided for each estimate. All analyses were performed using the survey package [5, 6] in *R version 2.11.1* [7].

## Results

*LTrAC 101:* This survey investigated the organizational structure and incentive methodology of liver transplant teams within their departments as shown in Fig. 10.1 [101] (Table 10.1).

Sixty-five percent (95% CI: 49–77%) of anesthesiologists within the US and 85% (64–94%) internationally received post-residency training with a focus on hepatobiliary anesthesiology, but did not participate in a designated liver transplant anesthesia fellowship program (Fig. 10.1 [101-1-A]) (Table 10.1). Sixty-eight percent (53–80%) of the US programs used supervised on-the-job training for liver transplant anesthesia for team members, but this occurred less frequently in the small volume centers. Almost 40% (26–54%) of US centers needed additional liver transplant anesthesia faculty. Respondents from centers located within the Southern US region reported the greatest need (68%, 43–85%). A written anesthesia transplant protocol was available in 80% (65–89%) of the US centers and the majority of the non-US centers (96%, 76–99%) (Fig. 10.1 [101-1-B]) (Table 10.1). All US programs and 76% of the international respondents reported having a separate LT anesthesia call team, and the call distribution was equal among physicians in 83% (69–92%) of US and 64% (44–80%) of the international centers. Forty-six percent (32–61%) of the US programs reported reduced participation in non-transplant-related departmental call. A majority of the US programs provide incentives either financially or in the form of post-call time off (84%, 70–93%) whereas only 64% (44–80%) of the international respondents reported doing so. Incentives were less frequent in US large volume centers compared to low and medium size centers (Fig. 10.1 [101-2-D]). Northeast US programs offered the most incentives in the form of post call time off (42% vs. <25% in all other regions) and financial sup-



**Fig. 10.1** LTrAC 101. Organizational structure. Organizational structure of the Liver Transplant Anesthesia team within the Department of Anesthesiology in International

and US liver transplant programs, further analyzed by US center transplant frequency and region

port (75% vs. 62.5% in West, 36% in the South, and 25% in the Midwest) (Fig. 10.1 [101-3-D]) (Table 10.1).

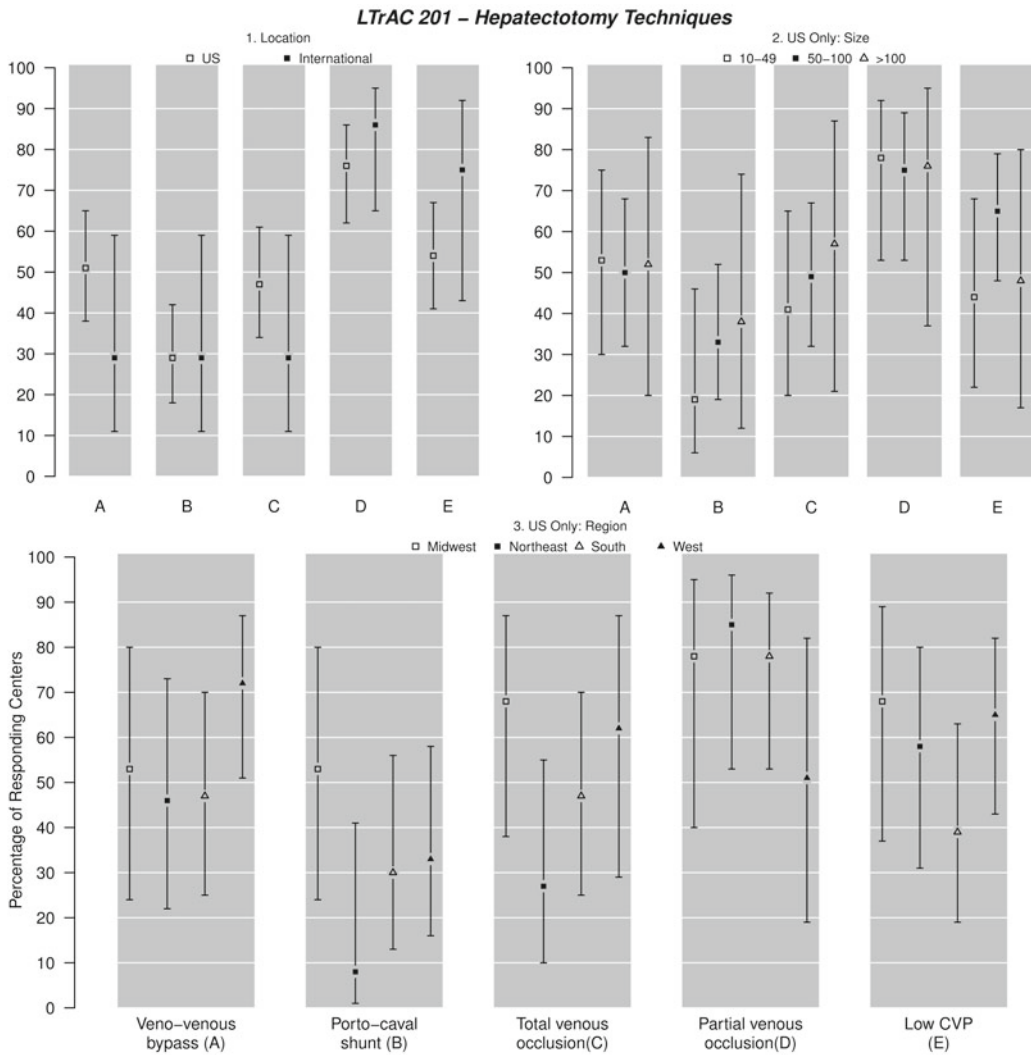
In 55% (40–68%) of the US programs anesthesiologists participated in LT patient selection committees of which 67% (32–90%), 55% (34–74%), and 46% (23–71%) occurred in large, medium, and small centers, respectively. LT candidates underwent a preoperative assessment by an LT anesthesiologist in all large volume centers. In low and medium volume

centers, LT anesthesiologists were involved in this assessment in 86% (56–97%) and 79% (57–91%), respectively. Involvement of the anesthesiologists in the postoperative ICU care of the LT patient was reported by 60% (40–77%) of the international respondents and only in 29% (17–44%) of the US centers. This practice was most frequent in mid volume (42%, 23–64%) and least in low volume centers (7%, 1–39%) and centers in the West (12%, 2–57%, Fig. 10.1 [101-3-E]) (Table 10.1). We assessed

**Table 10.1** Survey demographics

Survey; # responses (US;International)	LTrAC 101	LTrAC 201	LTrAC 202	LTrAC 301
# of US Centers <sup>a</sup> meeting inclusion criteria	85 (59;26) Yes: n=59 No: n=60	103 (85;18) Yes: n=60 No: n=59	104 (72;32) Yes: n=61 No: n=58	103 (80;23) Yes: n=61 No: n=58
Responding centers	71% (42/59)	72% (43/60)	66% (40/61)	64% (39/61)
<i>Exclusion</i>				
Private practice	–	–	–	–
Pediatric only	–	–	–	–
Other	–	–	–	–
<i>Size</i>				
10–49	58% (14/24)	62% (16/26)	52% (14/27)	54% (14/26)
50–100	83% (19/23)	83% (20/24)	75% (18/24)	71% (17/24)
>100	75% (9/12)	70% (7/10)	80% (8/10)	73% (8/11)
<i>Region</i>				
Midwest	50% (8/16)	56% (9/16)	44% (7/16)	67% (10/15)
Northeast	86% (12/14)	81% (13/16)	81% (13/16)	56% (9/16)
South	74% (14/19)	83% (15/18)	63% (12/19)	70% (14/20)
West	80% (8/10)	60% (6/10)	80% (8/10)	60% (6/10)

<sup>a</sup>A total of 119 US Centers were listed in the UNOS database during surveys 101 through 301



**Fig. 10.2** LTrAC 201-1. Hepatectomy techniques. Hepatectomy techniques used in international and US liver transplant programs, further analyzed by US center transplant frequency and region

interdepartmental morbidity and mortality conferences as a surrogate for interdisciplinary communication (hepatologists, surgeons, and anesthesiologists). Such conferences occurred in 80% (66–89%) of the US and 92% (72–98%) of the international programs regularly, more so in the Midwest (100%) and least in the West (62%, 26–89%, Fig. 10.1 [101-3-F]) (Table 10.1). Finally, departmental LT meetings as part of a quality improvement process occurred in 56% (41–69%) of US programs and in 82% (60–93%) of the reporting interna-

tional programs, least in medium volume (39%, 20–61%) and most in high volume (75%, 36–94%) programs.

*LTrAC 201*: Intraoperative monitoring and surgical preferences were the objective of this survey.

Surgical technique for recipient hepatectomy varies by personal or center preference. As shown in Fig. 10.2 [201-1-D], partial venous occlusion was utilized by 76% (62–86%) of all US responders although there was variation in preference by

region and center volume (Fig. 10.2 [201-2,3-D]). Just over half (51%, 38–65%) of the US centers employed veno-venous bypass for hepatectomy, whereas this technique was used in 29% (11–59%) of the international centers (Fig. 10.2 [201-1-A]). Within the US, this practice was independent of center's case volume or geographic location except for programs in the West. (72%, 51–87%, Fig. 10.2 [201-2,3-A]). Total venous occlusion followed similar trends and was used in 29% (11–59%) of the international and 47% (34–61%) of the US centers (Fig. 10.2 [201-1-C]), most commonly in large volume centers (57%, 21–87%, Fig. 10.2 [201-2-C]) and least in the Northeast (27%, 10–55%, Fig. 10.2 [201-3-C]).

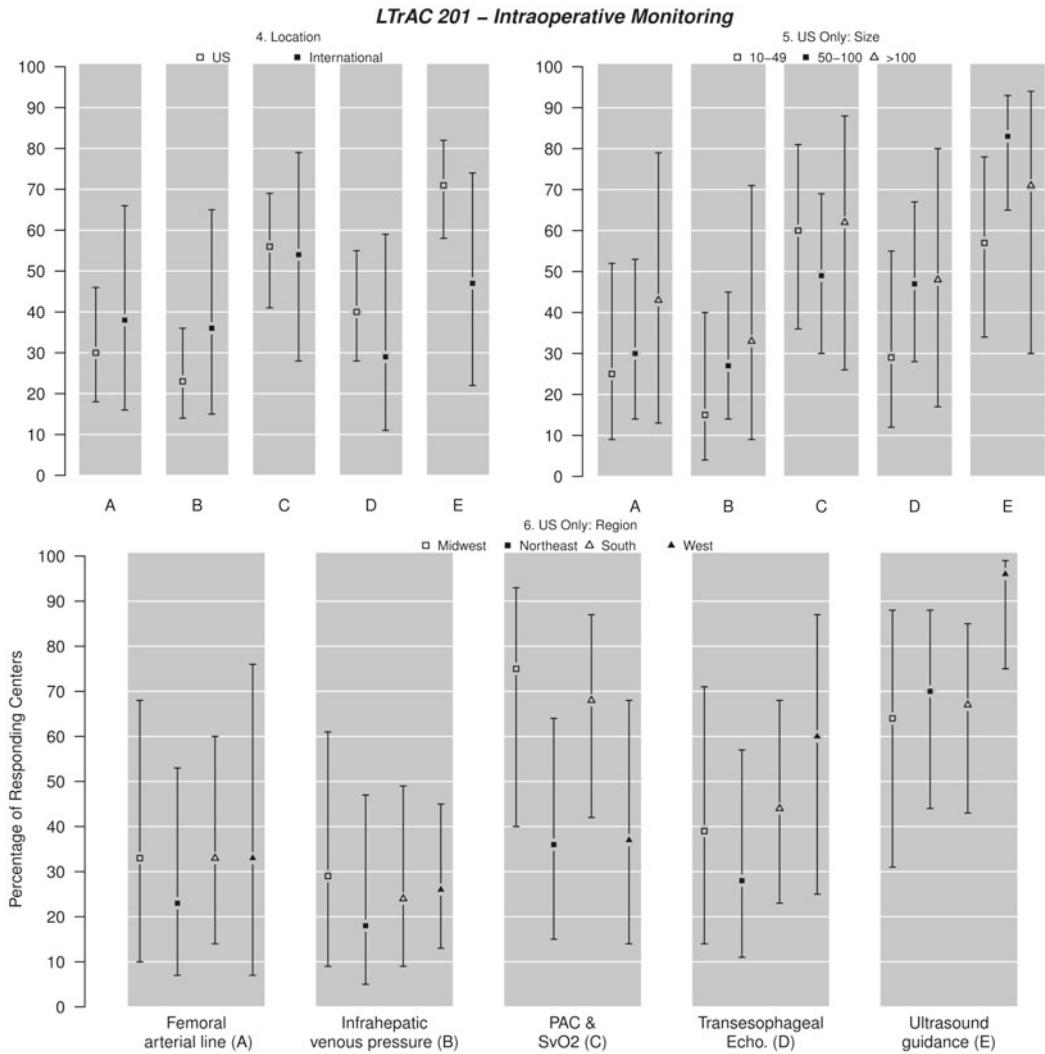
Temporary portacaval shunt was routine practice in 29% (11–59%) of the international centers and in 29% (18–42%) of the US centers (Fig. 10.2 [201-1-B]) where this technique was most common in the Midwest (53%, 24–80%) and least in Northeast (8%, 1–41%, Fig. 10.2 [201-3-B]). Similarly a low central venous pressure technique was practiced more frequently in the international centers (75%, 43–92%) compared to the US programs (54%, 41–67%, Fig. 10.2 [201-1-E]) where this was most common in the West (65%, 43–82%), Midwest (68%, 37–89%), and mid volume centers (65%, 48–79%) and least in centers in the South (39%, 19–63%, Fig. 10.2 [201-2,3-E]).

Use of a single radial arterial line for perioperative monitoring occurred in 83% (51–96%) of the international centers and 73% (58–84%) of the US centers where just over a third of the low volume centers (34%, 16–59%) and programs in the South (40%, 20–64%) routinely used two radial arterial lines. Femoral arterial line monitoring was utilized by 38% (16–66%) of the international and 30% (18–46%) of the US centers (Fig. 10.3 [201-4-A]), more so in the large volume centers (43%, 13–79%). Over one-third (38%, 25–52%) of all responders used two central lines and, this was more common in the small (42%, 22–64%) and large volume centers (43%, 13–79%) and in the South of the US (48%, 26–71%). Femoral venous catheters were utilized by 25% (8–57%) of the international centers and

10% (4–23%) of the US centers with no great variability by center size or region. Use of single rapid infusion catheter (RIC) as volume lines was similar across programs (international: 55%, 40–69%, US: 50%, 25–75%). Southern centers in the US were more likely to use two RICs (31%, 13–57%) compared to other regions (Midwest: 11%, 1–53%, Northeast: 15%, 4–47%, and West: 22%, 4–65%). Figure 10.3 [201-4,5,6] depicts variations in intraoperative hemodynamic monitoring within the US as well as between US and international centers. Infra-hepatic venous pressure monitoring was performed by 36% (15–65%) international and 23% (14–36%) US centers (Fig. 10.3 [201-4-B]) and less frequently in other centers. Pulmonary artery pressure monitoring, including mixed venous oxygen saturation (SvO<sub>2</sub>) monitoring were routine in just over half of all responders (Fig. 10.3 [201-4-C]). Although there were no major differences by center case volume (LV: 60%, 36–81%, MV: 49%, 30–69% and HV: 62%, 26–88%, Fig. 10.3 [201-5-c]), there was evidence of marked regional variation (Midwest: 75%, 40–93%; Northeast: 36%, 15–64%; South: 68%, 42–87%; West: 37%, 14–68%, Fig. 10.3 [201-6-C]). Intraoperative use of transesophageal echocardiography (TEE) was slightly more common in the US (40%, 28–55%) compared to the international centers (29%, 11–59%, Fig. 10.3 [201-4-D]). Within the US, TEE was preferentially used in the large (48, 17–80%) and mid volume centers (47%, 28–67%) compared to low volume centers (29%, 12–55%, Fig. 10.3 [201-5-D]). US regional differences showed greatest use of this monitor by centers in the West followed by centers in the South (Fig. 10.3 [201-6-D]). The primary anesthesiologists at large US centers performed the TEE in 43% (13–79%). Forty percent (16–70%) of the centers in the Midwest reported using transthoracic Echo, whereas the use of this monitor was less common elsewhere.

In more than 71% (58–82%) of the US centers and 47% (22–74%) of the international centers, ultrasound was applied to guide central line placement (Fig. 10.3 [201-4-E]). US regional and center size-based variations showed greatest use of this monitor by the mid volume centers (83,





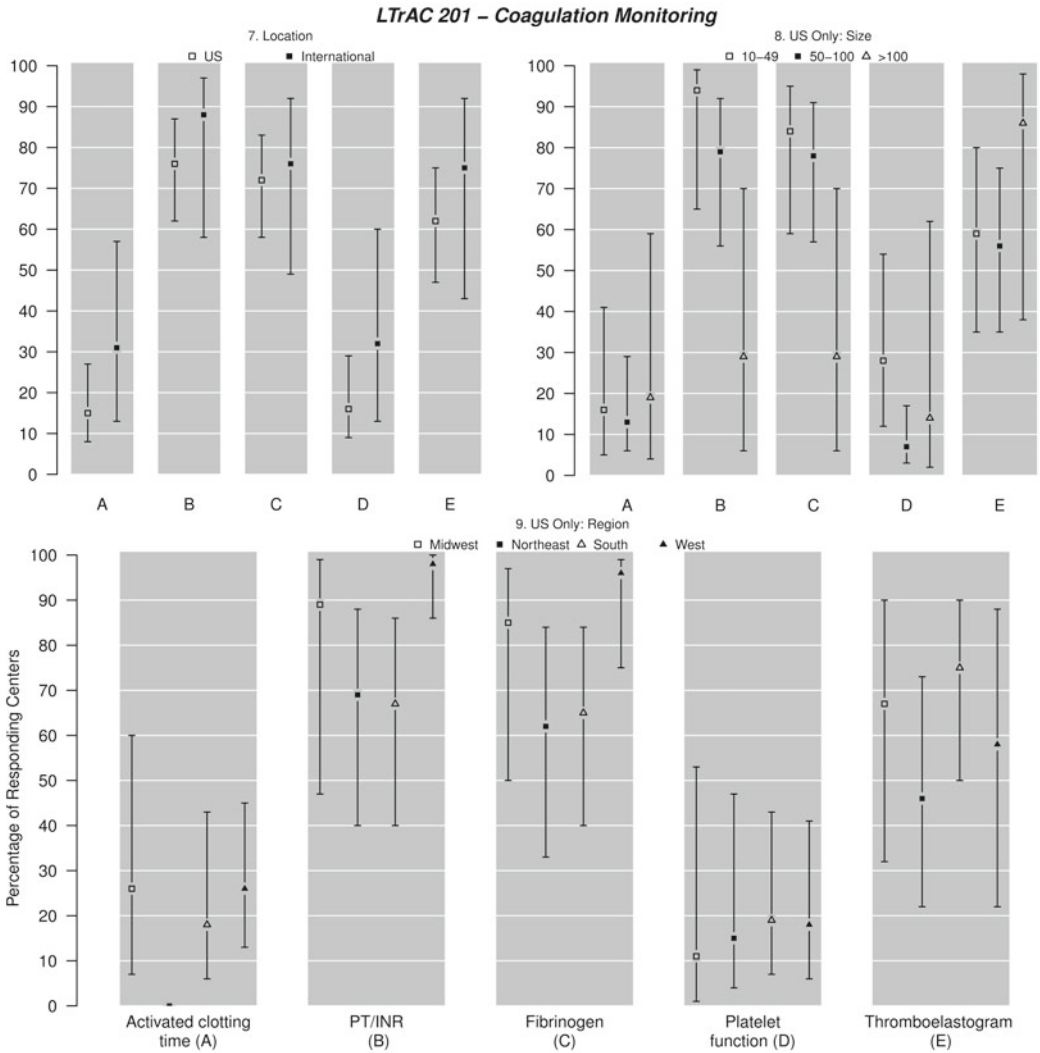
**Fig. 10.3** LTrAC 201–2. Intraoperative monitoring. Intraoperative hemodynamic and other monitoring modalities utilized in international and US liver transplant pro-

grams, further analyzed by US center transplant frequency and region. *PAC* Pulmonary artery catheter; *SvO2* mixed venous oxygen saturation

65–93%) and by those in the West (96, 75–99%, Fig. 10.3 [201-5,6-E]).

As shown in Fig. 10.4-[201-7,9], frequency of coagulation parameter monitoring varied considerably amongst centers. The activated clotting time was monitored in 15% (8–27%) of US centers and in 31% (13–57%) international centers (Fig. 10.4 [201-7-A]). Prothrombin time (PT) and international normalized ratio was monitored by 76% (62–87%) of the US and 88% (58–97%) of the international programs (Fig. 10.4

[201-7-B]). Two-thirds of the centers in the Northeast (69, 40–88%) and the South (67, 40–86%, Fig. 10.4 [201-9-B]) and 29% (6–70%) of the large volume centers (Fig. 10.4 [201-8-B]) routinely follow these parameters. Similar trends existed for fibrinogen level and partial thromboplastin time monitoring (Fig. 10.4 [201-7,9-C]). Intraoperative platelet function assessment was more than twice as frequent in international (32%, 13–60%) compared to US centers (16%, 9–29%, Fig. 10.4 [201-7-D]). Within the US,



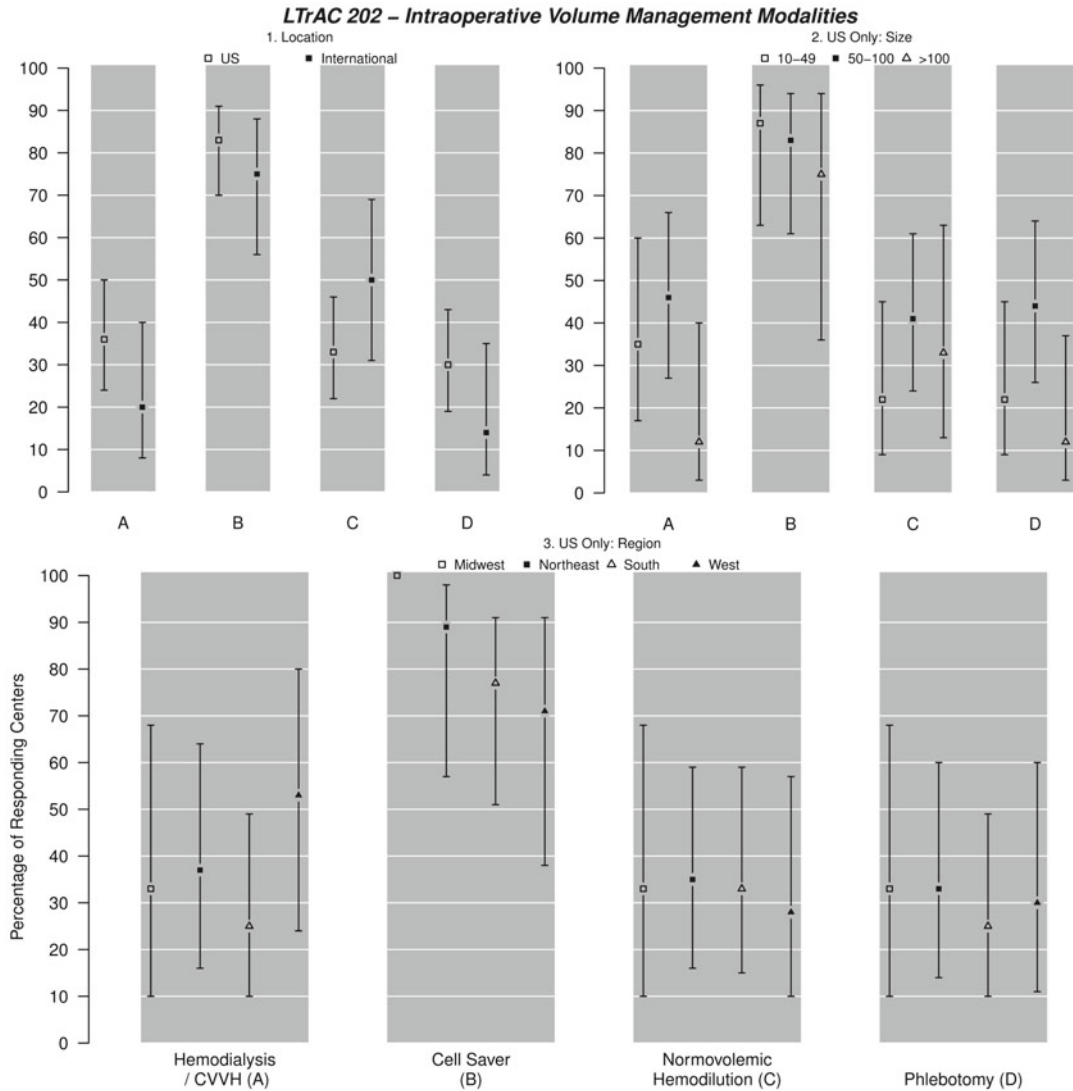
**Fig. 10.4** LTrAC 201–3. Coagulation monitoring. Intra-operative coagulation parameter monitoring modalities utilized in international and US liver transplant programs, further analyzed by US center transplant frequency and

region. *ACT* Activated clotting time; *PT* prothrombin time; *INR* international normalized ratio; *TEG* thromboelastogram

platelet function assay was followed most frequently in low volume (28%, 12–54%) and least in Midwest (11%, 1–53%) programs as shown in Fig. 10.4 [201-9-D]. Thromboelastogram was monitored more frequently in the international centers (75%, 43–92%) compared to US centers (62%, 47–75%, Fig. 10.4 [201-7-E]). This monitor was most frequently used in the large volume US centers (86%, 38–98%, Fig. 10.4 [201-8-E]) and least in the northeastern region of the US (46%, 22–73%, Fig. 10.4 [201-9-E]).

*LTrAC 202*: This survey examined routine intra-operative fluid, pharmacologic and coagulation management.

Fluid administration strategies include use of cell saver devices, normovolemic hemodilution, phlebotomy, and continuous renal replacement techniques. Figure 10.5 [202-1] shows the routine use of these modalities in international and US programs. Cell saver was the most frequently utilized technique, employed by 75% (56–88%) and 83% (70–91%) of international and US programs,

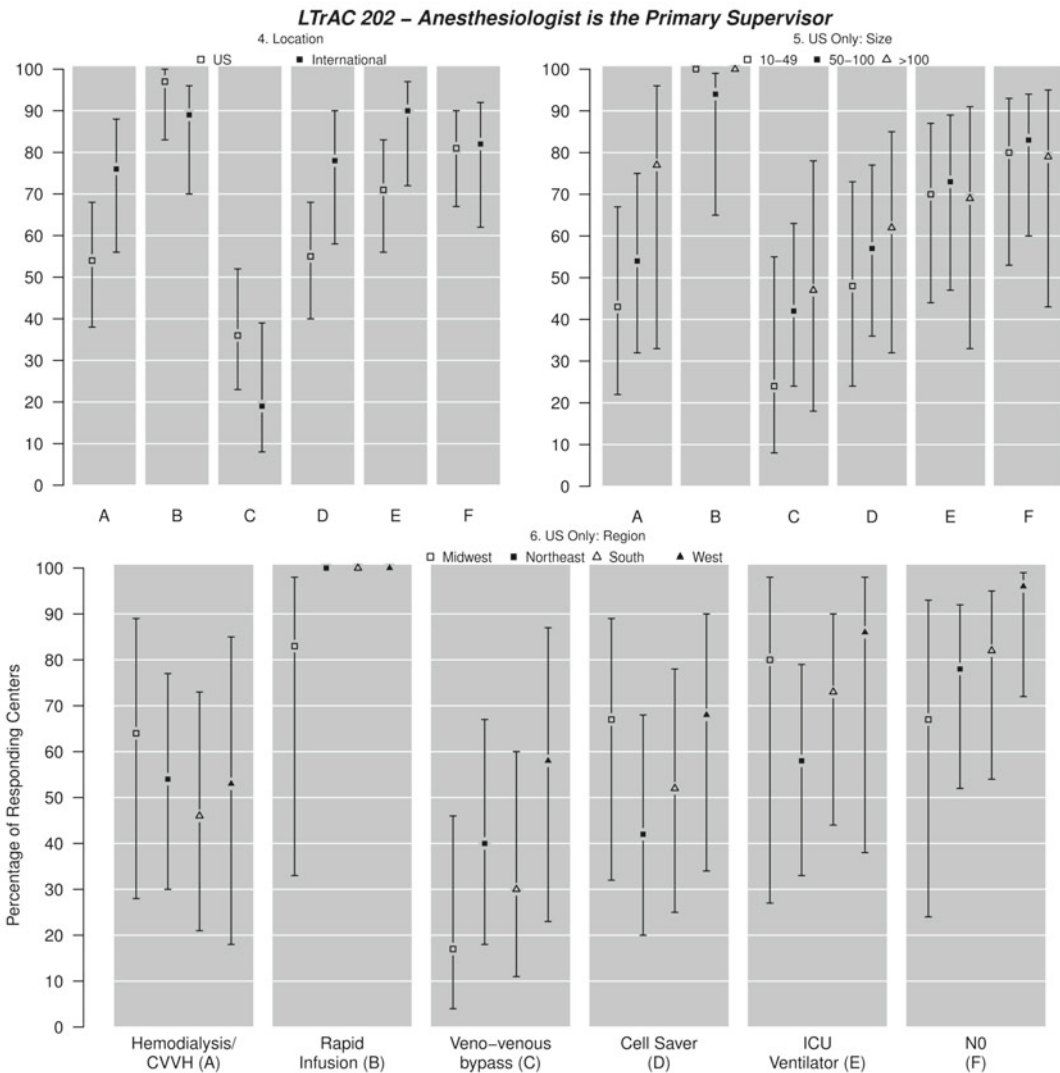


**Fig. 10.5** LTrAC 202–1. Intraoperative volume management strategies. Volume management modalities in international and US liver transplant programs, further analyzed by US center transplant frequency and region.

CVVH Intraoperative renal replacement strategies including hemodialysis and continuous veno-venous hemofiltration and dialysis

respectively (Fig. 10.5 [202-1-B]). The role of the anesthesiologist as the primary decision maker and supervisor for the intraoperative use of the above-mentioned techniques as well as the use of a rapid infusion device, veno-venous bypass, ICU ventilator, and nitric oxide is shown in Fig. 10.6 [202]. Direction and supervision of renal replacement therapies, veno-venous bypass, and cell saver devices by anesthesiologists in the US increased continuously with increasing transplant volume.

The most frequently administered crystalloid solution for routine intraoperative fluid replacement was normal saline internationally (82%, 62–92%) and in the US (81%, 68–90%) followed by a pH-adjusted crystalloid (Plasmalyte®) in 74% (53–87%) and 74% (59–85%) of international and US programs, respectively. Least favored for this purpose was glucose containing normal saline in the US (43%, 28–58%) and internationally (36, 19–57%). Most international

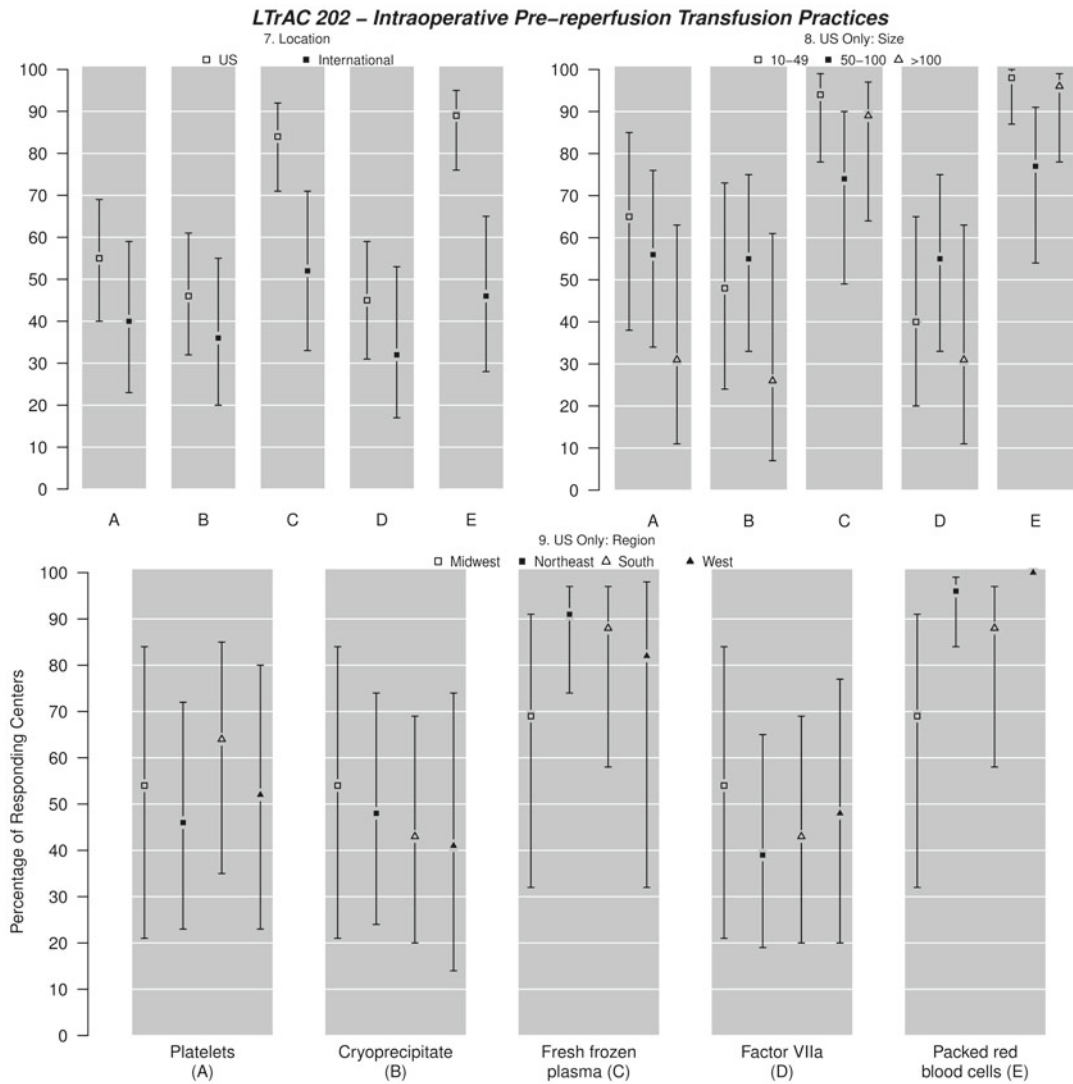


**Fig. 10.6** LTrAC 202–2. The anesthesiologist as the primary supervisor for various intraoperative management options in international and US liver transplant programs, further analyzed by US center transplant frequency and region.

CVVH Intraoperative renal replacement strategies including hemodialysis and continuous veno-venous hemofiltration and dialysis; ICU intensive care unit; NO nitric oxide administration

(62%, 42–78%) and US programs (85%, 70–93%) administered albumin routinely for volume expansion. Hydroxyethyl starch in saline (Hespan®) was routinely used in roughly 50% (~30–70%) of both, international and US centers, while Hydroxyethyl starch in balanced electrolyte solution (Hextend®) was employed routinely in 39% (22–59%) and 52% (37–67%) of international and US programs, respectively.

The routine administration of different blood products including packed red blood cells, fresh frozen plasma, cryoprecipitate (Cryo), and platelets (Plts) intraoperatively before reperfusion is summarized in Fig. 10.7 [202]. US programs routinely use blood products of all categories frequently, and so do international centers, but to a lesser overall extent. This same result was observed for blood product use in the



**Fig. 10.7** LTrAC 202–3. Intraoperative pre-reperfusion transfusion practices. Intraoperative pre-reperfusion transfusion practices in international and US liver transplant

programs, further analyzed by US center transplant frequency and region

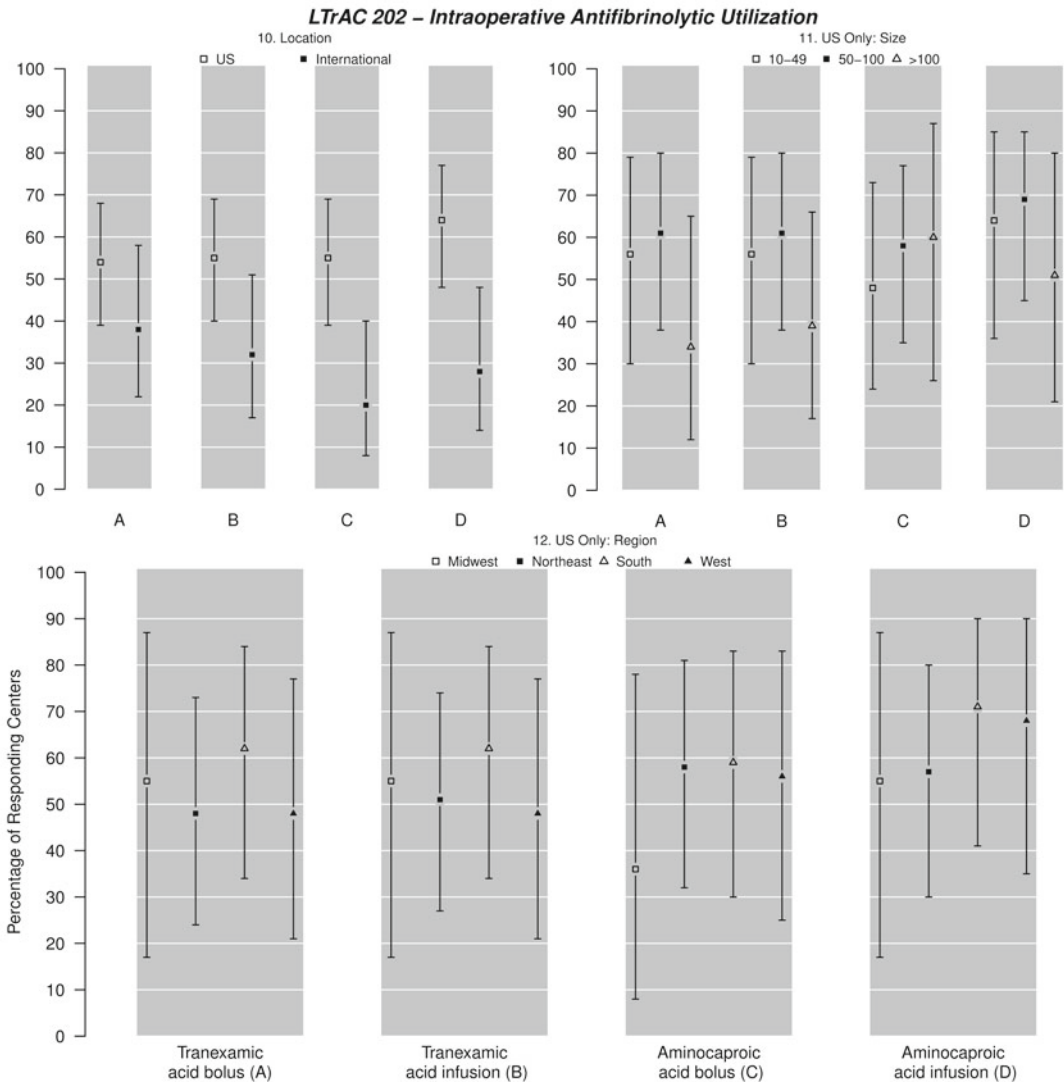
immediate preoperative and the post-reperfusion phase of LT.

Just more than half of US centers (54%, 39–67%) regularly employ recombinant factor VII (rFVII) in the post-reperfusion phase, while between 28% and 30% (~30%, 15–53%) of international programs used rFVII in each LT phase. The anesthesiologist was the primary decision maker for rFVII use in 66% (47–81%) and 70% (55–81%) of international and US programs, respectively, and its use was dependant on a proto-

col in 16% (6–37%) and only 9% (3–23%) of international and US centers, respectively. However, rFVII administration was protocolized in 33% (11–66%) of US high volume centers.

Antifibrinolytic infusion of either tranexamic or aminocaproic acid was part of routine practice in less international than US programs with limited variation between centers by transplant volume (Fig. 10.8 [202]).

Intraoperative use of inotropes and vasopressors including dobutamine, dopamine,



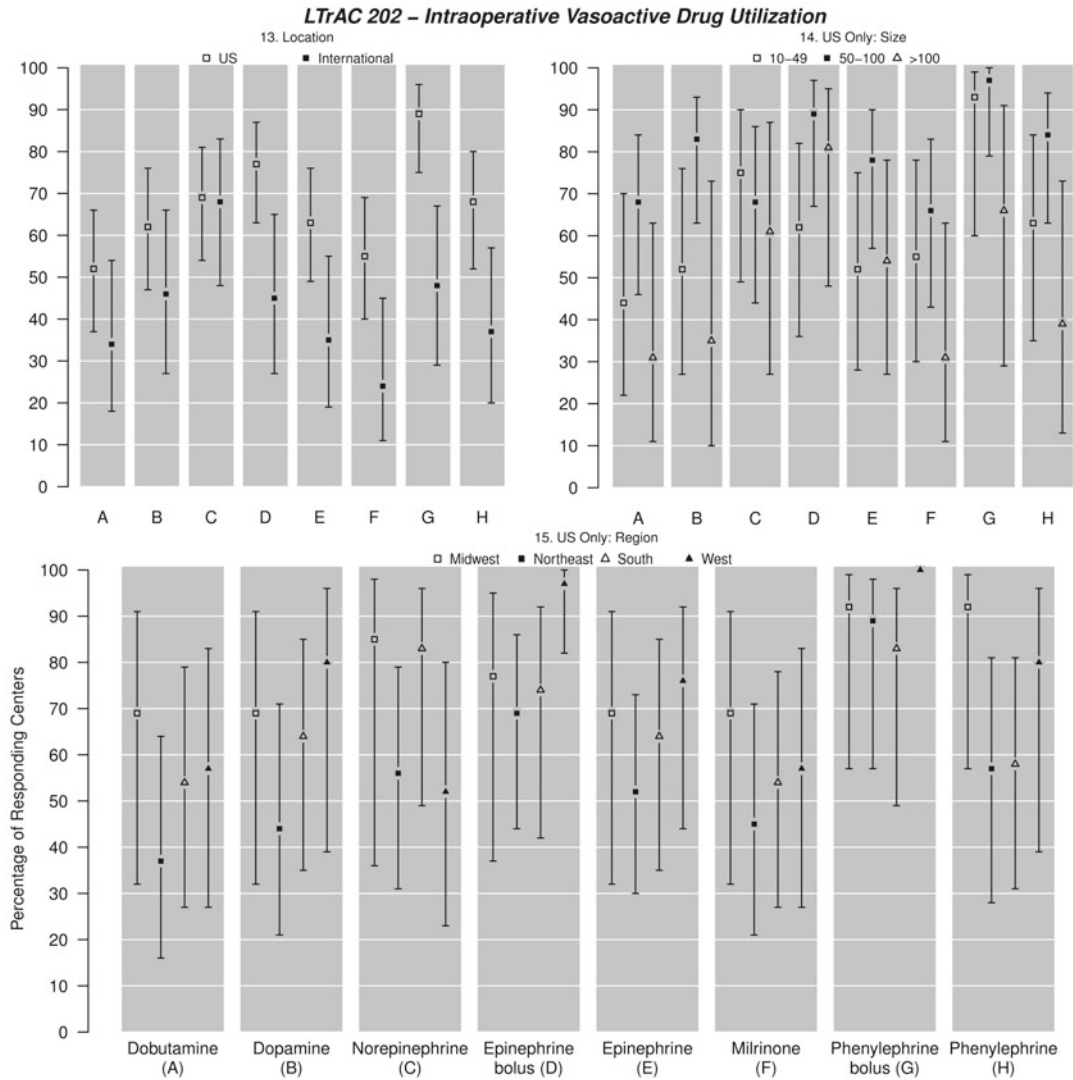
**Fig. 10.8** LTrAC 203-4. Intraoperative antifibrinolytic utilization. Use of tranexamic or aminocaproic acid either as bolus or infusion in international and US liver trans-

plant programs, further analyzed by US center transplant frequency and region

epinephrine, norepinephrine, milrinone, phenylephrine, and vasopressin was common internationally and in the US (Fig. 10.9 [202]). Norepinephrine infusions, phenylephrine bolus, and epinephrine bolus administration were the most frequently employed vasoactive drugs internationally (68%, 48–83%, 48%, 29–67%, and 45%, 27–65%, respectively) and in the US (69%, 54–81%, 89%, 75–96%, and 77%, 63–87%, respectively). Vasopressin was routinely used in 60% (45–74%) of US and 26% (12–47%) of

international centers. Dopamine administration was most frequent in the Western centers of the US (80%, 39–96%) and least in the Northeast (44%, 21–71%). With the exception of norepinephrine infusions, all vasoactive medications were less routinely used in international programs compared to the US. Epoprostenol (Flolan) administration was similar in international and high volume US programs 30% (15–51%) and 28% (9–60%), respectively and most frequent in medium size US centers (70%, 49–86%).



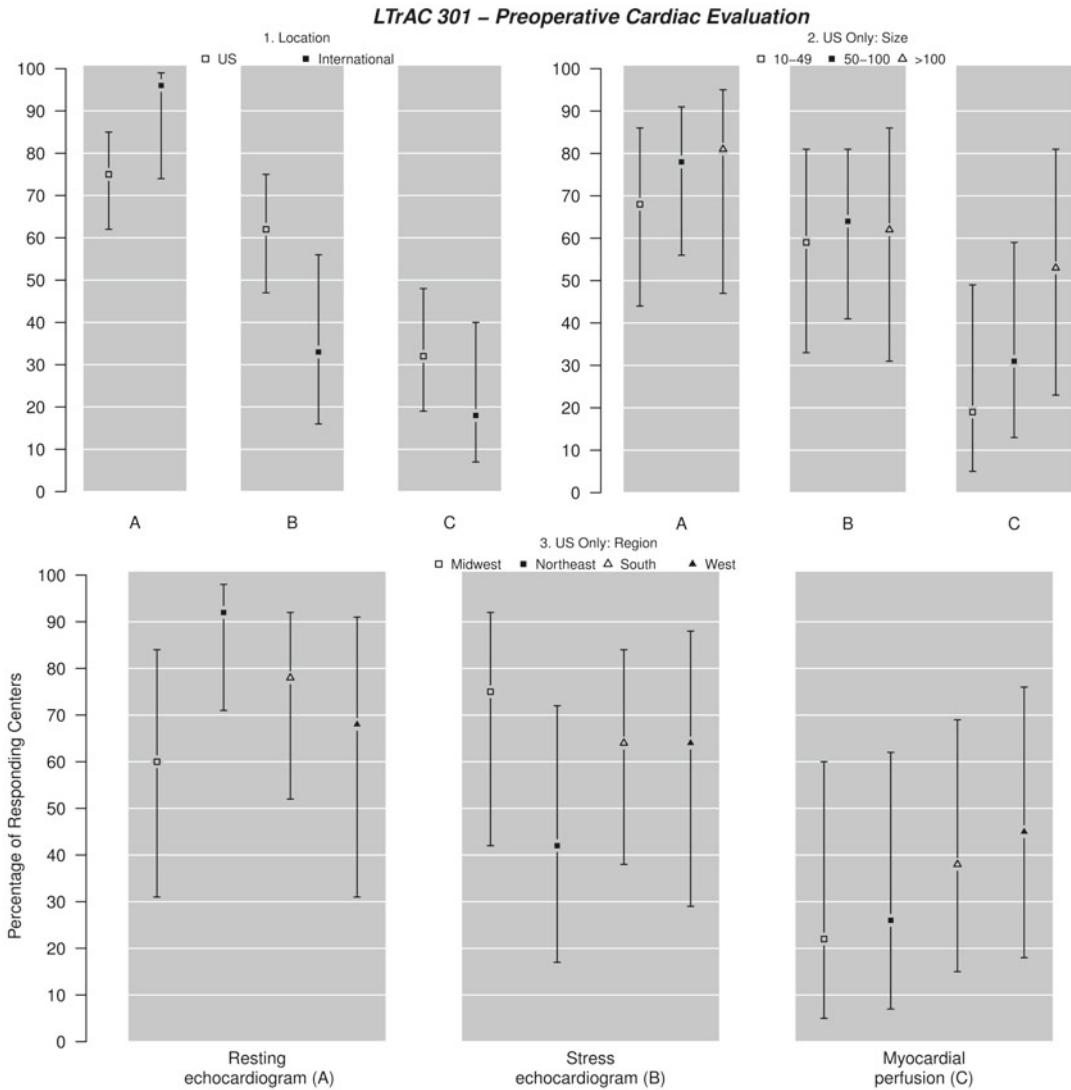


**Fig. 10.9** LTrAC 202–5. Intraoperative vasoactive drug utilization. Inotrope and vasopressor use in international and US liver transplant programs, further analyzed by US center transplant frequency and region

*LTrAC 301:* Qualifications of LT anesthesia directors, transplant team CME, pre- and postoperative care issues were the subject of this final survey.

In 38% (20–60%) of US and 78% (41–95%) of international programs, the directors of LT anesthesia teams needed special qualifications for their appointment such as postgraduate ICU, cardiac, or LT training, and this requirement was more frequent in small volume centers (58%, 18–90%). In almost all US and international centers this appointment was permanent rather than

on a rotating basis. A minimum number of LT cases were a condition to become the director in 67% (33–89%) of international but only 4% (1–17%) of US programs (survey prior to implementation of the ASA guidelines for Liver transplant anesthesia program directors). LT-related educational activities including journal club, grand rounds, and block rotations for faculty and residents occurred in 35% (18–56%) of international and 44% (32–57%) of US centers with predominance in medium and high volume programs.



**Fig. 10.10** LTrAC 301-1. Preoperative cardiac evaluation. Utilization of different types of cardiac testing for routine preoperative evaluation in candidates without a

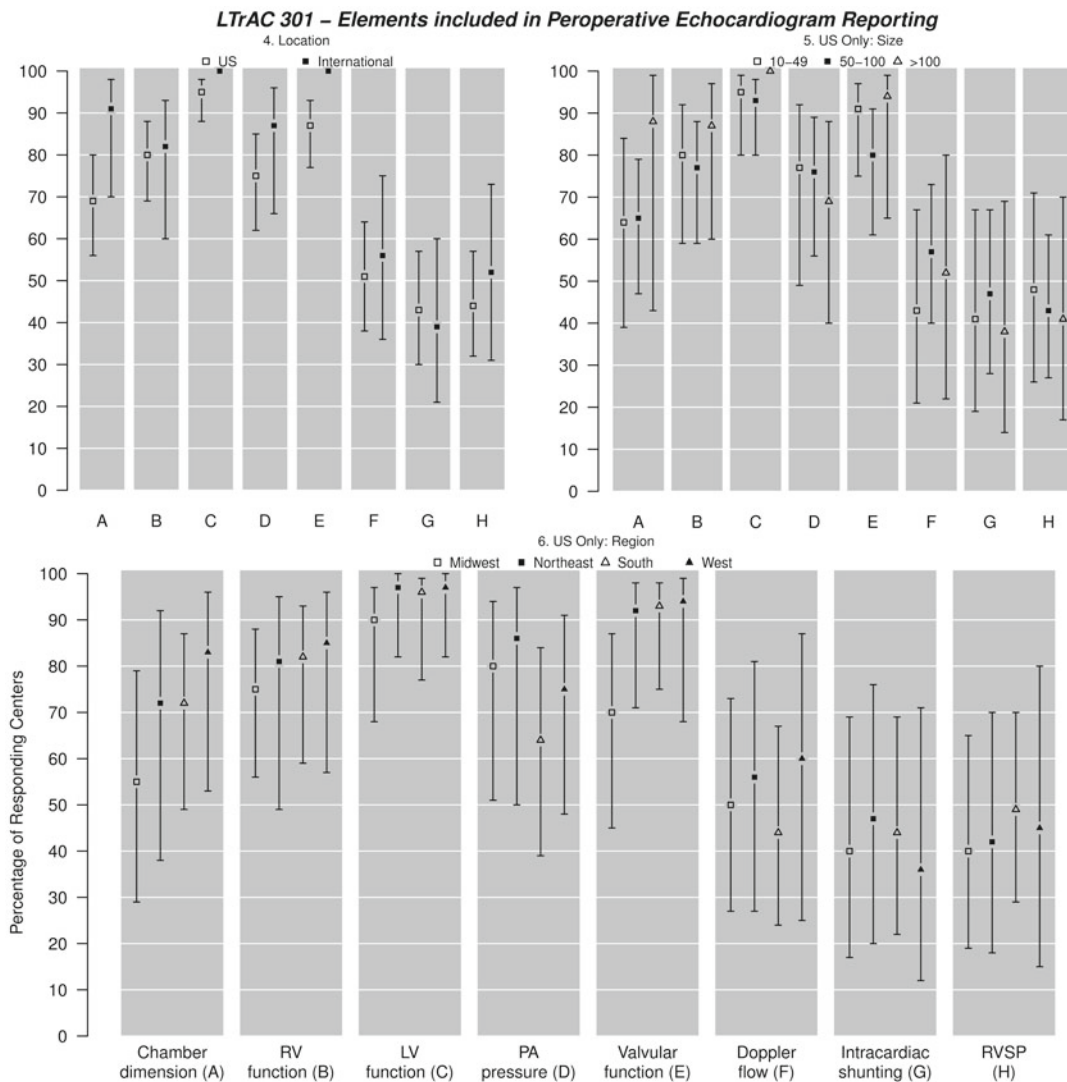
history of cardiac disease in international and US liver transplant programs, further analyzed by US center transplant frequency and region

Although directors participate in LT candidate selection meetings in 74% (52–88%) of international and 65% (51–77%) of US programs (increasingly with higher LT volume), regular attendance more than 50% of the time occurs in 56% (36–75%) of international and 18% (9–32%) of US programs and protected time for these meetings is provided by 44% (25–64%) of international and 25% (15–40%) of US centers.

four answer choices; every 6 months, annually, less than annually and “do not know”. Every 6 months was chosen by 55% (34–74%) of international program, while 27% (13–49%) did not reevaluate and 5% (1–27%) did not know. In the US, 16% (8–29%) reevaluated annually, and 40% (27–54%) and 33% (22–46%) did not reevaluate prior to transplant or did not know, respectively

The frequency of routine transplant candidate anesthesia reevaluation was examined providing

Routine cardiac work-up is shown in Fig. 10.10 [301]. Cardiac diagnostic tests are frequently used internationally and in the US.



**Fig. 10.11** LTrAC 301-2. Elements included in perioperative echocardiogram reporting. Routinely reported elements of echocardiograms in international and US liver transplant programs, further analyzed by US center trans-

plant frequency and region. *RV* Right ventricle; *LV* left ventricle; *PA* pulmonary artery; *RVSP* right ventricular systolic pressure

Information routinely provided by cardiac echo is demonstrated in Fig. 10.11 [301]. A pulmonary artery systolic pressure of  $\geq 40$  mmHg is the most frequent reason for right heart catheterization in international (52%, 32–72) and US centers (43%, 30–58). A normal cardiac echo is repeated every 6 months by the majority of international centers (30%, 15–52%) and annually in the majority of US programs (30%, 19–44%) with heterogeneity among respondents with

respect to immediate preoperative echo, no repeat echo at all, and not knowing whether or not a regular reassessment was performed at their respective center. Half of international (52%, 32–72%) and US (48%, 35–61%) programs agreed with the time intervals for repeat echo in their centers and international programs mostly consider biannual echoes appropriate whereas US centers would contend with an annual assessment.

Following booking of a transplant, communication and updates to the LT anesthesia team regarding changes in the recipient's location and health status, surgeon availability, and donor issues are consistently provided in more than 60% of international but less than 40% of US programs. The transplant coordinator or the surgeon or both are most frequently involved in this communication internationally and in the US.

An early extubation protocol (extubation within 6 h of LT) was used in 52% (32–72%) and 27% (16–41%) of international and US centers, respectively, least in low volume (4%, 0–22%) and most in medium volume (47%, 28–67%) programs. Regionally, early extubation increased from 11% (3–35%) in the Northeast to 30% (12–56%) in the South and Midwest and finally 39% (12–75%) in the West.

Following ICU transfer, the intraoperative anesthesiologist is involved in the extubation decision in less than 50% of international (44%, 25–64%) and US (31%, 19–45%) programs. An anesthesia provider routinely performs a 24-h post-transplant evaluation in 70% (48–85%) of international and 90% (81–95%) of US centers (usually attending of the case or resident, 96% (88–98%) within the US and 78% (57–91%) outside of the US).

Intraoperative anesthesia for emergent surgery for non-life-threatening conditions within 72 h of LT is provided by a LT anesthesiologist in 74% (52–88%) of international 30% (17–45%) of US centers and when the condition is life-threatening (i.e., bleeding, ischemic bowel) this percentage increases to 91% (70–98) internationally and 56 (42–69)% in US programs.

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## Discussion and Conclusion

The multidisciplinary clinical practice of liver transplantation has progressed in recent decades, improving organ allocation, immunosuppression, graft and patient survival and decreasing wait list mortality [4]. An unmet need remains to define and collect outcomes data related to specific perioperative anesthesia, surgical and intensive care practices [8, 9]. The growing liver transplant

recipient wait list worldwide demands optimal use of available organs in an evidence-based, resource-efficient best practice. The literature demonstrates a clear relationship between the case volume, anesthetic technique, and outcomes in surgical procedures other than liver transplantation [10–14]. Specifically in hepatic surgery evidence suggests that specific intraoperative anesthetic practices such as a “low CVP technique” [15], administration of specific vasopressors [16], early extubation following liver transplantation [17], and certain surgical techniques including veno-venous bypass and partial venous occlusion [18–28] can have a significant impact on patient and graft outcome.

LTrAC was established as an initial step to catalogue anesthetic practices in liver transplantation within the US and worldwide. Most of these practices are based on center and/or personal experiences and preferences, passed on to future liver transplant clinicians with little scientific evidence to support these practices. Furthermore, an accredited liver transplant anesthesia fellowship that could contribute to the definition of practice standards does not yet exist. Best practice recommendations for this specialty could emerge from verification of current practices against outcomes in multicenter studies so as to promote an increasingly evidence-based clinical practice. The results of LTrAC contribute to the determination of current practices and their difference between centers, regions, and continents. However, particularly the relatively low and heterogeneous response rate from international centers in these surveys needs to be considered when interpreting the comparative practices between the US and international programs. In addition, the geographic distribution of programs of different sizes may account for some of the apparent regional differences in practice as well.

Utilization of fluid management strategies varies between centers internationally and in the US with cell saver use as the overall most frequently employed technology, but distinctively less so in international and US high volume programs in sub-analysis. Cell saver use has been investigated in LT and reduced the intraoperative need for blood transfusions [29–34], and was cost

effective [30, 32, 33]. Its use does not appear to affect coagulation [35] and although contamination of the transfused blood occurs frequently, its use is not associated with positive blood cultures postoperatively [36]. The results of these studies support the use of cell saver in LT which is echoed by the current US and international practice pattern. However, use in transplant recipients with liver cancer leads to contamination with tumor cells even in the presence of microfilters and should be avoided [37]. This may explain the lower routine utilization rates in international and high volume US programs that may have a larger share of patients with liver cancers. The role of continuous renal replacement therapies, normovolemic hemodilution, and phlebotomy is much less clear and these modalities are much less practiced overall.

Fluid replacement and volume expansion is mostly achieved with normal saline, a pH-adjusted, balanced, salt solution or albumin in the US and internationally. Hydroxyethyl starches are less frequently used, as are all other types of crystalloid solutions. We did not explore the use of gelatin-based volume expanders, and the proportionate use of crystalloids vs. colloids and blood products was not determined.

Blood product administration was common routine during LT in US programs and more frequent in the US than internationally. The same trend was observed for antifibrinolytic and recombinant factor VII use. Interestingly more international and US high volume programs regulated factor VII use by protocol. The administration of prothrombin complex concentrate and other non-FDA approved agents was not explored in this survey series. However, the availability of these different medications able to modulate intraoperative coagulation may well explain the observed differences between US and non-US centers. While tranexamic acid (TA) appears to be safe and effective in reducing blood product transfusion requirements in LT, the evidence is less clear for aminocaproic acid (EACA) [38–41]. Although these agents are not as frequently used internationally than in the US overall, US programs administer EACA more frequently than TA while this practice is reversed in international

programs. Recombinant factor VII administration has been effective in reducing blood product administration and as a rescue treatment in high-risk LT recipients but may make little difference when used routinely for every LT [42–47].

Vasopressors and inotropes were frequently used routinely in all programs. Interestingly their administration is overall less common internationally and decreased with higher LT volume in the US suggesting that greater team experience may reduce the need for use of these drugs. Vasopressin was used twice as much in the US than internationally and surprising regional differences for different agents exist within the US particularly for dopamine. There are very few studies examining the benefits or detriments of specific inotropic and vasopressor agents during LT and this should be an area of active inquiry [37].

Requirements for special qualifications (i.e., fellowship) and a minimum number of LT cases in order to become the director of an LT anesthesia team were much more common internationally than in the US prior to approval of the guidelines for directors of liver transplant anesthesia by the ASA in the US in 2009 [48]. Similarly, director participation in LT selection meetings and protected time to do so was more prevalent internationally, whereas continuing educational activities for staff occurred more frequently in US programs. Evidence for a positive influence of LT anesthesia team education and expertise on LT outcomes is slowly emerging and will likely become more important for programs in the future [49–51].

Consensus or evidence in support of a specific frequency of routine LT candidate anesthesia reevaluation or repeat cardiac echo following a normal initial exam is lacking. Internationally biannual repeat evaluations are favored vs. once a year in the US.

Early extubation in LT recipients meeting protocolized criteria reduces mortality, ICU length of stay, and cost [17, 52–55]. Careful patient selection at the end of surgery considering MELD score, intraoperative blood loss, and hemodynamic stability and LT anesthesia team experience is critical for successful early extubation protocols [52, 56–58]. Use of early extubation

protocols are much more common internationally than in the US, where their application is disparate between different program sizes, and still far from routine and should receive more attention. Involvement of the LT anesthesia team for the care of recipients returning to the OR for emergent conditions is more common internationally than in the US. The impact of this practice on outcome is unclear.

## Summary

In several areas of anesthetic care for liver transplantation evidence for effective practices are emerging, including coagulation monitoring and management, LT anesthesia team education and experience, and early extubation. However, much of this available information has not yet been applied in most programs. Many facets of perioperative LT anesthesia care remain under explored, and practices within the US and internationally are very heterogeneous. Different practice patterns between international and US programs and regionally and by center size within the US are apparent and need further exploration to establish best practices.

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# Caval Cross-Clamping, Piggyback, and Venovenous Bypass

# 11

Ruairi Moulding and Paul Picton

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## Introduction

Early liver transplantation was marred by excessive blood loss and routinely required massive blood transfusion. Surgical techniques have evolved to improve patient safety and achieve better outcomes for the transplanted organ. In this chapter we review the physiology of caval cross-clamping and explore surgical options to safely establish hepatectomy and transplantation including piggyback technique and venovenous bypass (VVB).

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## Caval Cross-Clamping

The aim of caval cross-clamping is to eliminate hepatic outflow prior to hepatectomy. Traditionally two inferior vena cava (IVC) cross-clamps are placed, one below the diaphragm and one above the renal veins. Resection of the recipient's vena cava is achieved by dividing both the infra- and suprahepatic vena cava. Transplantation of the donor organ therefore requires both supra- and infrahepatic caval anastomoses, and complete caval occlusion occurs during the vast majority of the anhepatic phase.

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## Physiologic Effects of the Caval Cross-Clamp

The physiologic effects of caval cross-clamping can be described by considering the effect on each major organ systems (Table 11.1).

### Cardiovascular System

Patients with liver failure typically have hyperdynamic circulations (high cardiac output and low systemic vascular resistance (SVR)) which may coexist with low central blood volume [1, 2]. Cross-clamping of the IVC results in a large decrease in venous return, a reduction in pulmonary wedge pressure, and an ensuing reduction of cardiac output of up to 50% [3]. The extent of the subsequent effect on blood pressure (BP) is less predictable. Even with a 50% reduction in cardiac output, it is possible for blood pressure to be maintained (though usually not to pre-clamp levels) through compensatory mechanisms such as a significant increase in SVR and less so with an increase in heart rate. The effectiveness of compensation depends upon the intravascular filling status of the patient and the extent of collateral circulation and is influenced by associated comorbidities (particularly cardiac dysfunction) and the duration of cross-clamp. Patients with end-stage liver disease may suffer from depressed baroreflex sensitivity and exhibit a response similar to patients with autonomic nervous system imbalance. It has been suggested that such patients are unable to adequately compensate for

**Table 11.1** Physiological effects of caval cross-clamping

Cardiac	↓↓Venous return, ↓↓cardiac output, ↓mean blood pressure, ↑heart rate, ↑systemic vascular resistance,
Renal	↓perfusion pressure, ↓↓venous renal outflow
GI	↑venous congestion, ↓↓portal venous flow
Respiratory	↓pulmonary capillary wedge pressure, ↑ pulmonary vascular resistance, ↓mixed venous oxygen tension, ↓pulmonary venous oxygen tension
Neurologic	↓cerebral perfusion pressure

↓—Decreased

↓↓—Severely decreased

↑—Increased

hemodynamic changes resulting from lack of venous return, for example, during caval cross-clamping or during major hemorrhage [4].

Collateral circulation, mainly via the azygous system, is important in maintaining venous return in those patients in whom it is well developed. Patients with established portal hypertension therefore usually tolerate caval cross-clamping better than patients with acute hepatic failure, for example.

The use of trial clamping of the IVC has been employed to predict the need for VVB. If cardiac output fell by more than 50%, then VVB was deemed to be necessary. However, even with a reduction in cardiac output of greater than 50%, there is no change in perioperative morbidity or mortality [5]. In fact, the only hemodynamic parameters that are independently associated with negative surgical outcome are intraoperative severe hypotension (mean arterial pressure (MAP) < 40 mmHg) and severe pulmonary hypertension (mean pulmonary artery pressure (MPAP) > 40 mmHg) [6]. The majority of severe hypotension occurred at graft reperfusion and not during caval clamping. Most centers now consider the ability to maintain systemic blood pressure with caval clamping to be sufficient evidence of circulatory fitness to proceed without VVB.

### Pulmonary System

The pulmonary effects of caval clamping are highly dependent upon the acuity of the patients' liver disease [7]. Caval clamping in patients with acute liver failure causes a more profound deterioration in mixed venous oxygen saturation than in chronic liver failure patients, as well as a greater and more persistent rise in pulmonary

vascular resistance. A potential explanation is that patients suffering from acute liver failure lack the functional portocaval shunting seen in patients with chronic liver failure. All these changes are usually transient and reversible with reperfusion.

### Renal System

The development of postoperative renal failure requiring renal replacement therapy results in a significant increase in mortality following liver transplantation [8, 9]. It is vital to maximize any opportunity to prevent renal dysfunction during the perioperative period. Understanding potential renal stressors, many of which are predictable, such as caval cross-clamping is of paramount importance. Renal perfusion pressure may fall below the threshold of autoregulation during caval clamping. Venous renal outflow is obstructed, and even if renal arterial perfusion pressure is maintained, experimental data suggests that severe renal damage may still occur [10]. Preexisting renal dysfunction is likely to render the kidneys more vulnerable to this insult and may mandate combined liver–kidney transplant [11].

Systemic blood pressure may be maintained during caval cross-clamping by judicious use of fluid and/or vasoactive drugs. The reliance on vasoactive drugs for dissection and hepatectomy may reduce intraoperative blood loss and also help to reduce hepatic congestion at reperfusion by limiting infused volume. Controversy still surrounds the correct approach for an optimum central venous pressure (CVP) in order to reduce bleeding and transfusion requirements without compromising renal function. Investigators

studying historical data [12] advocate a low CVP technique using fluid restriction and even phlebotomy, liberal use of vasopressors and strict blood product replacement triggers. These studies have shown no increase in morbidity or mortality, including no increase in renal dysfunction postoperatively. Moreover they reported a rise in liver transplants without blood product usage from 19% to 81% and better long-term survival. Other investigators [8] evaluated data from two centers, one center using a low CVP approach (<5 mmHg) and one center using a “normal” CVP approach (7–10 mmHg), and also found a reduction in blood product usage with low CVP: however, peak creatinine, postoperative hemodialysis rates, and 30-day mortality were all higher with low CVP technique. It is physiologically plausible that a low CVP technique may worsen renal injury; however, only prospective trials will be able to determine an effect on outcome.

### **Gastrointestinal System**

Clamping of the venous drainage of the gastrointestinal tract (GI) via the IVC and portal circulation causes venous congestion of the GI tract. Engorged splanchnic beds are a cause of bleeding during dissection as well as bacterial translocation and endotoxin release [13, 14]. Splanchnic congestion has also been linked to the development of bowel edema, bile leak, and cholestasis [15]. When systemic blood pressure is low, the physiologic response redirects blood flow to the major organs, such as the brain and heart, by reducing non-vital blood flow to the GI tract, resulting in GI hypoperfusion. The deleterious effects may persist beyond the period of hypoperfusion. Strategies to maintain oxygen delivery and reduce splanchnic hypoperfusion, such as goal-directed therapy, have been advocated [16] to improve postoperative morbidity.

### **Neurologic System**

Patients with fulminant hepatic failure are at an increased risk of cerebral edema and raised intracranial pressure (ICP) [14]. The combination of caval clamp-associated low MAP and high ICP may exacerbate any preexisting cerebral dysfunction by reducing cerebral perfusion

pressure (CPP). However, it has been demonstrated that the use of vasoconstrictors to increase MAP during caval cross-clamp is sufficient to maintain CPP [14].

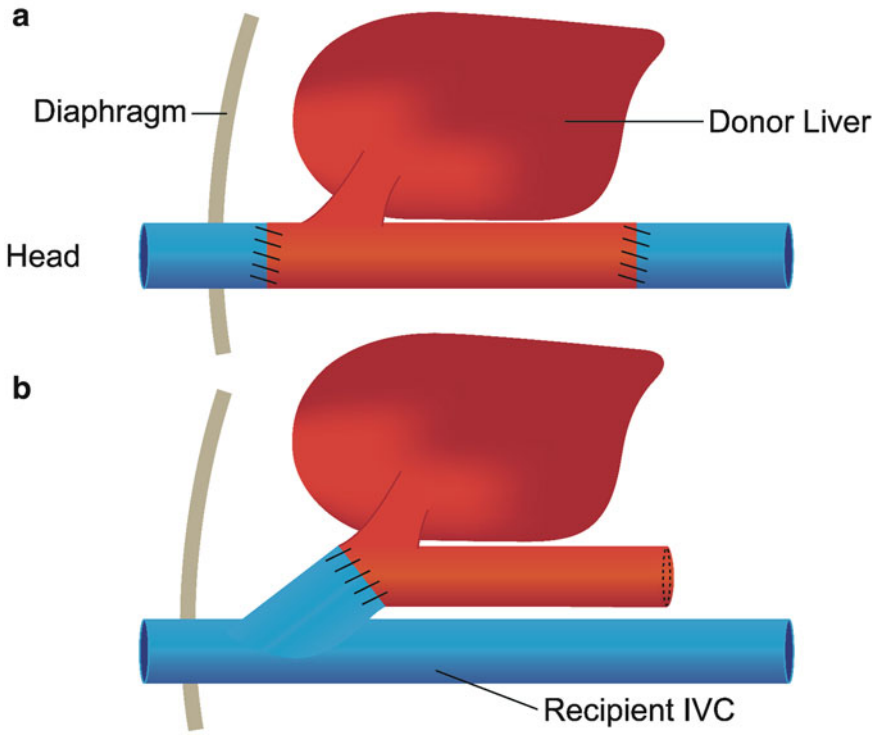
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## **The Piggyback Technique**

Piggyback liver transplantation was first described by Calne in 1968, soon after the introduction of human liver transplantation but did not gain popularity until Tzakis later described a series in 1988. The piggyback technique preserves the native retrohepatic IVC and avoids caval reconstruction and complete caval cross-clamping (Fig. 11.1).

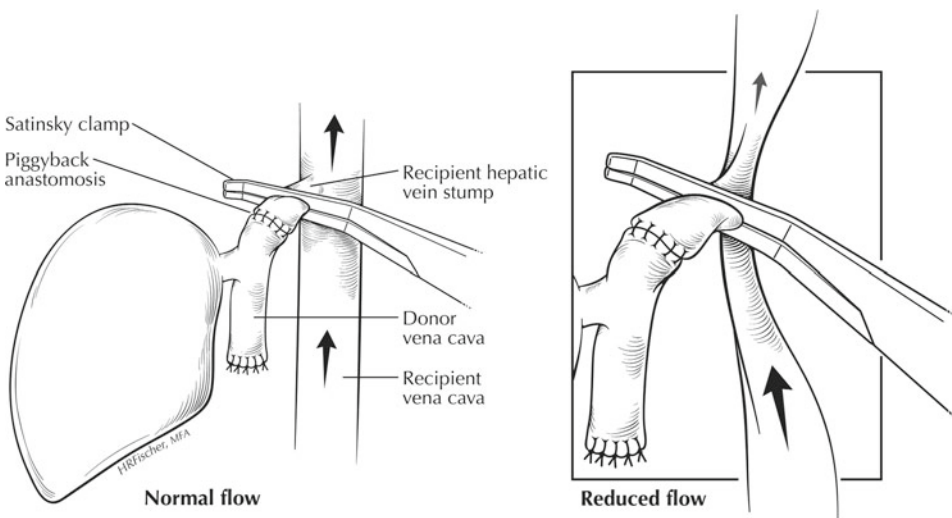
The piggyback technique is designed to preserve venous return to the heart by maintaining IVC blood flow during the anhepatic phase hence helping to ameliorate the physiological effects of caval cross-clamping. The hepatic veins are identified and occluded collectively by a partial IVC clamp which, when applied, allows sufficient venous return to avoid the sharp drop in cardiac output seen with a complete caval cross-clamp. Portal vein occlusion is still required and results in venous congestion of the gut and splanchnic edema. A temporary portocaval shunt may be used in conjunction with the piggyback technique to ensure portal venous flow during the anhepatic phase and potentially reduce portal venous congestion and hemorrhage. It should be noted that in certain circumstances, the caval clamp effectively completely occludes the IVC (Fig. 11.2), especially during periods of surgical manipulation. It is vital that anesthesiologists do not assume that piggyback clamp placement is non-consequential.

In several case series, authors have concluded that the piggyback technique can be used in nearly all liver transplantations [17–22], and the majority of re-transplantation [17, 18, 21]. The piggyback technique results in less bleeding, lower transfusion requirements, reduced warm ischemic time, reduced hospital and ICU length of stay (and reduced staffing and equipment costs when compared to veno-venous bypass) [23]. During piggyback liver transplantation, renal perfusion pressure is maintained towards normal and the sustained renal injury is decreased [10].



**Fig. 11.1** Conventional vs. piggyback technique. (a) The conventional technique of orthotopic liver transplantation requires complete caval cross-clamp and two cavo-caval anastomoses. (b) The piggyback technique preserves the

recipient's retrohepatic IVC and avoids the caval cross-clamp and anastomoses. The inferior portion of the donor IVC is sutured closed, and the upper portion is anastomosed to the native IVC via the recipient hepatic vein stump



**Fig. 11.2** Figure illustrating piggyback clamp placement with normal flow and with reduced flow as may occur especially during periods of manipulation



**Table 11.2** The potential advantages of the piggyback technique for orthotopic liver transplantation

Piggyback advantages
Avoids caval reconstruction
Avoids caval cross-clamping and maintains venous return
Avoids venous renal outflow obstruction
Less postoperative renal dysfunction
Reduced warm ischemic time
Reduced staffing and equipment costs
Reduced blood product use
Reduced bleeding
No complement activation via VVB
Shorter hospital stay
Shorter ICU stay

Outflow obstruction has been identified as a problem following piggyback transplantation, but a modification of this technique using a side-to-side cavocavostomy and exclusion of the right hepatic vein described by Belghiti in 1992 has largely prevented this complication (Table 11.2).

## Venovenous Bypass

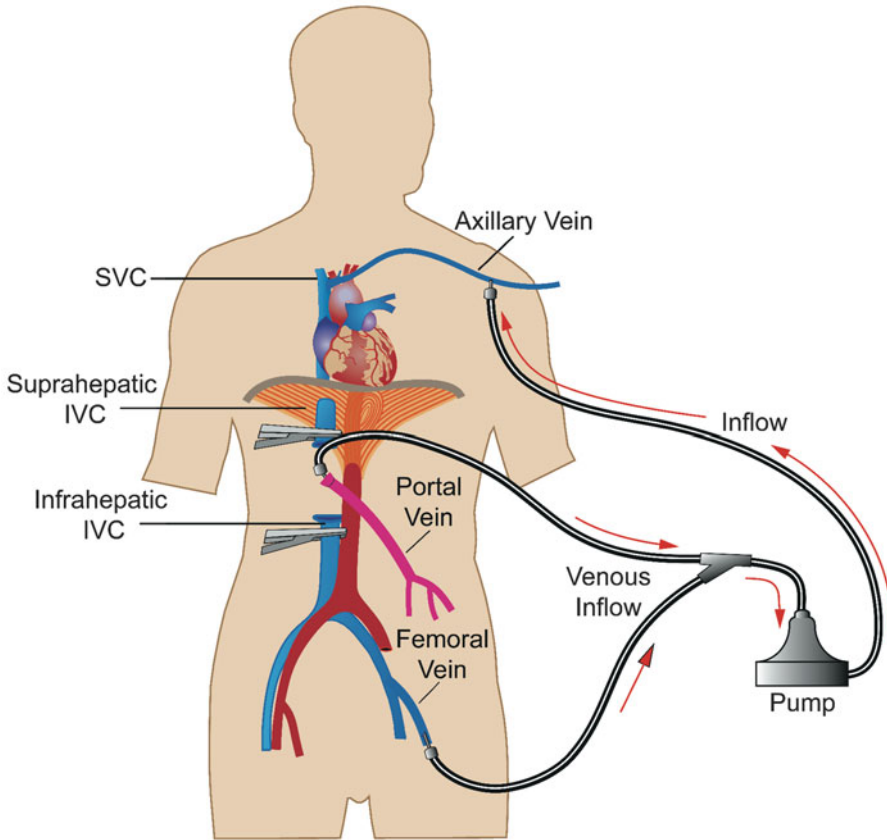
VVB was introduced in order to facilitate smooth hemodynamics for transplantation by providing adequate venous return during caval cross-clamping and to limit portal venous congestion. Initially VVB was provided by a passive extracorporeal connection between veins below the level of the liver (femoral/portal) and the major veins above the heart (axillary/subclavian/internal jugular). This passive circuit resulted in a high incidence of embolic events including fatal pulmonary emboli. Calne introduced partial cardiopulmonary bypass in 1979. However this circuit required systemic heparinization that frequently resulted in devastating hemorrhage. The addition of a centrifugal pump and heparin-coated tubing [24] allowed physicians to forgo systemic heparinization and resulted in fewer hemorrhagic complications (Fig. 11.3). In his original description Shaw suggested that VVB was particularly advantageous if a difficult surgical dissection of the native liver was expected because it provided sufficient time to complete the surgery unrushed and safely.

Very early studies comparing VVB with complete caval-clamping showed that VVB was associated with reduced requirement for postoperative dialysis [25] although subsequent studies have failed to show any difference [26].

VVB was initially also thought to reduce blood loss [24]. However, subsequent studies showed no advantage of VVB over the piggyback technique and also indicate that VVB may be associated with higher transfusion requirements secondary to platelet activation and hemolysis by the bypass tubing and pump [14, 17]. VVB has been proposed as a means of maintaining CPP and ameliorating ICP changes in patients undergoing liver transplantation for fulminant hepatic failure [14]. Others suggest that use of VVB in these situations may be redundant, and the use of appropriate vasopressors can provide adequate CPP even with caval cross-clamping and a 50% reduction in cardiac output [27]. It has also been suggested that VVB may actually cause a rise in PaCO<sub>2</sub>, causing vasodilatation and an increase in ICP [21]. No data yet exists on the effect of the piggyback technique on cerebral blood flow, CPP, or ICP [28]. Intraoperative hypothermia is associated with an increased postoperative morbidity, and VVB has been quoted as both a cause [27] (blood in the extracorporeal tubing cools down) and a cure [29] when a heat exchanger is added to the circuit.

VVB is associated with a complication rate of 10–30% [30] including inadvertent decannulation, thrombus formation in the circuit, air emboli, pulmonary emboli, lymphocele formation, brachial plexus injury, or hematomas, as well as complement activation predisposing towards the development of tissue injury and multiorgan failure. Resource allocation is a further issue, and the costs involved, both in manpower and equipment, are significant.

There are no current absolute indications for VVB, although some relative indications may warrant its use, for example, for patients with pulmonary hypertension, poor left ventricular function, severe portal hypertension, volume overload, fulminant hepatic failure, and renal failure, in patients with anatomical reasons for difficult dissection and to provide support for intraoperative failure of a transplanted liver.



**Fig. 11.3** Venovenous bypass circuit

It has been argued that the purported advantages of VVB are no longer valid in the context of the near-universal acceptance of the piggy-back technique, with or without portocaval shunting [27]. The majority of centers no longer use VVB routinely and reserve it for few, selected cases only.

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# Liver Transplantation: Hemodynamic Changes, Cardiac Output Monitoring and Inotropic Support

Anand D. Padmakumar and Mark C. Bellamy

## Introduction

Liver transplantation (LT) poses distinct challenges to the anesthesiologist. Patients presenting for LT constitute a high-risk surgical group with unique problems and require meticulous attention to their perioperative management.

End-stage liver disease (ESLD) is the most common indication for LT and presents complex pathophysiological changes involving various organ systems. The severity of such changes varies enormously between cases. A further level of complexity is seen in patients presenting with decompensated ESLD and in those presenting with acute hepatocellular failure. Cardiovascular, respiratory, renal, neurological, gastrointestinal and inflammatory changes all interact to produce a complex picture. Portopulmonary hypertension, ascites, varices and dyselectrolytemia are some of the myriad problems associated with liver disease that require special consideration before anaesthetising patients for LT.

In this chapter, we discuss cardiovascular changes occurring at various stages of LT, modes of hemodynamic monitoring and use of inotropes and vasopressors.

## Cardiovascular Changes During LT

### Physiological Considerations

To understand fully the hemodynamic changes during LT, it is worth considering the physiological principles of liver blood flow. In health, auto-regulation smoothes out potentially major changes in hepatic blood flow (HBF) and protects normal hepatic physiology and function. The precise mechanisms that regulate HBF are poorly understood. However, there are several hypotheses to explaining *intrinsic* and *extrinsic* factors affecting hepatic flow [1]. The liver has limited inherent ability to control portal venous blood flow (PBF); however, multiple integrated processes determine PBF, including anatomical and pathological changes altering portal vascular resistance.

*Intrinsic Factors*—PBF acts as a main intrinsic factor regulating HBF. The hepatic arterial blood flow buffers any changes in PBF through the “hepatic artery buffer response” to maintain a constant total HBF. This buffer response seems to be independent of the metabolic demands of the liver [2]. Myogenic and chemical mechanisms have been postulated to explain this mechanism. As in most other organs, the vascular resistance of the hepatic artery (HA) is inversely proportional to blood flow, and *adenosine* plays a key role in the chemical autoregulation of HBF. Sinusoidal adenosine concentrations, determined largely by portal venous washout, are inversely proportional to HA tone. Thus a reduc-

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tion in PBF causes accumulation of adenosine and ensuing local vasodilation of the HA [3]. The liver also has a unique property of matching its mass to the blood supply it receives by either *proliferation* or *apoptosis* of hepatic cells possibly mediated via portal flow-dependent growth factors. Adenosine furthermore activates the *hepatorenal reflex* causing fluid retention [4].

*Extrinsic Factors*—Animal experiments have revealed multiple extrinsic factors regulating HBF including:

- Sympathetic nervous system
- Catecholamines
- Gastrointestinal hormones (secretin, glucagon, cholecystokinin, etc.)
- Autacoids (histamine, serotonin, bradykinin, prostaglandins, etc.)
- Vasoconstrictor peptides (angiotensin-2 and vasopressin) [1]

## Hemodynamic Changes

Patients with ESLD demonstrate characteristic cardiovascular system (CVS) changes such as a hyperdynamic or hyperkinetic state secondary to a reduction in systemic vascular resistance (SVR) and a compensatory increase in cardiac output (CO) [5]. There may be a coexisting cirrhotic cardiomyopathy particularly in alcoholic liver disease, chronic portal and/or pulmonary hypertension, ascites, hypoproteinemia and dyselectrolytemia. These CVS changes worsen as disease progresses [6], and conditions inducing a neurohumoral stress response, such as trauma, surgery and sepsis, may induce or aggravate such complications as hepatorenal syndrome, variceal bleeding and circulatory failure [7].

## Pathogenic Mechanisms

Liu et al. have reviewed the pathophysiological processes contributing to the CVS changes in liver disease [7]. The salient features are summarised in Table 12.1.

The exact pathogenic mechanisms causing significant hemodynamic changes in the perioperative period of LT, however, remain unclear.

## Measurement of Cardiac Output

Although a full discussion of CO monitoring techniques is discussed elsewhere (Chapter 9) in this book, it is important to understand their importance and limitations. Estimation of CO is important as it helps guide fluid and inotrope management. Hypotension may result from low SVR, poor cardiac contractility, reduced stroke volume or a combination of these factors; (relative) bradycardia may also contribute to low CO, and hence hypotension even in the presence of adequate filling. This is particularly important in LT as bradycardic hypotension is frequently associated with high central venous pressure, which may compromise the pressure gradient between the portal and central venous systems, compromise graft blood flow in the immediate post-reperfusion phase and result in primary nonfunction.

Cardiac function may be further compromised by pleural or pericardial effusions or pre-existing pulmonary hypertension with right ventricular dysfunction. Furthermore, cardiac filling may be impaired by diastolic dysfunction, either *irreversible* (e.g. as a result of an established infarct with a fibrotic area), *mechanically reversible* (e.g. due to pericardial effusions) or *physiologically reversible* (e.g. lusitropic and pseudo-lusitropic effects secondary to the effects of transfusion on anemia-induced myocardial ischemia or due to ventricular septal shifts following “venodilatation”).

The method for CO monitoring selected should take account of the patient’s needs and the expected severity and nature of cardiovascular derangement. For example, the patients at risk of micro-embolic phenomena at reperfusion, or patients thought to have an inducible regional wall motion abnormality, or pericardial effusion, may be best monitored using trans-esophageal echocardiography (TEE) [8], but the patient with pulmonary hypertension, however, may benefit from the use of a pulmonary artery catheter (PAC). For routine use in patients with previously good cardiac function and no structural abnormality, pulse pressure or pulse power analysis

**Table 12.1** Proposed pathogenic mechanisms that contribute to hemodynamic changes in liver disease. cGMP—3', 5' cyclic guanosine monophosphate, CVS – cardiovascular system

Central neural activation	Plays a vital role in development of CVS changes in portal hypertension. Exact route of signaling from periphery to central nervous system remains unclear.
Endogenous cannabinoids (CB)	Lipid-like substances, acting on G protein-coupled receptors CB1 & CB2, show negative inotropic effect (for example, Anandamide levels increased in cirrhosis) and induce apoptosis in hepatocytes. This could alter microcirculation and lead to portal hypertension and hyperdynamic state.
Nitric oxide (NO)	Changes in NO activity affect CVS in different ways. Increased systemic NO production causes peripheral arterial vasodilation and negative inotropic effect. Cirrhotic rat models show reduced local expression of liver NO synthase and a corresponding drop in portal venous pressure
Carbon monoxide	Mainly produced by the action of heme oxygenase (HO), and activates soluble guanylate cyclase resulting in increased levels of cGMP. There is association between raised cGMP and heart failure in animal models of cirrhotic cardiomyopathy
Beta-adrenergic signaling	Expression and responsiveness of beta-adrenergic receptors and post-receptor signaling pathways are impaired at various levels in cirrhotic cardiomyopathy
Autacoids	Various potent autacoids (bradykinin, serotonin, histamine and prostaglandins) are less likely to play a significant role in systemic CVS changes due to their short half-life

may be sufficient, for example, using pulse contour cardiac output (PiCCO™) or lithium dilution cardiac output (LiDCO™) systems [9]. In the authors' institution, use of LiDCO™ is standard, with PAC and TEE when indicated.

## Classification of Inotropes and Vasopressors

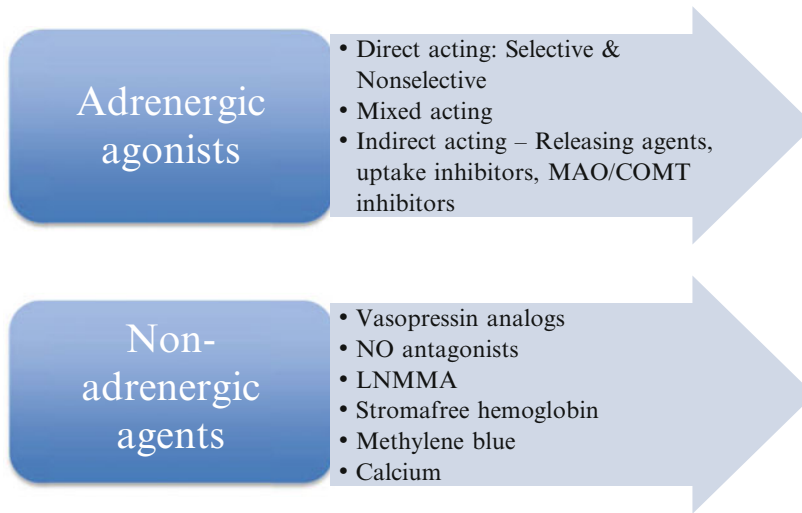
An understanding of the specific pharmacology of inotropes and vasopressors and the (sometimes subtle) differences between them increases their utility during LT in situations of varying physiological patterns and derangements at various stages of the transplant procedure. The key attributes of commonly used agents are summarised in Fig. 12.1.

Other agents with hemodynamic effect include vasopressin analogues such as terlipressin and octreotide. Both agents have important effects on reducing portal pressure and potentially limiting portal venous bleeding [10, 11] which can be of great value during the dissection phase of surgery. In addition, terlipressin has a direct vasopressor effect through its action on vasopressin

receptors [12], enhancing the effects of alpha-adrenergic agents. This may be particularly valuable in patients with low SVR, who may have exhausted pituitary stores of vasopressin and consequently show a reduced responsiveness to alpha-adrenergic stimulation. This effect has been observed in prolonged septic shock [13] and is also hypothesised as one cause of the vasodilatory state in liver failure [14]. Vasopressin or its analogues can be useful during liver transplantation to maintain SVR and is commonly used in the perioperative management of patients with hepatorenal syndrome.

Calcium supplementation is also frequently required during LT because the concentration of ionised calcium in the circulation falls rapidly, particularly during the anhepatic phase. This is due to chelation by citrate added to blood products at a time when there is no metabolic route for citrate [15]. Administration of calcium at this time, to maintain an ionised calcium value above 0.9 mmol per litre, has both a dramatic positive inotropic effect and a vasopressor effect and is of value in maintaining normal perfusion pressure [16].





**Fig. 12.1** Classification of vasopressors and inotropes. MAO – monoamine oxidase, COMT – catechol-o-methyl transferase, NO – nitric oxide, LNMMA – L-NG-monomethyl arginine citrate

Free radical scavengers such as mannitol and N-acetylcysteine have also been described as helping improve hemodynamic stability during LT, particularly in the period following graft reperfusion. Similar claims have been made for aprotinin, a broad-spectrum serine protease inhibitor, generally used for prevention of fibrinolysis and maintenance of clotting [17].

Methylene blue has been used as an inhibitor of the NO pathway and acts by inhibition of guanylate cyclase. Used as a bolus at the time of reperfusion, this may increase the blood pressure, but its overall effect on outcome is unclear [18]. The biological role of NO inhibition in sepsis is controversial as NO also appears to exert a protective effect.

### Clinical Features of Hemodynamic Disturbance and Their Management

Pre-existing cardiovascular changes in liver disease are further affected during induction and maintenance of anesthesia as intravenous and volatile agents frequently reduce CO and SVR. ESLD is associated with low SVR which may decrease even further with induction of anesthesia typically reaching a value around  $250 \text{ dyn s cm}^{-5}$ . This is in part offset by an

increase of CO which contributes to a “hyperdynamic state.” Nevertheless, the CO achieved is a reflection of the low SVR, a consequence of left shifting of pressure–volume loops and may coexist with reduced cardiac contractility. The extent to which the CO can compensate for a low SVR is further dependent on adequate ventricular filling, a function of venous return (dependent in part on vascular tone in capacitance vessels) and ventricular diastolic function. In ESLD, diastolic function may be abnormal due to cirrhotic cardiomyopathy [19], the presence of pleural or pericardial effusions, or myocardial ischemia. Consequently, close physiological monitoring and an intelligent approach to multimodal cardiovascular manipulation are required. The nature and magnitude of these CVS changes may necessitate intervention with fluids, inotropes or vasopressor agents. The hemodynamic changes during the various phases of LT and their causes are summarised in Table 12.2.

### Intraoperative Changes

Hemodynamic changes will be discussed in type and a suggested therapeutic/inotrope strategy in smaller font.

**Table 12.2** Cardiovascular changes during various phases of liver transplantation (LT). CO—cardiac output, PV – portal vein, IVC – inferior vena cava.

Phase of LT	CO	Causes for change in CO
Dissection/pre-anhepatic	↓	Hypovolemia, transient IVC compression, fluid shift with ascitic decompression
Anhepatic	↓	Reduced venous return due to clamping of PV and IVC, acidosis
Reperfusion/neohepatic	↑	Hyperkalemia, release of vasoactive substances, diuresis

During the course of the surgical dissection phase (pre-anhepatic phase), there may be further hemodynamic compromise due to decompression of ascites, hemorrhage and gut translocation. These issues are further exacerbated by lifting and rotation of the liver causing transient caval compromise. This may include introduction of portal bypass as part of the veno-venous bypass technique; complete cross-clamping of portal vein in techniques not using bypass, with consequent loss of venous return; or the creation of a portocaval shunt. The specific technique used, and therefore its hemodynamic consequences, will vary according to patient anatomy, surgeon preference and local protocol as discussed elsewhere (Chapter 11) in this book. Drainage of potentially massive ascites at the beginning of surgery is frequently accompanied by a reduction in aortocaval compromise and hence an improvement in overall systemic hemodynamics. This may further be enhanced by a reduction in pulmonary artery pressure (PAP); however, it is not uncommon to observe substantial hypovolemia at this time as well.

Prior to the anhepatic phase of the procedure, fluid and inotrope requirements vary considerably between patients. The principles of management are maintenance of an adequate perfusion pressure and hemodynamic optimisation. Significant volume loading may be necessary to achieve an optimal stroke volume. However, it is important also to pay attention to filling pressures and electrolyte changes; excessive elevation of filling pressure or PAP may both lead to reduced right ventricular performance and increased bleeding. For this reason, cardiovascular monitoring is important at this stage, and the use of inotropes or vasopressors may help mitigate excessive fluid administration. Agents commonly employed at this stage, both to help optimise stroke volume and to fine-tune fluid administration, include norepinephrine, phenylephrine or dopamine.

The problems of the dissection phase may be further exacerbated by portal hypertension and variceal bleeding. A logical combined approach to the hyperdynamic state similar to sepsis and bleeding secondary to portal hypertension is the use of vasopressin or a suitable analogue. Vasopressin by infusion, terlipressin and octreotide have all been used in these situations, and they have the advantage of enhancing catecholamine sensitivity while at the same time promoting splanchnic vasoconstriction and reducing portal hypertension. There may be an additional theoretical advantage in the reduction in portal flow around the time of graft reperfusion that may help minimise the potential for the “small for size” syndrome [20].

During the anhepatic phase, there is a progressive reduction in body temperature and worsening of coagulopathy and fibrinolysis. These effects interact with the hemodynamic situation. In those techniques involving partial caval clamping, either side clamping or cross-clamping in the absence of veno-venous bypass, there is additionally the effect of reduced venous return. While this can, to some extent, be offset by fluid administration, any improvement seen is generally transient and may overall contribute to a worsening of the clinical situation because gut edema and fluid overload may ensue which becomes manifest after clamp removal and graft reperfusion.

The extra fluid volume required to maintain hemodynamic stability has been estimated at around 4 L or more [21]. Vasopressors can be used to reduce fluid requirement to maintain hemodynamic stability during the anhepatic phase, especially in the presence of caval occlusion. Norepinephrine and phenylephrine by infusion are generally the drugs of choice; they help maintain blood pressure both by raising SVR and, importantly, through action on venous capacitance vessels resulting in modestly improved venous return and cardiac filling. This is particularly important in the presence of partial caval clamping. Hemodynamic consequences of IVC

occlusion, and therefore the effectiveness of alpha-agonists, are dependent on the extent to which the variceal circulation has resulted in collateralisation, facilitating venous return in the absence of vena cava flow.

At the time of graft reperfusion, caval blood flow is restored, resulting in an improvement in hemodynamics, but immediately thereafter is a return of blood flow from the graft. The initial stages are affected by the washout of cold fluid from the graft, potentially containing high concentrations of potassium and traces of preservation fluids which include adenosine in the case of University of Wisconsin solution. Therefore, the immediate effect is due to acute myocardial cooling and exposure to potassium and adenosine, possibly resulting in transient bradycardia, dysrhythmias and myocardial depression. As liver cell membranes become more functional, there is rapid sequestration of potassium into intracellular locations. Cardiac output rises, but the effects of complement activation and release of inflammatory mediators, together with generation of oxygen-derived free radicals, result in the "post-reperfusion syndrome" [22, 23]. This is characterised by hypotension and low SVR occurring five minutes or more after reperfusion and lasting at least 1 h [24].

A number of strategies may be employed to offset dramatic hemodynamic changes that can be seen at the time of graft reperfusion. The younger patient who is otherwise cardiovascularly fit or patients who do not have significant metabolic derangement and those where the graft ischemic time is particularly short may display only minimal and transient hemodynamic changes and require no specific inotrope or vasopressor at this time. However, such patients represent a minority in routine clinical practice.

In general, management of the immediate reperfusion phase consists of both pre-emptive and reactive elements. The pre-emptive element includes administration of a bolus of calcium, either as calcium chloride or gluconate, immediately prior to graft reperfusion. This has combined effects on protecting the myocardium against a potassium surge, while at the same time replenishing or restoring deficient calcium ion concentration to a physiological level. Hypocalcemia during the late anhepatic

phase is common, as a consequence of citrate accumulation, and this may be clinically significant<sup>19</sup>. A bolus of 10 mmol of ionised calcium at this stage is highly effective. In some cases, a bolus of sodium bicarbonate may also be of value to control peri-reperfusion hyperkalemia and helps maintain pH above 7.2. This is important to maintain vasopressor receptor responsiveness. Appropriately judging the use of these agents mandates blood gas analysis immediately prior to graft reperfusion.

The reactive components of management of the reperfusion process depend on the extent to which hypotension occurs. Small, incremental boluses of epinephrine may be required. Depending on the specific clinical situation, fluids may also be needed, for example, where the patient is relatively hypovolemic or if there is unexpected bleeding at reperfusion.

Cases who have been managed without venovenous bypass may have received significant fluid loading during the anhepatic phase, depending on the degree of vena caval occlusion and whether or not a temporary porto-systemic shunt has been created. As a result, there may be an increased venous return as the vena caval clamps are removed; such patients may show elevated right heart pressures in the seconds and minutes following liver reperfusion and therefore, fluid administration is inappropriate in this group. Epinephrine is generally a more suitable choice of agent rather than phenylephrine in this situation. Constriction of venous capacitance vessels can further contribute to fluid overload. Occasionally, it is necessary to combine epinephrine with a nitrate to achieve simultaneous improvement in cardiac function and venous offloading. This, however, is a strategy which requires considerable experience and very close monitoring. Injudicious use of nitrates at this stage can result in catastrophic hypotension.

Other agents that have been used experimentally to offset the hypotension and graft reperfusion include methylene blue, though there is very limited evidence to support the use of this agent and therefore, its use cannot be advocated in routine clinical practice.

Following reperfusion, reduction in SVR results in an elevation in CO. This, in turn, is accompanied by (and is related to) progressive elevation of PAP. This is probably a feature of a fixed or moderately elevated pulmonary vascular resistance in the presence of a rising CO [25]. An increase in left ventricular stroke volume is also frequently seen at this stage. Patients with pre-existing pulmonary hypertension or right ventricular dysfunction are at particular risk of

decompensation secondary to elevation of PAP with a subsequent shift of the right ventricular pressure flow-volume loop to the right. In these situations there is a substantial risk of right heart failure resulting in very high venous pressures and graft failure as a result of the loss of a pressure gradient between the portal and central circulations. Graft blood flow is further compromised by the potential low CO state and hypotension that can result from inadequate left ventricular filling secondary to right heart failure.

Standard management of persistent hypotension following liver graft reperfusion is the use of an alpha-agonist, commonly norepinephrine by infusion. Epinephrine may be a suitable alternative where a reduced or inappropriately low CO is also a feature. Patients who exhibit right heart failure at this time may benefit from administration of epinephrine and a nitrate. There may also, in such situations, be a role for dobutamines for inotropic support, but because of the vasodilatory properties of dobutamine, caution should be exercised. Dobutamine is unpredictable in this situation, as it is a racemic mixture, whose isomers exhibit a differential alpha-agonist effect.

An important and often overlooked contribution to maintain hemodynamic stability during vasodilating states and major hemorrhage is plasma viscosity (a function of hematocrit) among other factors. Although conventional teaching has been that a lower hematocrit is associated with reduced plasma viscosity and hence less tissue perfusion, current evidence questions this. At low plasma viscosity, reduced vascular shear results in altered signalling, probably via a NO pathway among others, which can in turn result in vasoconstriction and reduced tissue perfusion [26]. Maintaining an adequate hematocrit is also beneficial in preserving diastolic function and hence helping to avoid the catastrophic rise in right heart pressure, which could compromise hepatic perfusion at a stage when the liver is entirely dependent on portal venous flow.

Classically, diuresis is described during the neohepatic phase; however, this depends on the quality of the liver graft function, adequate perfusion pressure and the absence of preoperative renal impairment. Additionally, perioperative factors such as massive hemorrhage during the dissection phase may compromise renal function and limit the potential for a diuresis. To some extent, decisions on volume replacement

and potassium supplementation depend on observation of an adequate urine output and decreasing serum potassium at this stage of the procedure. Clearly, the inotrope and vasopressor requirements at the time of graft reperfusion differ from those required for support in the ensuing time period.

Cardiovascular changes persist well into the postoperative period. SVR remains low for up to 24 h after surgery, but they will gradually normalise over the next 24–48 h. The normalisation of SVR seems to be independent of the reduction in CO, which also self-corrects over a slightly greater time course. It is therefore not entirely clear whether the reduction in CO is compensatory or a consequence of separate neurohumoral regulation [27]. In patients with increased postoperative PAP and wedge pressure, these usually remain high for at least 4 days after surgery. Therefore, there is frequently an ongoing requirement for vasopressor support, although these can usually be decreased in the hours following surgery. Spontaneous improvement in mean arterial pressure and organ perfusion is associated with significant diuresis during the process of weaning from artificial ventilation. In most units, this is feasible within few hours after surgery. In units with fast track protocols, ventilation and extubation at the end of surgery are feasible when intraoperative fluid requirements and the absence of pulmonary fluid overload are taken into account [28]. Therefore, judicious use of inotropes and vasopressors at this stage of the procedure directly influences the need for postoperative ventilation and the time course of critical care unit discharge.

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# Coagulopathy: Pathophysiology, Evaluation, and Treatment

# 13

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## Abbreviations

AT	Antithrombin
CVP	Central venous pressure
DDAVP	Desmopressin
EACA	Epsilon-aminocaproic acid
EPCR	Endothelial protein C receptor
FFP	Fresh frozen plasma
INR	International normalized ration
PAI-1	Plasminogen activator inhibitor
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cell
TACO	Transfusion-associated circulatory overload
TAFI	Thrombin activatable fibrinolysis inhibitor
TEG	Thromboelastography
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TM	Thrombomodulin
tPA	Tissue plasminogen activator
TRALI	Transfusion-related acute lung injury

TxA	Tranexamic acid
VWF	von Willebrand factor

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## Introduction

For centuries from Hippocrates and Galen to Virchow and Morawitz, the process of hemostasis and its pathways has mystified us, and Roman numerals have comprised our understanding of hemostasis and coagulation. The reassuring “cascade” of events that has represented the process of coagulation and hemostasis has remained dogma until recently. We now know that hemostasis is a dynamic system comprised of “balanced” systems and cannot be explained away by a model of coagulation that is based on “cascades.” As we are forced to understand the “full” picture of hemostasis, we will evaluate coagulation in a more complete way.

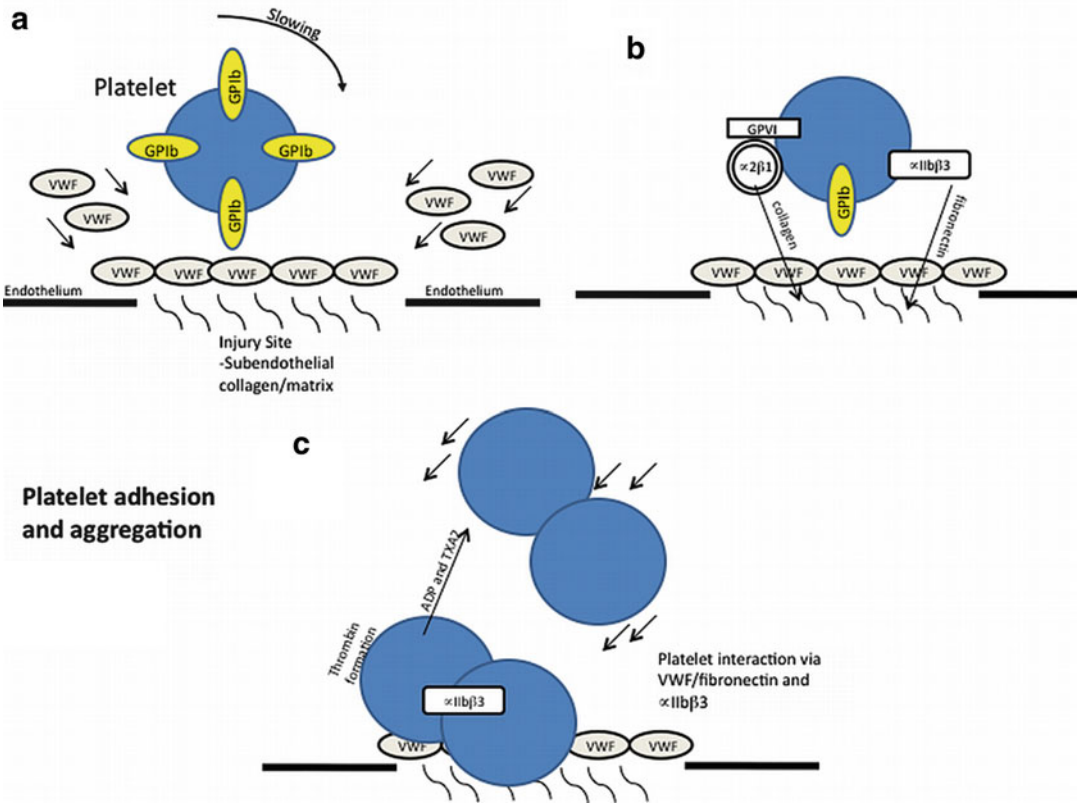
Nowhere are these complexities more apparent than in progressive liver failure. Dynamic changes occur at every level of this system from platelet dysfunction to imbalances in the coagulation cascade. These changes involve not only anti- but pro-hemostatic mechanisms. Whether planning an invasive procedure, major surgery, or liver transplant, there is much dilemma in how to properly handle these patients and their coagulopathic status. This chapter will explore the balance of hemostatic pathways and review the defects that occur in progressive liver disease. We will also portray the current state of how to evaluate and treat coagulopathy in this patient

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**Fig. 13.1** (a) Subendothelial collagen binds to von Willebrand factor (VWF) which momentarily interacts with platelets expressing glycoprotein GPIb. (b) This process slows the flow of platelets to create a more lasting attachment between the collagen-and platelet-expressed receptor  $\alpha 2\beta 1$  and glycoprotein VI or platelet integrin

$\alpha \text{IIb}\beta 3$  and fibronectin with collagen. (c) Glycoprotein VI on the platelet surface initiates a transmembrane signal, giving way to release of ADP, thromboxane A2, and alpha and dense granules by the platelet. Platelet aggregation can then occur

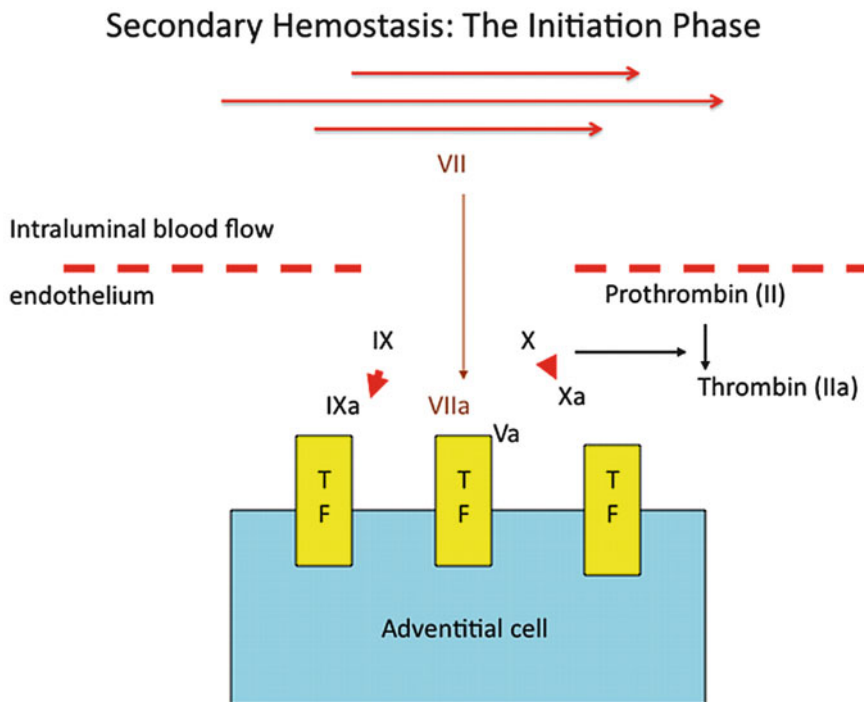
population with specific attention given to application towards liver transplantation.

## Physiology of Coagulation

### Primary Hemostasis

The initial step in the hemostatic pathway occurs by formation of the platelet plug. Platelet aggregation creates the scaffolding of which thrombosis can then occur. When the vessel wall is damaged, subendothelial collagen is exposed to von Willebrand factor (VWF) in the serum. VWF binds to the site of injury and will momen-

tarily interact with platelets expressing glycoprotein GPIb (Fig. 13.1a). This slows the flow of platelets until a more lasting attachment is made between the exposed collagen and platelet-expressed receptor  $\alpha 2\beta 1$  and glycoprotein VI, or platelet integrin  $\alpha \text{IIb}\beta 3$  and fibronectin with collagen (Fig. 13.1b). Glycoprotein VI on the platelet surface initiates a transmembrane signal, allowing activation and release of ADP, thromboxane A2, and alpha and dense granules by the platelet (Fig. 13.1c). Platelet-platelet interaction via integrin  $\alpha \text{IIb}\beta 3$  can then occur, leading to further platelet activation and aggregation. Meanwhile, the coagulation cascade is initiated, leading to platelet stabilization.



**Fig. 13.2** Endothelial damage–tissue factor (TF) interaction with factor VII, initiating the thrombin burst, promoting platelet activation, and activation of additional coagulation cofactors

## Secondary Hemostasis

Many interactions are occurring simultaneously at the site of endothelial damage. As platelets aggregate, the coagulation cascade initiates at the platelet surface to form a fibrin clot and reinforces platelet aggregation. When the endothelium is damaged, tissue factor (TF) is released into the bloodstream, binding to factor VII and initiating the thrombin burst. This initial generation of thrombin promotes maximal platelet activation [1], as well as activation of additional coagulation cofactors (Fig. 13.2). While this is not enough to generate a fibrin clot on its own, it primes the clotting system for a burst of platelet aggregation by activating factors V, VIII, and XI on the platelet surface [2–4]. Factor XI activates factors IXa and VIIIa, which then forms the FIXa/FVIIIa, tenase complex.

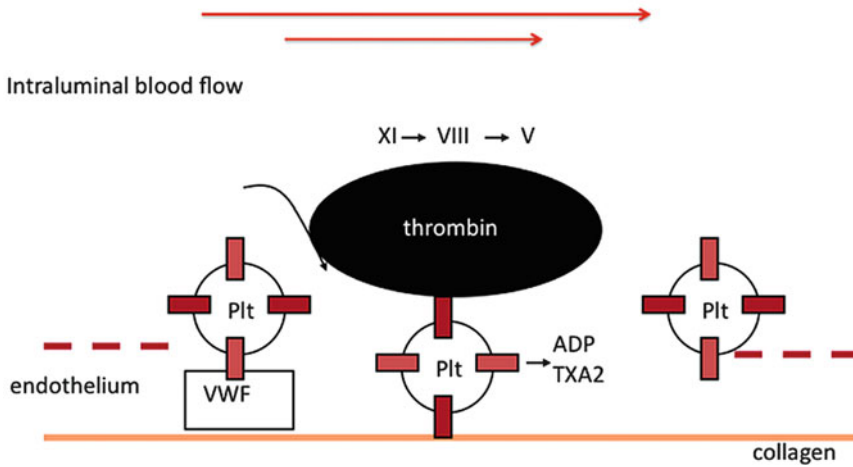
The tenase complex cleaves factor X into an activated form (Xa). Factor V is activated by

FXa. This creates the first sufficient amount of thrombin (IIa) to generate fibrin and stabilize the platelet plug. This is known as the “propagation” phase of thrombin generation (Figs. 13.3 and 13.4). Factor II is converted into factor IIa (thrombin), in turn cleaving fibrinogen into fibrin, which forms a strong meshwork to promote clot stability and thrombosis. The coagulation cascade only emphasizes the procoagulant factors of the hemostasis. Equally important to understand are those steps which provide balance and inhibit the prothrombotic steps of the coagulation cascade.

## Inhibition and Fibrinolysis in Coagulation

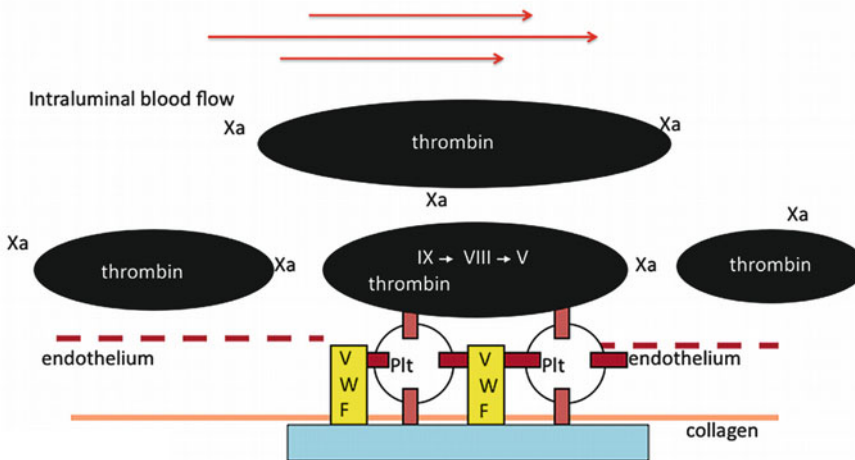
Hemostasis is composed of “forward” driving forces and those that “reverse” the process (fibrinolysis). Both forces maintain a balance and localize thrombosis to the site of injury, preventing

### Secondary Hemostasis: The Amplification Phase



**Fig. 13.3** Amplification phase—the tenase complex, FIXa/FVIIIa, cleaves factor X into an activated form (Xa). FXa activates factor V, which creates the first sufficient amount of thrombin (IIa) to generate fibrin and stabilize the platelet plug

### Secondary Hemostasis: The Propagation Phase

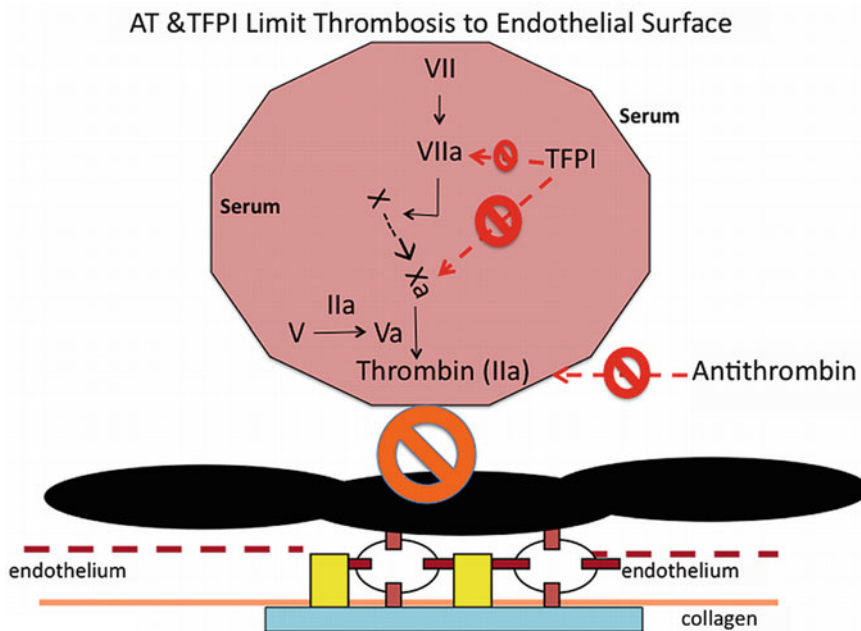


**Fig. 13.4** Propagation phase—the activity of the coagulation cascade continues to generate thrombin, creating a stable thrombin clot

uncontrolled thrombotic extension. Understanding this is crucial when assessing the coagulation status of the liver disease patient, since both pro- and anticoagulant factors are affected in this disease state. Thrombin generation is directly inhibited by tissue factor pathway inhibitor (TFPI) and antithrombin (AT) (Fig. 13.5). TFPI inactivates factors VIIa and Xa, and AT inactivates factor IIa (thrombin). TFPI is active in

serum, unable to inhibit at the cellular surface. This localizes thrombin generation to the surfaces of platelets and endothelium where damage is present [5, 6].

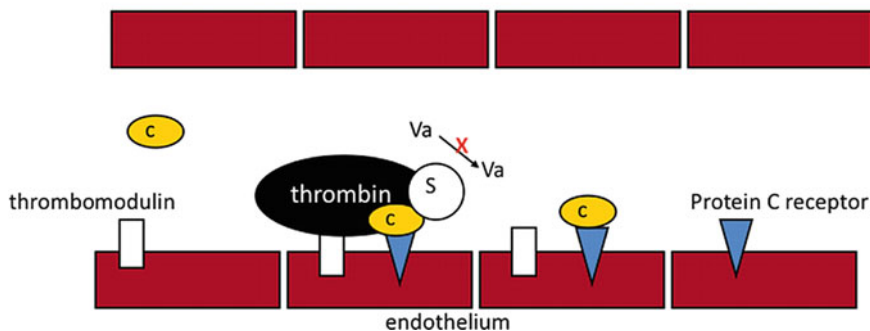
The vitamin K-dependent factors proteins C and S further regulate the coagulation cascade. Protein C is a protease [7] whose activity is enhanced by protein S, which together inhibit both factors Va and VIIIa. Protein C is bound to



**Fig. 13.5** Tissue factor pathway inhibitor (TFPI) inactivates factors VIIa and Xa, inactivating thrombin generation and antithrombin (AT) inactivates factor IIa (thrombin). TFPI is active only in serum and therefore

unable to inhibit at the cellular surface. This localizes thrombin generation to the surfaces of platelets and endothelium where damage is present

### Protein C and S: Antithrombotic Activity

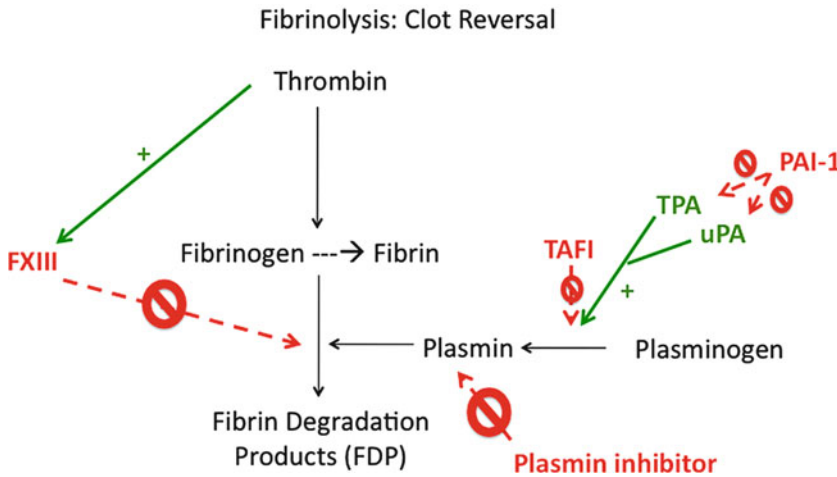


**Fig. 13.6** Protein C is a protease, enhanced by protein S, which together inhibit factors Va and VIIIa. Protein C is localized to the endothelial cell surface by the endothelial protein C receptor (EPCR). Thrombin escaping the site of

injury is bound to the endothelial surface receptor thrombomodulin (TM), forming a thrombin/TM complex, and can no longer carry out normal coagulant functions

the endothelial cell surface by the endothelial protein C receptor [8] further restricting thrombin generation to the site of damage. If thrombin escapes from the site of injury to intact endothelial cells, it will be bound to the endothelial surface receptor thrombomodulin (TM), forming a

thrombin/TM complex. This complex can no longer carry out normal coagulant functions [9] and will activate protein C to bind protein S and encourage further clot inhibition (Fig. 13.6). Other mechanisms further reverse fibrin production through a process called fibrinolysis.



**Fig. 13.7** Fibrinolysis—tPA released from endothelial cells, macrophages, and renal epithelial cells activates plasminogen to plasmin. FXIII inhibits the degradation of fibrin into fibrin degradation products. Thrombin activat-

able fibrinolysis factor (TAFI) inactivates the conversion of plasminogen into plasmin, by cleaving the C-terminal lysine and arginine residues on tPA and plasminogen preventing their binding to one another

These latter mechanisms (Fig. 13.7) utilize factors which include tissue plasminogen activator (tPA), plasminogen activator inhibitor (PAI-1), plasminogen, alpha2-antiplasmin, histidine-rich glycoprotein, and factor XIII, all of which except tPA and PAI-1 are synthesized in the liver [10]. tPA released from endothelial cells, macrophages, and renal epithelial cells activates plasminogen to plasmin. Plasmin is an enzyme capable of degrading fibrin into soluble fibrin degradation products. This process is regulated by inhibitory factors such as FXIII that inhibit the degradation of fibrin into fibrin degradation products and stabilize the fibrin meshwork, preventing over-fibrinolysis. Thrombin activatable fibrinolysis inhibitor (TAFI) inactivates the conversion of plasminogen into plasmin, by cleaving the C-terminal lysine and arginine residues on tPA and plasminogen and preventing their binding to one another.

When evaluating the effects of liver disease on the coagulation cascade, these inhibitory factors are often not considered. Unfortunately there is no simple way to test for their activity at the bedside. They are a major contributor to the overall coagulation status of the liver disease patient and need to be considered before treating coagulopathy.

## Hemostasis in Liver Disease

After reviewing normal hemostasis, we can explore how advanced liver disease affects this process. Because hepatic parenchymal cells synthesize so many of the pro- and anticoagulant proteins involved in coagulation, it is easy to understand how liver disease could disrupt hemostasis. As already mentioned, the coagulation cascade is not the only piece to this puzzle as factors such as hemodynamic disruption from stasis and portal hypertension, dysfibrinogenemia, production of endogenous heparinoids, platelet and endothelial dysfunction, renal failure, and increased susceptibility to infection all contribute to coagulopathy in liver disease. We are beginning to understand that each of these complications has direct implications towards the coagulopathic state of advanced liver disease.

## Coagulation Cascade and Liver Disease

The coagulation cascade is comprised of redundant steps that keep one another in balance. In a healthy person, only 20–50% of the normal level of procoagulant factors is required to achieve hemostasis [11] with a substantial amount of

overlap between pro- and anticoagulant factors, providing a buffering system for hemostasis in healthy individuals. This buffering system becomes more tenuous in patients with liver disease, and with advanced liver disease, it is increasingly difficult to balance this system as smaller changes of coagulant levels can cause significant changes within the entire system. Understanding this balance and how it is impacted in liver disease is helpful in assessing coagulopathy in these patients.

Traditionally prothrombin time (PT) and international normalized ratio (INR) have been used to assess the degree of coagulopathy in liver patients, and this reflects a shortcoming in our understanding and the barriers of our testing strategies. As PT and INR are mere measurements of “procoagulant” factors, it disregards the effect of liver disease on “anticoagulant” factors. In liver disease, all of the procoagulant factors except FVIII are reduced; however, procoagulants like FVIII and vWF can be increased in cirrhosis [12]. “Anticoagulant” factors such as protein C and S, of the coagulation cascade, are reduced in hepatic disease [13, 14] which is not reflected when measuring PT and PTT. As both sides of this system seem to be affected evenly, Tripodi demonstrated that thrombin generation may actually be normal in the setting of increased PT, PTT, and INR [15] and that there may be less hemostatic disturbance. The platform on which hemostasis balances is narrowed with liver disease, and it is easier to “tip” a liver patient towards one direction or the other. PT and PTT used by themselves may be inadequate in evaluating coagulation status in this clinical picture.

PT and INR only assess one part of the coagulation cascade—namely, vitamin K-dependent factors like FII, VII, IX, and X—as these tests were originally developed to measure the therapeutic effects of drugs like warfarin that affects vitamin K-dependent factors. In vivo hemostasis in liver disease involves deficiencies in fibrinogen, prothrombin, vitamin K-dependent factors, as well as protein C and S, and other “anticoagulants.” Furthermore, there are factors to consider beyond the coagulation cascade when assessing bleeding risk in liver disease patients.

## Platelet Function in Liver Disease

The platelet, the initial “plug” in primary hemostasis, provides the scaffolding for the coagulation cascade and thrombin generation. In liver disease, abnormalities in platelet number and function have been traditionally linked to impaired primary hemostasis [15]. Platelet numbers are decreased due to the effects of portal hypertension and increased sequestration in the spleen, and with worsening liver failure thrombopoietin levels decrease [16, 17] evidence of the importance of bone marrow production of platelets. Hepatitis C, alcohol toxicity, and nutritional folic acid deficiency compound this problem by depressing megakaryocytopoiesis [18–20]. The role of disseminated intravascular coagulation (DIC) as a cause of thrombocytopenia in these patients is contentious [21]; however, low-level consumption associated with DIC possibly decreases platelet life span as well [22].

Reduced platelet function further complicates impaired primary hemostasis, and there is strong evidence that platelet aggregation is reduced [23–25]. Platelet activation is affected by both intrinsic and extrinsic stresses. Intrinsically, decreased thromboxane A<sub>2</sub> synthesis, altered transmembrane signaling, and reduction in glycoprotein Ib and platelet integrin  $\alpha$ IIb $\beta$ 3 reduce platelet activation [25–32]. Extrinsically, elevated levels of nitric oxide and prostacyclin inhibit platelet function [33] as a result of endothelial dysfunction. The platelet phospholipid membrane may also be affected by abnormal high-density lipoprotein particles in plasma [34]. Moreover in liver disease, blood flow defects occur, and these may be compounded by low hemoglobin [35].

It is still not clear how these abnormalities affect bleeding time as there is some speculation that elevated levels of VWF compensate for these impairments [36]. In fact the elevation of VWF may actually lead to a higher rate of thrombin generation and clot formation [36]. We also know from groups like Tripodi and Porte that thrombin generation is not necessarily negatively affected and that under physiologic conditions of flow, platelets from a patient with hepatic cirrhosis can interact with collagen and fibrinogen as long as



platelet count and hematocrit are adjusted to levels found in healthy patients [37, 38].

## Hyperfibrinolysis in Liver Disease

The role of hyperfibrinolysis in patients with hepatic cirrhosis is controversial and widely debated in the current literature [39]. Whether hyper- or hypofibrinolysis occurs, it is agreed that it complicates the picture [40–43]. Hyperfibrinolysis appears to be more problematic as liver disease progresses [44–47], and low-grade fibrinolysis has been shown to occur in 30–46% of patients with end-stage liver disease [48].

Plasminogen, alpha2-antiplasmin, histidine-rich glycoprotein, factor XIII, and TAFI [49–58] are all produced in the liver, and therefore their levels are reduced in liver disease. However, increased levels of tPA and PAI-1 are present as these are not synthesized in the liver [59]. tPA is elevated most likely due to reduced hepatic clearance [10, 60], but PAI-1 levels seem to be better correlated by the clinical stage of the liver disease. PAI-1 is elevated in patients with chronic “smoldering” liver disease [45, 61] and is decreased in patients with severe liver failure [45, 62]. Patients with acute liver failure have a higher circulating amount of acute phase reactant PAI-1 and more of a shift towards hypofibrinolysis [63]. Therefore, theoretically, increased fibrinolysis should occur in patients with severe liver failure with an increased pool of tPA and depressed levels of PAI-1 and alpha2-antiplasmin to balance it.

Decreased levels of TAFI have also been linked to hyperfibrinolysis in cirrhosis [43]. Colluci and colleagues [64] demonstrated that TAFIa generation was low in cirrhosis due to decreased levels of TAFI concluding that depleted TAFIa was a significant contributor to hyperfibrinolysis. However, Lisman et al. [65] came to the conclusion that TAFI deficiency was not a significant contributor to hyperfibrinolysis in cirrhosis. This disparity may be due to the inability to test and measure global fibrinolysis, and newer methods of testing global fibrinolysis confirmed the presence of hyperfibrinolysis in chronic liver disease [66].

Fibrinolysis is important not necessarily because of its potential to initiate bleeding in a liver disease patient but because of the important role it plays in delaying primary and secondary hemostasis, contributing to the severity or recurrence of bleeding events. In liver transplantation, many studies report enhanced fibrinolytic activity during the anhepatic stage [67]. The lack of tPA clearance and the reduction of alpha2-antiplasmin may be responsible for this enhanced fibrinolysis [68]. After liver transplantation, fibrinolysis may persist for a prolonged time especially in case of early allograft dysfunction [68–70]. An initial rise of tPA during the anhepatic stage is followed by further increases after reperfusion in 75% of patients [71]. The importance of how to recognize, monitor, and further treat this dysfunction in moderate to severe liver disease is important and will be addressed later in this chapter.

## Endothelial Dysfunction and Liver Disease

Sinusoidal endothelial cells produce and release vasoactive substances that regulate intrahepatic vascular resistance [72]. Endothelial dysfunction is thought to be due to a defective vasodilatory response to acetylcholine and insufficient endothelial NO synthase to produce NO [73–75]. Increased production of thromboxane A2 also leads to increased intrahepatic resistance in advanced liver disease [76, 77]. Portal hypertension is the liver’s response to its inability to accommodate fluctuations in increased portal circulation.

As portal hypertension develops, deleterious processes such as splanchnic and then systemic vasodilatation occur. The endothelium in these two systems responds by producing more NO for arterial dilatation, and this will then lead to a hyperdynamic circulation, which is related to complications such as variceal bleeding, ascites, hepatorenal syndrome, and hepatopulmonary syndrome [78–80]. There are several proposed ways to monitor the response of the endothelium in liver disease, and these will be addressed later.

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## Evaluation

### Bleeding Time

Bleeding time is performed by inflicting a standardized cut on the volar aspect of the forearm while applying a blood pressure cuff to the upper arm. There are several limitations to the reproducibility to the test including the skill of the technician, skin thickness, ambient temperature, and endothelial dysfunction [81]. Bleeding time is not well validated [82] and for example studies using desmopressin (DDAVP) as treatment showed improved bleeding time but no effect on risk of variceal bleeding in liver disease patients [83–85]. This lack of correlation between bleeding time and risk of bleeding in this patient population makes this test less helpful in addressing this clinical conundrum.

### Platelet Function Analyzer-100

The noticeable difference between the platelet function analyzer-100 (PFA-100) and other tests of platelet function is that this *in vitro* test provides a quick way to quantitatively evaluate primary hemostasis under shear stress. The test measures platelet adhesion as blood flows through a collagen membrane under the draw of a vacuum. The time it takes to occlude the channel in the collagen membrane is a measurement of platelet adhesion [81, 86]. Data collected using the PFA-100 has not been overwhelmingly helpful; however, one study demonstrated that closure time was decreased if hematocrit was normalized in the blood of liver disease patients [87]. It seems that this test is not well accepted as a means to analyze platelet function.

### Prothrombin Time

The prothrombin time evaluates the extrinsic pathway of the coagulation cascade and is responsive to deficiencies in factors X, VII, V, II, and fibrinogen. The test was developed by Armand Quick and measures the time it takes a blood

sample to clot once thromboplastin and calcium chloride are added [25]. Results are typically measured in seconds but are commonly standardized with the international normalized ratio (INR). The INR was developed as a way to account for differences in reagents (thromboplastin) across different laboratories and was originally used to standardize treatment of patients using vitamin K antagonists like warfarin. The INR is an imperfect system, and in coumadinized patients, a variability of 13% has been observed depending on where lab samples are obtained from [88]. This difference is accentuated in liver disease patients, and mean INR variation increases further with advanced liver disease [89–92].

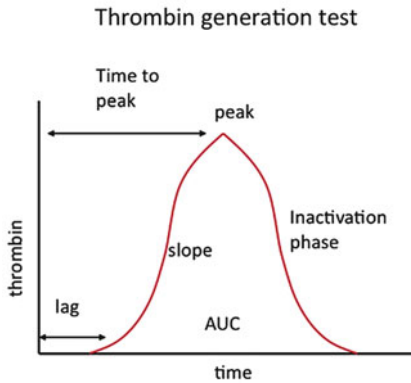
Not only are PT and INR variable, they also reflect an incomplete picture of coagulopathy in liver disease patients and are unreliable in this patient population [93–97]. This test does not reflect the parallel depletion of protein C and S *in vivo* [98] and is without sufficient levels of thrombomodulin for thrombin-mediated activation of protein C [15]. The PT is also limited by its inability to evaluate the role of platelet and endothelial dysfunction.

### Activated Partial Thromboplastin Time

The activated partial thromboplastin time (aPTT) allows for evaluation of the intrinsic pathway of the coagulation cascade and is increased with deficiencies of all coagulation factors except for factors VII and XIII. It represents the time (in seconds) for phospholipids, representing the platelet membrane, to generate a thrombus by activating factors like factor XII. It is often clinically used to monitor the anticoagulant effects of heparin in patients, though there is no standardization between laboratories. As previously mentioned, relying solely on this test to evaluate coagulation in liver disease patients is fraught with difficulties.

### Thrombin Generation Test

This test utilizes tissue factor and phospholipids to trigger thrombin generation and is arguably the



**Fig. 13.8** Thrombin generation test—thrombin generation in plasma where tissue factor (TF) and phospholipids are added to trigger coagulation. AUC (area under curve)=ETP (endogenous thrombin potential), or the amount of work that can potentially be done by thrombin. Proposed potential of this test is to quantify how much and how long thrombin is active

closest measurement of what occurs in vivo. Thrombin, a potent platelet activator, and phospholipids, representing the platelet surface, feed forward to allow for explosive thrombin generation. The thrombin generation test (Fig. 13.8) can measure this reaction with the thrombin vs. time generation curve. Once coagulation occurs, the initial part of the curve is the lag time, followed by the peak of thrombin, and time to peak. The area under the curve measures the effectiveness of thrombin generation in a system where both pro- and anticoagulants are examined as they operate in plasma. Reliability of the thrombin generation test is yet to be determined but may have acceptable levels of variation [99]. Further clinical studies are needed to evaluate the usefulness of the thrombin generation test as it applies to liver disease.

### Thromboelastography

Thromboelastography (TEG) provides a graphical representation of the viscoelastic changes that occur during coagulation in vitro (Fig. 13.9). A stationary pin is introduced into a sample of whole blood that oscillates back and forth six times per minute. Kaolin is added, initiating thrombin generation [100], and subsequently, fibrinogen is converted to fibrin. As fibrin is sta-

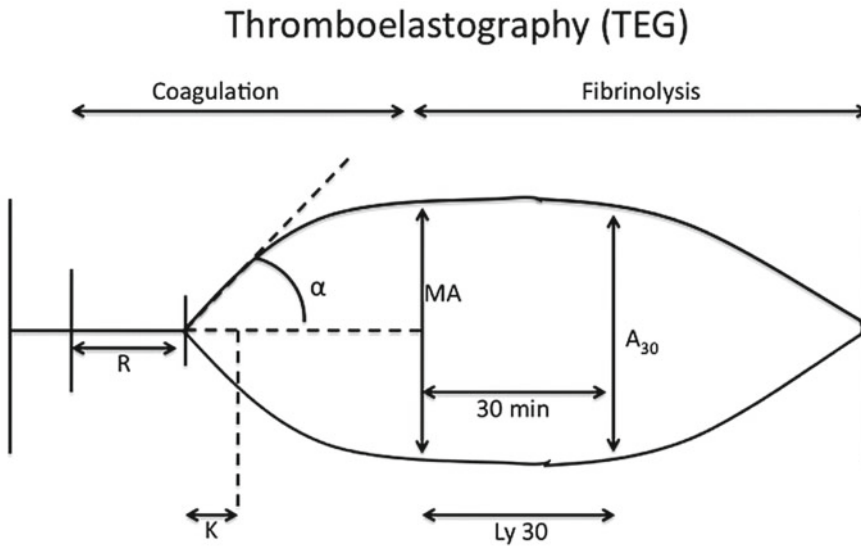
bilized by platelets [101] and the clot is strengthened, the pin detects viscoelastic changes and records these dynamic changes in a graph. The technique can provide continuous observation and quantitative measurement of different stages of hemostasis, including clot formation, strength, platelet function, and fibrinolysis. Technical difficulties have limited the use of TEG in the past; however, the combination of improved technology and materials has come closer to standardizing the technique, improving reproducibility. A modification of the TEG, the rotational thromboelastometry or ROTEM, uses a rotating sensor shaft rather than a rotating cup and is less sensitive and provides a simpler and standardized user interface. Liver transplantation was one of the first procedures to utilize TEG [102], and TEG and ROTEM are now increasingly used as standard tests to evaluate coagulation intraoperatively [103]. As the tests monitor different phases of hemostasis, intraoperative therapy can be individualized and reevaluated in a short period of time.

### Monitoring Fibrinolysis During Liver Transplant

Several studies have reported hyperfibrinolysis during the anhepatic stage when venous return is maintained via a venovenous shunt [104], as well as during graft reperfusion [68, 69]. Some attribute this to a decreased hepatic clearance of tPA, and Porte et al. demonstrated that tPA levels are increased during reperfusion in 75% of patients [71]. If a transplanted liver has sustained increased damage during transport due to ischemia, it may take longer for the hyperfibrinolysis to resolve. TEG remains a key instrument in monitoring every step of hemostasis during liver transplant; however, the below tests may be helpful as well.

### Prevention and Treatment Guidelines for Bleeding During Liver Surgery

While bleeding is inevitable during liver resection and transplantation, blood loss rates have decreased substantially as surgical technique and



**Fig. 13.9** Thromboelastography (TEG)—R reflects coagulation factor and platelet activities, K reflects activity of fibrinogen, factor II, and hematocrit effects. Alpha represents the clotting factor deficiency; MA indicates

platelet, fibrin, and factor XIII function. Ly 30 reflects fibrinolysis. A<sub>30</sub> further represents fibrinolysis and is the amplitude 30 min after MA

preventive measures through volume management have become more sophisticated (Fig. 13.10). Particularly pertinent in the coagulopathic liver disease patient, extensive bleeding may require transfusion of blood or blood products, which is associated with increased rates of morbidity and mortality [69, 105–109]. Recommendations regarding administration of blood products have improved in order to reduce these rates and should help guide the decision to treat coagulopathic processes during surgery. We will present these recommendations here.

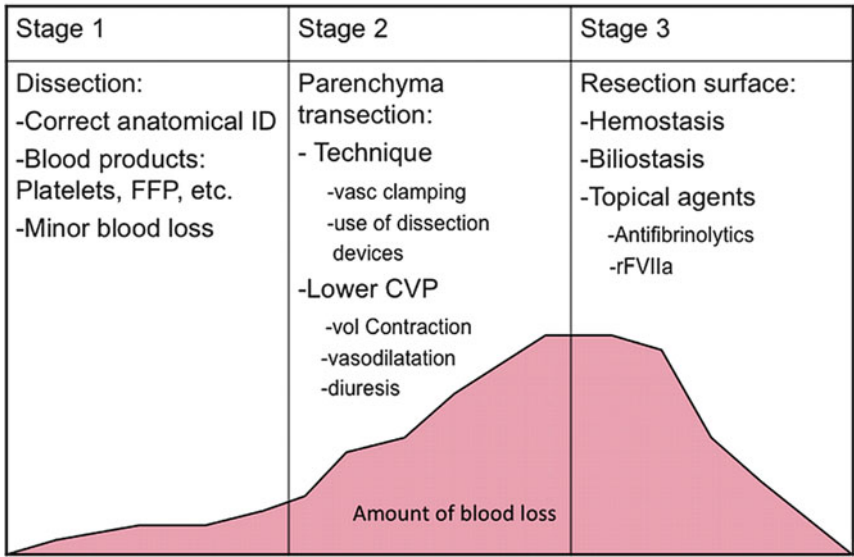
### Fresh Frozen Plasma

Fresh frozen plasma may be obtained from whole blood or via plasmapheresis and frozen within 8 h at  $-30^{\circ}\text{C}$ . FFP is a useful product as it contains both pro- and inhibitory factors of the coagulation cascade, acute phase proteins, immunoglobulins, and albumin [110], and it is often used to prevent or stop bleeding. Factor VIII is typically the only plasma protein whose level is quality controlled, and while coagulation factor content can be maintained for up to 5 days

at  $1-6^{\circ}\text{C}$ , there is evidence of fall in levels of FV and FVIII over time. Variability in factors represented between units exists, and heterogeneity reflects genetic differences between donors or adverse effects of the pathogen-eliminating techniques [111, 112]. One unit of FFP measures about 300 ml, and appropriate dosing is loosely agreed upon.

Most of the recommendations for dosing are based upon mathematical extrapolation of factor content and physiologic response to the effects of plasma infusion [113]. Data has been variable as to the efficacy of FFP as a therapeutic agent. A prospective evaluation of 324 units of FFP on 120 patients demonstrated only 15% of patients corrected halfway to normal PT and INR and 1% completely corrected with FFP transfusion [114]. Even more troubling in this study is that, retrospectively, there was no correlation between clinical bleeding and diagnostic test results. There was also no evidence of a dose-dependent response of plasma. Another study specific to liver disease patients found a median reduction of INR attained after FFP of 0.2 (range 0–0.7) [115]. Similar results have been attained, and other studies have looked at volume-related benefit,

### Management of Coagulopathy During Hepatic Resection



**Fig. 13.10** Bleeding occurs throughout the three stages of liver resection; however, blood loss rates increase during the transection of the liver parenchyma. The figure is

modified from Alkozai et al., indicating relative amounts of blood loss and some of modern techniques employed to reduce blood loss

demonstrating that at lower doses (12.2 ml/kg), there was less therapeutic benefit and increased harm when compared to higher doses (33.5 ml/kg) [116]. The recommended dose of FFP is 10–20 ml/kg until better defined with future studies.

While dosage remains an important issue, another difficulty is determining when to transfuse plasma and which diagnostic markers to use to guide transfusion. Massicotte et al. demonstrated that preoperative plasma transfusion did not decrease the need for intraoperative red blood cell (RBC) transfusion and found no difference in the number of plasma or RBC transfusion units between patients with an INR >1.5 and those with an INR <1.5 during 200 liver transplants [117]. They further demonstrated that transplant recipients who did not receive plasma with an INR >1.5 subsequently did not incur anymore RBC transfusion when compared to patients with an INR <1.5 [117].

FFP transfusion is certainly not without risk and may have the highest incidence of complications of all blood products in liver transplantation [118, 119]. The most important complications

relevant to liver disease patients are transfusion-related acute lung injury (TRALI), an inflammatory reaction producing non-cardiogenic pulmonary edema acutely within 6 h of transfusion [120], and transfusion-associated circulatory overload (TACO). TACO is an acute syndrome producing elevated blood pressure and dyspnea associated with large volume transfusions and is associated with prolonged hospital stay and increased mortality. Variable reporting of both syndromes has made it difficult to reliably determine the incidence [113]. TRALI has been related to female donors through England's Serious Hazards of Transfusion hemovigilance program [114], and as a consequence, male donors for plasma are preferred. Allergic reactions to FFP occur at a rate of 1–3% of all FFP transfusions [121], and of course there is a real risk of infectious complications related to FFP.

Despite the perceived and real risk of FFP infusion, plasma is no longer directly linked to decreased survival rate. Rather, there is known association between increased 1-year mortality, RBC transfusion, and Child-Pugh score, and plasma transfusion has been the variable with the

strongest association with blood transfusion [122]. In another retrospective study done by Massicotte et al. [123], the proposed sequence of events was that the patient with coagulation defects would receive plasma (10–15 ml/kg), the expanded volume would increase CVP, and this would worsen bleeding prior to the anhepatic phase. The resultant increased rate of bleeding associated with plasma infusion and subsequent blood transfusion is what is then thought to be responsible for an increased 1-year mortality in liver transplant patients.

While the American Society of Anesthesiology recommends transfusion of FFP for an INR greater than 2.0 in patients with excessive microvascular bleeding [124], better control of volume status and lower central venous pressure may be preferential over attempting to correct coagulopathy strictly defined by an INR of 2.0. For now with the current lack of adequate data, it is advised that INR of 2.0 with clinically significant bleeding may be an indication for FFP transfusion; however, more work is required in this area.

## Platelet Transfusion

Apart from the known role of platelets in primary hemostasis, platelets may actually play an important role in regulating inflammation, angiogenesis, tissue repair/regeneration, and ischemia and reperfusion injury [125–128], all of which are important factors during liver transplantation. It is therefore important for us to know which platelet levels to strive for pre-, intra-, and postoperatively independent of their role in hemostasis. Since there is currently no optimal way to monitor the function of primary hemostasis, it is difficult to predict optimal platelet thresholds for surgery.

What we do know about the thrombocytopenic liver patient is that primary hemostasis may not be as compromised as previously thought [14, 38]. Platelet levels are in a constant state of flux during and after orthotopic liver transplant due to hemodilution, immunologic reactions, and 30–55% reduction of levels during liver reperfusion secondary to entrapment in the liver [125, 129, 130]. Platelet levels constantly change and

additionally platelet function is also altered. These alterations in platelet function are due to the hyperfibrinolytic state after reperfusion, increased levels of tissue plasminogen activator released from the graft [71, 125, 131–134], and increased platelet activation after transplant. Factors indicating platelet activation and degranulation have been detected in serum and graft samples at elevated levels [125, 127, 129, 135]. Altered platelet function excludes a simple serum platelet count cutoff as the best way to guide transfusion thresholds.

Platelets should be used to minimize RBC transfusions, as there is a clearly demonstrated association between transplant complications and increased RBC transfusion [106, 136–139]. The known risks of TRALI and TACO are clearly recognized; however, the risks of platelet transfusion during liver transplantation are less well described. With improved surgical technique and perioperative strategies to minimize bleeding, the results of older studies that found an association between large volume platelet transfusions and poor survival after surgery are less helpful [106]. A recent retrospective study by Boer et al. identified RBC and platelet transfusions as risk factors compromising 1-year survival in first-time liver transplant patients, independent of markers for worse disease, such as model for end-stage liver disease (MELD) score [136]. This study evaluated 433 liver transplant patients and analyzed 26 variables, showing that 1-year survival risk was dose-related to platelet transfusion with a hazard ratio of 1.377 per unit of platelets transfused ( $P=0.01$ ) [136]. Platelet transfusion also appeared to have a negative impact on graft survival (and not only mortality), but this association was not present on multivariate analyses [136]. It is difficult to determine causality for poor outcomes of transplantation on platelet transfusion alone using retrospective studies. However, currently these results should be considered when administering platelets during liver transplantation. We recommend that platelet transfusion should be reserved for active bleeding and low platelet count and not be used prophylactically.

Patients with platelet counts greater than  $75 \times 10^9/l$  and an INR  $<1.5$  are at no increased



risk for bleeding during invasive procedures. Patients with a platelet count  $>50 \times 10^9/l$  without evidence of bleeding should not be transfused perioperatively, as platelet levels are not correlated with bleeding risk in invasive procedures such as paracentesis [110, 140]. Dosing of platelets should be tailored for each individual patient and preferably guided by bleeding, TEG, and whether or not a consumptive platelet process is present. Endogenously produced platelets typically survive around 10 days; however, transfused platelets do not last this long, with further reduced life spans if platelet consumption is present. Patients with platelet levels below  $100 \times 10^9/l$  have shorter platelet life spans when compared to patients with levels greater than this [141].

A single dose of random donor platelets contains approximately  $3 \times 10^{11}$  platelets, suspended in 50–70 ml of plasma. The optimal dose specific to liver patients has not been determined and often has more to do with individual patient requirements and resource availability as platelets are a limited resource [142–147]. The standard dose prescription for platelets is 10 ml/kg, with a maximum dose of five random donor platelet units. Single donor platelet apheresis units contain at least  $300 \times 10^9$  platelets, suspended in 200–400 ml of plasma [148, 149]. The hematology literature has found little difference in efficacy between different platelet preparations prepared from random donors versus those collected by apheresis [150, 151]. However, platelets obtained by apheresis are received from one donor and decrease the incidence of immune-mediated refractoriness. They are used preferentially in patients who may be refractory to random donor platelet units. Platelet transfusion is recommended when patient levels drop below the level of  $50 \times 10^9/l$  or if platelet count cannot be obtained and there is evidence of microvascular bleeding and coagulopathy.

### **Procoagulant Drugs and Liver Transplantation**

A limited amount of information is available on pharmacologic alternatives to blood product use.

Agents in this class of therapy target hemostasis, coagulation, and fibrinolysis and include DDAVP, aprotinin, lysine analogues, and recombinant-activated factor VII (rFVIIa).

### **Desmopressin**

DDAVP or 1-deamino-8-D-arginine is a synthetic analogue to vasopressin. It acts by releasing factor VII and VWF concentrations from endothelial storage pools into the serum. The effect is rapid and short-lived and has a decreased response over repeated use of the drug without adequate time for storage pools to re-accumulate. This agent has been used successfully in the treatment of minor to moderate bleeding during surgical procedures for patients with von Willebrand deficiency or hemophilia A. Dosing is usually  $0.3 \mu\text{g/kg}$  intravenously infused over 20 min.

There is very little literature supporting its use during a major operation such as liver transplantation; however, intranasal DDAVP was shown to be equally effective as blood product transfusion in achieving hemostasis in cirrhotic patients undergoing tooth extraction [152]. In this study, patients were matched evenly and there was no difference between groups transfused with platelets versus those given DDAVP, including MELD score, number of tooth extractions, and coagulation profile. For mild to moderate procedures like tooth extraction, patients receiving DDAVP received no rescue transfusions after the procedure, whereas one platelet-transfused patient required rescue transfusion [152]. Outcomes were considered the same between the two groups.

While results with DDAVP have been favorable in cardiac surgery patients on cardiopulmonary bypass [153, 154], recent randomized control trials did not show a beneficial effect of the agent in liver resection patients [155]. While DDAVP should provide some theoretical benefit to liver disease patients undergoing transplant surgery, we can currently not recommend to use DDAVP routinely as a primary hemostatic agent.

## Aprotinin

Aprotinin is an antifibrinolytic and a serine protease inhibitor. Aprotinin has an effect on a broad variety of systems and of most interest can neutralize trypsin, plasmin, and tissue and plasma kallikrein [156], helping to limit the hyperfibrinolytic state that occurs during liver transplantation. Early, nonrandomized control trials in Europe using aprotinin prophylactically in liver transplant patients showed promising results. However, further randomized studies failed to show significant benefit in blood transfusion rate between aprotinin-treated and control patients [157, 158]. The recent European multicenter placebo-controlled study tested aprotinin using doses that inhibit kallikrein and those that inhibit plasmin. The results were inconsistent, and the study concluded that perhaps surgical technique or perioperative interventions had more impact than the use of aprotinin [159]. Other studies have indicated a significant reduction in blood loss and transfusion requirements of around 30–40% with the additional benefits of improved hemodynamic stability, decreased use of vasoactive substances, and improved one-month graft survival with the use of aprotinin [156].

While aprotinin has been used widely in many transplant centers across Europe, appropriate dosing is subject to major debate. In general, it seems that improvements in operative and perioperative technique have contributed more greatly to reducing blood loss in patients undergoing liver resection. A Canadian randomized trial of cardiac surgical patients found an increased mortality with the use of aprotinin, and as a consequence the manufacturer has withdrawn aprotinin from the market.

## Lysine Analogues

Epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA) are synthetic analogues of the amino acid lysine, which competitively block lysine-binding sites on plasminogen to limit hyperfibrinolysis. The Cochrane group

meta-analysis found aprotinin and lysine analogues to have a nearly similar effect on limiting blood transfusion [160], and a recent randomized controlled trial among liver transplant patients failed to demonstrate a difference between TXA and aprotinin with regard to transfusion use [137]. EACA was first shown by Kine et al. to decrease the amount of residual bleeding during the hyperfibrinolytic state after liver transplantation in 20 of 97 liver transplant patients [161]. A standard dose of 1 g of EACA bolus was used. A more recent study compared EACA, TXA, and placebo used as prophylaxis to decrease transfusions during and after transplant and found that TXA was beneficial over EACA and placebo with no difference in RBC transfusion sparing effect between EACA and placebo [162]. Dosage for TXA has varied greatly, and different studies have shown reduction in transfusion at dosages of 10 and 40 mg/kg<sup>-1</sup>/h<sup>-1</sup> [162, 163].

Limited research of both of these agents makes it difficult to recommend specific doses, and further trials should be conducted. Also, comparative data is extremely limited between these two agents, and it is difficult to recommend using one over the other.

## Recombinant Factor VIIa

Recombinant factor VIIa (rFVIIa) has been approved for use in hemophilia patients with inhibitors in both surgical and nonsurgical settings. The agent is very similar to endogenous FVIIa and is thought to enhance thrombin generation at sites of endothelial injury. Two mechanisms have been suggested in rFVII-driven thrombin generation: A high concentration of tissue factor (TF) and rFVIIa accumulate at the site of vascular damage [164], which in turn activates factor Xa and triggers thrombin generation [165, 166]. The second proposed mechanism, rFVII, binds directly to the platelet surface, which then activates factor X [167]. The normal FVII:FVIIa ratio in the serum is 100:1 (10 and 0.10 nmol/l, respectively), and with rFVII infusion, FVIIa levels increase 100-fold to 3–20 nmol/l [168]. The agent seems to be well

tolerated, and widespread activation of coagulation resulting in DIC has not been noted. rFVII has been useful in off-label uses such as controlling bleeding in trauma, obstetrical complications, and surgical patients with complex coagulation disorders [169, 170].

rFVII corrects vitamin K-dependent decreases of coagulation factors [171, 172]. This has led to its use in liver patients with a depletion in vitamin K-dependent coagulation factors. rFVII is able to effectively reverse prolonged prothrombin time (PT) in cirrhotic patients without active bleeding [173], and Lisman et al. concluded that a single dose of rFVIIa could lead to stable clot formation in cirrhotic patients [174].

Results have been mixed when using rFVIIa in liver transplant patients. There are multiple case reports and series reporting efficacy of rFVIIa at varying doses such as 100 [175], 80 [176] or 68.4 µg/kg [177]. However, better information is derived from several randomized control and retrospective case control studies. Two retrospective case control studies concluded that administration of rFVIIa preoperatively decreased blood transfusion requirements in transplant patients [178, 179]. The dose of rFVIIa in one of these studies of 22 patients was 58 µg/kg. Two randomized control studies failed to show efficacy of rFVIIa in reducing transfusion requirements while using 20, 40, 60, 80, or 120 µg/kg bolus doses of rFVIIa when compared to placebo [180, 181]. A more recent randomized, double-blind trial found that patients undergoing orthotopic liver transplant who received 40 µg/kg of rFVIIa perioperatively required fewer transfused units of blood compared to placebo [182].

As we previously stated, prothrombin time does not necessarily correlate with improved coagulation profile in liver disease, and correction of prothrombin time does not necessarily decrease transfusion rate or improve outcome. While it seems that more randomized, controlled studies should be implemented, the current consensus European guidelines on the use of rFVIIa during liver transplantation or resection recommends that rFVIIa not be used routinely (grade B evidence) [183].

## Topical Agents in Hemostasis

Several types of agents are available for intraoperative topical application to stimulate hemostasis. Products that provide matrix for coagulation to occur such as collagen and cellulose, those that mimic coagulation like fibrin sealants, and products that combine the use of endogenous and exogenous coagulation factors are currently used during liver transplant surgery [133, 184]. Results are mixed showing that while there may be a decrease in blood transfusion intra- and perioperatively, there may actually be no mortality benefit [185, 186]. A 2003 Cochrane review [187] and much of the endoscopic literature supports the utility of fibrin sealants; however, a randomized study of 300 liver resection patients found no difference in total blood loss, transfusion requirement, or morbidity with or without the product.

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## Summary

Coagulation management is a fascinating and rapidly developing subfield in transplant hepatology. It extends across all fields of medicine presenting challenges for anesthesiologists, hepatologists, and liver transplant surgeons. As our understanding of the intricate imbalances comprising coagulopathy in the liver disease patient further develops, we will more effectively be able to perform invasive procedures and care for the liver transplant patients. As this field continues to develop, we owe it to one another as colleagues and to our patients to continue challenging present thinking. It is this spirit that will bring us to the new appreciation for the multifaceted and complex approach to coagulation disorders in liver disease.

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# Physiology, Prevention, and Treatment of Blood Loss During Liver Transplantation

# 14

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## Introduction

Historically, bleeding was one of the major challenges during liver transplantation. The first patient receiving a liver transplant in 1963 exsanguinated during the procedure [1], and massive perioperative blood loss remained a major clinical challenge until the 1980s. Most, if not all, liver transplant procedures required transfusion of blood products in those days, and transfusion requirements could exceed 100 units of red blood cell concentrates (RBCs), whereas mean transfusion requirements were around 20–40 units of blood products (RBC, fresh frozen plasma, platelet concentrates, cryoprecipitate) [2, 3]. Blood products were, and still are, costly and accounted for a significant part of the total costs of liver transplantation [4]. In the last 15–20 years, massive blood loss during liver transplantation has become rare, and a significant proportion of patients can nowadays be transplanted without any requirement for blood transfusion [5]. Improvements in surgical technique and anesthesiological management have contributed to this major reduction in blood loss, but in addition a better understanding of the nature of the abnormalities in the hemostatic system has led to a

more rational approach to the prevention of bleeding. Nevertheless, severe and uncontrollable bleeding still occurs occasionally and has to be treated appropriately.

This chapter will discuss causes of bleeding during liver transplantation, strategies to prevent blood loss, and treatment possibilities in case major bleeding does occur.

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## Hemostatic Alterations in Liver Disease and During Liver Transplantation

The liver is the site of synthesis of most proteins involved in initiation, propagation, and regulation of both coagulation and fibrinolysis. Consequently, major alterations in the levels of hemostatic proteins occur in patients with liver disease (Table 14.1) [6, 7]. In addition, a substantially decreased platelet count is present in a large proportion of patients, which may be accompanied by platelet function defects [8, 9]. Routine diagnostic tests of hemostasis such as platelet count, prothrombin time (PT), and activated partial thromboplastin time (APTT) are consequently frequently abnormal in a patient with liver disease. Abnormal test results have long been interpreted as suggestive of a bleeding tendency [10]. Recent advances in the understanding of both clinical and laboratory aspects of hemostasis in liver disease have led to an alternate view of the status of the hemostatic system in these patients [11]. We have coined this alternate view the “concept of rebalanced hemostasis” in patients

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**Table 14.1** Alterations in the hemostatic system in patients with liver disease that contribute to bleeding (left) or counteract bleeding (right)

Changes that impair hemostasis	Changes that promote hemostasis
Thrombocytopenia	Elevated levels of von Willebrand factor (VWF)
Platelet function defects	Decreased levels of ADAMTS-13
Enhanced production of nitric oxide and prostacyclin	Elevated levels of factor VIII
Low levels of factors II, V, VII, IX, X, and XI	Decreased levels of protein C, protein S, antithrombin, $\alpha_2$ -macroglobulin, and heparin cofactor II
Vitamin K deficiency	Low levels of plasminogen
Dysfibrinogenemia	
Low levels of $\alpha_2$ -antiplasmin, factor XIII, and TAFI	
Elevated tPA levels	

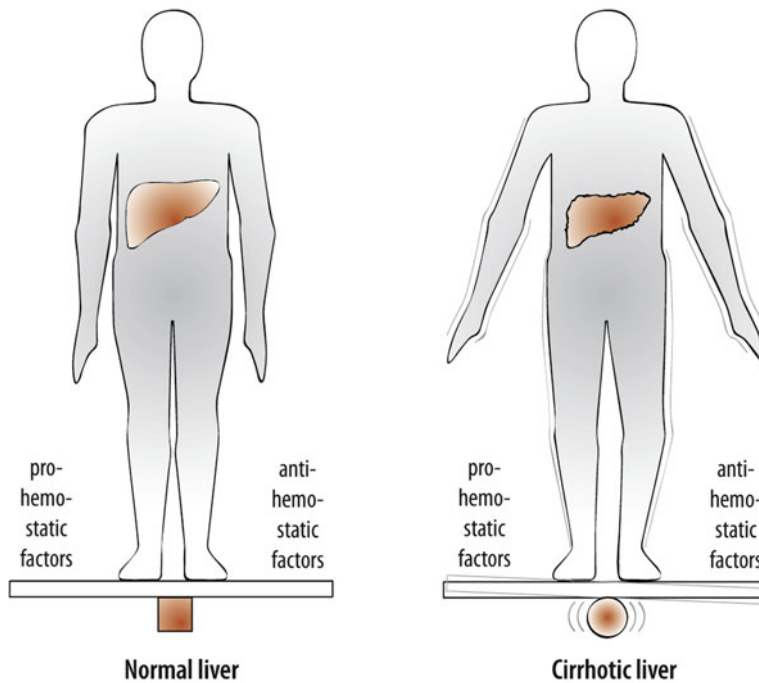
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with liver disease. The rebalanced hemostasis theory states that with liver disease, the hemostatic system is in a rebalanced status due to concomitant alterations in both pro- and anticoagulant pathways (Fig. 14.1). This balance is present in patients who may have severe abnormalities in routine hemostasis tests such as the PT (either expressed as seconds or as international normalized ration [INR]), APTT, and platelet count indicating that these tests do not reflect the true hemostatic status of patients with complex alterations of hemostasis, for example, seen with liver disease [10]. Patients with liver disease thus do not necessarily have a hemostasis-related bleeding tendency to a degree that is suggested by the low platelet count and/or prolonged PT. Many bleeding complications that occur are unrelated to deranged hemostasis, but rather related to complications of portal hypertension, such as esophageal varices [12, 13]. However, in patients with liver disease, the hemostatic balance is more easily disturbed as compared to healthy individuals, which may lead to bleeding but also to thrombotic complications (summarized in Table 14.1) [11, 14, 15]. Importantly, current laboratory tests, including many newly developed

point-of-care tests, fail to predict which patients are at risk for either bleeding or thrombosis.

A thorough review of the pathophysiology of coagulation in liver disease and during liver transplantation is found elsewhere (Chapter 13) in this book.

During liver transplantation additional changes in the hemostatic system occur. During the anhepatic phase there is a lack of synthesis of hemostatic proteins, but more importantly, these proteins (activated hemostatic proteins and protein-inhibitor complexes) accumulate in the circulation due to a lack of clearance by the liver. As a result, disseminated intravascular coagulation can develop, resulting in consumption of platelets and coagulation factors and accompanied by secondary hyperfibrinolysis. During reperfusion, hyperfibrinolysis may further develop as a consequence of release of tissue-type plasminogen activator (tPA) from the graft [16–18]. The degree of hyperfibrinolysis is related to the severity of ischemia/reperfusion injury of the hepatic endothelium, the source of tPA upon graft reperfusion [16, 19]. Moreover, the liver graft may release heparin-like substances which can inhibit coagulation [20]. In addition, hypothermia, metabolic acidosis, and hemodilution may adversely affect the hemostatic status during liver transplantation [5]. Although the additional changes in the hemostatic system during liver transplantation have long been held directly responsible for the bleeding seen in these patients, accumulating evidence suggests that many liver transplant recipients may remain in hemostatic balance throughout the procedure [10, 21, 22]. The hemostatic balance is clinically evident by an increasing proportion of patients that can be transplanted without any blood transfusion [5, 23–26]. Moreover, recent laboratory data indicate rebalanced platelet-mediated hemostasis as a result of a hyperreactive von Willebrand factor system, which is responsible for attachment of platelets to damaged vasculature [27, 28]. Despite profoundly prolonged routine laboratory tests of coagulation (PT, APTT), the coagulation potential appears preserved or even hyperreactive throughout the transplant procedure when tested with modern thrombin generation tests [21]. Finally, with improvements in



**Fig. 14.1** The concept of rebalanced hemostasis in patients with liver disease. In healthy individuals (left), hemostasis is in a solid balance. In patients with liver disease (right), concomitant changes in pro- and antihemo-

static pathways result in a “rebalance” in the hemostatic system. This new balance, however, presumably is less stable than the balance in healthy volunteers and may thus more easily tip towards either bleeding or thrombosis

graft preservation and the avoidance of prolonged cold ischemia times, hyperfibrinolysis is nowadays less frequently encountered.

Despite the observation that the hemostatic balance is frequently relatively well preserved during liver transplantation, there are individual patients with severe and uncontrollable bleeding that require substantial amounts of blood products. Causes of these bleeding complications and treatment possibilities will be discussed in this chapter. In addition, there is increasing recognition of the potential for perioperative thrombotic complications. A discussion on diagnosis and treatment of thromboembolic complications during and after liver transplantation is discussed elsewhere (Chapter 13) in this book.

### Causes of Bleeding During Liver Transplantation

Liver transplantation is a lengthy procedure with extensive surgical wound surfaces including transection of collateral veins. Bleeding

complications that may occur during the procedure are often due to surgical causes, and meticulous surgical hemostasis is important to limit blood loss. In addition, the presence of portal hypertension may contribute to bleeding and as will be discussed below. Avoidance of aggravation of portal hypertension by fluid restriction and maintenance of a low central venous pressure (CVP) may be required to reduce pressure-associated bleeding complications [23]. There is evidence that a liberal fluid management (including the liberal use of blood products such as fresh frozen plasma) may aggravate the bleeding tendency of patients during liver surgery by increasing CVP and splanchnic venous pressure [5, 23, 29–32]. Strategies to avoid this will be discussed below. Dysfunctional hemostasis may contribute to bleeding in some patients, and multiple potential causes may be present. Firstly, hypothermia, metabolic acidosis, and low ionized calcium levels directly affect the hemostatic system, and prevention and treatment of these complications is important to prevent bleeding [5]. Secondly,



although the role of thrombocytopenia and coagulation factor defects in bleeding during liver transplantation has never been convincingly shown, it has been established that hyperfibrinolysis is associated with an increased bleeding risk [16, 33, 34].

Earlier studies have suggested that patients with a more severe disease are at an increased bleeding risk; however, more recent studies have failed to provide proof for a correlation between disease severity and blood loss [35]. Even more, it has been demonstrated that over time a progressive decrease in transfusion requirements is observed despite a progressive increase in MELD score of the recipients [26]. The most important predictor of blood product use may be the center, or the surgical or anesthesiology team, which may indicate that surgical and anesthesiological factors rather than a defective hemostatic system are the primary cause for perioperative bleeding [36, 37].

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## Prophylactic Strategies to Prevent Blood Loss

Multiple reasons to support an active attitude towards prevention of bleeding during liver transplantation exist. Firstly, a dry surgical field is beneficial for the surgeon, and lack of bleeding complications will shorten the procedure. Second, excessive blood loss is associated with a worse outcome for multiple reasons, one being the direct detrimental effects of blood product transfusion [38–41]. Finally, reduction of transfusion requirements as well as reduction of the duration of surgery will save costs. Multiple prophylactic strategies to reduce or avoid bleeding exist, and the pros and cons of these strategies will be discussed in the following paragraphs.

## Blood Products

In the early days of liver transplantation, prophylactic administration of blood products prior to the procedure was the standard of care. It was believed that (partial) correction of abnormal

hemostasis tests prior to surgery would improve the overall hemostatic status of the patients, resulting in a reduced bleeding risk. Consequently, liver transplant procedures routinely started with administration of fresh frozen plasma (FFP) to correct the prolonged PT/APTT, platelet concentrates to reverse thrombocytopenia, and cryoprecipitate to increase the circulating level of fibrinogen [5]. Also, administration of RBCs to reverse anemia is believed to improve hemostasis by virtue of the pivotal role of red blood cells in platelet attachment to the damaged vasculature in flowing blood [42]. During the procedure, frequent monitoring of the hemostatic status by PT, APTT, platelet count, and fibrinogen measurements is performed to guide additional administration of blood products. Alternatively, thromboelastography may be used to guide transfusion [43–45].

Although prophylactic administration of blood products prior to and during liver transplantation is still common practice in many centers, little evidence for the efficacy of such a strategy exists, and there may be valid arguments against prophylactic administration of blood products [5, 12, 32, 46]. Administration of blood products is associated with the potential for volume overload and inevitably results in elevation of CVP and splanchnic venous pressure. This is particularly true in critically ill transplant recipients with a hyperdynamic circulation with increased cardiac output and active shunts between the systemic and portal venous circulation. In a patient with portal hypertension, elevation of CVP by administration of blood products may thus paradoxically induce bleeding by pressure effects rather than decreasing bleeding risk by improving the hemostatic status [30, 31]. Furthermore, administration of blood products is associated with adverse effects and affects morbidity and mortality [23, 24, 47–50], and normalization of routine laboratory tests is hardly ever achieved [51].

Rather than prophylactic administration of blood products in a patient that is not (yet) bleeding, a wait-and-see policy is increasingly used. In this scenario, the anesthesiologist and surgeon accept (profoundly) abnormal PT, APTT, platelet,

and fibrinogen levels, as they do not accurately reflect the hemostatic status and commence with the procedure only to initiate blood product transfusion in case of active bleeding complications [5, 32, 52]. Since abnormal preoperative hemostasis tests do not appear to predict perioperative bleeding risk and many centers can nowadays transplant a large number of patients without any blood transfusions, this wait-and-see policy appears justified [5, 23–26]. When active bleeding does occur, administration of blood products may be guided by laboratory tests or thromboelastography [43, 44]. Specifically, a profound thrombocytopenia in a bleeding patient may be reason for platelet transfusion, whereas a prolonged PT or INR may be reason to transfuse FFP. Furthermore, hypofibrinogenemia may prompt transfusion of fibrinogen concentrate or cryoprecipitate, whereas evidence of hyperfibrinolysis on the thromboelastograph may be a reason to start antifibrinolytic therapy. There is no clear evidence that laboratory-test-based transfusion is optimal in the context of liver transplantation. And, for example, whole blood transfusion is by some as an alternative. No consensus on on-demand transfusion strategies exists, and variability between centers is high [36, 40]. The ratio of blood products administered in bleeding patients is likely important, and some authors have even suggested that whole blood transfusion may be more appropriate than transfusion of individual blood components [53].

## Pharmacological Agents

A major advance in management of bleeding complications in liver transplantation has been the use of antifibrinolytic agents. The serine protease inhibitor aprotinin has been shown to reduce transfusion requirements during liver transplantation by around 30–50 % [33, 34, 54], and these findings also indicate that the hyperfibrinolytic status that can accompany liver transplantation is clinically relevant. Aprotinin not only inhibits the fibrinolytic protease plasmin but also has anti-inflammatory properties by virtue of inhibition of kallikrein and the protease-activated receptor type 1 [55].

Administration of aprotinin in liver transplant patients does not appear to be associated with side effects such as thrombosis or renal failure [56–58], which have been reported to occur in cardiac surgery. Despite the apparent excellent risk/benefit profile of aprotinin in liver transplantation, safety concerns in cardiac surgery have led to the withdrawal of aprotinin from the market both in the USA and Europe. The lysine analogues tranexamic acid and  $\epsilon$ -aminocaproic acid are potentially suitable alternatives for aprotinin [5]. Although both drugs are widely used, only tranexamic acid has been shown to reduce transfusion requirements in randomized studies [59–61]. It has to be noted that both tranexamic acid and  $\epsilon$ -aminocaproic acid are potent antifibrinolytic agents but lack the anti-inflammatory properties of aprotinin.

Other procoagulant drugs may also be beneficial in reducing bleeding. An initial non-controlled trial suggested recombinant factor VIIa (rFVIIa) to reduce transfusion requirements during liver transplantation [62, 63]. However, two subsequent randomized controlled trials did not show any benefit from rFVIIa administration, despite a profound correction of the PT [64, 65]. These findings illustrate that normalization of the PT does not translate in a reduction of bleeding risk, which is in line with the findings that the PT does not predict bleeding risk, and with the laboratory finding that the PT does not accurately reflect the hemostatic status in a patient with liver disease. Although prophylactic administration of rFVIIa does not reduce perioperative blood loss, rFVIIa may be an option as “rescue agent” in patients with intractable bleeding.

Improvement of platelet function parameters, in particular shortening of the bleeding time by administration of 1-deamino-8-D-arginine vasopressin (DDAVP), has not been shown to translate into clinical improvement of hemostasis. Several studies showed no effect of DDAVP on variceal bleeding or on blood loss in patients undergoing partial hepatectomy or liver transplantation [66], indicating that correction of the bleeding time may not necessarily result in improvement of hemostasis.

A pharmacological prohemostatic strategy that may have potential but have not yet been

tested in adequately powered clinical studies is the use of prothrombin complex concentrates (PCCs) to improve the coagulation status. The theoretical advantage of PCCs over FFP is the low volume of PCCs, which prevents the inevitable rise in CVP and splanchnic venous pressure that is accompanied by FFP infusion. On the other hand, PCCs only contain a selection of coagulation factors and its use may be associated with a thrombotic risk. Future randomized clinical trials (RCTs) will have to demonstrate safety and efficacy of PCCs in reducing bleeding during liver transplantation.

## Fluid Restriction

Emerging evidence indicates that the hemostatic balance during liver transplantation is relatively well maintained [10] and that portal hypertension, fluid overload, and hyperdynamic circulation are more important determinants of perioperative bleeding than possible coagulation defects [23, 67, 68]. Liver disease and portal hypertension are associated with increased plasma volume and disturbed cardiac function, and the administration of fluids results in a further increase in portal and CVP, promoting rather than preventing bleeding tendencies when surgical damage is inflicted [12, 29–32, 46, 67]. Avoidance of fluid overload by a very conservative transfusion policy and by restriction of infusion of colloids and/or saline thus likely reduces bleeding risk. A recent RCT compared a policy of restrictive transfusions and low CVP with a liberal transfusion policy and found that the former policy leads to a significant reduction in intraoperative blood loss and transfusion requirement, especially during the preanhepatic phase [69]. Liberal use of blood products, including preoperative correction of abnormal laboratory test values may thus even be counterproductive, as these blood products increase venous pressure and thereby “fuel the fire.” Some groups have taken more drastic steps to maintain a low perioperative CVP by combining fluid restriction protocols with preoperative phlebotomy [23, 68, 70]. One center has reported that ~80 % of patients could be transplanted without

the requirement for any transfusion when using fluid restriction in combination with preoperative phlebotomy [68]. It is important to realize that acceptance of a low hematocrit (20–25 %) is essential in such a strategy. A major concern regarding the use of fluid restriction protocols is the risk of complications such as air embolism, systemic tissue hypoperfusion, and renal failure [24, 68, 71, 72]. Although one non-controlled study showed an increase in renal failure using a low CVP strategy [72], a number of other studies, including one RCT, have concluded that fluid restriction during liver transplantation is safe and does not lead to an increased incidence of postoperative renal failure [23, 68, 69].

## Surgical and Anesthesiological Techniques

In general, the experience of the surgical team is an important determinant of perioperative bleeding, but specific improvements in surgical technique have also been instrumental in reducing blood loss [5, 32]. The introduction of the use of venovenous bypass in the 1980s has presumably contributed to a reduction of blood loss, as this technique results in avoidance of major hemodynamic changes during the anhepatic phase [73]. Subsequent introduction of the piggyback technique has led to a significant further decline in transfusion requirements [74, 75]. A major advantage of the piggyback technique with respect to blood loss is the avoidance of dissection of the retroperitoneum, which avoids dissection of multiple collateral veins in this area. More importantly, the piggyback technique has enabled reduction of intraoperative fluid load [74, 75].

Anesthesiological interventions to prevent excessive bleeding are maintenance of body temperature, pH, and ionized calcium level. For example, avoidance of hypothermia is accomplished by heating blankets and administration of fluids at 30° C [5, 72]. Frequent determination of serum-ionized calcium levels and aggressive replacement is key especially when large amount of RBCs are transfused. Citrate that acts as an anticoagulant in RBC by chelating calcium is

metabolized by the liver. With liver disease and especially during the anhepatic phase, plasma citrate levels may be high. Frequent calcium replacement is often required to maintain adequate ionized calcium levels.

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### Laboratory Monitoring of Bleeding and Transfusion

Traditionally, laboratory tests such as the PT, APTT, platelet count, fibrinogen level, and hematocrit were used to guide transfusion. Cutoffs for transfusion differ substantially from center to center, and it is becoming evident that there is little evidence to support blood product transfusion at certain laboratory thresholds (e.g., a platelet count below  $50 \times 10^9/L$  or a PT > 1.5–2 times the upper limit of normal) in the absence of active bleeding [32, 33, 40, 46]. Even in the presence of active bleeding, target laboratory values to be achieved have never been thoroughly established. However, aiming for a hemostatic profile of platelet count  $>50 \times 10^9/L$ , PT < 1.5–2 times the upper limit of normal, and a fibrinogen level of 1–2 g/L appears reasonable. Instead of using these classic laboratory values, the use of thromboelastography has been suggested to result in a more rational use of blood product transfusion although definitive data are lacking. The thromboelastography tracing can distinguish between a specific platelet or coagulation defect and is the only available rapid test that can indicate hyperfibrinolysis. Thromboelastography tracing can thus guide platelet, FFP, fibrinogen transfusion, and possibly antifibrinolytic therapy [43, 45]. Some centers use thromboelastography for prophylactic transfusion of blood products, whereas other centers only transfuse blood products in case of active bleeding. There are an increasing number of variations of the thromboelastograph on the market which differ in coagulation trigger (none, tissue factor, kaolin) or in additive that specifically neutralize specific components of coagulation (heparins, platelets, fibrinolysis). The true value of native or variant thromboelastography in guiding transfusion or predicting bleeding remains to be established.

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### Adverse Events of Blood Products

A large intracenter variability in blood product use during liver transplantation exists [36]. Part of this variability may be explained by differences in the surgical experience of the teams, but an important contributor to this variability is the lack of uniformity of transfusion protocols. An important difference between centers is the choice between prophylactic administration of blood products based on pre- and perioperative laboratory parameters and an on-demand approach in which blood products are only transfused when active bleeding occurs. When deciding to transfuse blood products, one has to weigh the possible (and in liver transplantation often uncertain) benefits against potential adverse events.

A number of adverse effects associated with blood product use are well recognized [48, 76]. Although the risk of viral transmission has not yet been fully eliminated, the chance of contracting a virus through blood product transfusion is extremely low, at least in the western world [39, 77]. Transmission of bacteria can still occur, in particular with transfusion of platelet concentrates which are stored at room temperature, which increases the risk of bacterial growth [49, 78, 79]. Hemolytic and allergic transfusion reactions have been well described but are fortunately relatively rare [76]. A recently recognized risk of blood product transfusion is transfusion-related acute lung injury (TRALI), an antibody-mediated transfusion reaction that is rare, but may be fatal [80]. The risk of TRALI appears highest with the use of FFP, in particular FFP from female donors [81–83]. Blood product administration results in depression of the immune response, which in theory may be beneficial with liver transplantation as it may contribute to prevention of rejection. However, transfusion-related immune modulation also increases the incidence of postoperative infections. Finally, fluid overload is an important potential complication of transfusion of blood products [50].

The introduction of transfusion-free liver transplantation has allowed us the assessment of the effects of blood product transfusion. Several

studies have demonstrated that blood product transfusion is associated with increased morbidity and mortality even after thorough adjustment for potential confounders [38, 84, 85]. Adverse events of transfusion are still observed at low doses of blood products. Furthermore, a dose effect has been demonstrated, indicating that in patients who received some blood products during the transplantation, further minimization of transfusion may be of the utmost importance [5].

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### **Conclusion: A Rational Approach to Prevention or Treatment of Bleeding**

Increasing laboratory evidence suggests that the hemostatic system in a patient with liver disease is in a rebalanced situation and consequently much more competent than suggested by routine laboratory tests such as the PT and platelet count. During liver transplantation, the hemostatic status appears to remain in balance, when tested by more sophisticated laboratory tests. These findings, combined with the clinical observations that an increasing number of centers report that a substantial number of patients can undergo a liver transplantation without any blood transfusion, suggest that dysfunctional hemostasis is not necessarily the prime cause for perioperative bleeding. Nevertheless, occasionally patients with dysfunctional hemostasis as the primary cause for excessive blood loss are encountered, and hyperfibrinolysis is often observed in these patients.

Clinical experience suggests that portal hypertension, fluid overload, and the hyperdynamic circulation are much more important determinants of bleeding than a dysfunctional hemostatic system. Volume contraction therefore may be vital in avoiding bleeding during transplantation. Volume contraction is achieved by restrictive use of fluids and blood products, avoidance of fluid overload, and a very restrictive use of blood products. Preoperatively, correction of a prolonged PT or decreased platelet count is not required and may even be counterproductive as transfusion of these products can result in elevation of the CVP and splanchnic venous pressure. Perioperatively,

transfusion of blood products should be restricted to situations in which active bleeding not of surgical origin occurs. Transfusion may be guided by laboratory values or thromboelastography, although little evidence for the efficacy of this strategy exists. The restrictive use of blood products may also be of benefit for long-term outcome, since multiple studies suggest that transfusion in liver transplant recipients is associated with increased morbidity and mortality. Antifibrinolytics may be used to reduce fibrinolytic bleeding, either prophylactically or on-demand, except in patients with a high thrombotic risk, such as patients with cholestatic disease who demonstrate hypercoagulability on the thromboelastograph. Finally, the acceptance of low hematocrit values (20–25 %) as part of a restrictive transfusion policy appears to be safe.

Although transfusion thresholds and protocols have not been established, it appears reasonable that, in case of larger transfusion requirements, RBC, FFP, and platelets should be concomitantly administered in physiological ratios. On-demand use of antifibrinolytics may be considered, especially with evidence of hyperfibrinolysis on thromboelastography. Also, the use of rFVIIa may be considered, but little data on efficacy and safety are available. This drug is also extraordinarily expensive. Additional studies on the optimal management of intractable bleeding during liver transplantation are required; however, it will be difficult to achieve adequate power for these studies.

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## Introduction

According to the United Network for Organ Sharing (UNOS) data, as of November 2012, 4,040 liver transplants have been performed with 16,053 patients on the waiting list [1]. The advances in patient and donor selection, surgical techniques, immunosuppression, organ preservation, and critical care management have made lifesaving liver transplantation possible to those with irrevocable liver damage and acute liver failure. Yet the scarcity of organs continues to be a major obstacle to greater application of liver transplantation (Fig. 15.1).

This disequilibrium between supply and demand has forced transplant programs to use more marginal donors to fulfill the ever-increasing organ demand. Though there is no consensus, advanced donor age, steatotic livers, donation after cardiac death (DCD), livers with seropositivity

for hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as occult malignancy constitute extended criteria donor (ECD) factors and have been considered contraindications for transplant until recently (Table 15.1). Many single-center experiences have illustrated that allocation of such livers provides an expansion of the donor pool and reduction of the wait-list mortality at the projected cost of inferior outcomes. In this chapter, we will highlight these “marginal” donor factors and the strategies that have enabled the use of these organs for select recipients.

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## Donor Demographics and Graft Outcome

### Age

Advanced donor age was previously thought to be a relative contraindication to transplantation due to increased risk of poor graft function. Evidence indicates that liver grafts from donor age 70 or greater have similar outcomes to that of younger donors [2]. Accordingly, the UNOS data has shown a steady increase in the upper age limit for livers used in transplantation. In 1995, 20.6% ( $n=795$ ) of the transplanted livers were above the age of 50, which has increased to 31.2% ( $n=1,244$ ) in 2010 [1].

Elderly donors need to be assessed on a case-by-case basis. Livers from donors with advanced age tend to be smaller, fibrotic, and less compliant although these morphologic changes do not

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**Fig. 15.1** Number of transplants and size of active waiting list (Source: 2009 OPTN/SRTR Annual Report)

**Table 15.1** Extended criteria donor characteristics that can affect severity of preservation injury in liver transplantation

Elderly donors (>65 years)	<ul style="list-style-type: none"> <li>More susceptible to ischemic endothelial injury</li> <li>Decreased ATP availability on reperfusion</li> <li>Less tolerant of prolonged cold ischemia</li> <li>May have decreased synthetic function and regenerative capacity</li> </ul>
Underlying liver histopathology	<ul style="list-style-type: none"> <li>Macrosteatosis → predisposes to early allograft dysfunction and primary nonfunction</li> <li>Ischemic changes/necrosis</li> <li>Significant alcohol abuse → steatohepatitis</li> <li>Hepatitis B and C activity/portal inflammation</li> <li>Fibrosis → may be associated with hepatitis C or alcohol abuse and may affect long-term outcomes</li> </ul>
Ischemia associated with donor injury	<ul style="list-style-type: none"> <li>Donation after cardiac death → frequently profound ischemia injury</li> <li>High-dose vasopressors</li> <li>Prolonged or uncorrected hypoxemia or acidosis</li> </ul>
Biochemical changes	<ul style="list-style-type: none"> <li>Hypernatremia</li> <li>Rising transaminases or bilirubin</li> </ul>

necessarily equate to impaired functional capacity. The liver is known to be resilient when facing the forces of aging as well as possesses functional reserve and regenerative capacity that allow it to function effectively. Cumulative experiences with advanced age donors relate excellent outcomes especially with minimal cold ischemic time (CIT) and legitimize the use of such organs in this era of organ shortage and aging donor population [3–5]. Careful attention by the donor surgeon is paramount in selecting appropriate elderly donor organs that may have features of fibrosis or steatosis [6]. Transmission of occult malignancy is another consideration owing to the higher incidence of unrecognized malignancies in the elderly, which will be elaborated later in this chapter.

Caution must be exercised in the use of elderly donors in HCV-positive recipients. Livers with advanced donor age (>60 years) increase the risk for deleterious histologic outcomes and graft failure due to disease recurrence [7–9]. Interestingly, recipients with hepatitis C and concomitant hepatocellular carcinoma seem to better tolerate early intervention with interferon and to be in healthier conditions which may translate to better outcomes when organs from advanced donor age are used [10].

## Steatosis

About 20–25% of deceased donor liver allografts are steatotic. The mechanism of hepatic dysfunction in fatty livers is multifaceted. The fatty vacuoles in the hepatocytes increase the cell volume and compromise the sinusoidal space [11]. This alters the microcirculation of the liver. Moreover, fatty livers are less tolerant of ischemia/reperfusion injuries associated with cold preservation [12]. Kupffer cell dysfunction, endothelial cell necrosis, and intensified leukocyte adhesion and lipid peroxidation are also characteristics of steatotic graft dysfunction [13].

There are two histologic patterns of fatty infiltration observed in donor liver biopsies: microvesicular steatosis, in which the cytoplasm contains diffuse small droplet of fat vacuoles, and macrovesicular steatosis, in which large vacuole

deposits displace the nuclei [14, 15]. The presence of macrosteatosis adversely affects the function of the graft [14, 16], while the presence and extent of the microsteatosis does not appear to affect the graft function. Grafts with less than 30% of macrosteatosis can be safely used for transplantation, whereas grafts with macrosteatosis of 30–60% are at high risk for graft dysfunction and should be used only after careful evaluation by an experienced surgeon. Grafts with over 60% macrosteatosis are at very high risk for primary nonfunction (PNF) and should be discarded.

## Prolonged Cold Ischemic Time

Even in the era of modern preservation techniques, solutions and modulation of the hepatic microenvironment, it is of paramount importance to minimize the CIT. Ample evidence points to the rapidly increasing incidents of PNF, early allograft dysfunction (EAD), and declining graft viability with 14–16 h of cold ischemia [17, 18]. Beyond the immediate anoxic injury and EAD, prolonged cold ischemia is also associated with long-term biliary complications [19]. Extensive anoxia may also induce immunogenicity of the grafts and contribute to acute and chronic rejection of the grafts [20]. In marginal grafts with risk factors such as steatosis, donation after cardiac death (DCD), and donors with advanced age [21], the CIT should be further minimized to under 6–8 h.

## Hepatitis B Virus and hepatitis C Virus Seropositive Donors

The fear of transmission of HBVs and HCVs made using such organs controversial. The reported risk of HBV transmission in the recipient is very variable and ranges widely between 15% and 95% [22, 23]; however, it is clear that the transplantation of HBV core antibody seropositive (HBcAb<sup>+</sup>) grafts increases the risk of infection. Recipients positive for antibodies against both hepatitis surface antigen (HBsAb) and core antigen (HBcAb) have been most resistant to HBV reactivation with HBcAb<sup>+</sup>

grafts, whereas those with no serologic indications for HBV immunity or infection were most susceptible [24–28]. Fortunately, prophylactic lamivudine and hepatitis B immunoglobulin (HBIG) have minimized the risk of HBV transmission by HBcAb+ grafts in both HBV-naïve and HBV-positive recipients [29–31]. Investigations on HCV-positive vs. HCV-negative grafts demonstrate no disparity in graft function and short-term patient survival when used in HCV-positive recipients [32–34]. There is also evidence that using grafts from donors with dual seropositivity for both HBV and HCV has no effect on graft function and 5-year survival outcome [35]. HBcAb+ and HCV-positive allografts will continue to be utilized in patients undergoing transplantation for HBV and HCV, respectively, and HBcAb+ grafts may even be applied to HBV-naïve patients with appropriate prophylaxis.

Hepatitis C recurrence in HCV-positive recipient is inevitable with comparable patient outcomes between HCV-positive and -naïve grafts [32–34]. Hepatitis C viremia persists in 95% of transplant patients due to HCV cirrhosis [36], and graft damage by HCV is expedited, particularly with HCV-1b, compared to the indolent course of de novo hepatitis C infection in immunocompetent patients [37]. Approximately 25% of HCV transplants experience recurrence of cirrhosis within a median time interval of 5 years [7] and subsequent decompensation 1 year later [38]. Retransplantation for hepatitis C is controversial and has suboptimal outcomes [39]. Unlike the breakthroughs in HBV prophylaxis, prophylactic HCV antiviral therapy with ribavirin and interferon- $\alpha$  combination or monotherapy in transplant patients has disappointing results, and posttransplantation HCV prophylaxis is currently not the standard of care [40–42]. Treatment of HCV recurrence with combination therapy produced varying degrees of sustained virological response [43–45] with adverse effects of anemia as well as acute and chronic rejection attributed to ribavirin and interferon- $\alpha$ , respectively [46]. In the absence of effective prophylaxis, risk/benefit stratification of prophylaxis, and definitive treatment, HCV-positive allografts transplant in HCV-naïve recipients or HCV-positive recipients with undetectable viral load should be

avoided. Newer anti-HCV agents, including the protease inhibitor, telaprevir, hold promise for improving posttransplant outcomes in HCV patients undergoing orthotopic liver transplant.

## Donation After Cardiac Death

The utilization of donation after cardiac death (DCD) livers has escalated steadily, comprising approximately 5% of liver transplants now [47]. A wider application of DCD has been hindered by its well-known inferior outcomes when compared to standard criteria donor (SCD) [48–51], mainly as a sequela of ischemic cholangiopathy and diffuse intrahepatic biliary strictures [51–53]. Unlike the neurologic death in most deceased donors where a controlled withdrawal of cardiopulmonary support and aortic cross-clamping minimize warm ischemia time (WIT), DCD has prolonged warm ischemia time by virtue of the necessary intervention and observation of the patient for any possibility of resuscitation.

A retrospective analysis of 1,567 patients who received DCD livers has delineated the recipient and donor characteristics for morbidity and mortality [54]. Male gender, recipient age over 55, hepatitis C seropositivity, African-American race, the need for hospitalization and life support at the time of transplant, and MELD score greater than 35 in recipients were all attributed to graft failure. Donor age greater than 55, weight greater than 100 kg, increasing cold, and WIT also correlated with morbidity. There were several predictors of posttransplant mortality, namely, recipient factors of age greater than 55, hospitalization at the time of transplant as well as donor factors of weight greater than 100 kg, and prolonged CIT.

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## Donor Risk Index

In 2006, Feng et al. described a scoring system that identified donor-specific risk factors and quantified their effect on outcome [55]. The donor risk index (DRI) was developed by retrospectively analyzing data over 20,000 liver transplants from the Scientific Registry of Transplant Recipients (SRTR) from



**Table 15.2** Donor risk index = exponent of the sum below

Age	0.154 If $40 \leq \text{age} < 50$	0.274 If $50 \leq \text{age} < 60$	0.424 If $60 \leq \text{age} < 70$	0.501 If $70 \leq \text{age}$
Cause of death (COD)	0.079 If COD = anoxia	0.145 If COD = CVA		0.184 If COD = other
Donor race	0.176 If race = African-American		0.126 If race = other	
Donation after cardiac death	0.411 If DCD			
Partial/split transplant	0.422 If partial/split			
Donor height	0.066 $170 - \text{height}/10$			
Area of organ sharing	0.105 If regional share		0.244 If national share	
Cold ischemic time	0.010 $\times$ cold time			

1998 to 2002. The authors identified seven risk factors that had an independent association with increased graft loss: age, African–American race of the donor, donor height, cause of death of the donor, and partial or split liver transplant (SLT). Two non-donor factors, CIT and sharing of grafts outside the local organ sharing area, were also significantly and independently associated with increased graft failure and therefore included in the calculation of the DRI. The DRI is calculated according to Table 15.2. It should not be the only criterion to accept or decline an organ; however, it may help decisions by quantifying the donor quality and allows comparison between centers and regions.

## Malignancy

The incidence of untoward transmission of donor malignancy is extremely low. Though the reports have been increasing since the creation of Disease Transmission Advisory Committee in 2005, only four proven and one conjectured donor-transmitted malignancy in all solid organ transplant were recorded in 2007 [56]. CNS tumors, such as medulloblastoma and glioblastoma multiforme [57], along with non-CNS tumors including high-grade melanoma and choriocarcinoma, were associated with highest transmission risk [58]. Allografts with lymphoma often culminate in dire outcomes, and vigilance should be exercised to diagnose occult lymphoma in donors and to avoid the use of such grafts [59].

## Alternative Procurement Techniques: Split, Reduced, and Adult Living Donor Liver Transplant

The scarcity of organ donors has expedited the technical advances in split liver transplant (SLT). SLT can expand the donor pool as each donor liver can benefit two patients, most commonly one pediatric from left lobe or segments and one adult from the right. Results from SLT technique unfortunately have been accompanied by its own set of morbidities, including parenchymal leakage of bile, thrombosis of hepatic artery, infection secondary to the necrotic tissue remnant, and poor graft function due to insufficient hepatic volume [10]. Early reports on the outcomes from SLT from optimal allografts paralleled that of the whole organ transplant of ECD in terms of graft failure and mortality [10, 60]. More recent investigations found that SLT renders long-term outcomes comparable to standard criteria donor (SCD) and holds promise for another potentially underutilized organ resource [61]. The future of SLT will be the refinement of full left lobe and right lobe split liver transplantation for two appropriate-sized adult recipients, which is currently at an exploratory stage. Further understanding of small for size syndrome, portal hyperperfusion, and flow modulation combined with improvements in liver preservation may allow safe right/left lobe splits for two adults in the future. Experiences gained from reduced liver transplant from an adult donor to a pediatric recipient have refined the SLT technique.

Adult-to-adult living donor liver transplant has shown excellent outcomes. While donor morbidity remains a concern with few well-publicized donor mortalities, a subanalysis of adult-to-adult living donor liver transplant (A2ALL) trial illustrated that donor serologic markers of liver function and transaminases, with the exception of platelet count, returned to baseline within a year post-donation, suggestive of good hepatic functional recovery [62].

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## Organ Preservation

Since the beginning of orthotopic liver transplantation, the optimization of the graft has been a collaborative effort between donor and recipient sites. Interventions to optimize the graft condition can take place as preconditioning, organ preservation, and post-conditioning in the donor site, as well as *en route* to the recipient site and during the process of transplantation. Injuries to the allograft can occur in at least three phases: warm ischemia, cold ischemia, and reperfusion. Warm ischemia starts with aortic cross-clamping or withdrawal of cardiac support in brain death or impaired hemodynamic status in the donation after cardiac death (DCD). Cold ischemia is iatrogenic, initiated by the flushing of the liver with cold preservation solution. Reperfusion injury is incurred when the allograft is connected to the recipient, and the blood circulation is resumed. The scope of this chapter will be to describe the pathophysiology of organ preservation injury and techniques to minimize such insults, which is of particular interest in optimizing the use of ECD livers.

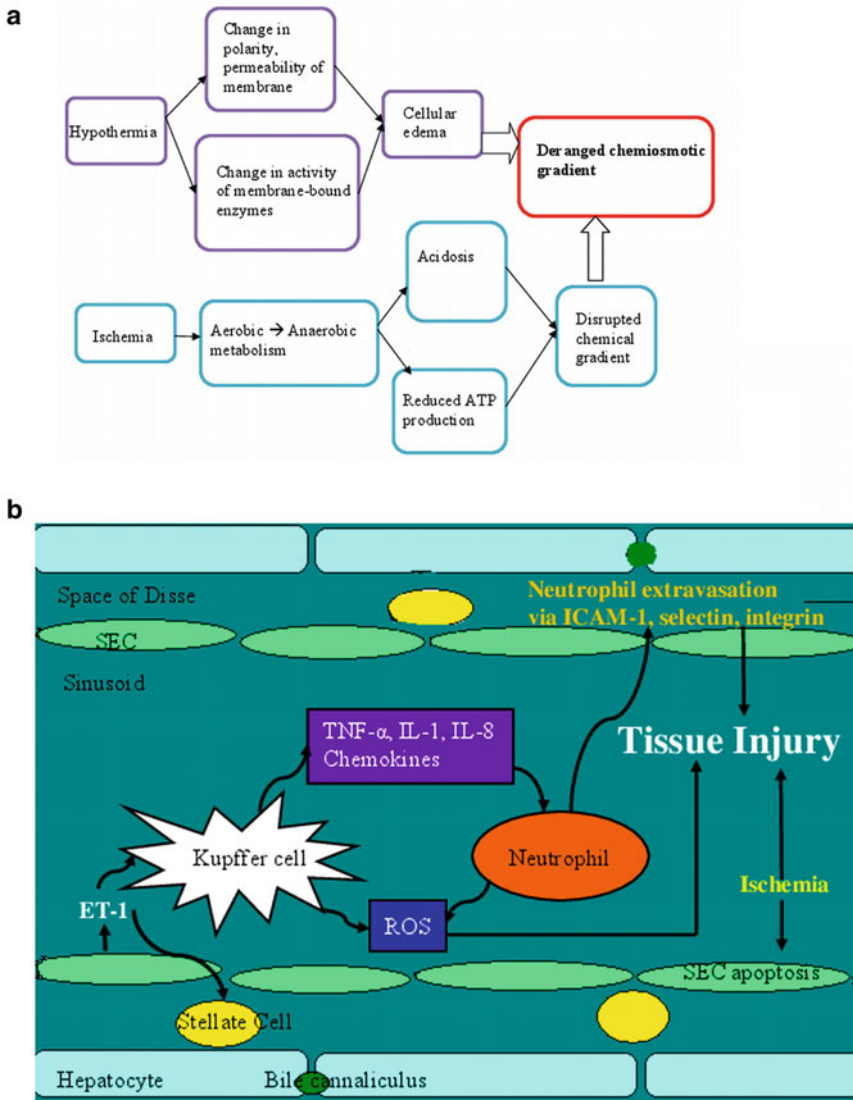
## Mechanism of Ischemia and Reperfusion Injury

Understanding organ preservation warrants the appreciation of the complexity of ischemia/reperfusion injury (IRI) (Fig. 15.2). As the metabolic rate and ATP requirement for cell sustainment drop precipitously with decreasing temperature, most organ preservation techniques incorporate hypothermia as standard protocol.

However, this artificial cellular ambience of hypothermia and anoxia results in the disruption of chemiosmotic gradients and structural integrity of the membrane phospholipid bilayer. Hypothermia alters the polarity and permeability of plasma membrane as well as the activity of membrane-bound enzymes culminating in cell swelling. Ischemia necessitates the transition from aerobic to anaerobic metabolism, creating acidosis and reducing ATP production. Consequently the activity of enzymes such as  $\text{Na}^+\text{-K}^+\text{-ATPase}$  and  $\text{Ca}^{2+}\text{-ATPase}$  that maintain the chemiosmotic gradient diminishes, exacerbating the disrupted ionic traffic. Calcium influx in particular induces calmodulin and phospholipase activation, alteration in mitochondrial activity, and vasospasm by its action on myofibrils, prolonging and exacerbating ischemia. Hence, the preservation solution is hypertonic and contains impermeants in order to minimize cellular edema.

On a cellular level, ischemia and reperfusion activate Kupffer cells, which release chemokines like tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Subsequent release of interleukin-8 (IL-8) recruits neutrophils to the ischemic area. The interaction between neutrophils and sinusoidal endothelium occurs via intercellular adhesion molecule-1 (ICAM-1), selectin and integrin, which results in extravasation of inflammatory cells. Lysosomal enzymes, hydrogen peroxide, nitric oxide, and endothelin perpetuate further structural destruction [63]. Sinusoidal endothelial cells (SECs) are known to be more susceptible to cold ischemia than warm ischemia [64, 65]. There is growing evidence that both cold and warm ischemia also damage biliary epithelial cells [66].

Interestingly, more damage is incurred during reperfusion than ischemia. For instance, though cold ischemia damages sinusoids, mounting evidence points to the notion that reperfusion results in apoptosis of sinusoidal endothelial cells [67]. Such fatal injuries occur mainly via reactive oxygen species (ROS) such as superoxide radical, hydroxyl, and hydrogen peroxide [68], synthesized from Kupffer cells, neutrophils via cytosolic xanthine oxidase [69]. Such a sudden and tremendous oxidative stress eclipses the endogenous



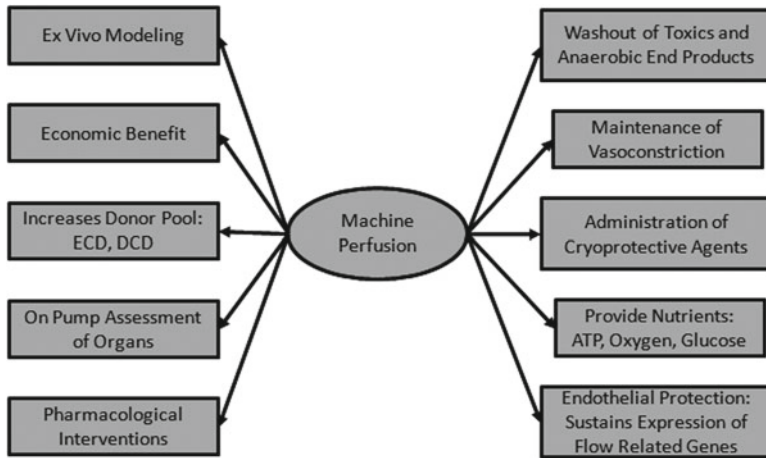
**Fig. 15.2** (a) Simplified diagram of preservation injury due to hypothermia and ischemia. (b) Simplified schematic of ischemia/reperfusion injury. Ischemia-reperfusion activates Kupffer cells which release TNF- $\alpha$ , IL-8, and other chemokines. Neutrophil is activated, recruited, and infiltrated the sinusoidal endothelial layer to damage

hepatocytes. ROS from Kupffer cell and neutrophil incur tissue injury. Endothelin (ET-1) activates Kupffer cells as well as stellate cell (Ito cell) resulting in vasoconstriction and further ischemia. Lysosomal enzymes, nitric oxide (not shown), and complement activation also contribute to further injury (SEC: sinusoidal endothelial cell)

antioxidants such as superoxide dismutase, glutathione, catalase, and beta-carotene [70]. The consequent damages are observed in different levels. ROS destroys the microvasculature in liver, perpetuating local anoxia after reperfusion [71], impairs mitochondrial function, and induces lipid peroxidation [72]. Reperfusion injury is also mediated by cytokines and nitric oxide [68].

### Organ Preservation: Modalities to Attenuate Ischemia/Reperfusion Injury

As previously mentioned, IRI are correlated with PNF, EAD, acute as well as chronic rejection and intrahepatic biliary stricture. Hypothermia reduces the metabolic rate at the cost of chemiosmotic derangement. Hence, a successful organ



**Fig. 15.3** Advantages of hypothermic machine perfusion. The left column lists outcome benefits, while the right column outlines mechanistic advantages

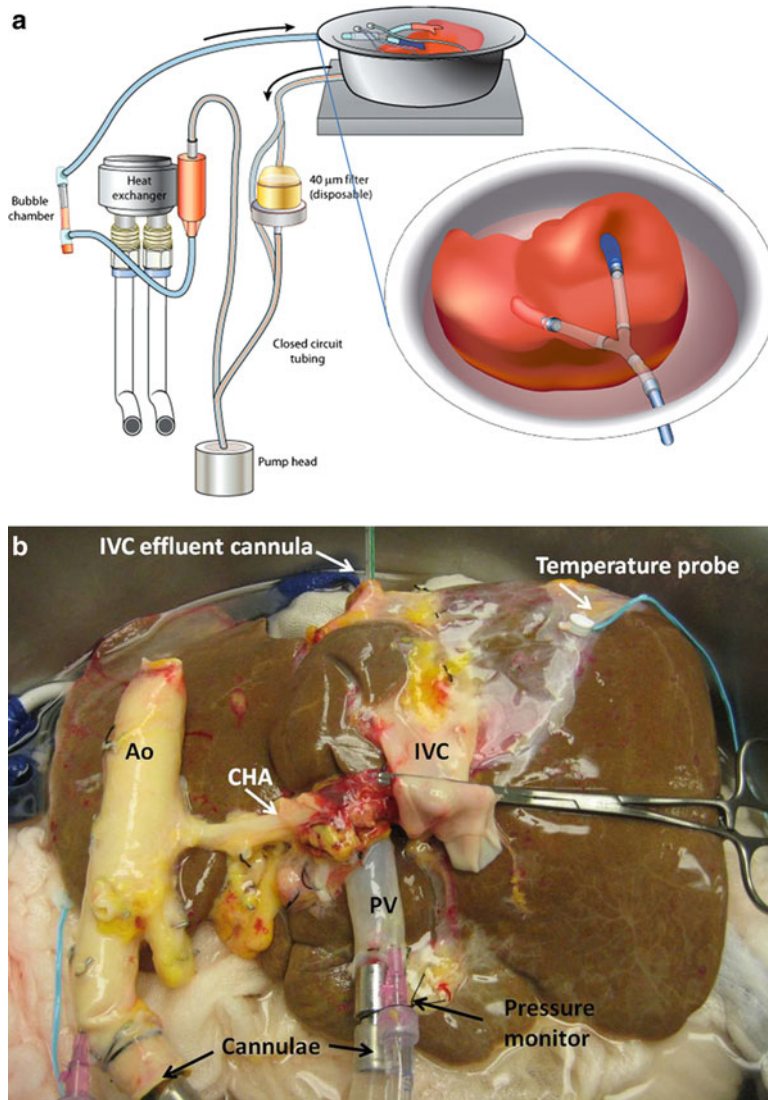
preservation technique entails a balance of attenuating metabolic strain by hypothermia and ameliorating IRI, which has propelled the evolution of preservation solutions. Euro-Collins solution simulates the intracellular chemiosmotic composition in order to mitigate cell swelling. However, the demonstration of its maximal potential in ex vivo rat model of liver preservation was only 8 h [73]. Other preservation solutions, such as histidine-tryptophan- $\alpha$ -ketoglutarate solution [74], University of Wisconsin solution (UW) [75], Celsior [76], and Polysol [77], further ameliorated IRI in standard cold storage (SCS) and hypothermic machine perfusion (HMP) in different organs including liver. A novel solution called Vasosol is charged with enhanced vasodilatory and antioxidant capacity with evidence of improved early graft function and survival benefits in humans [78]. Despite the variety in preservation solution, the essential components include buffers and impermeants to diminish cellular edema, enriched with metabolic substrates, amino acids, free radical scavengers, as well as vasodilators.

A notable advance in liver preservation is hypothermic machine perfusion (HMP). Although the inception of organ preservation (kidney) by Dr. Belzer in 1967 utilized the machine perfusion technology, the convenience of standard cold storage had largely replaced HMP until recently [78, 79]. The advantages of HMP are (1) continu-

ous supply of metabolic substrates for ATP production, (2) washout/dilution of waste products such as lactic acid and ROS, (3) assessment of organ viability and functionality prior to transplant, and (4) intraoperative therapeutic interventions including downregulation of the mRNA from precursors of IRI such as TNF- $\alpha$ , IL-8, and ICAM-1 (Fig. 15.3). Interest in HMP techniques for the liver has recently returned due not only to its superiority to SCS in preserving SCD liver but also to improved outcomes including reducing IRI, PNF, and EAD in ECD livers, which has been delineated in rodent [77, 80] and swine studies [81]. A seminal work by Guarrera et al. demonstrated in their phase I clinical trial that HMP of SCD human liver grafts results in shorter postoperative recovery time, diminished biliary complication, and attenuated serum markers of IRI [78, 82] (Fig. 15.4). Currently, a phase II clinical trial probing the effects of HMP on ECD livers is approaching completion with excellent results thus far. Reconditioning livers through HMP is the key to salvaging marginal organs and extending liver transplant to more patients.

### Future Directions in Liver Preservation

The most promising advance in the imminent future will be the development of portable HMP appara-



**Fig. 15.4** (a) Schematic diagram of hypothermic machine perfusion. (b) Liver graft undergoing hypothermic machine perfusion (*Ao* Aorta; *CHA* common hepatic artery; *IVC* inferior vena cava; *PV* portal vein)

tus which will minimize IRI due to CIT and provide a vehicle for multicenter trials and subsequent application of liver HMP in clinical practice.

The HMP protocols will also need to be optimized. This implicates enhancing perfusate, optimizing temperature, perfusion pressure, and flow. Perfusate will undergo further evolution with anti-apoptotic drugs, vasodilators, inhibitors of inflammatory cytokines, antioxidants, and matrix metalloproteinase inhibitors [83]. Although studies agree on the benefits of HMP, there is discor-

dance as to the optimal temperature and perfusion pressure. More in-depth investigation in not only organ preservation but also reversal of IRI, biliary complications, and other damages already present in ECD livers should be explored.

Other technical advances such as perioperative carbon monoxide inhalation [84, 85] and pharmacological or ischemic preconditioning [86] of liver may be incorporated in to HMP protocol to further potentiate its effect. Studies of normothermic machine perfusion of rat [87] and



porcine liver [88] as well as normothermic extracorporeal membrane oxygenation of human livers open a new possibility of normothermic preservation, especially of DCD livers [89].

The future of organ preservation will more aggressively incorporate therapeutic interventions into HMP. Though a more sophisticated HCV prophylaxis regimen has produced significant sustained viral response rates, there is an urgent need for new therapeutic methods. Our laboratory is also working on lentiviral transduction with RNAi which can inhibit viral entry to the cell and impose a selective mutational pressure on HCV and induce a nonviable HCV strain, thus attenuating damage caused by hepatitis C recurrence [90]. IRI may be further mitigated by introducing superoxide dismutase gene by adenovirus [91]. Novel therapeutic interventions to “defat” steatotic allografts, leading to improved graft function are also being explored in a small animal model.

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## Summary

Improvements in donor management, organ preservation and attenuation of IRI hold promise in allowing safe expansion of the donor pool and improvement of outcomes in Liver Transplantation.

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## History of Pediatric Liver Transplantation

The history of pediatric liver transplantation started with the first unsuccessful liver transplantation in 1963. The following eight pediatric patients survived the initial transplantation, only to face difficulties with immunosuppression. The introduction of cyclosporine A in 1978 made acceptable long-term survival rates possible [1], and liver transplantation became standard of care in the 1980s for liver failure and end-stage liver disease. The resulting shortage of organs for small children triggered surgical innovations in the late 1980s and early 1990s such as living-donor liver and split liver donations. The introduction of the pediatric end-stage liver disease (PELD) score in 2002 shifted wait-list priority for organ allocation from time on the waiting list to the severity of the disease. This evolution over almost 50 years led to today's excellent long-term outcome after pediatric liver transplantation with 1- and 5-year survival rates of 90% and 85%, respectively [2]. Problems related to life-long immunosuppression and donor scarcity are remaining challenges.

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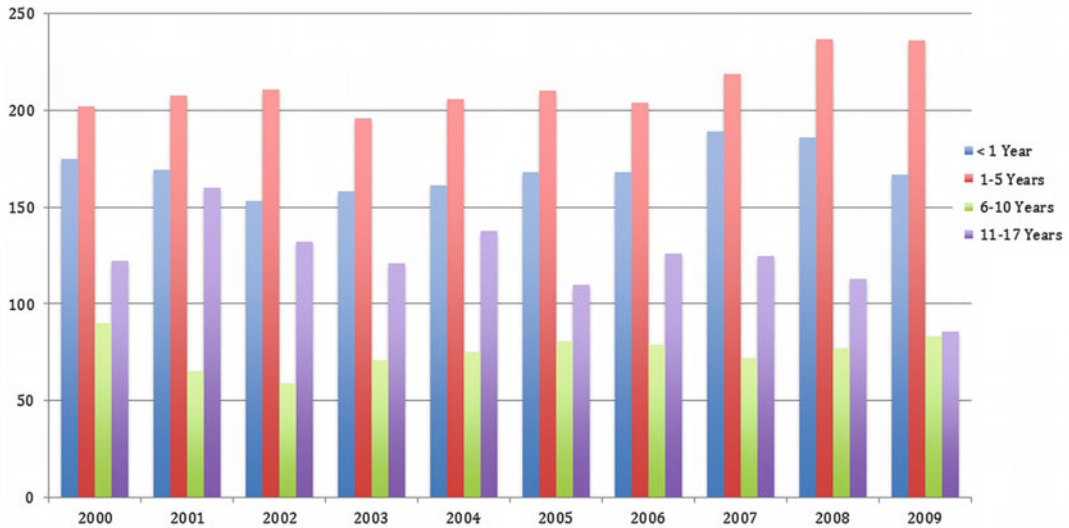
## Allocation of Organs for Pediatric Liver Transplantation

In the United States, the allocation of organs is overseen since 1986 by the Organ Procurement Transplantation Network. Organ allocation was initially based on time on the waiting list and home, hospital, or ICU location as a surrogate for the severity of illness. However, studies found that wait-list time had no correlation with death, except with status 1 patients. Until 2002, patients needing liver transplants were grouped into four medical urgency categories, and this system did not take the urgency or the actual severity of the illness in consideration. In 1995, a group of transplant physicians from the United States and Canada formed a collaborative research group, the Studies of Pediatric Liver Transplantation (SPLIT), to share data and create a national database of pediatric liver transplants. Based on the data from the SPLIT group, the PELD score was established in 2002 [3]. The PELD score was developed to predict the mortality or ICU admission of a patient within the next 3 months without a liver transplantation using growth failure, albumin, bilirubin, INR, and age at the time of listing and is valid for patients younger than 12 years [4].

The PELD score is calculated using the following formula:

(Scores for patients listed for liver transplantation before the patient's first birthday continue to include the value assigned for age (<1 year) until the patient reached the age of 24 months.)

PELD score =
$0.480 \times \text{Log}_c$ (bilirubin mg/dL)
$+ 1.857 \times \text{Log}_c$ (INR)
$- 0.687 \times \text{Log}_c$ (albumin g/dL)
+0.436 if the patient is less than 1 year old
+0.667 if the patient has growth failure (>-2 standard deviations)



**Fig. 16.1** Age distribution of pediatric liver transplantation in the US from 2000 to 2009

The score is multiplied by 10 and rounded to the nearest whole number. Additional points are given for hepatic-pulmonary syndrome, urea cycle defects, and hepatic neoplasms [5].

In general, pediatric organs are given to pediatric patients. Patients with acute liver failure with an expected life expectancy of 7 days or less are categorized as status 1 (usually less than 1% of all listed patients), and these patients have the highest priority independent of PELD score. Most patients who received allocated organs achieved high PELD scores through special exception points or received transplants as status 1 patients.

The introduction of the PELD score led to fewer healthy patients on the waiting list as there was no benefit in listing patients early in their disease process. Initially there was concern that

this system would lead to worse outcomes, since organs are allocated to sicker patients; however, the SPLIT research group demonstrated that posttransplant survival was similar with either allocation system [6].

### Age Distribution

One-third of all transplanted pediatric patients were younger than 12 months; 14% were older than 13 years (Fig. 16.1). Sixty-five percent of patients under one were transplanted for biliary atresia. The most common indication for patients older than 13 years was unspecific type of cirrhosis; fulminant liver failure as an indication for liver transplantation was highest in this age group [7].

## Indications for Pediatric Liver Transplantation and Their Implications

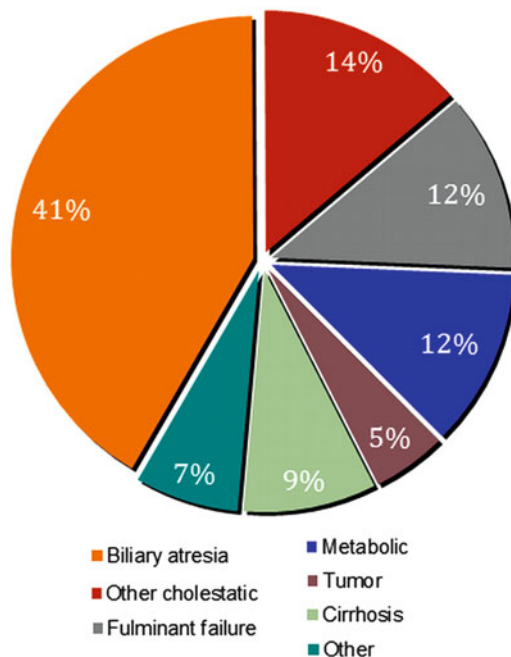
Indications for pediatric liver transplantation can be divided into four general categories: cholestatic liver disease, metabolic liver disease, fulminant hepatic failure, and liver tumors. The SPLIT group organizes the US and Canadian database of pediatric liver transplants and collects data on more than 80% of all pediatric liver transplants in the US and Canada; the following epidemiological data is extracted from the SPLIT database [7] (Fig. 16.2).

### Cholestatic Liver Disease

Biliary atresia is the indication for almost half of all pediatric liver transplants and other cholestatic liver diseases such as Alagille syndrome and sclerosing cholangitis; progressive familial intrahepatic cholestasis accounts for 15% of all pediatric liver transplantations. Liver transplantation is considered curative for patients with cholestatic liver disease; however, some patients may develop a recurrence of cholestatic disease due to autoantibodies that interfere with the canalicular function in the graft [8].

### Biliary Atresia

Biliary atresia is an inflammatory destruction of both intra- and extrahepatic bile ducts in neonates. The obliterative process is thought to begin in the neonatal period in patients with isolated biliary atresia, whereas syndromic biliary atresia is thought to begin at an earlier stage of the development in the embryo [9]. The presenting signs and symptoms are persistent jaundice, pale stools, dark urine, failure to thrive, and coagulopathy unresponsive to vitamin K. Late signs are hepatosplenomegaly and ascites, suggestive of progressing cirrhosis. The diagnosis is usually made in early infancy with a percutaneous liver biopsy.



**Fig. 16.2** Indications for pediatric liver transplantation

Biliary atresia is the most common indication for pediatric liver transplantation. Left untreated, it is usually lethal within 3 years. Up to 20% of patients have other congenital abnormalities, including splenic malformation, situs inversus, or absence of an inferior vena cava (IVC). Standard of care in industrialized countries is a Kasai portoenterostomy, which is a palliative procedure in which a Roux-en-Y loop is anastomosed to the exposed ductules at the surface of the porta hepatis. Long-term outcome is thought to be better the earlier the Kasai procedure is performed. Although controversial, studies show that procedures done after day 90 of life have shorter native liver survival and worse bile drainage; best results are achieved if the procedure is done within the first 30 days of life [10]. Successful portoenterostomies drain bile and will normalize plasma bilirubin level within 6 months of the procedure. Possible postoperative complications include bile leaks, ascending cholangitis, and later fat malabsorption and malnutrition. Up to 80% of patients who underwent a successful Kasai procedure survive with a native liver for longer than 10 years. Despite adequate bile drainage, the disease will



**Table 16.1** Metabolic diseases of the liver

Structural damage to liver	Extrahepatic damage	Causes hepatic adenomas or hepatocellular carcinoma
Alpha-1-antitrypsin deficiency	Urea cycle disorders	Glycogen storage disease types I and III
Cystic fibrosis	Hyperoxaluria	Hereditary tyrosinemia
Wilson disease	Tyrosinemia type I	Galactosemia
	Familial hypercholesterolemia	Alpha-1-antitrypsin deficiency
	Organic acidemias	PFIC type II

progress with worsening portal fibrosis, cirrhosis, and portal hypertension to a point at which a liver transplantation is indicated. Patients who are diagnosed late with biliary atresia and already have cirrhosis may undergo a liver transplantation without prior Kasai procedure. Patients with biliary atresia splenic malformation syndrome will require preoperative imaging study to evaluate the anatomy of the portal vein.

The anesthesiologist will encounter patients with biliary atresia prior to the transplantation for liver biopsies and for esophago-gastro-duodenoscopies to rule out or treat esophageal varices. Patients undergoing a liver transplantation after a Kasai procedure will have greater blood loss during the pre-anhepatic phase because of adhesions. After reperfusion, there is no need to create a new Roux-en-Y limb as the existing limb from the Kasai procedure can be used.

## Metabolic Disease

Metabolic disease is the indication for 13% of all pediatric liver transplants. The metabolic diseases can be divided into (A) diseases that lead to structural liver damage with or without extrahepatic injury, (B) metabolic defects that are expressed in the liver but cause injury to other organ systems, and (C) metabolic defects that can cause hepatic neoplasms [11, 12] (Table 16.1). Patients with primary hepatic metabolic disease such as Wilson disease,  $\alpha$ -1-antitrypsin deficiency, tyrosinemia, and cystic fibrosis present with end-stage liver disease or liver failure at the time of transplantation. Extrahepatic injury can be significant, as in cystic fibrosis, where pulmonary disease is the leading manifestation in many patients. Only a

subgroup of patients with cystic fibrosis have hepatic disease, and of those, only few progress to liver failure.

Wilson disease is an autosomal recessive disorder of the copper metabolism with an incidence of 1:30,000; it is the cause of 5% of all cases of acute liver failure. Patients who are diagnosed prior to fulminant liver failure and receive pharmacological treatment have an excellent prognosis. Copper-induced injury leads to liver failure, neuropsychiatric decline, hemolysis, proximal renal tubular dysfunction, and other systemic manifestations. Patients with Wilson disease may only have mild hepatic disease with progressive neuropsychiatric deterioration and have chronic active hepatitis. They may present in their teens with an acute deterioration that leads to fulminant hepatic failure. Severe hemolysis at this time can be treated by removal of copper from the circulation. The mortality of acute liver failure with Wilson disease without a liver transplantation is almost 100% [13], and long-standing neurological deficits appear to persist despite liver transplantation.

In patients with primary nonhepatic disease (ornithine transcarbamylase deficiency, familial hypercholesterolemia, primary hyperoxaluria type 1, or organic acidemia) the indication for transplantation is not liver failure or end-stage liver disease; the liver is structurally normal in these patients and only lacks one specific function. The purpose of the liver transplant is to prevent extrahepatic damage. Transplantation is curative for extrahepatic complications of these patients, and outcome is excellent. This can be considered as a crude form of gene therapy to prevent the accumulation of toxic metabolites [12]. Timing of the transplantation is difficult in this setting.

Metabolic diseases that cause hepatic adenoma or hepatocellular carcinoma include, among others, glycogen storage disorders, hereditary tyrosinemia, galactosemia, and alpha-1-antitrypsin deficiency. In patients with adenomas, auxiliary transplants are avoided due to the risk of progression to hepatocellular carcinomas. Glycogen storage disorders pose a special challenge for the anesthesiologist: glycogen deposits can cause myocardial hypertrophy, subaortic stenosis, and macroglossia, which can make airway management extremely difficult. Patients are at risk for hypoglycemia and lactic acidosis and usually receive a glucose-containing solution during the preoperative fasting period. Indications for transplantation are large or multiple adenomas and poor metabolic control.

### **Fulminant Hepatic Failure**

Fulminant hepatic failure accounts for 11% of pediatric liver transplantations. Often no diagnosis can be found, and an unspecified viral etiology is assumed. Sometimes, due to the time constraints and urgency of transplantation, metabolic diseases or autoimmune hepatitis cannot be ruled prior to transplantation [14]. Patients with fulminant hepatic failure are generally older and have worse long-term outcome.

### **Liver Tumors**

Liver tumors account for 4% of all pediatric liver transplantations, with hepatoblastoma as the most common pediatric liver tumor. If the tumor is unresectable after appropriate systemic chemotherapy, liver transplantation can be offered and metastatic disease unresponsive to chemotherapy is not necessarily a contraindication to transplantation.

### **Total Parental Nutrition-Induced Liver Failure**

Intestinal failure from either congenital abnormalities or after bowel resections may require chronic total parental nutrition (TPN) administra-

tion that may lead to TPN-induced liver disease. TPN-induced liver disease is seen in 40–60% of pediatric patients receiving chronic TPN. The TPN-induced liver dysfunction in pediatric patients differs significantly from adults: in adults, steatosis is more common, whereas infants often present with cholestasis. Biliary sludge formation and cholelithiasis are seen in both populations [15]. An earlier small-bowel transplant in a TPN-dependent infant may avoid a combined liver and small-bowel since early TPN cholestasis is reversible after cessation of TPN [15].

### **Hepatic Encephalopathy**

Hepatic encephalopathy has a different pathogenesis in children compared to adults. In adults, it is usually seen in a setting of chronic liver failure and cirrhosis, whereas in children, hepatic encephalopathy is usually due to acute or chronic liver failure. Cerebral edema is seen at earlier stages in children and frequently not recognized in a timely manner. Supportive care for patients with hepatic encephalopathy should address fluid management and potassium, sodium, and glucose control. To achieve normovolemia, it is usually necessary to restrict fluid intake. Hypokalemia and alkalosis impair ammonia detoxification and increase renal ammonia production, which may worsen the hepatic encephalopathy. Artificial hepatic support is an unproven therapy in children.

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### **Intraoperative Anesthetic Care for Pediatric Liver Transplantation**

Anesthetic management for liver transplantation varies depending of the age group. For the ease of discussion, patients can be divided in three groups: Infants and Toddlers, Preteens, and Teens

#### **Infants (0–1 Year) and Toddlers (1–3 Years)**

Infants typically present with biliary atresia and a history of a failed Kasai procedure. Inhalational induction of anesthesia can be used, if there are

no contraindications such as a full stomach, massive ascites, or actively bleeding gastroesophageal varices. The airway is secured with a conventional uncuffed endotracheal tube or an endotracheal tube with a high-volume/ low-pressure cuff. Historically cuffed endotracheal tubes were avoided in prepubescent patients because the use of a low-volume/high-pressure cuff may result in mucosal ischemia and subglottic stenosis. However, uncuffed endotracheal tubes may affect oxygenation and ventilation perioperatively: with large volume fluid administration, pulmonary compliance worsens, airway pressures rise, and then leakage around the endotracheal tube may also increase [16]. Cuffs made from polyurethane such as the Microcuff® have high-volume/low-pressure characteristics, which make them ideal in smaller patients. The leak around the cuff should be maintained under 25 cm H<sub>2</sub>O and may need to be checked frequently as the airway can become more edematous. Surgical exposure, ascites, pleural effusions, and organomegaly cause a reduction of FRC; PEEP and higher airway pressures may need to be applied to ensure adequate oxygenation.

Gastric emptying can be delayed; the presence of massive ascites with an associated increase in intra-abdominal pressure further increases the risk of pulmonary aspiration and a rapid sequence induction of anesthesia is commonly performed in this scenario.

Central vascular access is usually obtained after the airway is secured, either using a Broviac catheter or a conventional central line. Broviac catheters are long and have a small lumen, which precludes rapid infusion of fluids or blood products. Therefore, adequate peripheral access is also required. Peripheral intravenous lines should be placed in the upper extremity because there might be inadequate drainage in to the central circulation during caval cross-clamping. Obtaining intravenous access can be a challenge in these patients who have had multiple central line placements in the past. At times, a venous magnetic resonance study or venous Doppler study can be obtained preoperatively to verify patency of the veins. The use of an ultrasound machine in the

OR can be helpful to establish not only central access but also peripheral access in the antecubital veins. An arterial line can be established in either extremity; the upper extremity is preferred because of the possibility of intraoperative partial aortic occlusion from aortic side clamping.

Infants typically tolerate cross-clamp of the IVC with only minimal hemodynamic support, and most infants only require a dopamine infusion and optimization of their intravascular volume to tolerate the cross-clamp. Venovenous bypass is not routinely done in this age group because of the risk of thromboembolic complications due to low flow in the extracorporeal circuit; if cross-clamping of the vena cava is not tolerated, the piggyback technique as described earlier in this book can be used [17].

Infants are at higher risk for hypothermia due to the larger skin surface to body mass ratio and the inefficient shivering thermogenesis. Infants have to rely on non-shivering thermogenesis, which may persist up to the age of 2 years. Placing the cold donor organ in the abdominal cavity of an already hypothermic infant will result in an even lower core temperature that may be difficult to correct. Warming the operating room, use of radiant heat lamps, convective forced-air warmers, and airway humidifiers can prevent hypothermia. Placement of temperature probes in the rectum in addition to the esophagus helps recognizing erroneous temperature readings when the cold organ is placed in the immediate vicinity of the esophageal temperature probe.

Arterial blood gases with a hemoglobin level should be sampled hourly because bleeding is frequently unrecognized and difficult to estimate in this age group. Transfusion of FFP and platelets should be restricted because of the constant threat of hepatic artery thrombosis. It is not uncommon to start a heparin infusion if the hepatic artery anastomosis is felt to be at a higher risk of thrombosis. Arterial blood gases analysis should also include glucose and electrolyte determinations: decreased glycogen storage capacities in infants and prior infusion of glucose-containing fluids such as TPN predispose these patients to hypoglycemia and may make a

glucose infusion and monitoring necessary. Hyperkalemia is of similar concern as in adults especially during reperfusion and needs to be treated aggressively.

Although some infants can safely be endotracheally extubated at the conclusion of the procedure, most anesthesiologists choose to keep the patient intubated during the early postoperative phase. Postoperative ventilation provides time to ensure adequate diuresis, reduction of possible airway swelling, and stable hemodynamics and hemostasis and facilitates optimal imaging studies.

Patients as small as 1.7 kg have successfully undergone a liver transplantation; however, meticulous surgical technique and anesthetic care are necessary to ensure the success of the operation in this extreme patient group. Anesthetic issues that are similar to those encountered with premature neonates such as glycemic management, avoidance of hyperosmolar medications, ventilatory management, and the neonatal circulation need to be considered. A Broviac catheter should be placed preoperatively in very small and/or premature neonates to allow adequate central administration of fluid and vasoactive medication.

### **Pre-teenager (4–9 Years)**

Preteens can receive large bore central venous lines, but usually it is not necessary or feasible to place a pulmonary artery catheter. Preteens have normal shivering thermogenesis but still have a larger skin surface to body mass ratio and require meticulous temperature management. Unlike adults, pre-teenagers do not commonly have cirrhotic cardiomyopathy.

### **Teenager**

Hemodynamic perturbations seen with teens during liver transplantation are comparable, but still less grave than with adults; however, the anesthetic setup and management are similar to the management of adults. Teenagers usually have

good cardiac reserves and a very compliant ventricle with exceptions such as patients with familial hypercholesterolemia, who may have significant coronary artery disease and myocardium at risk. Large bore central venous access, with the possibility to float a pulmonary artery catheter, is mandatory. Pulmonary artery catheters or other measures of ventricular filling can be used in teenagers with significant cardiac disease or pulmonary hypertension as described for adults elsewhere (Chapter 9) in this book. Transesophageal echocardiography may be a good monitoring option in teenagers of appropriate size.

Patients with complex congenital heart disease pose a special challenge. A multidisciplinary effort is necessary to ensure that all team members clearly understand the cardiac physiology and to prioritize the repair of the cardiac lesion vs. addressing the liver disease with the liver transplantation. Patients with congenital right to left shunts are at risk for paradoxical emboli during reperfusion of the graft and throughout the procedure, and meticulous de-airing of the caval anastomoses as well as all intravenous fluid lines is paramount.

Heterotaxy syndrome is an abnormal arrangement of thoracic and/or abdominal viscera with a wide array of anatomical abnormalities. Patients with heterotaxy syndrome may have, in addition to congenital heart defects, an abnormal vascular anatomy. The hepatic segment of IVC can be present or absent (so-called interrupted IVC). The hepatic veins can be normal (join the IVC just proximal to the IVC-atrial junction) or can connect independently to atria. An interrupted IVC with hemiazygos continuation might be advantageous for the intraoperative management since cross-clamping the suprahepatic IVC may not lead to a significant decrease of venous return. Extrahepatic portosystemic shunts should be ruled out in all patients with heterotaxy syndrome. Congenital extrahepatic shunts decrease the metabolism of galactose and ammonia by bypassing mesenteric circulation through the liver and can cause encephalopathy. Newborn screening for elevated galactose levels can be positive because of congenital extrahepatic portosystemic shunts [18].

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## Postoperative Care

Concerns in the immediate postoperative period care are similar to patients who underwent major abdominal procedures and remained intubated. Additional considerations specific to liver transplantation are the detection of graft-related complication such as hepatic artery or portal vein thrombosis, rejection, or infectious complications.

If the abdominal wall cannot be closed initially, tracheal extubation is deferred until after closure of the abdomen and other related procedures. The higher rate of re-explorations in infants and better pain management and imaging of intubated patients make it prudent not to extubate the patient too prematurely. In patients with relative large grafts, special care must be taken to rule out abdominal compartment syndrome. Increasing airway pressure, respiratory insufficiency from worsening ventilation–perfusion mismatch, hemodynamic compromise from compression of the vena cava, and worsening abdominal distention are signs of abdominal compartment syndrome and should prompt urgent evaluation and possible re-exploration. If not addressed rapidly, the high airway pressures may cause further hemodynamic compromise and increase intracranial pressure. Renal function may deteriorate due to compression of the renal veins. With a normal postoperative course, renal dysfunction is not as frequent as in the adult population; however, reduced perfusion pressure, impaired venous return, and renal vasoconstriction from calcineurin inhibitors may precipitate renal injury and lead to renal dysfunction.

Due to intraoperative fluid administration fluid overload is common, and fluid shift in the early postoperative period may require aggressive diuresis. Extensive use of loop diuretic, however, may lead to (contraction) metabolic alkalosis and may cause hypoventilation in the extubated child.

There are three categories of graft-related problems in the early postoperative period: vascular complications, biliary complications, and allograft rejection.

Patient with any of the complications may present with cholestasis, elevation of hepatocellular enzymes, lethargy, and fever. Urgent diagnosis of the specific cause is required to initiate timely treatment. Doppler ultrasound may help exclude vascular complications and identify fluid collections from bile leaks. Vascular and biliary complications frequently require re-explorations. Rejections are not common very early after surgery; however, treatment should be commenced rapidly either when there is a high level of suspicion or after a biopsy confirmed the rejection [19].

## Vascular Complications

In pediatric patients, hepatic artery thrombosis is the most common serious postoperative complication and up to four times more frequent than in adult patients due to the smaller size of the vessel. Early occlusion of the hepatic artery leads to graft necrosis and may cause graft loss if not addressed immediately. Daily routine Doppler ultrasound examinations are recommended to verify a patent vessel.

Patients with biliary atresia typically have a hypoplastic portal vein and may need a replacement of the portal vein up to the superior mesenteric vein and the splenic vein. These patients are at a higher risk for portal vein thrombosis with an incidence of up to 10%. Portal thrombosis is treated with revision of the anastomosis or percutaneous interventions such as angioplasty or stent placement. Portal thrombosis in the late postoperative period becomes clinically apparent by splenomegaly, thrombocytopenia, and gastrointestinal hemorrhage. If there is still an open lumen, percutaneous techniques can be used, but with complete thrombosis, portal venous shunt placement may be needed.

## Biliary Complications

The incidence of biliary complications is up to 30% in pediatric liver transplant recipients, and it is the most common surgical complication in patients receiving reduced sized organs [20]. Most biliary complications are bile leaks; biliary

strictures are less common [21]. In the early postoperative period, bile can be found in the abdominal drains, if a bile leak is present. The vascular supply of the extrahepatic bile ducts is quite precarious, and bile leaks are at times caused by hepatic artery thrombosis, leading to necrosis of the bile duct and leakage of bile into the abdominal cavity. Biliary strictures present with recurrent cholangitis, elevate alkaline phosphatase and GGT, and dilated intrahepatic biliary ducts on ultrasound examination. Biliary complications almost always require surgical re-exploration if endoscopic interventions are not successful or feasible.

## Rejection

Hyperacute rejection is rare, usually occurs very early, and is caused by antibodies that bind to the endothelial epithelium of the graft. It can lead to intraparenchymal vascular thrombosis and rapid graft loss. Acute rejection presents with irritability, fever, increased bilirubin, transaminases, and leukocytes. A confirmatory liver biopsy is usually necessary. Treatment consists of a course of steroids over 3–6 days followed by a steroid taper.

## Primary Nonfunction

Twenty-five percent of postoperative graft loss is due to primary nonfunction requiring re-transplantation and is associated with 67% mortality [22]. These patients present with worsening coagulopathy, acidemia, rising liver enzymes, and cholestasis without a clear etiology. If not re-transplanted in time, the disease may progress to fulminant liver failure and death.

## Infectious Complications

Induction immunosuppressive therapy in the early postoperative period renders patients at high risk for gram-negative enteric bacteria, enterococci, and staphylococci. Indwelling catheters should be removed as soon as possible. Epstein–Barr virus,

cytomegalovirus, and herpes simplex virus are the most common causes of a viral infection postoperatively. An antifungal prophylaxis may be given even before the transplantation, whereas most centers reserve prophylaxis only for high-risk patients. Diagnosis and treatment of infectious complications is similar to adults described elsewhere (Chapter 33) in this book.

## Outcome

In the SPLIT database, the overall 1- and 5-year patient survival was 89.8% and 84.8%, and graft survival among the 5-year survivors was 93% and 88%, respectively. Twelve percent of 5-year survivors needed a second liver transplantation, and 2% needed a third transplantation [23]. Posttransplant lymphoproliferative disease was seen in 6% of patients, and 60% of patients experienced an episode of acute cellular rejection within the first 5 years [23]. The reported incidence of renal insufficiency in long-term survivors varies between 13% and 32% [24].

Providing perioperative care for patients undergoing a liver transplantation is one of the most satisfying challenges of a pediatric anesthesiologist. Anesthetizing young, critically ill patients with highly complex diseases undergoing urgent and major surgery is even more rewarding considering the excellent long-term outcomes.

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Geraldine Diaz

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## Introduction

The number of orthotopic liver transplants performed (LT) in combination with transplantation of other solid organs has increased [1], and multiple factors have contributed to this. First, the last decade has seen a dramatic improvement in the medical management of patients with cirrhosis. The introduction of beta-blockade to decrease portal hypertension, widespread application of endoscopic modalities to treat esophageal varices, use of TIPS (transjugular intrahepatic portosystemic shunt), and effective medications to control hepatitis B viral replication have increased the life expectancy of patients with cirrhosis. As a result of improved life expectancy, patients with end-stage liver disease at times present with additional organ-system failures. A second contributing factor for increasing combined organ transplantation is the dramatic improvement in the outcomes of single-organ transplantation. The natural progression of these successes in abdominal and thoracic solid organ transplantation is the extension of these techniques to the arena of dual-organ transplantation.

Combined solid organ transplantation creates an entirely new dimension to the practicing anesthesiologist. These procedures are a

significant clinical challenge and require unique clinical considerations. Perioperative management must be “tailored” to the underlying etiology of organ failure, severity of illness, and the patient’s estimated physiologic reserve. This chapter will discuss the three most common combined solid organ transplant procedures involving the liver and their anesthetic implications.

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## Combined Liver–Kidney Transplantation

In the last 10 years, we have seen a substantial improvement of outcome after simultaneous liver–kidney transplantation (CLKT) [1, 2]. Improved medical management of the patient diagnosed with hepatorenal syndrome (HRS) awaiting liver transplantation as well as the implementation of the Model for End-Stage Liver Disease (MELD) system for liver allograft allocation in February 2002 [3] contributed to this success. The MELD score is a disease severity instrument derived from serum bilirubin, the international normalized ratio (INR) of prothrombin time, and serum creatinine which predicts the 90-day mortality from liver failure [4]. As the MELD is derived from historic data, it is considered by many to be overweighted toward renal function because HRS was a leading contributor to wait-list morbidity and mortality prior to advances in critical care and the implementation of continuous renal replacement therapy. The MELD score is discussed in detail elsewhere (Chapter 28 and others) in this book.

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HRS is a serious complication of advanced liver disease, with an annual incidence of 8% in patients with cirrhosis who develop ascites [5]. HRS results from activation of the sympathetic nervous system and renin–angiotensin–aldosterone system causing renal vasoconstriction, a compensatory response to the profound systemic arterial vasodilatation and decrease in effective central blood volume seen in patients with portal hypertension [5–7]. The result is decreased renal perfusion and glomerular filtration rate; however, tubular function is preserved [5, 7]. HRS is classically thought to be reversible following liver transplantation and is not a recognized indication for CLKT [3]. However, improvements in medical management, critical care, and (continuous) renal replacement therapy have dramatically prolonged the period that patients with HRS can wait for an allograft. This prolonged wait time has increased the incidence of liver transplant candidates diagnosed with HRS who may be considered for kidney transplantation following LT. Identification and selection of appropriate candidates for CLKT remains a clinical challenge despite multiple consensus conferences [8, 9]. This dilemma stems from an absence of reliable instruments to determine the etiology and reversibility of renal failure. Patients with prolonged HRS requiring renal replacement therapy may be indistinguishable from patients with irreversible renal failure. Recent consensus reports by the International Liver Transplantation Society and United Network for Organ Sharing have proposed the following criteria for CLKT:

- End-stage renal disease requiring 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
- Acute kidney injury with a requirement for dialysis at least two times per week for more than 6 weeks [8]

### Preoperative Evaluation

The preoperative evaluation should include an understanding of the etiology of liver and kidney disease, associated complications such as uremic

or hepatic encephalopathy, pericardial effusion, cirrhotic cardiomyopathy, hepatopulmonary syndrome, and coagulopathy. The anesthesiologist should query the duration of dialysis and the last hemodialysis session of the patient. Recent serum electrolytes must be obtained and reviewed prior to surgery.

Central venous access can be difficult in this patient population. Venous access should include a dialysis catheter and central lines for volume and pharmacologic resuscitation. Because of the nature of kidney and hepatic failure, these patients have inherent problems with vessel patency. Therefore, venous imaging such as real-time ultrasound or magnetic resonance mapping (MRI) as part of the preoperative evaluation of CLKT candidates can facilitate choosing the best route for venous access.

### Intraoperative Management

The allograft with the least cold-ischemic tolerance should be transplanted first. In CLKT, the surgery therefore usually begins with the liver transplant procedure followed by renal allograft transplantation. The surgeries are typically sequential; however, if necessary the liver transplant procedure can be completed and the patient stabilized in the intensive care unit prior to performing the kidney transplant procedure. This can be a very effective strategy when the liver transplant procedure is complicated by coagulopathy, hypothermia, hemodynamic instability, high vasopressor requirements, or early hepatic allograft dysfunction. Resuscitation in the intensive care unit for several hours often optimizes the patient prior to returning to the operating theater for completion of the CLKT through a separate skin incision.

Rapid sequence induction is preferred in CLKT secondary to delayed gastric emptying in patients with renal and hepatic failure [10]. Venous and arterial catheter placement should be discussed with the surgeon to optimize vascular access for the transplant procedure as it is very unpleasant to discover a venous or arterial catheter in the vascular clamp when implanting a

kidney! The anesthesiologist needs to clarify where the kidney will be implanted (left lower quadrant, right lower quadrant, or intra-abdominal) and avoid that area for venous and arterial access. Two arterial catheters, radial and femoral, are used in most centers. Radial arterial monitoring alone should be interpreted with caution as aortic pressure can be underestimated in hypotensive states, particularly at hepatic allograft reperfusion [11, 12]. The systolic pressure within the femoral artery is often higher than that of the radial artery, and the observed difference can be antagonized by the use of vasopressors [12]. Pulmonary artery catheter (PAC) and continuous transesophageal echocardiography permit measurement of cardiac pressures, evaluation of ventricular function, and detection of air or thrombotic emboli.

### **Liver Transplantation in the Presence of Renal Failure**

CLKT challenges the anesthesiologist with the presence of hepatic and renal failure. LT in the presence of renal failure is difficult as renal disease impairs acid–base physiology, hemostasis, and the ability to compensate for acute volume/electrolyte shifts secondary to blood transfusion and reperfusion [13]. Anesthetic management often requires the utilization of intraoperative continuous renal replacement therapy, aggressive red cell washing prior to transfusion, frequent laboratory analysis, venting of the hepatic allograft prior to reperfusion, and volume resuscitation guided by TEE and PAC pressures. Our group has also found flushing the hepatic allograft with low-potassium histidine–tryptophan–ketoglutarate (HTK) preservation solution prior to implantation to be particularly effective at reducing hemodynamic instability associated with allograft reperfusion. Frequent coagulation studies, clinical assessment of coagulation, and the use of thromboelastogram data guide transfusion therapy [14]. Desmopressin increases factor VIII levels and von Willebrand antigen and therefore should be considered for patients with uremic coagulopathy [13].

### **Renal Transplantation in the Presence of a Newly Transplanted Liver**

Similar concerns arise for renal transplantation in the presence of a newly transplanted liver. Aggressive fluid resuscitation during kidney allograft implantation may result in congestion of the hepatic allograft. The use of diuretics such as mannitol and furosemide during renal transplantation may also compromise hepatic function. Heparin is frequently administered during renal transplantation to ensure graft vessel patency and may be dangerous in the setting of hepatic allograft dysfunction.

Anesthetic considerations include judicious fluid resuscitation guided by monitoring TEE, PAC pressures, and urine output. The use of diuretics should be discussed with the surgeons and often depends on the function of the newly transplanted liver. Heparin administration should also be discussed and is often omitted in CLKT. Vasopressors should be avoided due to the potentially deleterious vasoconstrictive effects on the newly transplanted hepatic and renal allografts [15].

### **Postoperative Management**

The complexity of the postoperative period for the CLKT patient is related to the duration of surgery and the recovery of two allografts [16]. Hepatic allograft dysfunction manifests as persistent acidemia, coagulopathy, hypoglycemia, and encephalopathy [17]. Renal allograft dysfunction is associated with anuria or oliguria, acidemia, and electrolyte abnormalities. Hypotension is common in the postoperative period and may result from hypovolemia, hemorrhage, myocardial ischemia, arrhythmias from electrolyte/acid–base abnormalities, and vasodilatory shock. An echocardiogram to supplement PAC data may be helpful in the diagnosis and treatment of hypotension. Judicious vasopressor administration is paramount to optimize perfusion to both allografts. Assessment of abdominal drains and measurement of serum and abdominal drain hemoglobin concentrations can help with the diagnosis of ongoing hemorrhage. TEG and coagulation

studies should guide transfusion therapy. Obtaining a renal and hepatic ultrasound may demonstrate abnormalities in blood flow and trigger re-exploration. CLKT recipients often require a brief period of renal replacement therapy until the transplanted kidney regains sufficient function to cope with volume overload and the necessary diuresis often seen after liver transplantation.

Resolution of encephalopathy secondary to uremia and hepatic failure depends upon allograft function. Persistent encephalopathy may contribute to difficulty with weaning from mechanical ventilation and increases the risk of aspiration [10].

Immunosuppressive therapy and especially the use of nephrotoxic calcineurin inhibitors should be decided by a team of hepatologist, surgeons, nephrologist, and intensivists, and no unilateral changes in the immunosuppressive protocol should be done without agreement of all participating specialties.

## Combined Heart–Liver Transplantation

Combined heart and liver transplantation (CHLT) was originally described by Starzl et al. [18] in 1984 and has been successfully reported in adults and children [19–21]. CHLT is an uncommon procedure, with less than 50 procedures reported in the United States by the United Network for Organ Sharing Scientific Registry of Transplant Recipients (SRTR) database [1]. This, in part, reflects the significant surgical and medical challenges of identifying appropriate candidates who will tolerate such an extensive procedure.

Historically, there were few indications for CHLT, and definitive dual-organ candidacy criteria have not been established (Table 17.1). Indications for CHLT can be broadly categorized as a procedure to optimize the performance of a single organ, characterized by single-organ failure with minimal portal hypertension, or true dual-organ failure, characterized by concomitant cardiac, and liver failure, with portal hypertension and its complications (Table 17.1).

Reported outcomes of CHLT have been excellent. Porrett performed a review of the SRTR

**Table 17.1** Indications for combined heart–liver transplantation

I. Procedure to “optimize” performance of a single organ (Heart failure secondary to a metabolic defect in the liver)
Familial hypercholesterolemia
Homozygous beta-thalassemia
Familial amyloidotic polyneuropathy
Familial hypertrophic restrictive cardiomyopathy
II. True dual-organ failure (Heart and liver failure)
Hemochromatosis
Cryptogenic cirrhosis/cardiomyopathy
Alcoholic cardiomyopathy/cirrhosis

(Scientific Registry for Transplant Recipients) data which included 33 patients who underwent CHLT between 1992 and 2004 and reported 1-year and 3-year survival of 80 and 70%, respectively [22]. Current UNOS (United Network for Organ Sharing) policy underserves the CHLT population by not permitting the cardiac and liver allografts to be allocated as a single unit. Thus, it is very difficult for the recipient to be in the same allocation position on separate cardiac and liver allograft match lists. As a result, less than 30% of patients listed nationally for CHLT receive transplantation, and the overall mortality in this population is *greater* than that predicted by the sum of MELD and cardiac status scores [22].

## Preoperative Evaluation

Understanding the etiology of cardiac and hepatic failure is essential to the successful performance of CHLT. The indication for CHLT often will provide a clue as to the difficulty of the planned surgery. If the indication is to optimize the performance of a single organ, as in amyloidosis and familial hypercholesterolemia, the operative course will be much less difficult due to absence of portal hypertension. However, when the indication is true dual-organ failure, as in hemochromatosis or alcoholic cardiomyopathy, the surgery will be much more challenging secondary to the physiology of cirrhosis.

## Surgical Plan

No consensus has emerged regarding the ideal surgical technique for CHLT. Reported operative strategies range from complete cardiac transplantation with sternal closure before proceeding with the abdominal dissection to maximal abdominal dissection before initiating CPB [23, 24]. Shaw et al. [25] described the first three cases of CHLT in 1985 using CPB during cardiac transplant and venovenous bypass including portal vein decompression during the liver transplant portion. The authors suggested that venovenous bypass augmented cardiac support and enhanced hemodynamic stability during liver transplantation. However, Shaw et al. acknowledged that CPB induced coagulopathy, hypothermia, acidosis, and platelet dysfunction that required several hours to correct. Subsequent strategies to reduce hemorrhage advocated separate thoracic and abdominal transplant operations with interruption of extracorporeal circulation and heparin neutralization [24]. Although this technique reduced the period of anticoagulation, it significantly increased hepatic allograft cold ischemia. Conversely, Offstad et al. have advocated complete abdominal dissection prior to sternotomy [23]. This technique facilitates abdominal dissection without the presence of anticoagulation but significantly adds to the length of the total operative procedure as well as the cold ischemia time of both allografts. While no superior approach has emerged, it is critical that coordination between the cardiothoracic anesthesiologist, liver anesthesiologist, cardiothoracic surgeon, liver transplant surgeon, and perfusionists occur prior to surgery. Discussions should include surgical sequence, cardiopulmonary bypass (CPB), use of venovenous bypass, placement of bypass cannulas, placement of central venous catheters, PAC, arterial lines, heparin use, and reversal.

## Intraoperative Management

The successful performance of CHLT mandates attention to unique anesthetic considerations.

Two extensive operative procedures must be performed on a patient with limited physiologic reserve as a result of combined cardiac and hepatic failure. The cardiac transplant is initially performed to minimize the ischemia time of the heart and also because the failing heart will poorly tolerate the fluid shifts and hemodynamic instability associated with hepatic reperfusion.

## Cardiac Transplantation in the Presence of Liver Failure

The physiology of portal hypertension complicates the anesthetic management of cardiac transplantation. Gastric and intestinal motility are impaired with hepatic cirrhosis secondary to electrolyte disturbances and ascites [10]. While rapid sequence induction is ideal to prevent aspiration in the presence of a full stomach, it may cause hemodynamic instability among patients with cardiac failure. Cirrhotic patients demonstrate a hyperdynamic state characterized by low systemic vascular resistance and high cardiac output [26]. Increased vasopressor requirements during the cardiac transplant procedure should be expected in the presence of cirrhotic physiology. Balanced anesthesia using opioids, benzodiazepines, and muscle relaxants may be supplemented with low-dose volatile anesthetics to minimize vasopressor requirements and avoid hypotension associated with higher concentrations of volatile anesthetics [27].

Patients with liver failure suffer from impaired acid–base regulation, hypothermia, thrombocytopenia, and clotting factor deficiencies [10]. This further complicates the cardiac transplant procedure. Astute acid–base and volume management are prerequisites, in addition to metabolic support, to avoid disseminated intravascular coagulopathy, metabolic acidosis, associated arrhythmias, and increased pulmonary vascular resistance [28].

Vaso-mediated pulmonary hypertension or portopulmonary hypertension (PPHTN) can be exacerbated during hepatic allograft reperfusion and precipitate right ventricular dysfunction. Pulmonary arterial catheterization permits



immediate recognition of pulmonary hypertension and response to pulmonary vasodilators, while TEE is helpful in evaluating right ventricular function.

### **Liver Transplantation in the Presence of a Newly Transplanted Heart**

Liver transplantation incurs unique demands upon the newly transplanted heart. The cardiac allograft shows a normal Starling relationship between end-diastolic pressure and cardiac output [29]. As a result, the cardiac allograft is preload dependent and limited in its tolerance of the sudden declines in total venous return with clamping of the inferior vena cava [28]. In addition, large transfusion requirements associated with LT and ischemia reperfusion injury predispose to elevated pulmonary vascular resistance, right ventricular systolic dysfunction, and increased myocardial demand. Satisfactory right ventricular function is prerequisite to maintain adequate cardiac output, hemodynamic stability, and end-organ perfusion. Therefore, pulmonary artery pressure monitoring and TEE are integral to intraoperative volume management.

Reperfusion of the hepatic allograft is associated with electrolyte abnormalities, acidosis, hypothermia, and ischemia/reperfusion injury [30]. The “cytokine storm” triggered by ischemia/reperfusion increases cardiac demand and may precipitate arrhythmias in the newly transplanted heart. Venovenous bypass offers the theoretical advantage of attenuating sudden declines in venous return and hemodynamic instability secondary to allograft reperfusion [31]. Furthermore, judicious fluid management combined with immediate correction of electrolyte and acid–base abnormalities are essential to optimizing cardiac and hepatic performance.

### **Postoperative Management**

The postoperative course of the CHLT recipient depends on the patient’s functional status prior to transplantation, intraoperative complications, and

the immediate function of both allografts. Successful recovery of a CHLT recipient requires meticulous, coordinated care balancing the interests of the cardiac and hepatic transplant teams. Integration, communication, and a precise treatment plan for nurses and intensivists are essential.

Hemodynamics should be monitored utilizing a PAC and arterial catheter. Transthoracic or transesophageal echocardiograms supplement these data and should be obtained as necessary. PAC pressures, mixed venous oxygen saturation, arterial pressures, liver function tests, and urine output are principal determinants for discontinuing inotropic and vasopressor support. Chest tube output must be monitored closely and frequent laboratory tests obtained within the initial 24 h including arterial blood gas, lactate, liver function tests, complete blood count, and coagulation panel. A hepatic ultrasound is frequently obtained to evaluate vascular flow and patency within the hepatic allograft [17].

Early cardiac function dramatically affects the newly transplanted hepatic allograft. Right ventricular failure secondary to prolonged CPB, ischemia/reperfusion injury, or increased pulmonary vascular resistance is very concerning as right ventricular failure precipitates hepatic congestion and allograft dysfunction. Biventricular failure results in systemic hypotension with increasing vasopressor requirements that are deleterious to the hepatic allograft.

Persistent coagulopathy from CPB and hepatic dysfunction may manifest as continued abdominal and thoracic hemorrhage. Close attention to abdominal drains, chest tube output, wound dressings, and hemodynamic values can prevent hemorrhagic shock. Cardiac tamponade must be suspected in the setting of acute hypotension, elevation with equalization of diastolic pressures, or decreased chest tube output [32].

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### **Combined Lung–Liver Transplantation**

Combined lung–liver transplantation (CLLT) is uncommon with less than 25 procedures reported in the United States [1]. Thus, true performance benchmarks have yet to be established. Barshes

et al. have reported 1- and 5-year patient survival from the SRTR of 79 and 63% that is comparable to outcomes of isolated liver or bilateral lung transplantation [33]. In this cohort, the majority of patients are children or young adults under age 30 years. As found in CHLT, there is increased wait-list mortality and no prioritization under current UNOS allocation policy [34].

Indications for CLLT can be broadly categorized as end-stage lung disease with advanced liver disease, as in cystic fibrosis and alpha-1 antitrypsin deficiency, or end-stage liver disease with secondarily compromised lung function found in PPHTN and cirrhosis-associated hypoxemia with intrapulmonary shunting [33]. By far, the most common indication for CLLT is cystic fibrosis. Hepatic multilobar cirrhosis occurs in 20–30% of cystic fibrosis patients typically in the first decade of life [35]. The characteristic early hepatic lesion is focal biliary fibrosis which is thought to result primarily from the accumulation of abnormally tenacious bile in intrahepatic ducts that impedes bile flow and leads to biliary cirrhosis [34]. Hepatocyte function as estimated by serum albumin, prothrombin time, and transaminase may be normal or slightly impaired despite advanced multilobar cirrhosis [36]. However, progression to portal hypertension, hypersplenism, variceal bleeding, and ultimately end-stage liver failure occurs.

A less frequent indication for CLLT is PPHTN, with 3.5–8.5% prevalence among candidates awaiting liver transplantation [37, 38]. Mild PPHTN (mPAP 25–35 mmHg) is reversible with liver transplantation, but more severe PPHTN (mPAP > 45 mmHg) is a contraindication to liver transplantation given the high intraoperative mortality due to heart failure [39]. Pirenne reported two cases of CLLT for cirrhosis and severe refractory PPTHN: The first case resulted in fatal heart failure occurring after liver reperfusion, and the second patient successfully received en bloc heart–lung transplant followed by liver transplant due to anticipated risk of intraoperative heart failure after liver reperfusion [24].

## Preoperative Evaluation

It is imperative to determine the etiology and severity of pulmonary *and* hepatic disease. Coordination between the thoracic anesthesiologist, liver transplant anesthesiologist, thoracic surgeon, liver surgeon, and perfusionist is essential during the preoperative period with discussions focused upon surgical sequence, catheter placement, CPB, venovenous bypass, and incision location. Lung transplantation is performed first followed by liver transplantation. Various surgical sequences have been reported including (1) integrated, concomitant dissection of the chest and abdomen prior to CPB, initiation of CPB, followed by en bloc combined thoracic and liver transplantation [40], and (2) completion of thoracic organ implantation and discontinuation of CPB before laparotomy, abdominal dissection, and LT [34]. The latter technique decreases hepatic warm ischemia by permitting liver allograft preparation during the thoracic dissection. In this sequence, abdominal dissection occurs after reversal of heparin.

There is wide variation in the frequency of CPB utilization during lung transplantation. One-lung ventilation without CPB may avoid the dilutional coagulopathy and thrombocytopenia secondary to CPB, which may be beneficial in the setting of coagulopathy of liver disease. However, all CLLT cases reported in the literature utilized CPB [24, 33, 34, 40].

## Intraoperative Management

Intraoperative monitoring should include an arterial catheter, pulmonary arterial catheter (PAC), and TEE. The PAC is positioned only to the central venous position during the initial placement, and further relocated into the pulmonary artery after unclamping of the pulmonary arteries. Balanced anesthesia with opioids and volatile agents provide hemodynamic stability.

The most common intraoperative complication reported in CLLT is pulmonary hypertension associated with reperfusion of the liver allograft. Zimmerman et al. reported

successful management of severe pulmonary hypertension in a 14-year-old girl with cystic fibrosis utilizing prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) and dobutamine administered via a PAC [41]. Pirrene reported a fatal case of right heart failure occurring after liver allograft reperfusion, despite the utilization of portal and systemic venovenous bypass [24].

## Postoperative Management

Intricate coordination between the pulmonary and hepatic transplant teams is essential as their clinical goals are frequently contradictory. While the pulmonary transplant team frequently advocates early intravenous fluid restriction to avert pulmonary edema and facilitate early extubation, the liver transplant team will be concerned about hypoperfusion of the new liver allograft. Open discussion and data-driven management are critical to a successful outcome. Laboratory values, including arterial blood gas, lactate, and liver function tests, are helpful in assessing lung and liver allograft function. Bronchoscopic examination is performed routinely or when clinically indicated. Doppler ultrasonography of the hepatic artery and portal vein is also helpful in the postoperative period.

## Conclusion

Notable achievements in the performance of isolated solid organ transplantation have broadened the indications for these procedures and stimulated the performance of multiorgan transplantation. Transplantation of the liver with additional thoracic or abdominal organs is increasing in frequency. Prerequisite to the successful performance of these procedures from an anesthesia/critical care perspective is an intricate understanding of the disease and its pathophysiology and seamless communication between all clinical parties to reduce organ ischemia, facilitate optimal allograft function, and minimize morbidity.

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Cynthia Wang and Randolph Steadman

The model for end-stage liver disease (MELD) is a system for scoring the severity of liver disease. The model was developed in 2000 to predict survival in patients undergoing transjugular intrahepatic portosystemic shunt placement. In 2002, the Organ Procurement and Transplantation Network adopted the MELD score as the standard for prioritization of graft allocation for liver transplantation [1–3]. With few exceptions (hepatocellular carcinoma and acute liver failure), those patients with highest MELD scores have the highest priority for organ allocation for orthotopic liver transplantation (OLT) in many countries, including the United States. Since the implementation of the MELD system, wait-list mortality has significantly decreased, waiting time to liver transplantation has been reduced by over 100 days, and the MELD score has proven to be a good marker for 1-year posttransplantation survival [4–7]. The MELD score is a composite of three laboratory values: the international normalized ratio (INR) [8], serum creatinine, and serum bilirubin [9].

$$\begin{aligned} \text{MELD} = & 9.6 \times \log_e (\text{creatinine}) \\ & + 3.78 \times \log_e (\text{bilirubin}) \\ & + 11.2 \times \log_e (\text{INR}) + 6.43 \end{aligned}$$

Any laboratory value below one is set at one for the purpose of MELD calculation to prevent negative MELD scores. For serum creatinine levels above four mg/dl or for patients requiring dialysis twice or more per week, a creatinine value of 4.0 is entered in the formula [10].

Patients with high MELD scores (MELD > 30) who present to the operating room for OLT have characteristics that are associated with greater perioperative challenges and risks as compared to patients with lower MELD scores [11, 12]. Although these characteristics are often directly associated with the MELD score (i.e., renal insufficiency and coagulopathy), there are also MELD-unrelated factors in this patient population that contribute significantly to perioperative risk.

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## Renal Insufficiency

The etiology of preoperative renal insufficiency in patients awaiting liver transplantation is often multifactorial and presents a unique cadre of clinical considerations in the perioperative period. Patients with end-stage liver disease (ESLD) and coexisting renal failure are at higher risk of death while awaiting transplantation when compared to patients with ESLD who have preserved renal function [13, 14]. It is estimated that survival in

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patients with cirrhosis and renal failure is approximately 50% at 1 month and 20% at 6 months [15]. Posttransplantation, these patients are also at higher risk for postoperative complications, prolonged hospitalization, and decreased survival.

OLT is a complex and lengthy procedure associated with major hemodynamic alterations, fluid shifts, and metabolic derangements. These changes are less well tolerated in patients presenting to the operating suite with preexisting renal dysfunction whether or not they have been receiving renal replacement therapy (RRT) preoperatively [16].

The intravascular volume status of cirrhotic patients with renal dysfunction is difficult to assess. Cirrhotic patients are prone to systemic vasodilatation, extravasation of intravascular volume due to low oncotic pressure, and decreased effective circulating blood volume. Volume overload can occur in patients with renal insufficiency, particularly prior to the institution of RRT. More commonly, however, the patient in renal failure on RRT who presents for liver transplantation is either euvoletic or hypovolemic at the time of surgery. Regardless of the patient's initial volume status, fluid management is very challenging in this patient population. The potential for massive blood loss and high transfusion requirements during surgery in an oliguric or anuric patient dictates close monitoring of intravascular volume status. While there is no evidence that the use of an intraoperative pulmonary artery catheter improves outcome, many clinicians consider it a helpful guide to fluid management during surgery. Intraoperative use of transesophageal echocardiography as a monitor to assess volume status is increasingly used during liver transplantation and may be especially useful in patients with high MELD scores and/or significant comorbidities. Central venous pressure (CVP), though frequently monitored and recorded during liver transplant procedures, is not an accurate reflection of intravascular volume status. Multiple studies have shown that there is no correlation between CVP and effective circulating blood volume [17]. Vigilant monitoring of fluid administration is crucial, especially during periods of sudden

fluctuation in volume status, that is, during clamping of the vena cava and portal vein prior to hepatectomy, venting of the liver prior to reperfusion, and during brisk blood loss in the dissection phase.

Even in patients with preexisting nonoliguric renal insufficiency, it is prudent to note that the circulatory and hemodynamic disturbances associated with the transplant procedure can worsen renal dysfunction. These patients may become oliguric intraoperatively, most commonly during the anhepatic and neohepatic phases. There is no evidence that renal protective measures such as mannitol, furosemide, and dopamine have any benefit [18, 19].

Metabolic abnormalities during liver transplantation are more frequent and challenging in patients with preexisting renal dysfunction. Reperfusion of the newly transplanted graft is associated with an influx of potassium, lactic acid, and inflammatory mediators into the circulation. The hyperkalemia and acidemia encountered upon reperfusion can be fatal, especially in patients with compromised renal function who are unable to compensate for these intraoperative physiologic changes. Furthermore, if the patient has received large volumes of banked blood, potassium can be dangerously high by the time of reperfusion, further increasing the risk for life-threatening arrhythmias [20]. Patients with significant acidemia or electrolyte disturbances may not be able to tolerate reperfusion. These situations must be anticipated, and intraoperative RRT should be considered upon arrival to the operating room so that sufficient time (at least 1–2 h) is allotted to correct the acidosis and/or hyperkalemia prior to reperfusion. Intraoperative continuous venovenous hemodialysis (CVVHD) is frequently used; however, it may be less effective than single-pass conventional hemodialysis in correcting acidemia and electrolyte disturbances over a limited time period [21]. Large-bore venous access is required for CVVHD or single-pass hemodialysis and should be placed prior to surgery.

Combined liver–kidney transplantation is indicated in cirrhotic patients with preexisting chronic renal disease whose renal failure is not expected to improve after successful



**Table 18.1** Indications for combined liver and kidney transplantation

I. Advanced liver disease with chronic kidney disease
(a) <i>Coincidental</i> Glomerulonephritis/glomerulopathy (membranous, membranoproliferative, IgA nephropathy, focal glomerulosclerosis, anti-GBM disease, scleroderma, SLE, diabetes mellitus) Interstitial renal disease (chronic pyelonephritis, analgesic nephropathy, sickle cell anemia, renal transplant failure, sarcoidosis) Structural (obstructive uropathy, medullary cystic disease, nephrolithiasis, malignant hypertension, renal artery thrombosis)
(b) <i>Associated</i> Polycystic disease Glomerulonephritis/glomerulopathy associated with viral hepatitis (HBV, HCV) HCV chronic liver disease in chronic renal failure patients on hemodialysis (HD)
(c) <i>Calcineurin inhibitor (CNI) toxicity</i>
II. Advanced liver disease with acute renal failure/acute chronic Hepatorenal syndrome (HRS) Acute tubular necrosis (ATN)
III. Metabolic
(a) <i>Affecting both organs</i> Sickle cell disease Alpha 1 antitrypsin deficiency Glycogen storage disease type I
(b) <i>Affecting mainly kidney, liver serving as a gene therapy for correcting the metabolic disorder</i> Primary hyperoxaluria I Amyloidosis Hemolytic-uremic syndrome Methylmalonic acidemia
IV. Miscellaneous Immunoprotection of kidney in positive cross-match Abdominal fibromatosis COACH syndrome Acute intoxication of chromium-copper

Table 2 in [22]

transplantation of a new liver. Indications are listed in Table 18.1. In patients who have developed renal disease as a result of liver failure, that is, in these patients with hepatorenal syndrome, the guidelines for combined transplantation are less well defined. The determination to perform a combined liver–kidney transplant in these patients is generally based on the length of time the patient has been on RRT prior to surgery. The length of time on RRT and hence the time at which renal failure is

considered irreversible has been described from 1 to 12 weeks. Patients who required dialysis longer than 3 months prior to liver transplantation have an increased survival with combined liver–kidney transplant compared to isolated liver transplantation (87% vs. 75%,  $P=0.02$ ) [15]. It has been recommended that patients with severe renal dysfunction defined by a glomerular filtration rate  $<30$  mL/min, and those with rapidly progressing renal disease, should be considered as candidates for combined liver–kidney transplantation [23]. More about combined liver–kidney transplants is found elsewhere (Chapter 17) in this book.

## Coagulopathy and Transfusion

Liver transplant surgery is often associated with massive blood loss and transfusion, factors that are associated with poor postoperative outcomes. Massive transfusion is associated with a higher incidence of postoperative infections, hemolysis, allergic reactions, and death [24–26]. Patients with high MELD scores are at greater risk of requiring large volumes of intraoperative transfusions [27]. Highly elevated INR is indicative of more advanced coagulopathy, and increases of INR and creatinine, both components of the MELD score, are associated with elevated intraoperative blood loss and transfusion requirements [28].

In addition to elevations of INR, patients with high MELD scores often have lower preoperative hematocrit and fibrinogen levels [11]. There is a positive correlation between MELD score and transfusion requirements during OLT. Single-center studies have demonstrated that patients with MELD scores greater than 30 require on average 5 more units of packed red blood cells and 7 more units of fresh frozen plasma when compared to patients with lower MELD scores [12]. Transfusion requirements for cryoprecipitate and platelets were also doubled in this patient population. Furthermore, patients with high MELD scores also received rescue antifibrinolytic agents more frequently than those with lower MELD scores.

The use of recombinant factor VIIa in OLT is controversial. Though factor VIIa may reduce transfusion requirements in selected cases, several randomized trials have failed to show a benefit [29–31]. Data on the use of recombinant factor VIIa in patients with high MELD scores is limited. Liver failure and high MELD scores are associated not only with coagulopathy but also hypercoagulability since production of anticoagulant factors is reduced as well. Use of recombinant factor VIIa in ESLD may predispose these patients to the development of fatal thromboembolism if administered indiscriminately.

Yet, massive bleeding and transfusion requirements during OLT exacerbate complex circulatory and metabolic derangements and are associated with reduced graft and patient survival [32]. Despite the fact that many cirrhotic patients have a prolonged INR due to the inability of the liver to synthesize coagulation factors, patients with severe liver disease are also at increased risk of hypercoagulability secondary to abnormal polymerization of clot and accelerated intravascular coagulation. These disturbances in coagulation are often exacerbated by sepsis, circulatory failure, or blood loss necessitating massive transfusion [25, 33]. Inherited thrombophilias such as protein C and S deficiencies, antithrombin deficiency, factor V Leiden, and lupus anticoagulant may also increase the risk of perioperative thrombotic events, increasing the morbidity of liver transplant recipients [34, 35].

It is prudent to ensure adequate venous access and a sufficient supply and easy access to banked blood products for patients with high MELD scores. Particular attention must be paid to the presence of other factors that may exacerbate the potential for intraoperative bleeding, such as a history of, prior abdominal surgeries and/or significant portal hypertension. Monitoring coagulation status by following fibrinogen, PT, PTT, INR, and platelet levels at frequent intervals during the operation may help guide transfusion therapy. Although thromboelastography (TEG) is not used routinely at all institutions, it may provide insight into the patient who is hypercoagulable or has fibrinolysis. However, the sensitivity and

specificity of TEGs is not well defined, and abnormal TEG tracings are not always associated with an abnormal coagulation status [36, 37]. Likewise, thrombocytopenia related to hypersplenism is not typically associated with bleeding.

In the high MELD patient, volume replacement therapy is best managed with a combination of packed red blood cells and fresh frozen plasma. In the setting of poor hemostasis and ongoing coagulopathy due to hypofibrinogenemia and thrombocytopenia, cryoprecipitate and platelets may also be administered. However, there is no absolute transfusion threshold for these products, and transfusion practices may vary by center. The excessive use of crystalloid and colloid solutions may lead to worsening of preexisting coagulopathy by hemodilution. Intraoperative blood salvage is used at some institutions during OLT; however, it should not be used in patients with hepatocellular carcinoma or in patients with bacterial peritonitis due to the possibility of bacterial contamination. The use of leukocyte depletion filters with intraoperative blood salvage devices may reduce the complications associated with allogeneic transfusion [38].

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## Severity of Disease

In addition to MELD-related indicators of liver disease (INR, creatinine, and bilirubin), the MELD score has been shown to correlate with MELD-unrelated markers that indicate severity of liver disease. Patients with high MELD scores have a higher incidence of ascites and more frequently require preoperative ventilatory and vasopressor support, all markers for advanced disease. These patients also have longer preoperative hospital stays, predisposing them to additional comorbidities prior to liver transplantation [11, 12]. Intraoperatively, patients with high MELD scores have demonstrated a greater need for fluid boluses and vasopressor infusions. The need for vasopressors in this patient population may be exacerbated by the increased incidence of intraoperative blood loss. Vasopressor use may be problematic, causing decreased hepatic perfusion and potentially worsening outcome [12].

Ascites alone is associated with increased requirements for intraoperative vasopressors.

High MELD scores are also associated with excessive changes in cerebral blood flow during transplantation which may affect the ability to assess the etiology of mental status changes. It has been demonstrated that both a high MELD score and pretransplantation mechanical ventilation are predictive of postoperative altered mental status [39]. Brain perfusion scans during OLT have suggested that patients with high MELD scores experience cerebral hyperperfusion intraoperatively that may cause neurological damage through cerebral hypertensive episodes. These neurological complications can be devastating and a major source of postoperative morbidity and mortality [39, 40].

Other MELD-unrelated factors such as hypertension, diabetes mellitus, and coronary artery disease exhibit little variation between patients with high vs. low MELD scores. Nevertheless, understanding both MELD-related and MELD-unrelated factors that contribute to increased perioperative risk and postoperative morbidity and mortality can help guide management, resource utilization, and steps to improve patient outcomes.

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## Organ Allocation

Despite the reduction in wait-list mortality since the introduction of the MELD system, the scarcity and quality of donor organs remains a major concern when allocating organs to patients awaiting liver transplantation. The disproportion between organ demand and supply continues to increase, and the current system for organ allocation does not take into account the quality of the donor organ. Centers may avoid accepting extended criteria donor organs for the sickest patients with the highest MELD scores. Extended criteria organs include those that come from older donors, donors who have undergone a period of mechanical ventilation and/or hospitalization in an intensive care unit prior to procurement, organs with evidence of high-grade steatosis, or grafts with exceedingly long warm and/or cold

ischemia times. The defining features of the extended criteria organ are not standardized between studies [41–43].

In light of the scarcity of organs, the use of grafts donated after cardiac death (DCD) has become increasingly common. For DCD grafts, death is declared on the basis of cardiopulmonary criteria rather than based upon the cessation of brain function. This subjects the organ to additional warm ischemia time due to an often unspecified period of hypotension. Higher incidences of non-anastomotic biliary stricture, hepatic artery thrombosis, hepatic abscesses, and primary graft nonfunction have been described in patients who have been transplanted with DCD organs [44]. Traditionally, DCD organs have been avoided in the sickest patients with the highest MELD scores, and matching DCD organs with patients with lower MELD scores may be the best way to utilize this resource effectively [45–49].

Recently, these donor and graft characteristics have been used to create a mathematical model known as the donor risk index (DRI). Organs with a high DRI are associated with higher rates of graft failure. Recent evidence has also suggests that patients with high MELD scores experience a greater survival benefit when transplanted with low DRI grafts. The survival benefit remains, but is less, when high MELD recipients are transplanted with high DRI grafts [50–53].

Living-donor liver transplantation is another source of organs, though living donation presents a risk to both the donor and the recipient. Recent studies that have compared the differences in survival between patients with high and low MELD scores receiving adult-to-adult living-donor liver transplants have suggested that there is no difference in survival between the low MELD group and the high MELD group [54, 55]. However, these findings are based on studies with limited sample sizes, and further studies of the use of live donors for patients with high MELD scores are needed before any definitive conclusions can be drawn [56]. However, living-donor liver transplantation may be a viable option when considering the high wait-list mortality of patients with MELD scores above 30 [57].

## Conclusions

The patient with a high MELD score who comes to the operating suite for an OLT presents a unique set of challenges in the perioperative period. A thorough understanding of the impact of the MELD score on the management of these patients is crucial in navigating through a technically complicated surgical procedure that is physiologically taxing but lifesaving for the patient.

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# Perioperative Considerations for Transplantation in Acute Liver Failure

# 19

Christopher P. Snowden and David M. Cressey

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## Introduction

In contrast to the intensive care management of the patient with acute liver failure (ALF), the perioperative anesthetic management of emergency liver transplantation for ALF has received limited attention in the medical literature. Although many of the principles regarding recipient management can be transferred from the intensive care unit (ICU) setting into the intraoperative period, the liver transplantation procedure (including transfer to operating room) creates concerns that require specific anesthetic management. Ultimately, this will allow a smooth transition throughout the procedure and into the recovery phase.

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## Patient Population

The paucity of literature concerning the anesthetic management of ALF patients may in some part be explained by the fact that they comprise only 7% [1] to 10% [2] of liver transplantation recipients. Paracetamol poisoning remains a major etiological factor for ALF in adult patients in North America and Europe, estimated at 46% and 61% of USA [3] and UK [4] cases, respectively. This is reflected in a predominantly younger age group of ALF patients, with minimal evidence of chronic liver disease presenting for emergency liver transplantation. There is also a relatively low incidence of other co-morbid disease including ischemic heart disease or chronic pulmonary conditions that may increase perioperative risk. However, the rapid onset of preoperative multiorgan failure (MOF), especially involving cardiovascular, renal and cerebrovascular dysfunction, creates specific practical and physiological challenges for the transplant anesthesiologist.

Even with the development of MOF, the current outcome of patients with ALF who undergo transplantation is excellent and in some series (especially following paracetamol poisoning) rivals that of elective liver transplantation for chronic disease. One study reported patient survival at 1, 3 and 5 years as 72%, 70% and 67%, respectively [5]. This is in part due to appropriate early identification of patients who may require transplantation, in addition to aggressive intensive care therapy from the

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outset. Identification of patients too sick to survive the transplantation procedure or who are likely to have poor post-operative survival (i.e. recidivist heavy intake alcoholics, active repeat suicide risk) may also improve outcome figures. In addition, when time from listing to organ procurement is prolonged, some degree of self-selection will occur, whereby supportive measures are not able to maintain a rapidly deteriorating patient. This often leaves the more physiologically adaptable patients to receive the available organs. If artificial liver support and bridging therapies improve, it may be possible to support ever sicker patients to facilitate transplantation. However, at present, there is no evidence to suggest existing bridging therapies affect outcome in ALF [6].

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## Preoperative Considerations

Preoperative management of the ALF patient in the ICU is particularly relevant to the transplant anesthesiologist, and early communication with the intensivist is important prior to and following listing for transplantation. Patient transfer is potentially destabilising and must be performed carefully. The specific supportive measures for MOF will already have been established in ICU as part of preoperative optimisation. Maintenance of these modalities into the operating room environment, including inotropic and vasopressor infusions, protective ventilatory strategies and renal support, is important in maintaining stability for the forthcoming operative period. Relevant practical considerations prior to transfer of the patient to the operating room are shown in Table 19.1. All infusions should be continued to ensure stability and nearly completed drug infusions changed prior to transfer. Ventilation is optimally provided by portable mechanical ventilation given the inherent variation in manual ventilation with the risk of hypercapnia and intracranial hypertension. Patients with established lung injury require maintenance of appropriate positive end-expiratory pressure levels. Head positioning including 15° head raise in the neutral position must also be ensured to avoid intracranial pressure (ICP) elevation. Many centres prefer not to use continuous

muscle relaxation in the ICU to reduce the risk of developing polymyopathy. However, muscle paralysis prior to operating room transfer will reduce the risk of surges in ICP associated with valsalva maneuvers caused by coughing and allow more consistent ventilation during transfer. Where continuous veno-venous hemofiltration (CVVH) has been in use on the ICU and is to be recommenced in the operating room, it is advisable to electively “wash back” the circuit prior to transfer, as mechanical cranking of circuits during transfer is impractical.

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## Pre-emptive Total Hepatectomy

Where total cardiovascular or neurological collapse secondary to liver failure seems imminent and where a donor organ is not yet available, the possibility of elective total hepatectomy with portocaval shunting prior to liver transplantation should be considered. It has been stated that “toxic liver syndrome” could be treated by means of this strategy [7, 8]. In most reports, this procedure has demonstrated a stabilising effect on the neurological status in patients with ALF [9, 10]. In contrast, the effect on cardiovascular stability has been variable [11, 12]. This procedure provokes some difficult ethical issues, as once the liver is removed, the patient clearly has no hope of survival beyond a limited timescale without a donor organ being implanted. If there was any doubt that the patient might have a chance to survive without a transplant, then the ethic of “do no harm” may be evoked. In our institution, hepatectomy has only been used in extreme cases where a suitable donor organ is known to be available and harvest is imminent or, more frequently, where the donor organ has been already viewed and deemed macroscopically usable.

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## Liver Transplantation Procedure

### Surgical Considerations

The type of surgical procedure for emergency liver transplantation will depend on regional surgical

**Table 19.1** Key discussion points prior to transfer of patients to the operating theatre

Factor to consider	Discussion points
Invasive access/monitoring	Vascular access and line position related to theatre requirements, available method of cardiac output assessment, presence of ICP measurement device, access for established continuous veno-venous hemofiltration (CVVH)
Ventilation parameters	Modes and pressure settings required to maintain adequate oxygenation and PaCO <sub>2</sub> levels, availability of these same ventilation modes in theatre, the presence/absence of permeability pulmonary edema
Stability issues	Cardiovascular and ICP stability prior to theatre transfer, response to therapy
Renal support	Overall fluid balance, details of CVVH flow rates
Sedation and paralysis	Regimes, recent administration of paralysis agent
Coagulation issues	Adequacy of preoperative correction, availability of pre-ordered blood products

experience and expertise. No published study has demonstrated an advantage of any one surgical technique for ALF. Wherever a conventional caval clamping technique is used without veno-venous bypass, it is the authors' opinion that this is likely to be more of a challenge from a cardiovascular and neurological perspective than other techniques due to instability from decreased venous return and the requirement for increased fluid transfusion [13]. However, institution of veno-venous bypass remains a balance between the benefits gained in cardiovascular stability vs. the risks of complex line insertion and prolonged surgery.

## Anesthetic Considerations

The primary considerations for the anesthesiologist involved in transplantation for patients with ALF in addition to those for non-emergency transplantation are those of:

- (a) Cerebrovascular stability (closely linked to cardiovascular stability)
- (b) Avoiding coagulopathy
- (c) Use of intraoperative CVVH
- (d) Potential for use of marginal donor organs and ABO-incompatible donor organs
- (e) Acceptance of requirement for extended post-operative recovery

## Cerebrovascular Stability

Patients with fulminant hepatic failure (FHF) and encephalopathy may have impaired cerebral

autoregulation, and variations in mean arterial pressure will tend to result in marked changes in cerebral blood flow (CBF). It follows that cardiovascular stability during transplantation is of paramount importance to the maintenance of cerebral perfusion pressure (CPP). A decrease in cerebral compliance leading to an increase in ICP may occur through either excess CBF or an increase in interstitial fluid secondary to endothelial leak. Alternatively, ICP rises may be secondary to ischemia. Gaining a balance between the two distinct entities is critical to cerebral protection during transplantation.

Many patients with ALF have evidence of cerebral "luxury" perfusion and cerebral hyperaemia secondary to reduced cerebrovascular resistance. It has been demonstrated that ICP surges in FHF are likely to be due to an increase in CBF [14]. Intraoperative measurements of the ICP, cerebral metabolic rate of oxygen (CMRO<sub>2</sub>) and CBF during transplantation in patients with FHF have also demonstrated that ICP is more usually related to rises in CBF than ischemia induced by reduction in CPP secondary to systemic hypotension [15]. Therefore, although a threshold CPP must be maintained, relative hypertension during and after reperfusion may be more detrimental in terms of increasing the risk of increased microvascular pressure, cerebral hyperperfusion and ultimately cerebral edema. Unfortunately, intraoperative changes in ICP are often hemodynamically silent. Direct measurement of the ICP may be advantageous in the setting of liver transplantation, but the advantages of being able to act swiftly on an incipient rise in

ICP must be balanced against the definite risk of intracerebral hemorrhage secondary to coagulopathy.

Changes in ICP are often temporally predictable during different stages of emergency transplantation. Lidofsky [16] demonstrated that peaks of ICP occurred during the dissection, anhepatic and early reperfusion phases. However, in more recent reports [17, 18], the increases in ICP seem to occur more consistently in the reperfusion and dissection phase only with either a stabilisation or more often a reduction in pressure during the anhepatic phase. These differences may be due to a requirement to increase central venous pressure to maintain venous return prior to the development and use of VVB during the anhepatic period. The temporal changes during the transplantation procedure have been attributed to various mechanisms including early inflammatory substances released from the failing liver, de novo cytokine production from the newly perfused liver and cerebral hyperperfusion secondary to an increase in venous return [19].

Although temporal ICP rises during the procedure are somewhat predictable, the cerebral response of an individual patient is variable. In an early report [20], all patients maintained a higher ICP throughout the procedure when compared with preoperative ICU values. Detry et al. [17] suggested that those patients who developed preoperative rises in ICP may be at greater risk of intraoperative changes of ICP presumably representing reduced cerebral compliance in these patients. However, this finding has not been universally accepted. Individual variation may be explained by the complex relationship between CBF, CPP and cerebrovascular resistance in patients with abnormal autoregulation, which in itself is not an “all or nothing” phenomenon.

Given this degree of variation in ICP response during transplantation, the management of phasic ICP changes during the procedure is complex. The use of moderate hypothermia to control changes in ICP has been applied to patients with FHF [21]. Jalan et al. [18] have shown that moderate hypothermia abolished ICP variability throughout the transplantation procedure in patients even when preoperative control was very

difficult. Other evidence suggests that hypothermia may reinstate cerebral autoregulation and reduce cerebral hyperperfusion [22, 23]. The significance of these changes has not been demonstrated in an outcome study, but hypothermia seems a reasonable therapeutic strategy where ICP control is troublesome.

Whilst hypothermia can be used as an important baseline strategy for reducing surges in ICP, other manipulations may also be important. Variations in ICP during the early dissection phase can be reduced by expeditious hepatic artery/portal vein clamping. The development of an anhepatic state often promotes a reduction in the requirement for vasoconstrictors and inotropes [24], enabling better cardiovascular stability. Furthermore, rapid fluid removal via CVVH and mild hyperventilation in anticipation of increased CO<sub>2</sub> production may attenuate increases in ICPs at reperfusion. If acute rises in ICP occur, standard active measures including the use of mannitol and single-dose ibuprofen remain the emergency measures of choice. Management of increased ICP is described in more detail elsewhere (Chapter 23) in this book.

## Coagulopathy

Given that the vast majority of procoagulant and anticoagulant stimulatory and inhibitory factors are either synthesised or metabolised in the liver (von Willebrand factor, tissue plasminogen activator (t-PA) and thrombomodulin being amongst the exceptions), the development of ALF can lead to complex multifactorial coagulopathy. Although spontaneous hemorrhage is relatively uncommon in ALF in the ICU, early correction of coagulopathy is important when operative intervention is imminent. Standard methods of correction utilise FFP, cryoprecipitate and platelets guided by laboratory studies. However, this may lead to excess blood product transfusion. Indeed, the balance between blood product transfusion to control coagulopathy and replace blood loss in the setting of cerebral dysfunction remains a constant threat to stability throughout the transplantation procedure. The emphasis is on using blood

conservation techniques to avoid the large volume transfusion whilst maintaining coagulation stability with alternative coagulation strategies and the minimal use of selective blood products.

Thromboelastography (TEG) can provide a measure of overall clot formation and function, including the presence of hyperfibrinolysis, within 20–30 min. TEG-guided therapy as a whole (including determining the need for platelets, FFP and cryoprecipitate) may reduce transfusion requirement by up to 33% [25]. Other methods to avoid excess transfusion in acute liver transplantation include the use of cell salvage, relative hypotension and controlled hypovolemia [26]. Whilst cell salvage is ideally suited for transplantation for ALF, the need to maintain optimal cardiovascular stability for neurological protection and reduction of the effects of MOF means hypotensive, and hypovolemic approaches are not ideal in these circumstances.

In the pre-reperfusion phase of transplantation, the emphasis is on maintaining adequate coagulation control secondary to the complete loss of liver function whilst maintaining adequate circulating volume when blood loss is prominent. The development of recombinant factor VIIa provides an alternative to large-scale transfusion, and several studies support the use of recombinant factor VIIa in acute liver transplantation [27, 28]. Within 15 min of an intravenous dose of recombinant factor VIIa, almost complete correction of prothrombin time may be achieved. This effect seems to persist until reperfusion [29], and the judicious use of factor VIIa has demonstrated a reduction in transfusion requirement in some studies [30]. The main concern with the use of VIIa (and indeed any procoagulant) is an increase of thromboembolic events and of especially hepatic artery thrombosis (HAT). HAT post-transplant is associated with a high risk of graft loss and greatly increased mortality. Therefore, any actions to correct coagulopathy must be balanced against the risk of excessive procoagulation. Whilst several studies report no increased incidence of thromboembolic complications with VIIa, others suggest caution in its use [31].

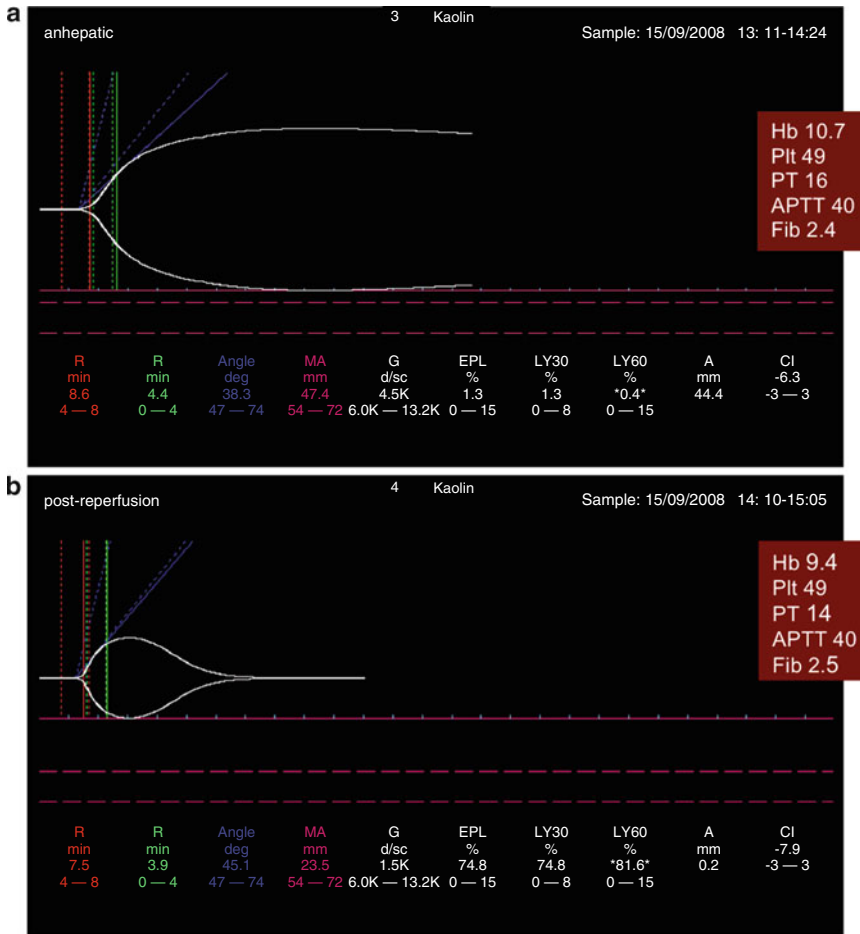
Post-reperfusion, primary hyperfibrinolysis is a common cause of coagulation dysfunction with

a quoted incidence of 80% and 40% being severe [25]. This is due mainly to an imbalance between hepatic metabolism of t-PA and synthesis of plasminogen activator inhibitor-1 (PAI-1). During the anhepatic phase, t-PA breakdown in the liver ceases [32]. Immediately post-reperfusion, a large release of t-PA into the circulation from the donor liver endothelium, accumulated during the cold ischemia period, accentuates [33] t-PA excess and overwhelms activity of plasminogen activator inhibitor-1 (PAI-1) [34]. Factor VIIa has no effect in reducing hyperfibrinolysis [35]. Furthermore, standard laboratory coagulation studies will not identify fibrinolysis, and TEG is invaluable in this phase (see Fig. 19.1). Spontaneous recovery from hyperfibrinolysis during post-reperfusion commences after 30–60 min but does not return to normal before 2 h [25]. In the presence of brisk hemorrhage, which may be related to hyperfibrinolysis, waiting for spontaneous recovery may allow consumptive and dilutional coagulopathies to supervene. As a result, early therapy based on regular assessment of the TEG trace is appropriate.

Before aprotinin (a serine protease inhibitor which prevents plasminogen splitting to form plasmin) was removed from the market in 2008 following the BART study [36], its prophylactic use in all liver transplantation as the first-line anti-fibrinolytic agent was well supported and was shown to significantly reduce transfusion requirements [37]. Now the two available lysine analogues (which inhibit conversion of plasminogen) tranexamic acid and epsilon aminocaproic acid (EACA; unlicensed in Europe) are the agents of choice. An intravenous dose of either given prophylactically prior to reperfusion or, preferably, after establishing the presence of hyperfibrinolysis using TEG can provide rapid reversal of that aspect of coagulopathy.

## Perioperative Fluid Balance

The initiation of CVVH in the ICU in patients with renal impairment has become a standard procedure in patients with ALF to allow fluid management, ICP control and enable coagulation



**Fig. 19.1** TEG traces. (a) Anhepatic phase represents a relatively normal clotting profile with minor abnormalities associated with a corrected coagulation state in a patient with ALF. (b) After reperfusion in the same patient, marked hyperfibrinolysis associated with reperfusion of the donor liver is clearly demonstrated. The initial forma-

tion of clot with line divergence is followed by rapid return of the two lines to a single straight line indicating clot lysis. The standard laboratory results for a blood sample taken simultaneously with the TEG sample are displayed. Note the minimal change of laboratory results despite a radical change in coagulation status

control. The decision to continue CVVH in operating room has been previously hampered by the accuracy and reliability of fluid removal of the CVVH machines. Some centres described the use of hemofiltration filters in parallel to the VVB circuit in a modified CVVH system [38]. Advances in CVVH technology have made it more attractive to continue standard CVVH during the transplant, although optimal intraoperative regimes have not been defined [39]. Intraoperative CVVH adds to the complexity of the transplant procedure with more staff and

operating room equipment required. However, our institution regards intraoperative CVVH an important component in the success of present and future transplantation of ALF patients with MOF and established acute renal failure (and potentially with the use of marginal donor livers). The continuous exchange regime has likely been started in the ICU preoperatively already; in our centre, an exchange rate of 35 mL/kg/h using lactate-free solutions is standard. Furthermore, the ability for rapid fluid removal with CVVH allows the immediate transfusion of significant

blood products and better control of ICP pressure spikes, anhepatic acidosis and pre-reperfusion hyperkalemia [40].

### **Marginal Donors and ABO Incompatibility**

Rapid deterioration and profound MOF seen in ALF may restrict the choice of donor organ availability within the period where successful transplant for these patients can be achieved. As a result, clinicians may decide that use of marginal donor organs or ABO-incompatible organs is necessary for survival. For the transplant anesthesiologist, this may provide greater challenges. Marginal donor organs may produce more profound reperfusion-related physiological effects. Recovery of function with its attendant improvement in coagulopathy and other physiological parameters may also be greatly delayed in a sub-optimal donor liver. If size matching has not been perfect, either “small for size” syndrome or difficulties closing the abdomen may be encountered. Indeed, splitting the donor liver is sometimes necessary to obtain a size match. In the unstable ALF transplant recipient with difficult ICP control and impaired respiratory function, attempting to close an abdomen over an oversized liver may create major physiological difficulties. The resultant increase in abdominal pressure may impair diaphragmatic excursions and potentially reduce perfusion pressures to the new liver and other intra-abdominal organs (i.e. gut and kidneys). Furthermore, the increase in intra-thoracic pressure required to maintain ventilation may have an adverse effect on ICP control. It may be prudent to opt for a delay in total abdominal closure for 24–48 h with surgical packs or vacuum-type dressings in place to minimise the deleterious impact.

In the UK, major blood group (ABO) incompatibility (i.e. “A” donor with “O” recipient) liver transplantation is not considered an appropriate use of a limited resource, as survival results are inferior to group matched transplants. Only one such UK liver transplant has been reported under exceptional circumstances in a patient with ALF.

Minor ABO incompatibility (i.e. “A” recipient receiving an “O” liver) is accepted and more likely to occur for ALF treatment due to time restraints. The main concern is a graft-versus-host reaction caused by passenger lymphocytes released from the donor liver producing anti-A antibodies, resulting in the potential for recipient red cell hemolysis. If marked hemolysis occurs, this is treated by transfusing donor-compatible red cells (to which the A recipient will not produce antibody), B-cell suppression, IVIg and plasmapheresis. In other countries (e.g. Japan), ABO-incompatible transplantation is an accepted method using a live-related donor when ABO-compatible donors are not available. With enhanced immunosuppression using mycophenolate mofetil (MMF), aggressive use of B lymphocyte suppression (i.e. with rituximab) and removal of preformed immunoglobulins with plasmapheresis, immunoabsorption and IgG, it is possible to provide conditions for successful transplant. In ALF, there may be no other choice, and the relative increased risk is no longer a concern for the recipient. In these cases, particular attention to the use of appropriately matched blood products is vital.

### **Realistic Expectations of Delayed Recovery**

It is important to be realistic about the recovery of the patient with established ALF even after seemingly successful liver transplantation. Preoperative severe organ dysfunction, delayed new liver function, continuing raised ICP, pulmonary edema and persistent renal failure are all reasons why recovery will be delayed. This requires continual supportive ICU care.

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### **Summary**

Patients with ALF make up only 7–10% of liver transplant recipients but create unique perioperative challenges for the anesthesiologist. Advances in supportive ICU care have improved the likelihood of patients surviving until a donor



organ is procured, but where pre-morbid organ failure and imminent demise seems likely, “bridging” therapies including total hepatectomy must be considered. If emergency liver transplantation is performed, cerebrovascular stability remains a priority. The use of moderate hypothermia seems to abolish ICP variability and may constitute an important therapeutic strategy in high-risk patients. However, this has not been subjected to a rigorous clinical trial. In addition, the early initiation of the anhepatic state will improve the patients’ cerebrovascular stability. Surges in CBF are often more relevant to increases in ICP, whereas CPP is usually maintained even during periods of systemic hypotension due to the reduction in cerebrovascular resistance seen in ALF patients. Management of the complex coagulopathies with ALF is a challenge in itself and can be enhanced by the use of TEG monitoring. Intraoperative fluid balance and early post-reperfusion hepatic function are important to intraoperative success. The pressure to use marginal donor organs not perfectly matched to the recipient can provide additional intraoperative challenges. Delayed post-operative recovery needs to be anticipated and managed appropriately.

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## Introduction

Renal injury and failure is a frequent and potentially devastating complication of liver cirrhosis and patients awaiting liver transplantation [1]. When renal injury progresses to failure, the prognosis for patients with concomitant cirrhosis is poor [2]. Preoperative renal dysfunction is also associated with significantly worsened outcomes in patients who undergo liver transplantation [3]. In 2002, the United Network for Organ Sharing (UNOS) modification to the Model for End-Stage Liver Disease (MELD) scoring system was implemented for prioritizing patients on the liver transplant waiting list due to its ability to predict survival for patients with end-stage liver disease [4]. It replaced the Child-Pugh scoring system. Both UNOS and Eurotransplant now use the MELD for allocating organs to patients awaiting liver transplantation. Serum creatinine, a marker

of renal function, is one of only three variables used in the MELD score, highlighting the importance of renal function for survival in the face of liver disease. The use of the MELD scoring system has increased the number of patients with acute kidney injury (AKI) and chronic kidney disease (CKD) who undergo liver transplantation [5]. Additionally, now more than 10% of patients who undergo liver transplantation have a serum creatinine of greater than 2 mg/dL and more than 5% undergo transplantation while receiving renal replacement therapy (RRT) [3]. Preoperative renal function is one of the most important predictors of posttransplant survival. These facts reinforce the importance of renal function and dysfunction in patients with advanced liver disease.

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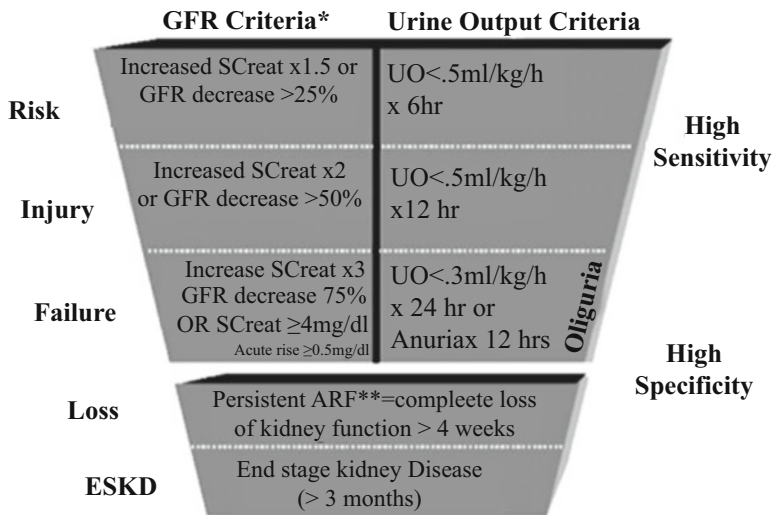
## Defining Renal Failure

Arriving at a standardized definition of renal failure has been surprisingly difficult. Renal failure is commonly divided into either acute renal failure (now termed acute kidney injury or AKI) or CKD (previously termed chronic renal insufficiency or chronic renal failure) [6]. More than 35 definitions have existed for renal failure [7]. The absence of a consensus definition has had a negative impact on basic science as well as clinical research in the field of AKI. There has never been a consensus on the most effective way to assess renal function, either by defining which markers best assess renal func-

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**Fig. 20.1** RIFLE criteria (risk, injury, failure, loss of function, end-stage kidney disease (with *Open Access* permission [9]))

tion or which level of a biomarker defines normal from abnormal renal function. Only recently has there been a unified definition for classifying and diagnosing AKI. The diagnosis of AKI requires both a patient's clinical history and relevant laboratory data. The Acute Kidney Injury Network (AKIN) introduced specific criteria for the diagnosis of AKI including a rapid time course (less than 48 h) and a decrement of kidney function [8]. Furthermore, a reduction of kidney function was defined as either an absolute increase in serum creatinine of >0.3 mg/dL, a percentage increase in serum creatinine of >50%, or a reduction in urine output to a level of <0.5 mL/kg/h for more than 6 h. Prior to the introduction of AKIN criteria, the Acute Dialysis Quality Initiative (ADQI) uniformly defined and staged AKI using the RIFLE criteria [9]. The five categories of RIFLE criteria represent three grades of increasing severity of AKI (*risk*, *injury*, and *failure*) and two outcome classes (*loss* and *end-stage kidney disease*). Absolute increase of serum creatinine, percentage increase in creatinine, percentage reduction in glomerular filtration rate (GFR), and decrement in urine output over time define the categories. Figure 20.1 summarizes the RIFLE criteria. Rather than reductively equating renal function and serum creatinine, the RIFLE criteria attempt to standardize the definition and severity of

renal injury and facilitate evaluation, treatment, and communication among healthcare providers. A recent study demonstrated the utility of the RIFLE criteria as a predictor of mortality in patients with cirrhosis admitted to the intensive care unit (ICU) [10].

### Acute Kidney Injury in Cirrhosis and Hepatorenal Syndrome

AKI is a rapid loss of kidney function and is commonly categorized into three broad categories: pre-renal, intrinsic-renal, and post-renal kidney injury. Acutely, renal function can deteriorate over a period of hours to days most often as a result of multiple insults. Pre-renal causes of kidney injury include any mechanism that decreases the effective blood flow to the kidney. Common causes of pre-renal kidney injury include dehydration, hypovolemia, hemorrhage, hypotension, and heart failure. Pre-renal injury is often rapidly reversible when the underlying mechanism is corrected; thus, glomerular or tubular injury can be avoided. However, prolonged pre-renal azotemia may progress to intrinsic AKI. Intrinsic causes of kidney injury can result from direct injury to the glomeruli, tubules, or interstitium of the kidney. Common causes of intrinsic kidney injury include glom-

**Table 20.1** Major diagnostic criteria of hepatorenal syndrome (HRS)

Major diagnostic criteria of HRS [14]		
Hepatic failure and ascites		
Creatinine >1.5 mg/dL		
No shock, ongoing bacterial infection, nephrotoxic agents, or fluid losses		
No improvement after diuretic withdrawal and fluid resuscitation		
Proteinuria <500 mg/day, normal renal sonography		
HRS	Type I	Type II
Serum creatinine	>2×baseline or >2.5 mg/dL (221 μmol/L)	>1.5 mg/dL (133 μmol/L)
Creatinine clearance	<20 mL/min	<40 mL/min
Onset	<2 weeks	>2 weeks
Median survival	1 month	6 months

erulonephritis (GN), acute interstitial nephritis (AIN), and acute tubular necrosis (ATN) [6]. Infection and sepsis are common causes of AKI in a patient with cirrhosis who present for liver transplantation. Cirrhotic patients are at high risk for sepsis from a multitude of causes including, but not limited to, spontaneous bacterial peritonitis, pneumonia, or central-line-associated bloodstream infection [11]. Additionally, these patients are often chronically ill and at risk for toxin-mediated ATN from aminoglycoside antibiotics, intravenous contrast agents, or nonsteroidal anti-inflammatory medications. Post-renal kidney injury involves obstruction at any point along the urinary outflow tract by, for example, malignancies, stones, or a hypertrophied prostate. Treatment of any type of kidney injury is centered on treating the underlying etiology while providing supportive care and avoiding nephrotoxic substances and further renal insult. Patients with liver cirrhosis are at risk for all three types of AKI, but they can also develop a unique entity known as hepatorenal syndrome (HRS) [12]. HRS is a form of pre-renal AKI caused by circulatory dysfunction secondary to an imbalance of circulating vasodilatory and vasoconstrictive substances. This dysfunction is the result of a decrease in systemic vascular resistance resulting primarily from splanchnic vasodilatation due to nitric oxide, prostaglandins, and other vasoactive substances released in patients with portal hypertension and advanced cirrhosis [13–15]. Vasodilatation thus triggers

the activation of the renin-angiotensin system and, along with sympathetic stimulation, results in intense renal vasoconstriction. In compensated cirrhosis, cardiac output and plasma volume both increase to restore effective arterial volume and thereby renal perfusion and function is preserved. However, in decompensated cirrhosis, cardiac output and heart rate maximized and cannot increase further to augment blood pressure, resulting in a further increase in circulating vasoconstrictors and renal vasoconstriction, sodium and water retention, and ascites formation [1]. This results in decreased renal perfusion pressure and reduced GFR. Two types of HRS exist: type 1 HRS is characterized by a rapid decline in renal function, while type 2 HRS entails a more chronic deterioration in renal function that is associated with ascites formation. Differentiating HRS from ATN can be difficult because diagnosing the former involves excluding other causes of AKI and there is no single test that confirms HRS [16]. Although mortality is very high among patients with cirrhosis and renal failure, patients with type 1 HRS have the worst prognosis—a 50% survival rate of 1 month and 20% survival rate of 6 months [17]. Therapeutic options are limited for patients with HRS. While albumin combined with vasopressin (or one of its analogues such as terlipressin) is of some benefit, optimal medical management should include the evaluation for liver transplantation [18].

Diagnostic criteria for HRS are summarized in Table 20.1.

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## Assessment and Management of Acute Kidney Injury in Cirrhosis: Preoperative Approach

Managing AKI in patients with cirrhosis depends not only on the cause but also on the severity of the injury. The most practical way to assess renal function is by measurement of factors included in the RIFLE criteria: serum creatinine, GFR, and urine output. Although commonly used and widely accepted, serum creatinine is unfortunately insensitive and not linearly related to GFR [19]. However, GFR is impractical to measure. Moreover, in patients with advanced liver disease, serum creatinine is often an unreliable indicator of renal function due to a decreased amount of creatinine production with reduced muscle mass [20]. Therefore, a normal or low serum creatinine is likely to overestimate GFR. Urine output may not be a reliable marker of renal function or injury as many patients receive chronic diuretic therapy. Recently, there has been a promising search for biomarkers of renal function and injury. Serum cystatin C, a protein produced by all nucleated cells at a constant rate independent of age, sex, race, or muscle mass, is a more accurate marker of GFR than creatinine [21]. Further studies are needed to test its clinical utility. Neutrophil gelatinase-associated lipocalin (NGAL) is a protein that is produced by renal tubular cells in response to renal injury [22]. It can be detected easily in the urine within minutes of induced injury and has been shown to be highly sensitive and specific to AKI—levels are much less increased in CKD. Although it has been used in a variety of clinical scenarios, further research is necessary before it can routinely be used in clinical practice.

Patients with advanced liver disease and those presenting for liver transplantation may have kidney injury with a wide variety of causes and severity. Unfortunately, despite the countless studies, there is no proven preventative measure or treatment for AKI [19]. Therefore, the management of AKI centers on identifying and treating the underlying etiology, providing renal support including maintaining renal blood flow

and oxygen delivery, and avoiding nephrotoxic agents. Most commonly, pre-renal causes of AKI in cirrhotic patients include hypovolemia secondary to bleeding, fluid losses, reduced oral intake, or diuretic administration. Gastrointestinal bleeding, including esophageal variceal bleeding, can occur as a consequence of portal hypertension. Excessive fluid losses from the gastrointestinal tract (e.g., due to diarrhea of an infectious etiology or from excessive lactulose administration) or renal fluid loss secondary to excessive diuresis can cause pre-renal injury [1]. Treatment of pre-renal injury can be simple but requires quick recognition of the cause and appropriate treatment to avoid a more permanent renal injury. Discontinuation of diuretics and optimization of fluid status and renal blood flow with the administration of isotonic crystalloid or colloid solutions may be necessary to prevent progression of the injury. There is little convincing evidence favoring colloids or crystalloids; however, some studies suggested that 6% of hydroxyethyl starch should be avoided in the setting of AKI [23, 24]. In more acute situations of hypovolemia, for example, due to gastrointestinal bleeding, rapid administration of plasma expanders and/or blood products may be needed to reverse hemodynamic instability. Sepsis should always be considered as a cause of renal injury in cirrhotic patients [25]. Early and aggressive treatment should be initiated if sepsis is suspected including source control, appropriate antibiotics, early goal-directed therapy [26], lung protective ventilation in the setting of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) [27], the avoidance of severe hyperglycemia [28], early enteral nutritional, and potentially steroid therapy for adrenal insufficiency or refractory vasoplegia [29]. Bacterial infections should be treated rapidly and appropriately [30]—initial empiric therapy is often dictated by local and hospital antibiograms. “Renal-dose” dopamine remains in use as it often increases urine output and may increase cardiac output and therefore renal perfusion in patients with low cardiac output and/or bradycardia. However, multiple large randomized controlled trials demonstrated that there is no role for dopamine in prophylaxis or treatment



of AKI [31–33]. Loop diuretics can be used in the setting of AKI as long as euvolemia is restored prior to their administration to avoid further renal hypoperfusion and exacerbation of AKI. Loop diuretics have multiple effects on the injured kidney. They may relieve obstructed tubules by clearing necrotic cells. They increase prostaglandin synthesis which, in turn, can increase renal blood flow while decreasing active tubular sodium reabsorption, thus decreasing metabolic demand [19]. However, most large studies have shown no direct effect of loop diuretics on prevention or treatment of AKI [34]. Many vasoactive drugs have been studied as possible prevention or treatment of renal injury. Studies of renal vasodilators such as dopamine, prostaglandins, and fenoldopam have been either too small or discouraging [35], and vasopressors can be effective in AKI, primarily in the setting of HRS type 1 [1]. Vasopressors reverse splanchnic vasodilatation and the restore of central blood volume and renal perfusion. Several different vasoconstrictors such as terlipressin (a vasopressin analogue), octreotide, norepinephrine, or midodrine have been studied, and results from recent randomized controlled trials were especially promising for the use of vasopressin analogues, with possibly added benefit with coadministration of intravenous albumin [18, 36]. However, vasopressin analogues are not yet considered first-line therapy as their use is associated with serious cardiovascular and ischemic adverse effects with an incidence of greater than 10% in some studies. Overall, vasopressin analogues can be effective in 40–50% of patients with HRS, but in these studies, there was no 3- and 6-month mortality benefit [1].

Despite maximum pharmacologic therapy, AKI and/or HRS can cause renal function to decline to a point of metabolic disarray, acidosis, severe electrolyte abnormalities, and/or volume overload. Once renal function has reached this level of severity, the patient should be treated with RRT. Although there are several renal replacement modalities, three major types exist—intermittent hemodialysis (iHD), peritoneal dialysis (PD), and continuous renal replacement therapies (CRRT). iHD, the standard treatment

for severe acute renal failure for more than four decades, is most often used in patients without acute hemodynamic abnormalities. Peritoneal dialysis is often used in patients with CKD but contraindicated in patients with ascites. There is little data validating one method over another, and there is debate over the timing and dosage of RRT in the perioperative period [6]. The RRT modality used is often determined by institutional experience and can be quite variable. However, most would agree that CRRT, particularly continuous venovenous hemodialysis (CVVHD), is the most commonly used and safest modality for patients in the perioperative period with a tenuous hemodynamic status. Regardless of the method of RRT, complications such as bleeding, infection, and hypotension should be recognized. In addition to RRT, there are other nonpharmacologic therapies used in patients with combined kidney and liver dysfunction. Placement of a transjugular intrahepatic portosystemic shunt (TIPS) can improve renal perfusion and GFR [37, 38]. Unproven and experimental artificial liver support systems currently under clinical investigation include the Molecular Adsorbent Recirculating System (MARS), single-pass albumin dialysis (SPAD), and the Prometheus System, and their effect on renal function remains to be seen [39].

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### **Liver Transplantation: Intraoperative Management of Renal Function**

Liver transplant remains the preferred treatment of advanced cirrhosis. Although discussed elsewhere (Chapter 17) in this book, patients with combined renal and liver failure should be considered for combined liver-kidney transplant (CLKT) [40]. It is not clear which patients benefit from CLKT, but consideration of the type of renal failure, particularly the presence of HRS, along with the severity and duration should be made. Without CLKT, renal function often improves after liver transplantation [1]. As stated before, patients present for liver transplant with varying types and severities of kidney dysfunction and may only have mild and short-lived elevations of

creatinine or they may present with severe AKI requiring CRRT. The intraoperative management of these patients is complex, and conventional anesthetic goals can often have detrimental effects on kidney function. As with any surgery, maintaining a normal blood pressure and euvolemia to ensure adequate perfusion and oxygen delivery to all tissues is paramount. Volatile anesthetics as maintenance of anesthesia can decrease GFR primarily as a result of decreased systemic vascular resistance [19]. This may be exacerbated by hypovolemia and antidiuretic hormone (ADH) secretion as a response to surgical stress [41]. Furthermore, sevoflurane may theoretically cause a fluoride compound A-induced renal injury [42], but there is no evidence that this is clinically relevant and most consider sevoflurane safe for patients with renal dysfunction. Intraoperative positive pressure ventilation reduces cardiac output, renal blood flow, and thus GFR through activation of the sympathoadrenal system. Although not specific to liver transplantation, anesthesiologists should be aware of any medications that may accumulate or have adverse effects in patients who have renal dysfunction—barbiturates, benzodiazepines, succinylcholine, morphine, meperidine—and most nondepolarizing neuromuscular blockers should be used with caution.

Although the details of the traditional phases of liver transplantation are discussed elsewhere (Chapter 8) in this book, it is evident that liver transplantation is a lengthy procedure and associated with hemodynamic instability, bleeding, coagulopathy, transfusion, and metabolic disarray, all of which can cause or exacerbate kidney injury. The role of the anesthesiologist, among others is to maintain adequate intravascular volume and hemodynamic stability, ensure renal perfusion, and minimize further renal injury. Vascular occlusion of the portal triad and interruption of the inferior vena cava are often part of the surgical procedure and, in the absence of venovenous bypass, result in a significant decrease in cardiac preload and cardiac output and, therefore, renal perfusion [43]. Fluid management strategies such as “low-CVP” techniques and conservative fluid management to prevent liver

congestion, bleeding, and transfusion requirements may have detrimental effects on renal perfusion and predispose patients to perioperative kidney injury [44, 45]. Significant alterations in the acid–base balance occur intraoperatively, and two of the most critical phases of liver transplantation, the anhepatic and neohepatic phases, are associated with significant and serious lactic acidosis, often demonstrated by a base deficit of less than  $-10$  to  $-12$  mmol/L [46]. Correcting acidemia and base deficit may help prevent the many serious manifestations of reperfusion of the donor liver, such as severe acidosis, hypotension, hyperkalemia, myocardial depression, arrhythmias, and cardiovascular collapse. Sodium bicarbonate can be administered during the anhepatic phase to prevent a further deterioration of a severe metabolic acidosis during reperfusion. The anesthesiologist must be cognizant of potential adverse effects such as hypercarbia, hyponatremia, rebound alkalosis, and worsening intracellular acidosis [46]. Tris-hydroxymethyl aminomethane (THAM) is a buffer that appears to safely control acidosis during the reperfusion phase of liver transplantation and is considered by some an alternative to sodium bicarbonate. However, THAM accumulates in patients with renal dysfunction, and its ubiquitous use cannot be recommended. Severe bleeding is frequently encountered during liver transplantation requiring massive transfusion of blood products. Blood transfusion in patients with renal failure may cause hyperkalemia, and this may further be exacerbated by reperfusion of the graft. It should be aggressively treated by insulin-glucose to drive extracellular potassium into cells, calcium to ameliorate the effect of potassium on the myocardium, and loop diuretics to increase renal potassium secretion. However, preexisting kidney dysfunction or AKI might make the loop of Henle resistant or unresponsive to loop diuretics. Vasopressors are often required during liver transplantation to treat hypotension and vasodilation, and norepinephrine and arginine vasopressin are the two most commonly used agents. GFR is determined by the net difference in arterial pressure between the afferent and efferent arterioles across the glomerular capillary bed known

as the transcappillary filtration pressure. In normal kidneys norepinephrine can constrict the glomerular afferent arteriole, decrease the filtration pressure, and therefore contribute to and prolong the course of acute renal failure. (Yet some pre-clinical evidence suggests that in a vasodilatory state, norepinephrine may actually increase filtration pressure.) Arginine vasopressin has been shown to constrict the glomerular efferent arteriole and therefore increases filtration pressure and consequently the GFR rate. To guide hemodynamic management, invasive monitors should be used including an arterial line, a central venous catheter, a pulmonary arterial catheter, and/or a transesophageal echocardiography probe as discussed elsewhere (Chapter 9) in this book. Additionally, since patients are ventilated and paralyzed, pulse pressure variation and stroke volume variation can help guide hemodynamic management [47, 48]. Obviously, urine output must be closely monitored with a Foley catheter. Frequent point of care assessment of the acid–base status and electrolyte balance aids in determining if renal replacement is needed.

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### Renal Replacement Therapy During and After Liver Transplantation

RRT, either iHD or CRRT, may be required in the perioperative period [49]. Sustained low-efficiency dialysis (SLED) is a hybrid form of RRT that is essentially a slower version of iHD using the same machinery with lower blood flow, longer dialysis sessions (8–10 h vs. 3–4 h), and possibly less hypotension [50]. As stated before, CRRT is preferred in the perioperative setting due to its hemodynamic stability. It has yet to be determined (but is an active area of investigation) which patients will benefit most from intraoperative CRRT. There are several forms of CRRT including, but not limited to, slow continuous ultrafiltration (SCUF), continuous venovenous hemofiltration (CVVH), CVVHD, and continuous venovenous hemodiafiltration (CVVHDF). These forms of RRT use the principles of ultrafiltration, hemofiltration, and/or hemodialysis for solute and fluid removal. CVVHD is the

preferred method during liver transplantation because of its ability to control both fluid and solute clearance. It has proven to be safe and can be used to achieve intraoperative even or negative fluid balance [49]. For the patient undergoing liver transplantation, CVVHD requires a large bore double lumen catheter that allows blood flows of 150–300 mL/min and countercurrent dialysate flows of 2–6 L/min without the need for anticoagulation [19, 49]. Dialysis catheters should be placed in the upper body especially if the vena cava is likely to be clamped. Most commonly CRRT is continued through the postoperative period until renal function has recovered or the patient can be transitioned back to iHD from a hemodynamic standpoint.

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### Summary

Renal dysfunction in the setting of liver dysfunction is an important cause of morbidity and mortality in the perioperative of liver transplantation. All types of renal injury can coexist with advanced cirrhosis, and recognizing and treating the underlying etiology is of paramount importance. In addition, HRS should be treated appropriately, although liver transplantation is the only long-term treatment. Unfortunately, there is no therapy that prevents or treats AKI. As a result, perioperative management of AKI should include maintaining renal blood flow, renal perfusion, normovolemia, and preventing further injury. Liberal use of intraoperative CRRT is probably the safest way to manage severe volume, hyperkalemia, and metabolic abnormalities and should be liberally utilized even if it may be logistically challenging.

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## Introduction

In order to properly discuss the anesthetic management of patients with cardiac comorbidities undergoing liver transplantation (LTx), we will first briefly describe the cardiovascular changes that occur as a result of liver failure, including hemodynamic changes and cirrhotic cardiomyopathy. We will then concentrate on the following comorbidities: coronary artery disease (CAD), valvular heart disease, and hypertrophic obstructive cardiomyopathy (HOCM). Preoperative diagnosis of cardiac comorbidities is essential to ensure preoperative optimization and proper intraoperative management and helps in determining the potential need for combined cardiac surgery and LTx. Poor left ventricular function (ejection fraction <35%) or severe cardiac disease that cannot be improved or corrected is considered to be contraindication for LTx, and only rarely can a patient with these conditions be considered for combined heart Tx/LTx [1].

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## The Cardiovascular Changes in End-Stage Liver Disease

Severe liver disease results in significant changes in the circulation and cardiac function, which can be summarized as a hyperdynamic circulation; this is characterized by increased cardiac output, heart rate, and blood volume; peripheral vasodilation; and low systemic blood pressure [2]. With mild liver dysfunction, the cardiovascular changes may be nearly imperceptible clinically; however, the circulatory effects may already have well progressed. The arterial compliance increases, and the overall systemic vascular resistance (SVR) decreases incrementally, corresponding to the degree of liver failure. As liver dysfunction progresses, the circulatory burden of biologically active compounds such as estrogen, bradykinin, prostacyclin, nitric oxide (NO), and vasoactive intestinal peptide exerts a predominantly vasodilator effect on the vascular smooth muscle. These and other vasodilating substances are overproduced or cleared less (as a result of reduced metabolism in the diseased liver or due to bypassing the liver); furthermore, there may be an increased sensitivity to their vasodilatory effects. In addition, peripheral arteriovenous communications form, and the sensitivity to vasoconstrictors such as norepinephrine, vasopressin, and endothelin-1 decreases due to a reduced number of receptors in combination with post-receptor defects.

Although SVR decreases in patients with severe liver disease, not all vascular beds are

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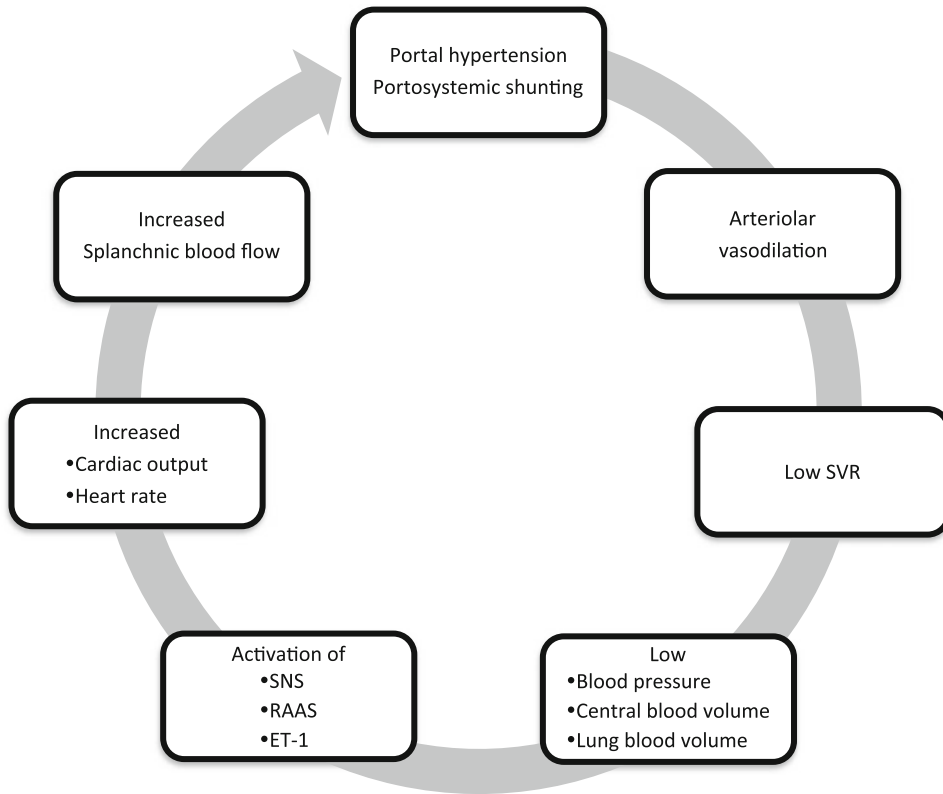
affected in the same way. As the primary disturbance in end-stage liver disease (ESLD), portal hypertension develops as a result of increased hepatic vascular resistance at the level of the sinusoids and is a direct consequence of local structural changes (fibrosis and regeneration nodules) and sinusoidal vasoconstriction (locally decreased NO production and increased local release of and sensitivity to vasoconstrictors such as endothelin, angiotensin II, catecholamines, and leukotrienes). The splanchnic circulatory response to portal hypertension is characterized by a massively increased local production of NO resulting in severe vasodilation of the splanchnic circulation. In addition, splanchnic vessels are less responsive to vasoconstrictors and release of substances such as vascular endothelial growth factor result in the creation of portosystemic collaterals. Other vascular beds, however, undergo vasoconstriction as a result of activation of compensatory mechanisms (see below).

The severe splanchnic vasodilatation leads to intravascular volume redistribution, which results in a reduction in central and arterial blood volume and an increase in noncentral blood volume (mainly splanchnic system) (Fig. 21.1) [3]. This is detected by central baroreceptors and leads to an activation of compensatory mechanisms, mainly the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS). There is also an initial increased release of vasopressin by the pituitary gland and an increased concentration of circulatory endothelins. In combination with the reduction in SVR, the stimulation of the SNS and RAAS results in a large increase in stroke volume and cardiac output. Eventually, with progressive liver failure, the SNS and RAAS become maximally stimulated, and the increase in cardiac output and vasoconstriction in certain vascular beds is insufficient to maintain an effective circulatory volume and compensate for the massive vasodilation of the splanchnic system. As a consequence, blood pressure gradually decreases and progressive autonomic dysfunction and baroreceptor insensitivity will further exacerbate this inadequate compensation.

Activation of the SNS and RAAS can be detrimental to the function of other organs. Indeed, the persistent sympathetic stimulation results in

vasoconstriction of coronary, cerebral, and renal vessels. This is most apparent in the kidneys, where reduction of blood flow in addition to a reduced circulatory volume may result in the progression to hepatorenal syndrome with fluid retention, hyponatremia, and ascites formation.

Although activation of the SNS results in a persistent state of sympathetic stimulation, it does not necessarily lead to a better myocardial performance. On the contrary, ESLD may cause progressive myocardial dysfunction called cirrhotic cardiomyopathy. Cardiac dysfunction in liver disease unrelated to alcohol was first described by Ma in 1996 and consists of systolic dysfunction, diastolic dysfunction, and electrophysiologic abnormalities [4]. Despite increased cardiac output in ESLD, the systolic contractility and diastolic relaxation are attenuated. Furthermore, repolarization changes such as prolonged QT interval (which may improve after  $\beta$ -blocker therapy) and reduced inotropic and chronotropic response to  $\beta$ -adrenergic stimulation may occur. Although cirrhotic cardiomyopathy is usually not apparent at rest, it becomes noticeable during cardiac stress (increase in preload or afterload). For example, cardiac dysfunction may become clinically relevant for the first time after transjugular intrahepatic portosystemic shunt (TIPS) placement or in the early postoperative period after LTx. The cause of cirrhotic cardiomyopathy is multifactorial; this includes circulating myocardial depressant substances (tumor necrosis factor- $\alpha$ , bile acids, endotoxins, cytokines, carbon monoxide, endogenous cannabinoids, etc.) and downregulation of  $\beta$ -receptors (reduced  $\beta$ -receptor density, desensitization of  $\beta$ -receptors, and abnormal excitation–contraction coupling). Furthermore, morphologic changes in the heart such as cardiac hypertrophy and patchy areas of fibrosis and subendothelial edema may occur and further contribute to the systolic and diastolic dysfunction. One of the early indicators of cirrhotic cardiomyopathy is diastolic dysfunction, which can be seen in many patients with ESLD. Typically there is a decreased E/A ratio on Doppler echocardiographic examination of the blood flow through the mitral valve; the E wave represents early passive transmitral flow, while the A wave represents



**Fig. 21.1** Pathophysiology of hemodynamic changes in cirrhosis: Systemic overproduction of vasodilators results in arteriolar vasodilation and low systemic vascular resistance (SVR), resulting in low blood pressure. Redistribution of blood results in a reduction in central blood volume and lung blood volume. Consequently, there is activation

of sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS) and increased plasma concentrations of endothelin-1 (ET-1). This leads to increases in cardiac output, heart rate, plasma volume (fluid and water retention), and splanchnic blood flow

transmitral flow as a result of atrial contraction. It is unclear whether diastolic dysfunction is a good marker for the degree of cirrhotic cardiomyopathy or whether it correlates well with systolic dysfunction; however, there is evidence that diastolic dysfunction precedes systolic dysfunction [5].

## Coronary Artery Disease

### CAD Does Occur in Patients with ESLD

In the 1960s and 1970s, it was thought that patients with severe liver disease had a low incidence of CAD, based on a lower incidence of hypercholesterolemia, increased levels of circulating estrogen (resulting in protection against

atherosclerosis), and decreased SVR thereby eliminating, at least in theory, hypertension as risks factors for CAD [6]. However, there is increasing evidence that the prevalence of CAD in patients with ESLD is higher than previously thought and maybe even higher than in the general population (20% vs. 12%, respectively) [7, 8]. Obesity, nonalcoholic steatohepatitis (NASH) and other inflammatory liver conditions, and advancing age of the LTx candidate have lead to an increasing prevalence of atherosclerosis [9, 10]. Interestingly, the prevalence of CAD is much higher in patients with alcoholic liver disease (31%) and NASH (27%) than in patients with cirrhosis due to other causes (2.4%) [11]. This could be related to a higher incidence of smoking, diabetes mellitus, older age, and hypertension in

patient with alcoholic liver disease and NASH, but it is unlikely that these risk factors by themselves can account for the higher incidence of CAD. There is also evidence that while light to moderate alcohol intake reduces the risk for CAD, heavy episodic alcohol drinking may actually increase its risk [12]. The prevalence of CAD in patients with viral cirrhosis, however, is lower than in patients without cirrhosis [13, 14]. Although there is limited comparative data about the prevalence of CAD in patients with cirrhosis with different etiologies, one must assume that CAD has a higher overall incidence in patients with ESLD than in the general population, mainly due to the high incidence of CAD in patients with alcoholic liver disease and NASH.

The reported prevalence of significant CAD (defined as at least one coronary artery stenosis  $\geq 50\%$ ) in patients with ESLD varies widely from 2.5 to 27%. There are several reasons for this variability. First, most studies have looked at a relatively small number of patients and second some studies based the diagnosis of significant CAD on abnormal screening tests such as positive dobutamine stress echocardiography (DSE). Third, the only method to determine the true incidence of CAD is by coronary angiography, and in most studies, coronary angiography was only performed in the subgroup of patients with abnormal screening tests or with multiple risk factors for CAD [15–17]. Interestingly, Carey found an incidence of CAD of 27% in 37 LTx candidates older than 45 years who underwent coronary angiography without consideration of other risk factor [18]; these results raise doubt on the appropriateness of risk stratification of patients that were referred to coronary angiography in other studies; however, this study was limited due to its small sample size (37 patients). Therefore, the true incidence of CAD in patients with ESLD remains unknown.

### **Consequence of CAD in Patients Undergoing LTx**

Why is there so much emphasis on the preoperative diagnosis of CAD? LTx is a procedure that creates a substantial stress for the heart with

virtually unavoidable episodes of often severe tachycardia and hypotension. Furthermore, plaque rupture resulting in acute coronary artery thrombosis and myocardial infarction may be related to a chronic inflammatory state. Episodes of hypercoagulability further increase the perioperative risk through intracoronary thrombus formation triggered by an area of coronary atherosclerosis. Therefore, CAD is considered to increase the peri- and postoperative risk. In 1996, Plotkin et al. reported a 50% 3-year mortality rate after LTx in patients with CAD, irrespective of whether the management of CAD was medical or surgical [19]. Management options for CAD have evolved since then and we can now choose among medical management, percutaneous transluminal coronary angioplasty (PCTA), coronary stenting with bare metal or drug eluting stents, coronary artery bypass surgery (CABG), and off-pump CABG (OPCAB), with cardiac surgery being performed before LTx or as a combined procedure. As a result, a more recent study demonstrated an improved outcome, although the mortality rates were still higher than in the general LTx population: 1-year mortality rate of 12.9% vs. 2.4% and 3-year mortality rate of 26.2% vs. 7.1%, respectively [20]. Postoperatively, CAD continues to be a significant cause of mortality after otherwise successful LTx [21].

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### **Preoperative Evaluation**

Preoperative risk stratification is guided by traditional CAD risk factors that include age  $>50$  years, diabetes mellitus, peripheral vascular disease, and history of CAD [22]. Interestingly, acute renal failure also increases cardiovascular risk in LTx patients [23]. Patients with no prior screening tests but several risk factors for CAD had a 26% incidence of moderate or severe CAD during coronary angiography, suggesting that CAD is quite common in patients with ESLD [17]. However, not all LTx candidates can or should undergo coronary angiography as the procedure is associated with significant risks such as femoral artery and renal injury [24, 25]. However, LTx candidates often present with a poor

functional status and hepatic encephalopathy, making the clinical diagnosis of significant CAD through eliciting signs and symptoms or exercise tolerance challenging and nearly impossible. For the same reasons, exercise testing is rarely feasible. Therefore, there is a real need for improved understanding who should receive what screening test and who should then undergo coronary angiography.

### **Dobutamine Stress Echocardiography**

DSE is the most frequently used screening test for CAD in LTx candidates. Dobutamine is administered at an increasing dose in an attempt to achieve 85% of the predicted maximal heart rate. The associated increase in myocardial oxygen demand attempts to mimic the physiologic stress that the myocardium undergoes in the perioperative period. Obstructive CAD is detected by regional wall motion abnormalities in the myocardial territories at maximal heart rate. Several studies show that a negative DSE is highly predictive of a myocardial injury-free perioperative course [15, 16, 26–28], and thus, a normal DSE has a good negative predictive value (range 89–100%). The negative predictive value, however, is reduced from 86 to 80% when non-diagnostic tests (due to inability of up to 50% of patients to reach the target heart rate) are included [29]. Others found an even lower negative predictive value (75% and 79%) [30, 31]. Another interesting finding is that patients who did not reach the target heart rate during DSE (“chronotropic incompetence”) had a higher incidence of cardiac complications up to 4 months after LTx [27]. The positive predictive value of DSE is not nearly as good, ranging from 22 to 44% [15, 16, 26, 28, 30, 31]. Therefore, an abnormal DSE is not necessarily caused by significant CAD. It has been suggested that the positive predictive value may be improved by the use of real-time contrast myocardial echocardiography for patients with intermediate risk factors for CAD [31]. The wide variability among various studies likely arises from differences in institutional protocols in selecting patients for DSE, coronary angiography,

and definitions of outcomes. For example, CAD can be defined as coronary obstruction >50% vs. >70%, perioperative myocardial infarction can be diagnosed based on different troponin cutoffs, and end point could be cardiac mortality or any-cause mortality. In addition, many patients failed to achieve the predicted maximal heart rate, rendering the ability of interpreting the DSE rather marginal [27, 30]. This may be the result of the use of  $\beta$ -blockers as part of medical management of portal hypertension, in addition to downregulation of  $\beta$ -receptors in ESLD (see above). Withholding  $\beta$ -blockers before the test and the administration of atropine has been recommended to reduce the number of inconclusive tests due to submaximal heart rates [27], but withholding  $\beta$ -blockers may increase the risk of variceal bleeding [32]. Because of the relatively poor predictive value of DSE in predicting perioperative cardiac events or early mortality, some clinicians deem alternative or additional screening tests for CAD necessary in order to avoid unnecessary coronary angiographies. However, in our opinion, it is still much better to obtain some false-positive screening test results (resulting in unnecessary coronary angiographies) than too many false-negative results resulting in patients accepted for LTx with unrecognized significant CAD. Also, no other screening test has a better positive predictive value than DSE at this time.

### **Myocardial Perfusion Scan**

Single photon emission computed tomography (SPECT) myocardial perfusion scintigraphy is another screening test for CAD. It uses exercise, dobutamine, or vasodilators such as adenosine or dipyridamole to stress the myocardium and determines the relative blood flow to different areas of the myocardium. Defects in perfusion can be classified as fixed (scar) or reversible (presumably ischemia), and defects in at least three segments (out of 17 or 20) are indicative of at least moderate risk for CAD [33]. Overall, the positive predictive value (range: 15–50%) and the negative predictive value (range: 77–99%) are

worse than for DSE [34–37]. These results are worse than those in patients without liver disease; this can be attributed to the decreased baseline arterial vascular resistance in patients with ESLD, as the typical response of the coronary arteries to vasodilators may not be achieved [35]. In addition, false-positive tests could be the result of abnormal coronary microvascular tone [38], which has also been observed in patients without severe liver disease [39]. This abnormal microvascular (coronary) blood flow (in the presence of normal coronary angiography) may be associated with a higher perioperative morbidity and mortality rate, sepsis, and graft failure [40]. Furthermore, ascites may result in attenuation artifacts in the inferior wall that may mimic ischemia or scar tissue [36]. Therefore, a high number of false-positive results makes this test less accurate [37], and myocardial perfusion scan may be only indicated as a screening test in patients with several risk factors for CAD who do not tolerate or have an inconclusive DSE.

### **Computerized Tomography (CT) Coronary Angiography and Coronary Artery Calcification**

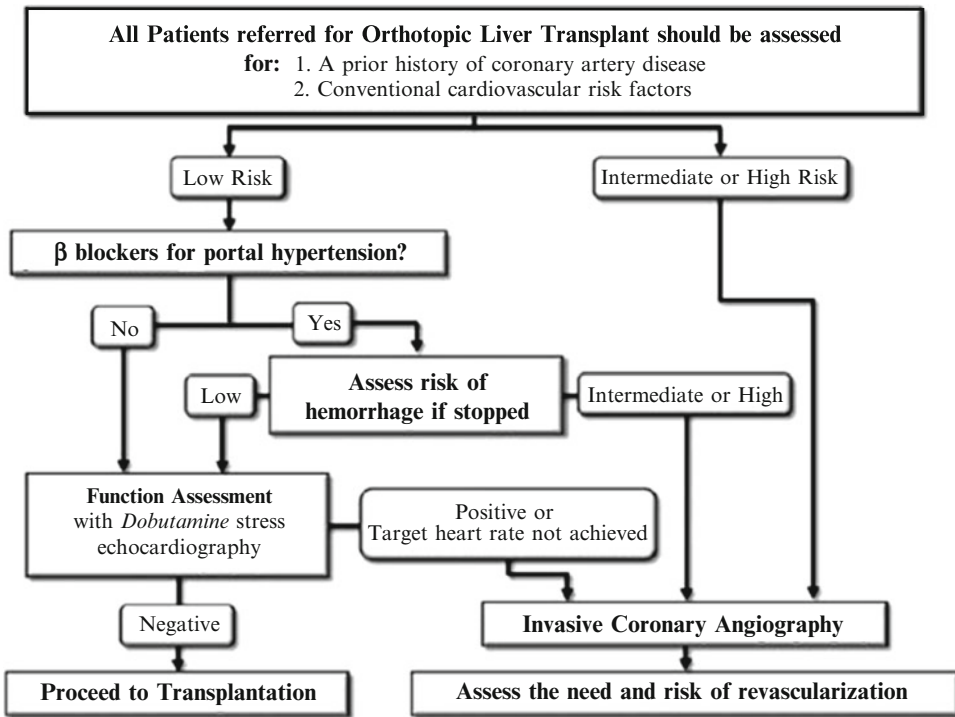
Coronary artery calcification (CAC) determined by multisection CT reflects the degree of calcification of coronary atherosclerotic lesions and may be an indicator of the degree of coronary obstruction. There is a good correlation between the CAC score and the presence of risk factors for CAD [41, 42], but currently, no studies compare the CAC scores to traditional contrast coronary angiography in the catheterization laboratory, nor are there any outcome studies. However, not all plaques are calcified and using the same test CT coronary angiography theoretically allows the detection of noncalcified plaques [41]. Again, there are no studies that compare abnormal CT coronary angiography tests with traditional contrast coronary angiography, and therefore, the usefulness of CT coronary angiography in patients with ESLD remains to be determined.

In conclusion, the currently available screening tests for CAD are not very good. Both DSE and myocardial perfusion scan have a good negative predictive value, but the positive predictive value is not nearly as good, although slightly better for DSE than for MPS. There is little experience with CT coronary angiography, and it is therefore difficult to estimate its ability as a screening test for CAD in LTx candidates. Since DSE gives additional information about cardiac function, valvular disease, hypertrophic cardiomyopathy, peak right ventricular pressure, and hepatopulmonary syndrome, it seems to be the preferred screening test at this time [8]. An excellent algorithm to screen for CAD has recently been presented by Ehtisham et al. [8] (Fig. 21.2).

### **Invasive Evaluation of CAD (Diagnosis)**

Coronary angiography using the standard dye technique in the catheterization laboratory is considered the gold standard for detection of CAD. A positive screening test for CAD should be followed by coronary angiography to confirm the presence of CAD considering the relatively low positive predictive value of these screening tests. Infrequently, coronary angiography is performed in candidates with several cardiac risk factors (e.g., diabetes, age >50 years, hypertension, smoking, family history of CAD, and hypercholesterolemia) even in the presence of a normal screening tests. This may be justified in patients with >2 risk factors for CAD [17], especially in patients with alcoholic liver disease and NASH, as the incidence of CAD is significantly higher in these patients.

Cardiac catheterization and coronary angiography are associated with a higher number of complications in patients with ESLD compared to patients without ESLD: patients with ESLD may have less renal function reserve, resulting in a higher incidence of renal dysfunction, and there is an increased incidence of bleeding complications at the site of vascular access [25]. Using the radial artery for vascular access is becoming more popular as it may have a reduced complication rate.



**Fig. 21.2** Coronary artery disease in orthotopic liver transplantation: Pretransplant assessment and management (from Ehtisham et al. [8]; with permission)

## Management of CAD

If significant CAD is diagnosed preoperatively, the coronary status of these patients should be optimized prior to LTx because if left untreated the perioperative mortality is excessively high [43]. The best strategy to accomplish this has not been determined, since no randomized controlled trials have compared percutaneous revascularization to surgical techniques in this population. The main therapeutic options besides medical management are placement of coronary stents, coronary artery bypass grafting (CABG), and off-pump coronary artery bypass (OPCAB).

## Coronary Stent Placement

Although coronary stent placement is an effective method of revascularization it is not without risks in patients with ESLD. Antiplatelet therapy is required after stent placement in order to

maintain patency and this further increases the risk of bleeding complications. However, the potential for clot formation is not as abnormal in patients with ESLD as previously thought [44], at least in part due to increased concentration of von Willebrand factor [45]. Most commonly bare metal stents are used instead of drug eluting stents because bare metal stents are covered faster by an endothelial layer and therefore do not require prolonged dual antiplatelet therapy (1 month vs. 12 months). The disadvantage of bare metal stents is the higher long-term restenosis rate, but this may not result in a higher incidence of acute myocardial infarction or death. Just like with coronary angiography, there are similar risks associated with arterial vascular access.

## CABG

Coronary artery bypass grafting (CABG) may be the only option in patients with significant CAD



that cannot be corrected by coronary stent placement. However, CABG in patients with ESLD and CAD prior to LTx is associated with a high mortality, mainly as the result of postoperative liver failure [46–49]. Other complications include renal failure, infections, and bleeding [46, 47, 49, 50]. Patients with mild cirrhosis (Childs A) have up to 25% morbidity (usually late postoperative liver failure and wound infections) but a low incidence of mortality [51]. Patients with moderate cirrhosis (Childs B) have a morbidity of almost 100% and mortality of up to 30%. Non-pulsatile blood flow during cardiopulmonary bypass results in systemic inflammation further contributing to liver dysfunction or liver failure. CABG is therefore an unattractive option for myocardial revascularization in patients with ESLD awaiting LTx. A better alternative may be simultaneous CABG/LTx, with the cardiac procedure performed first, resulting in excellent results, although it requires significant multidisciplinary coordination and cooperation from the cardiac surgical team [52].

## OPCAB

Off-pump coronary artery bypass (OPCAB) offers several theoretical advantages over CABG: no need for cardiopulmonary bypass and therefore less requirement for anticoagulation and better pulsatile organ perfusion. Therefore, if CAD is the only cardiac lesion to be corrected, then OPCAB would theoretically offer significant advantages, especially in patients with ESLD [47]. While some studies confirmed this [48, 53, 54], others found no improvement in incidence of hepatic dysfunction and overall mortality when OPCAB was used [55].

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## Valvular Disease

Mild or moderate valvular disease in patients with ESLD is usually well tolerated. The incidence of mild or moderate tricuspid and mitral regurgitation is higher than in the general population [56] possibly due to cirrhotic

cardiomyopathy and subsequent ventricular remodeling. These conditions require no special consideration perioperatively, although patients may require more blood transfusions and inotropic support [56]. Also, patients with severe valve disease with mild liver disease tolerate cardiac surgery better with a somewhat increased complication rate similar to patients with mild liver disease undergoing CABG [47, 50].

Perioperative management of patients with severe valvular disease and severe liver disease is very complex. If an attempt is made to surgically correct the valvular disease using cardiopulmonary bypass prior to LTx, the outcome will be as poor as the results of CABG in patients with ESLD [47, 48, 50]. Few patients underwent such an operation successfully [57, 58], and other options need to be explored. Percutaneous balloon valvuloplasty, avoiding cardiopulmonary bypass, could be used to correct severe mitral or aortic stenosis. Another option is a simultaneous valve replacement and LTx, although this requires a thoracoabdominal incision, cardiopulmonary bypass at the time of LTx, and initiation of immunosuppression [59].

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## Hypertrophic Obstructive Cardiomyopathy

HOCM is characterized by an asymmetrically hypertrophied non-dilated left ventricle, potentially causing left ventricular outflow tract (LVOT) obstruction. It has a genetic inheritance pattern, although it can be the result of de novo genetic mutation, and has an incidence of about 0.2% of the general population [60]. Although frequently asymptomatic, some patients develop anginal chest pain, dyspnea, or syncope, and it can progress to congestive heart failure or sudden death as a result of dynamic LVOT obstruction, mitral regurgitation, diastolic dysfunction, myocardial ischemia, or arrhythmias [60]. LVOT obstruction caused by septal hypertrophy becomes hemodynamically more significant in the presence of systolic anterior motion (SAM) of the anterior mitral leaflet that prevents complete ejection of the stroke volume and results in

a sudden drop in cardiac output. Echocardiography is the most useful method of diagnosing HOCM as it allows visualization of the HOCM, diagnosis of SAM, and estimation of the degree of obstruction [60]. Volume status, afterload, and myocardial contractility all affect the degree of LVOT obstruction and mitral regurgitation. Specifically, low SVR and a hyperdynamic left ventricle will worsen LVOT obstruction especially in hypovolemic patients. The hemodynamic goal is to prevent conditions that would result in obliteration of the LV cavity and ultimately LVOT obstruction. Such treatment modalities are focused on increasing LV cavity size by avoiding hypovolemia and reducing contractility with  $\beta$ -blockers. Myectomy and alcohol septal ablation are reserved for patients with drug-refractory heart failure symptoms [60].

HOCM poses a particular difficulty for patients with ESLD as some of the circulatory abnormalities in ESLD promote LVOT obstruction. LVOT obstruction can be diagnosed by DSE, but the incidence seems to be quite variable ranging from low (two out of 157 patients developed high LVOT gradients during DSE) [27] up to 43% of all patients [61]. It is possible that the diagnosis of LVOT obstruction with DSE depends on if one is actually looking for LVOT obstruction. A LVOT gradient of >35 mmHg has resulted in denial for transplantation, even though the reported perioperative mortality is not increased [61]. Options for patients rejected for LTx because of a high LVOT obstruction include myectomy and alcohol septal ablation. Myectomy in patients with ESLD may be a poor choice with high mortality rate mainly resulting from the need for cardiopulmonary bypass [47], although a combined myectomy-LTx can be an option. Alcohol septal ablation is less invasive but may be associated with several complications as well [62], and currently, there are only a few case reports of patients with ESLD who received alcohol septal ablation prior to LTx [63, 64].

Although ESLD and LTx result in hemodynamic conditions that worsen LVOT obstruction, these patients can be transplanted safely when meticulous hemodynamic management is used, such as intraoperative avoidance of inotropic agents (epinephrine) and hypovolemia. TEE

monitoring is essential in order to avoid hypovolemia and to closely follow the degree of LVOT obstruction and SAM [65–67]. During the anhepatic stage, venovenous bypass facilitates the avoidance of hypovolemia, while hypotension should be rapidly and aggressively treated with potent vasoconstrictors such as norepinephrine or vasopressin and volume. Also, calcium should be administered slowly in order to avoid a hypercontractile state [68].

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Mercedes Susan Mandell and Masahiko Taniguchi

Liver disease affects the function of all other organ systems, and cirrhosis can be thought of as a systemic disease that produces multisystem organ failure as a principal cause of death. The lung is particularly sensitive to changes in hepatic function and respiratory failure is a common complication of advanced liver disease. Historically, while physicians recognized an association between lung and liver disease, this association was considered to be rare. But more recent studies have shown that symptoms such as hypoxemia at rest occur in at least 27–33% of liver transplant candidates [1]. Hypoxemia is caused by a wide variety of diseases. Some pulmonary diseases occur more commonly in patients with liver disease than in the general population. These pulmonary defects can affect the perioperative management of patients and may influence the decision to proceed with transplantation. This chapter will present an overview of the changes in lung mechanics and gas exchange that occur in patients with liver disease and cover some of the more common causes of pulmonary disease in cirrhotic patients.

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## Pulmonary Function in Patients with Cirrhosis

Patients with liver disease have well-documented defects in respiratory mechanics, the alveolar blood supply, and in gas exchange at the alveolar surface [2]. Patients may have abnormalities in one or all of these important functions. Thus, patients with cirrhosis can suffer from hypoxemia even when there is no identifiable pulmonary disease process. Respiratory mechanics are commonly compromised by portal hypertension, anasarca, and an increase in the size of the abdominal organs, and symptoms suggestive of restrictive lung disease may develop. There are significant reductions in the chest wall motion, the normal underlying lung recoil and excursion of the diaphragm, caused by an increase in the size of the abdominal organs and/or increase in the abdominal blood volume. The enlarged abdominal volume pushes the diaphragm upwards and holds the ribs in a more horizontal position thereby increasing the resting diameter of the chest wall [3]. The consequent reduction in lung volumes and chest wall excursion limits the expansion and elastic recoil of the lung. This in turn reduces respiratory volumes, and especially the functional residual volume falls, while closing capacity increases [4].

All these changes reduce respiratory reserve and place patients at risk of developing hypoxemia. Additional complications such as ascites and pleural effusions further impair the normal



**Table 22.1** Patients with liver disease usually have mixed obstructive and restrictive pattern of pulmonary function tests conducted by spirometry

Pulmonary function tests (spirometry)	Restrictive pattern	Obstructive pattern
FVC	Decrease	Decrease
FEV1	Normal decrease	Decrease
FEV1/FVC ratio	Normal	Decrease
TLC	Decrease	Normal or increased

Ascites and pleural effusion cause restrictive changes in pulmonary function tests where the lungs cannot fully expand. This is reflected in the fall in the total lung capacity and the lung volumes and capacities that make up the total lung volume. The forced expiratory volumes are either normal or slightly decreased. In contrast, some patients may demonstrate a predominant obstructive pattern due to liver disease. In this case, the lung volumes increase, while the expiratory flow rates decrease. The ratio between the forced expiratory volume in 1 s and the forced vital capacity helps determine if a restrictive or obstructive pattern predominates. The ratio is normal in a pure restrictive pattern but is reduced in an obstructive pattern

expansion and elastic recoil of the lung and chest wall. Patients also develop symptoms of small airway obstruction due to edema and compression of the lower airway [2]. There is a reduction in expiratory flow volumes: the ratio between the volume that can be forcibly expired in 1 s as a percentage of the total forced vital capacity ( $FEV_1/FVC$ ) is commonly reduced. A similar reduction is seen in the forced expiratory flows in the small airways ( $FEF_{25-50}$ ) [5]. The mixed restrictive-obstructive pattern observed in pulmonary function tests correlates with the severity of illness, and patients in child's class B and those with ascites tend to have a greater impairment [5] (Table 22.1).

Defects in gas exchange produce an increase in the gradient between the alveolar and arterial concentration of oxygen (A-a gradient) in a large number of patients with liver disease [3]. Hypoxemia ( $PaO_2 < 80$  mmHg) has been reported in up to one-third of transplant candidates and correlates with the severity of liver disease as measured by the Child-Pugh score and the model for end-stage liver disease (MELD) [1]. There are three well-recognized mechanisms that explain the increase in A-a gradient in patients with liver disease: an imbalance in match between alveolar ventilation and perfusion, true shunt where there is perfusion without alveolar ventilation, and diffusion defects [6, 7].

Patients with liver disease have a mismatch between alveolar ventilation and capillary perfusion. Compression of the lung tissue by organomegaly, ascites, and pleural effusion explains

some of the ventilation-to-perfusion mismatch. A fall in functional residual capacity along with an increase in closing volume favors a drop off in alveolar ventilation due to simple mechanical compression of the alveoli. This leads to a mismatch between the ventilation and perfusion ratio. However, evidence suggests that the ventilation-to-perfusion imbalance in most patients is mainly due to changes in the pulmonary microvascular tone [8]. The hypoxic pulmonary vasoconstrictive reflex is attenuated and pulmonary capillaries fail to constrict in response to a hypoxic stimulus. Because autonomic dysfunction underlies this defect, greater degrees of ventilation-to-perfusion mismatch and hypoxemia are more commonly seen in patients with greater severity of illness [9].

There is little question that intrapulmonary shunts contribute to an increase in the A-a gradient and hypoxemia in patients with liver disease [10]. Harmonic imaging by echocardiography has revealed the presence of intrapulmonary shunting in up to 80% of patients assessed for liver transplantation [11]. Intrapulmonary shunting has also been observed by the multiple inert gas elimination technique [12]. In this case, blood completely bypasses ventilating units and empties into the arterial system causing pure venous admixture. When shunting is associated with clinical hypoxemia, patients are diagnosed with the hepatopulmonary syndrome (HPS).

There are also defects of the actual transfer of gases across lung tissue. Investigators have reported a notable decrease in the diffusing



capacity of the lung for carbon monoxide (DLCO) [13]. The DLCO is a single-breath pulmonary function test that estimates two components: the rate of gas exchange across the alveolar membrane and the binding of carbon monoxide to the hemoglobin molecule. The latter is a function of the rate of binding of carbon monoxide to hemoglobin and the alveolar capillary hemoglobin volume. The inverse correlation between the A-a gradient and DLCO in patients with cirrhosis suggests that mechanisms influencing the DLCO play an important role in oxygen exchange [9]: As the A-a gradient increases, the DLCO falls. Several hypotheses aim to explain why the end capillary partial pressure of a gas would not be equal to its alveolar value [14]. One possible reason is a diffusion-perfusion defect where the central stream of red blood cells in dilated capillaries does not have time to equilibrate with the alveolar oxygen [15]. Elevated cardiac output associated with the hyperdynamic state of hepatic cirrhosis may cause a rapid transit of blood through dilated alveolar vessels. The transit time exceeds the time needed for the alveolar blood to fully equilibrate with the alveolar oxygen content. Other theories propose that there is thickening of the capillary-alveolar interface [16] or a decrease in capillary blood flow despite an increase in central blood volume occurs [9]. Overall, an increase in the A-a gradient and hypoxemia is usually caused by multiple mechanisms in patients with liver disease (Fig. 22.1).

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## Diseases of the Hepatopulmonary Axis

Certain pulmonary diseases have a higher than expected incidence in patients with liver disease. Some of these are acquired while others have a clear genetic pattern of inheritance. The acquired diseases tend to fall into one of three categories: pulmonary vascular diseases, parenchymal disease, and diseases of the pleural space. Although inherited diseases can be roughly categorized in a similar manner, their classification is often not as clear as the principal disease process tends to affect multiple aspects of lung function.

## Inherited Diseases

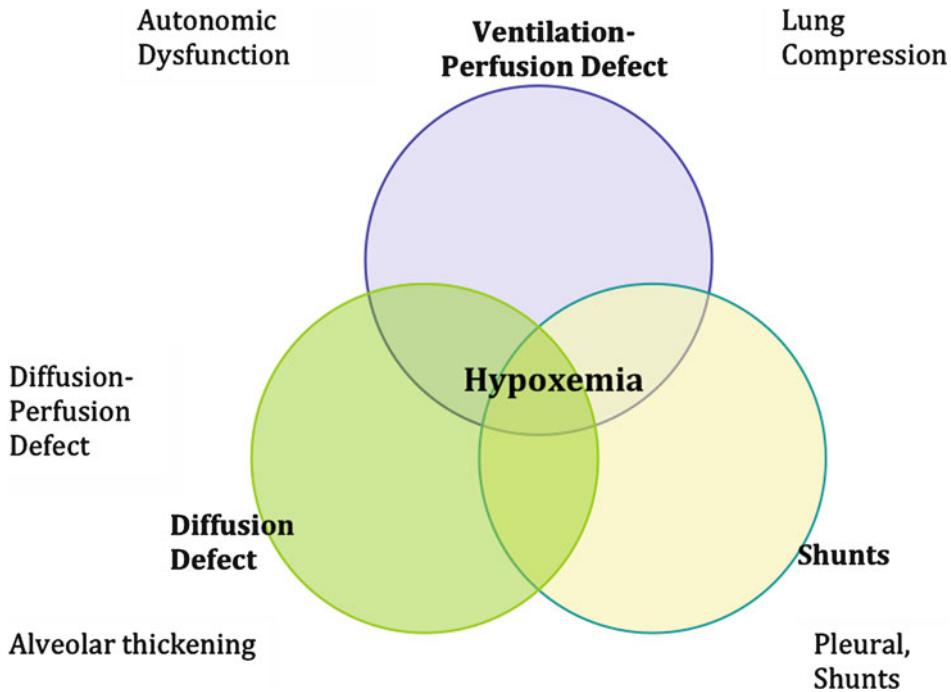
### Cystic Fibrosis and Alpha<sub>1</sub>-Antitrypsin Disease

The most common inherited diseases that affect both the lung and liver are  $\alpha_1$ -antitrypsin and cystic fibrosis [17]. Both are autosomal recessive disorders. Cystic fibrosis occurs in 1 in 3,000 births, while severe  $\alpha_1$ -antitrypsin is present in 1 in 3,500 births [18, 19]. The majority of patients with cystic fibrosis have some degree of hepatobiliary disease during their lifetime. In contrast, liver disease is rare in  $\alpha_1$ -antitrypsin.

Patients with cystic fibrosis have a predicted mean survival of 37.4 years [20]. The disease is caused by a lack of the cystic fibrosis transmembrane conductance regulator, and multiple organ systems are affected. Nearly 90% of patients are diagnosed under age 10 with symptoms of exocrine pancreatic insufficiency and pulmonary disease [21]. A second group of patients are diagnosed with cystic fibrosis as adults. The latter patients tend to have milder lung disease and predominant pancreatic insufficiency [22]. Patients who are diagnosed in adulthood tend to have long survival and are less likely to require lung transplantation.

Elevation in the serum levels of the aminotransferases and gamma glutamyl transferase is common in cystic fibrosis but often not clinically significant [23], and only less than one-third of patients with cystic fibrosis develop detectable hepatobiliary disease [24, 25]. Focal biliary cirrhosis is the most common lesion in these patients [23]. Severe liver disease is associated with only a few of the more than 1,500 known mutations in the cystic fibrosis transmembrane conductance regulator. Although clinically significant disease develops in 5–7% of patients with focal biliary cirrhosis [25, 26], complications of portal hypertension are rare [27, 28]. Currently, the only available treatment for liver disease due to cystic fibrosis is ursodeoxycholic acid [29].

All patients with hepatobiliary disease due to cystic fibrosis also have lung disease. The lower airways become obstructed by viscous secretions, and patients experience multiple episodes of infection [30]. This leads to parenchymal



**Fig. 22.1** Three principal causes of hypoxemia and a widened A-a gradient in patients with liver disease. All three mechanisms may be present in the same patient

destruction, severe obstructive disease with diffuse loss of lung volumes, and finally respiratory failure. The majority of patients have chronic lower airway infections with *Staphylococcus aureus*, *Hemophilus influenzae*, and *Pseudomonas aeruginosa* as the most common organisms. There are no clear pulmonary criteria that predict post-transplant survival in these patients, and chronic colonization and infection with bacteria does not seem to impact transplant outcome.

The 1- and 5-year survivals following liver transplantation in pediatric patients are 91% and 75%, respectively [31], and the perioperative morbidity and mortality are mainly related to lung disease [32]. There is not as much experience with liver transplantation in adult patients with cystic fibrosis; however, investigators have only reported a 40% survival rate at 5 years [33]. Patients died from a variety of problems.

Alpha<sub>1</sub>-antitrypsin is an autosomal recessive disease where each allele contributes 50% of the circulating enzyme. The normal gene product is designated as PiM [19]. Defects in  $\alpha_1$ -antitrypsin

are the most common metabolic cause of liver disease in neonates and children [34]. Adults are usually affected in the fifth decade [35]. The genetic variants that are associated with lung or liver disease are PiS (expressing 50–40%  $\alpha_1$ -antitrypsin) and PiZ (expressing 10–20%  $\alpha_1$ -antitrypsin). The most common deficiency types that cause disease are PiSS, PiSZ, and PiZZ [36].

Alpha<sub>1</sub>-antitrypsin inhibits neutrophil elastase. Failure to inhibit elastase causes early onset panlobar emphysema. The accumulation of  $\alpha_1$ -antitrypsin polymers in hepatocytes causes liver disease when the S and Z gene are co-inherited [37, 38]. These two genes code for errors in the steps that transport  $\alpha_1$ -antitrypsin out of the hepatocyte. Approximately 37% of asymptomatic PiZZ patients have cirrhosis at the time of death [39]. Other factors such as male gender and obesity increase the risk of hepatic disease [40].

The common environmental and genetic factors that predispose patients to develop lung and/or liver disease are unknown. Patients with liver disease due to  $\alpha_1$ -antitrypsin have an increased

incidence of cholangiocarcinoma and hepatocholangiocarcinoma. Patients with emphysema due to  $\alpha_1$ -antitrypsin deficiency have been treated with intravenous  $\alpha_1$ -antitrypsin augmentation therapy [41]; however, there is no medical treatment for liver disease due to  $\alpha_1$ -antitrypsin deficiency. Liver transplantation is curative since the new liver synthesizes normal  $\alpha_1$ -antitrypsin and patients have an excellent outcome with similar 1-, 3-, and 5-year survivals as those reported for all liver transplants in the United States [42].

### Autoimmune Diseases

Autoimmune diseases often affect both the lung and liver [43]. For example, one quarter of patients with rheumatoid arthritis have lung disease including chronic pleural effusions and interstitial pneumonitis, pulmonary fibrosis, and pulmonary hypertension. These patients also have an increased incidence of autoimmune hepatitis and nodular regenerative hyperplasia. Liver and lung disease also occur in patients with dermatomyositis, scleroderma, and systemic lupus erythematosus. Furthermore, drugs used to control symptoms of autoimmune disease can independently cause liver disease, and cases of acute and chronic hepatic injury have been described with the use of most anti-inflammatory drugs including high dose nonsteroidal anti-inflammatory drugs, methotrexate [44], and tumor necrosis factors inhibitors [45].

Primary biliary cirrhosis is similar to other autoimmune diseases in that a sibling has a 10.5% relative risk of developing the disease [46], and more commonly in females than in males. The disease is characterized by autoantibodies to mitochondrial antigens [47]. It causes progressive destruction of small and medium intrahepatic bile ducts and can lead to cirrhosis. There is an association between primary biliary cirrhosis and other autoimmune diseases and thyroiditis, Sjogren's syndrome, scleroderma, and rheumatoid arthritis occur more frequently in patients with primary biliary cirrhosis [48]. In fact, a crossover syndrome between primary biliary cirrhosis and autoimmune hepatitis has been reported [49]. Consequently, the pulmonary

manifestations can be complex. There is an increased incidence of lymphocytic interstitial pneumonia, intrapulmonary granulomas, bronchiolitis obliterans, obstructive airway disease, and pulmonary hypertension [50]. The high incidence and diverse presentation of lung disease in patients with autoimmunity indicates that a careful preoperative evaluation of pulmonary function is warranted in these patients.

The 5-year survival of patients with autoimmune hepatitis after liver transplantation is 75%, similar to patients with alcoholic liver disease [51]. However, this is significantly worse than the 5-year survival of 83% reported in a multicenter study for patients with primary biliary cirrhosis [51]. Young patients with autoimmune hepatitis had moderately better survival than patients over the age of 50. Infectious complications were a major cause of mortality, and pulmonary disease did not have a significant effect on overall outcome. Even though patients with primary biliary cirrhosis had better survival, approximately 9–35% of patients will have recurrent disease [52].

### Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease) is a group of autosomal dominant disorders that are characterized by the presence of abnormal arteriovenous malformations [43]. A number of organs systems can be involved aside from the lung and liver, such as skin, brain, and the gastrointestinal tract. The liver is affected in up to 84% of patients [53]; however, only 5–8% have symptomatic liver disease [54]. High-output cardiac failure is the most common clinical presentation and is caused by significant shunting through the arteriovenous malformations in the liver [55].

Patients with lung arteriovenous malformations experience hypoxemia. There is an increased incidence of arterial embolic complications including stroke and brain abscess due to direct arteriovenous connections. Complications in 15–45% of patients who have pulmonary arteriovenous malformation [56] include hemoptysis, spontaneous hemothorax, and severe pulmonary hypertension [57]. Pulmonary hyper-

tension occurs in patients with liver involvement secondary to high cardiac output. Some patients with hereditary hemorrhagic telangiectasia develop a plexogenic pulmonary arteriopathy that is identical to portopulmonary hypertension (POPH). An overall median survival of 87% has been reported at 47 months following transplantation.

## Acquired Diseases

### Diseases of the Pleural Space

Hepatic hydrothorax is the most common acquired pulmonary complication of cirrhosis, occurring in 4–6% of all patients [58]. The diagnosis is made when there is a pleural effusion (>500 mL) with no evidence of primary lung or heart disease. In the majority of patients, the effusion is right-sided and usually occurs in patients with ascites. Congenital fenestrations in the tendinous part of the diaphragm allow the passage of ascites fluid. Elevated intra-abdominal pressure combined with cyclic negative intrathoracic pressure will cause a unidirectional flow of ascites into the pleural space. Hepatic hydrothorax rarely occurs on the left because there are fewer fenestrations as the hemidiaphragm is thicker and more muscular.

Patients with hepatic hydrothorax have an increased risk of developing spontaneous bacterial empyema [59]. The effusion is initially treated in the same way as ascites, with diuretics and by restricting sodium intake. If these treatments fail, thoracentesis is an option but has been associated with an increase in infectious complications [58]. The application of biologic glue or sclerosing agents to seal diaphragmatic defects using video-assisted thoracoscopic surgery has a high rate of success [60]. Transjugular intrahepatic portosystemic shunting has also been used successfully to control hepatic hydrothorax [61]. A large effusion may impede positive pressure ventilation during liver transplant surgery and may require insertion of a chest tube for drainage at the beginning of surgery.

### Parenchymal Diseases

A large number of infectious and immune-mediated diseases affect the lung parenchyma. Patients with liver disease have changes in their immune system that makes them susceptible to pulmonary infections and complications. With hepatic cirrhosis, there is an increased incidence of pulmonary infections with bacterial, fungal, viral, and mycobacterial species; additionally, complications such as bronchitis obliterans are more common than in the general population [62].

Immune-mediated lung injury has been reported in patients with hepatitis C and in patients receiving interferon antiviral therapy. Fibrosing alveolitis has been reported in patients with hepatitis C [63]. This serious complication is probably due to mixed cryoglobulinemia caused by an innate immune response to infection with hepatitis C. Similar lung pathology has been observed in patients receiving treatment with sirolimus [64] and pegylated interferon [65].

### Portopulmonary Hypertension

Pulmonary hypertension is a rare but severe and potentially life-threatening disease. It occurs with increased frequency in patients with portal hypertension. It is estimated that up to 6% of all patients on liver transplant waiting lists have POPH [66, 67]. The diagnostic criteria include a mean pulmonary artery pressure greater than 25 mmHg, with a normal pulmonary capillary wedge pressure (<15 mmHg), a pulmonary vascular resistance greater than 240 dynes  $\text{s cm}^{-5}$ , and the presence of portal hypertension [68]. Most cases are initially found on screening echocardiography. Systolic flow through a regurgitant tricuspid valve correlates with the systolic pressure gradient between the right ventricle and the right atrium. When right atrial pressure is known (or estimated) right ventricular systolic pressure (RSVP) can be calculated. RSVP is equal to the systolic pulmonary pressure in the absence of pulmonary stenosis. RSVP great than 50 mm Hg is associated with 97% sensitivity and 77% specificity for a diagnosis of POPH by right heart catheterization [69].

All patients placed on the waiting list for liver transplantation should be screened for POPH using a resting echocardiogram and follow-up right heart catheterization if the estimated RSV  $\geq 50$  mmHg because there are no diagnostic clinical symptoms of POPH. Fatigue and dyspnea on exertion are the most common complaints and are not easily distinguished from general symptoms of liver disease. Patients with syncope or chest pain usually have severe POPH and right heart failure, but the absence of these symptoms does not preclude a diagnosis of POPH.

The etiology of POPH is still uncertain. Investigators think that genetic predisposition interacts with the hyperdynamic circulation to cause disease [70]. There are significant changes in the function of the vascular endothelium in the pulmonary circulation, and these changes lead to progressive vasoconstriction, inflammation, angiogenesis, and in situ thrombosis. If left untreated, most patients will progress to right heart failure and death [71]. Three molecular pathways in the lung vascular endothelium are affected: nitric oxide, endothelin, and prostacyclin [72] with a decrease of vasodilatory mediators (nitric oxide and prostacyclin) and an increase in vasoconstrictors (endothelin). Medical therapy is aimed at restoring a normal balance of these mediators, and patients have been successfully treated with endothelin receptor antagonists, prostacyclin derivatives, and drugs that increase the amount of nitric oxide.

Without any intervention, half of the patients with POPH die within 1 year of their diagnosis [73, 74]. With medical treatment, approximately 45% of patients are alive at 5 years and 67% of patients who received both medical therapy and liver transplantation were alive at 5 years. This is in sharp contrast to patients who were transplanted without medical therapy; only 25% of these patients survived 5 years. Overall surgical survival is affected by the severity of POPH, and mean pulmonary artery pressures over 35 mmHg are associated with an increased risk of mortality. Similarly right ventricular performance also predicts outcome, and preserved right heart function correlates with a better outcome [75].

Patients with POPH in the United States receive additional MELD points for the allocation of organs if their mean pulmonary artery pressure is 35 mmHg or less with or without medical treatment [76]. The priority given to patients with POPH is based upon better outcomes in patients with lower pulmonary artery pressures. The long-term outcome of POPH patients is still confusing. Some patients may have a complete resolution of the disease, while others experience a worsening of their disease [77, 78]. Still others remain stable but do not show any significant improvement, and in rare cases, there is new onset POPH following transplantation. To date, there are no patient characteristics known that predict long-term outcome.

### Hepatopulmonary Syndrome

Hypoxemia occurs in up to 33% of patients with liver disease [79]. Hypoxemia caused by pulmonary capillary dilation is diagnostic for HPS. HPS is the most common form of pulmonary vascular disease in patients with cirrhosis. Diagnostic criteria include a room-air PaO<sub>2</sub> <80 mmHg, the presence of intrapulmonary shunting, and a diagnosis of portal hypertension with or without cirrhosis. Investigators also use the alveolar-arterial oxygen gradient in addition to arterial oxygen concentration as a diagnostic criteria for hypoxemia as it is more sensitive and adjusts for changes in arterial carbon dioxide (PaCO<sub>2</sub>). PaCO<sub>2</sub> is often decreased in patients with liver disease due to hyperventilation. Approximately 30% of patients with advanced liver disease are diagnosed with HPS using these criteria.

HPS can be divided into mild, moderate, severe, and very severe based upon the degree of hypoxemia (Table 22.2). This classification is important as it correlates with patient survival and transplant outcome [79]. Standard arterial oxygen measurements should be performed with the patient in the sitting position. Pulmonary vascular dilation and shunting primarily occurs in the bases of the lung in patients with HPS, and there can be a marked difference of the arterial oxygen partial pressure in supine compared to sitting patients. The decrease in oxygenation with upright position is called orthodeoxia and

**Table 22.2** The classification of hepatopulmonary syndrome into severity of disease

Severity of disease	PaO <sub>2</sub> mmHg	A-a gradient
Mild	≥80	≥15
Moderate	≥60 to <80	≥15
Severe	≥50 to <60	≥15
Very severe	<50	≥15

There are four classifications of HPS based upon the arterial oxygen partial pressure. All severities of disease require that the A-a gradient is greater than 15. *A-a* alveolar-arterial gradient; *HPS* hepatopulmonary syndrome

commonly occurs in HPS. It is caused by an increase in perfusion through intrapulmonary shunts in the bases of the lung due to gravitational forces with the upright position.

Pulmonary function tests are not diagnostic for HPS. The only consistent finding is a low diffusing capacity, but this has low specificity. Intrapulmonary shunts are the hallmark of HPS and are identified by one of two methods [80]. Contrast-enhanced transthoracic echocardiograph with agitated saline is the most commonly used method. Microbubbles from the saline appear in the left heart in approximately 3–6 beats following the opacification of the right heart. This distinguishes HPS from right to left intracardiac shunts where bubbles are observed in the left heart within 1–2 beats following opacification of the right heart. Echocardiography cannot estimate the severity of disease but is less invasive than the injection of technetium-labeled macroaggregated albumin particles. With this technique, the amount of radiolabel technetium-labeled albumin that accumulates over the brain allows an estimate of the severity of disease. However, technetium scanning cannot determine the site of shunting and therefore cannot distinguish intracardiac defects from intrapulmonary shunts.

The principal defects in HPS are an increase in the number of pulmonary precapillary and capillary vessels in combination with vasodilation. Investigators have also identified anomalous pleural, pulmonary, and portopulmonary arteriovenous connections. In addition, patients with HPS have a reduction in their pulmonary vascular tone and impaired pulmonary vasoconstriction in response to hypoxemia [81]. These latter findings suggest the presence of autonomic dysfunction of the pulmonary circulation in patients with HPS,

and it is possible that some of the severity of disease is related to the degree of autonomic dysfunction.

Patients with HPS are hypoxemic due to three causes: There is a ventilation-to-perfusion mismatch due to a selective increase in pulmonary blood flow in areas of low ventilation [81]. Investigators also think that a diffusion-perfusion defect is caused by blood in the center of enlarged vessels that does not have adequate time to equilibrate with the alveolar oxygen [6]. Furthermore, there is direct arteriovenous admixture due to the presence of anatomic shunts. Ventilation-perfusion mismatch and shunts explain the presence of orthodeoxia [82]. Patients respond to an increase in inspired oxygen concentration when mismatching predominates as a cause of hypoxemia. A diffusion-perfusion defect probably predominates in severe cases of HPS and is made worse by the concomitant increase in cardiac output which further decreases the capillary transit time and therefore the time available for oxygen equilibration.

A selective increase in the pulmonary production of nitric oxide is one of the key pathological changes underlying the development of HPS [83]; however, HPS does not appear to be solely due to nitric oxide overproduction as inhibitors of nitric oxide do not entirely reverse hypoxemia [84]. Additionally to this and possibly other unknown mechanisms, an increase in endothelin B type receptors in the pulmonary circulation of patients with HPS further causes pulmonary vascular vasodilation and hypoxia [85].

Currently, the only definitive treatment for HPS is liver transplantation. The median survival in patients with HPS without a transplant is only 24 months with a 5-year survival of 23% [86]. Patients with similar characteristics but without



HPS had a median survival of 87 months, and 63% were alive at 5 years [87]. The outcome is worse with a PaO<sub>2</sub> less than 50 mmHg at the time of diagnosis or a macroaggregated albumin shunt fraction greater than 20% [88]. The cause of death is usually multifactorial with complications due to liver disease predominating. There are a few reports of improved hypoxemia after transjugular intrahepatic portosystemic shunting [89] or after cavoplasty in patients with HPS due to Budd-Chiari syndrome [90].

Patients with HPS have a high risk of perioperative death [91], and a 29% perioperative mortality is associated with a PaO<sub>2</sub> less than 50 mmHg [92]. Life-threatening decrease in oxygenation can occur anytime during surgery and in the early postoperative period. Due to the increased risk of early death, patients with HPS receive additional MELD points in the United States when the PaO<sub>2</sub> is less than 50 mmHg. There are a few case reports of ameliorating oxygenation using inhaled nitric oxide [93]. Nitric oxide is thought to vasodilate apical vessels and therefore may improve ventilation-to-perfusion matching.

## Summary

An intricate link between pulmonary and liver function exists, and abnormalities of the circulation and neurohormonal balance of patients with liver disease cause lung disease. Some diseases such as hydrothorax and pneumonitis are acquired and result from liver dysfunction. Other diseases such as cystic fibrosis and  $\alpha_1$ -antitrypsin are genetically based, and the coexisting lung injury is part of the wider disease process. Diseases such as POPH and HPS are acquired but probably have a genetic predisposition. The wide variety of lung diseases associated with liver dysfunction makes the preoperative assessment, selection, and perioperative management of transplant recipients challenging for anesthesiologists and intensivists. As newer medical therapies continue to emerge, they will change the outcomes of patients with combined pulmonary and liver disease. Thus, the perioperative care of the liver transplant patient is

a work in progress that will improve through advances of the scientific knowledge that underlies this unique specialty practice.

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# Liver Transplantation: The Patient with Severe Co-morbidities, CNS Disease and Increased Intracranial Pressure

Chris Willars and Georg Auzinger

## Intracranial Hypertension in Acute Liver Failure

### Etiology and Pathophysiology of Encephalopathy and Cerebral Edema in Acute Liver Failure

Intracranial hypertension (ICH) is a common cause of death in acute liver failure (ALF) [1]. The concept cerebral edema and hyperemia as a cause of the acute rise in intracranial pressure (ICP) in ALF is relatively novel and was first described in the early 1970s [2]. ICH is present in up to 75% of ALF patients with grade IV encephalopathy [3] and leads to decreased cerebral perfusion and risk of transtentorial herniation. The onset of ICH in ALF is rapid and allows insufficient time for adaptive processes. The underlying etiology is likely to be multifactorial.

### Etiology: Cerebral Cytotoxic Edema

In an analysis of 165 patients with ALF of varying etiology [4], a high arterial ammonia concentration was an independent risk factor for severe encephalopathy and ICH. A level of  $>100 \mu\text{mol/L}$  predicts the onset of severe encephalopathy with 70% accuracy, and ammonia levels of  $>200 \mu\text{mol/L}$  are associated with the develop-

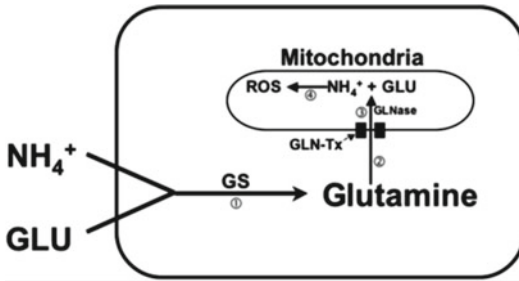
ment of ICH and the possibility of herniation. Furthermore, patients who develop ICH tend to have persistently high ammonia levels. Higher MELD (Model for End-Stage Liver Disease) scores, younger age and requirement for vaso-pressors or renal replacement therapy are additional independent risk factors for hepatic encephalopathy [5].

Ammonia plays a crucial role in the development of cerebral edema because astrocytes take up ammonia produced by bacteria in the bowel and convert it into glutamine, which has considerable osmotic activity. Ammonia also causes additional changes in neurotransmitter synthesis and release, mitochondrial function and neuronal oxidative stress. The net result is astrocyte swelling and cerebral edema [6]. Brain glutamine concentrations are increased in animal models of fulminant hepatic failure (FHF) [7] and also in samples taken post-mortem from patients with FHF [8]. Cerebral microdialysis studies in patients with ALF confirm a strong correlation of arterial ammonia concentrations with brain glutamine content [9]. ICP correlates with brain glutamine, and arterial ammonia levels and persistent elevations of both parameters may identify individuals at risk of ICH (Fig. 23.1).

Gene expression may also be altered in response to the onset of FHF, particularly those genes coding for astrocytic proteins. These proteins have important roles in the regulation of cell volume and in neurotransmission. The expression of the astrocytic/endothelial glucose transporter gene, the aquaporin-4 water

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**Fig. 23.1** Detoxification of ammonia to glutamine mediated by glutamine synthetase (GS) and subsequent creation of reactive oxygen species (ROS) following transport into the mitochondria. GLN-Tx—glutamine transporter, GLNase—glutaminase

channel and glutamate transporter gene have been specifically studied and demonstrated to be altered in FHF; however, the significance of any of these processes in isolation remains unknown.

Alterations in cerebral hemodynamics are common in acute and FHF and are discussed below. Blood–brain barrier injury, increased cerebral blood flow and hyperemia accompany astrocyte swelling and contribute to the rise of ICP. Blood flow is coupled to cerebral metabolic rate and changes in ventilation and acid–base status, and increases in blood flow can potentiate cerebral edema independently of astrocyte glutamine concentration [10].

In summary, cerebral edema may be vasogenic with inflammatory disruption of the blood–brain barrier, allowing extracellular edema formation (hind > forebrain), or cytotoxic with an increase in intracellular water as a result of defective osmoregulation (mainly forebrain). Evidence of predominant cytotoxic edema formation in ALF is based on findings of diffusion-weighted MRI scanning [11]. The diffusion coefficient that quantifies movement of water molecule across cell membranes is significantly lower in ALF patients with resolution of abnormal findings following recovery of liver failure.

### Etiology: Cerebral Blood Flow

FHF is associated with an accumulation of toxic metabolites and a massive systemic inflammatory

response with the release of a vast quantity of pro-inflammatory cytokines [12]. Alterations of cerebral blood flow are directly attributable to this inflammatory milieu: Cerebral edema is diminished in anhepatic rats compared with those with experimentally induced FHF [13]. Intrasplenic transplantation of allogeneic hepatocytes prevents development of ICH in pigs with acute ischemic liver failure and transient hepatectomy, and formation of a portacaval shunt has been used successfully in ALF patients with intractable ICH as a bridge to transplantation. The observation that ICH occurs with FHF, but not chronic liver disease, lends further weight to this ‘toxic liver hypothesis’. ICP measurements during transplant surgery have demonstrated that ICP increases during the manipulation and dissection of the necrotic liver [14], but then decreases during the anhepatic phase and following graft reperfusion. Evidence from case reports [15] suggests that the levels of pro-inflammatory cytokines are diminished following removal of the toxic liver.

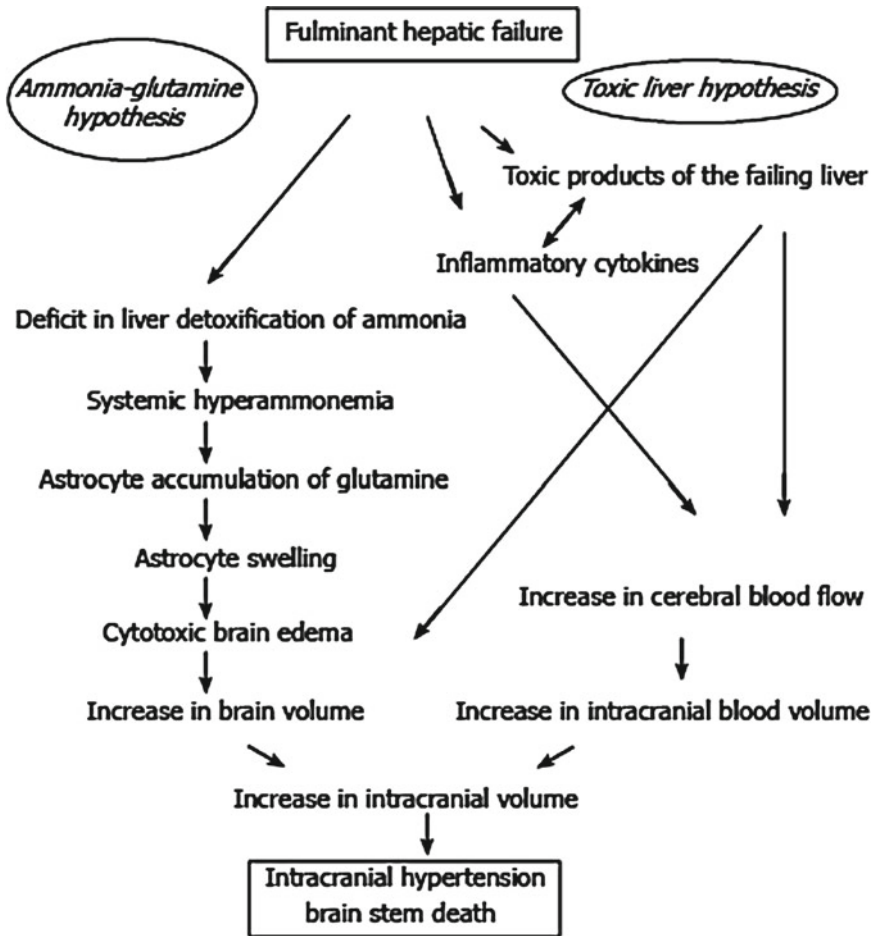
Loss of autoregulation can further lead to increased cerebral blood flow and blood volume and therefore ICH. This concept is supported by findings from animal models and seen in patients with FHF [16]. The loss of autoregulation has been attributed to the effects of nitric oxide (NO) on the cerebral vasculature, but it may be that elevated NO levels only occur secondary to increase in cerebral blood flow rather than as a primary and causative phenomenon [17]. Other pro-inflammatory mediators such as  $\text{IL-1}\beta$ ,  $\text{TNF}\alpha$  and  $\text{IL-6}$  may also cause cerebral vasodilation and ICH [18].

### Pathophysiology of Intracranial Hypertension

Normal ICP is approximately 7–15 mmHg in a supine adult. Definitions of ICH vary, but a pressure of >20 mmHg for a period of 20 min or more can be considered as an episode of significant ICH. Accurate measurement of ICH requires the insertion of an ICP monitor. The US ALF group recommends ICP monitoring for patients with advanced hepatic encephalopathy who are awaiting OLT and osmotic therapy for  $\text{ICP} \geq 25$  mmHg [19].

According to Monro and Kellie, the cranial compartment is essentially an incompressible





**Fig. 23.2** Etiology of ICH. Uptake and detoxification of ammonia to osmotically active glutamine by astrocytes, leading to cerebral edema (the ammonia-glutamine hypothesis). Loss of cerebral autoregulation leading to

increased CBF secondary to circulating inflammatory mediators (the toxic liver hypothesis), with disruption of the blood–brain barrier and vasogenic edema formation

box with a fixed internal volume. Blood, CSF and brain tissue (~90% of the total) exist in a state of volume equilibrium and are relatively incompressible, such that any increase in the volume of one of the cranial constituents must be compensated for by a decrease in the volume of another.

CT studies [20] in FHF have demonstrated that ventricular spaces are either unchanged or compressed, and therefore, the expansion of the CSF component is not responsible for rises in ICP. Rather, the radiological appearances are consistent with acute cerebral edema. Brain edema has been demonstrated in rabbits with galactosamine-induced fulminant hepatitis [21]

and ammonia-induced cerebral edema in rats. Hyperemia due to defective autoregulation or circulating inflammatory mediators may further compound the rise in ICP. The main complication of profound ICH is diencephalic transtentorial herniation, causing:

- Posterior cerebral artery insufficiency with temporal, thalamic and occipital infarction
- Compression of the cerebral aqueducts and subarachnoid space with resultant obstructive hydrocephalus
- Brain stem compression, ischemia and death

To summarise, two predominant mechanisms are thought to underpin the rise in ICP seen in FHF [22] (Fig. 23.2):

- The uptake and detoxification of ammonia to osmotically active glutamine by astrocytes, leading to cytotoxic cerebral edema (the ammonia-glutamine hypothesis)
- The loss of cerebral autoregulation leading to increased CBF secondary to circulating inflammatory mediators (the toxic liver hypothesis) with disruption of the blood–brain barrier and vasogenic edema formation

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## Monitoring

### Cerebral Perfusion Pressure

ICH compromises cerebral perfusion pressure (CPP) given their relationship:  $CPP = MAP - ICP$  ( $MAP$ —mean arterial pressure).

A sustained decrease of CPP to less than 40 mmHg for 2 h or more is associated with a poor outcome, although there are reports of complete neurological recovery despite prolonged periods of perfusion pressure below this threshold [23]. Whilst every attempt should be made to maintain cerebral perfusion within well-defined limits in our own experience, a transient decrement in cerebral perfusion should not be interpreted in isolation as a marker of poor prognosis.

### Diagnosis and Multimodality Monitoring

ICH should be suspected in any patient who presents with hepatic encephalopathy in the context of acute or fulminant liver failure and/or significantly elevated arterial ammonia levels. Usually patients with ALF and rapidly evolving encephalopathy will require endotracheal intubation with subsequent sedation and mechanical ventilation. Under these circumstances, the only reliable early monitor of raised ICP—the patient's own conscious level—has been lost, although clonus, hypertonicity and decerebrate posturing may still be detected. Pupillary changes, systemic hypertension and reflex bradycardia are late changes, and radiographic changes are non-

specific. A relatively 'tight' brain is often seen on CT imaging but correlates poorly with severity of cerebral edema or the presence of ICH.

### ICP Monitoring

Insertion of an ICP monitor (after correction of coagulopathy) and jugular bulb oximetry readings allow for continuous monitoring of ICP and give an indication of the cerebral oxygen supply/demand relationship. ICH may develop rapidly and is subject to flux. Inadequate sedation, seizure activity and worsening edema/hyperemia can cause sudden and potentially dangerous surges in ICP. Continuous monitoring enables rapid detection of ICH and allows the physician to target therapy accordingly. ICP monitoring further allows estimates of the likely neurological outcome. In practice, clinical signs do not adequately quantify ICP. Similar to trials of traumatic brain injury (TBI), evidence from randomised controlled studies were not able to demonstrate a clear survival benefit of ICP monitoring in patients with ALF. In addition, the procedure carries an, although in expert hands small, yet significant bleeding risk [24]. Furthermore, a lack of consensus over the therapeutic goals has done little to promote the role of ICP monitoring in ALF. A recent study of 332 patients with ALF reported the experience with ICP monitoring in 24 centres [25]. ICP monitoring was used in only 92 patients (28% of the cohort), and 10% of these experienced intracranial hemorrhage. The 30-day survival for liver transplantation recipients was similar in both monitored and unmonitored groups (85% vs. 85%). A retrospective analysis of over 200 patients in our institution demonstrated much lower rates of associated hemorrhage of 0.8% [26].

Monitoring modalities differ between centres: Extradural monitoring is less accurate and associated with significant baseline drift, but penetration of the dura is associated with higher rates of bleeding. Patients whose ICP is monitored undergo more treatment interventions, but it is not clear whether these interventions are associated with better neurological outcomes.

## Jugular Bulb Oximetry

Blood from the cerebral venous sinuses drains into the internal jugular vein. Monitoring of oxygen saturation in the jugular bulb allows an estimation of the balance of global oxygen supply vs. demand ratio and hence of cerebral metabolism.

Both intermittent sampling and continuous monitoring may be used, although the latter requires the insertion of a fibre optic catheter. The normal range for jugular venous oxygen saturations ( $S_{jvO_2}$ ) is 60–75%. Desaturations to less than 55% are indicative of cerebral hypoperfusion due to inadequate CPP or a sign of increased cerebral oxygen uptake as seen with seizure activity. High saturations >80% are found during cerebral hyperemia or with inadequate neuronal metabolism/neuronal cell death, respectively. High jugular venous saturations are equally associated with poor outcome as low values [27]. The major drawback of  $S_{jvO_2}$  is that it provides an estimate of global oxygenation and metabolism, and smaller areas of critical ischemia may not affect overall cerebral venous oxygen content. However, rises in ICP, effect of hyperventilation therapy, hypotension and cerebral vasospasm may all be detected with  $S_{jvO_2}$ .

$S_{jvO_2}$  is reduced in the following clinical scenario:

- Cerebral vasoconstriction (e.g. as a result of hyperventilation and hypocarbia)
- Hypoxemia
- Anemia
- Diminished CPP
- Inappropriately high CPP and vasoconstriction induced by exogenous vasoconstrictor
- Seizure activity

$S_{jvO_2}$  is elevated in:

- Hyperemia
- Vasodilation (e.g. as a result of hypoventilation and hypercarbia)
- Brain death

## Transcranial Doppler

Transcranial Doppler ultrasound (TCD) is a simple and non-invasive method of quantifying blood

flow velocities in the basal cerebral arteries (most commonly the middle cerebral artery). Cerebral blood flow is calculated from the mean flow velocity if the cross-sectional area of the targeted artery is known; thus,

$$\text{CBF} = \text{mean flow velocity} \times \text{area of artery} \\ \times \cosine \text{ angle of insonation}$$

Successive measures of CBF are only comparable if the angle of insonation and the diameter of the target vessel remain the same. Varying vessel diameters with vasospasm are a potential source of error. An increase in flow velocities is seen with hyperemia and increased cerebral blood flow and during episodes of cerebral vasospasm. In order to differentiate between these two very different phenomena, the ratio of middle cerebral artery to extracranial internal carotid artery flow can be determined. The MCA velocity is normally about 60–70 cm/s with an ICA velocity of 40–50 cm/s. The MCA/ICA ratio is therefore  $1.76 \pm 0.1$ . An MCA velocity >120 cm/s is considered significantly elevated and when accompanied by a high MCA/ICA ratio likely due to vasospasm. If MCA/ICA ratios are lower, hyperemia is the more likely diagnosis.

## Non-invasive Monitoring of ICP

Non-invasive monitoring of ICP with computed tomography, MRI, PET scanning or transcranial Doppler is inaccurate, noncontinuous and often impractical in advanced stages of ALF. Tympanic tonometry has been demonstrated to be inaccurate compared with direct ICP measurement but may be useful in detecting changes in ICP. The optic nerve sheath distends when CSF pressure is elevated. Measurement of optic nerve sheath diameter may therefore be an acceptable surrogate for the measurement of raised ICP. MRI and ocular sonography following TBI have demonstrated a correlation between nerve sheath diameter and presence of ICH. This method of assessment is user dependent but non-invasive and can be performed at the bedside. At present, its use in ICH related to FHF has not been fully

evaluated; it may be a useful adjunct if the indications for ICP monitoring are unclear, or in quantifying the risk of ICH and identifying those patients who are most likely to benefit from direct monitoring.

## Preoperative Management

Accepted strategies for the reduction of ICH include specific therapies targeting ICP and the reduction of the volume of brain tissue, as well as general measures to protect against secondary brain damage following the primary insult (Rosner's conjecture). This should embrace all the factors responsible for causing secondary insult via cerebral ischemia.

Medical management thus falls under a number of broad titles:

- General supportive measures
- Prevention and treatment of raised ICP
- Achieving an appropriate CPP
- Specific medical therapies
- Anticipation and management of complications

An ICP >15 mmHg is considered abnormally high. Various authors have suggested different thresholds for treatment under different circumstances. The Brain Trauma Foundation [28] suggests a treatment threshold of 20 mmHg, whilst the US Acute Liver Failure Study Group [19] suggests treating ICP of 25 mmHg and above. The limits within which CPP should be maintained are also not clearly defined.

## ICP-Targeted Therapies

The majority of treatment strategies are similar to those described in the neurosurgical literature, but many of the pathophysiological mechanisms of cerebral edema in ALF are unique and not applicable to other patient groups.

## Positioning and Environment

The head of the bed should be elevated at ~30° to facilitate venous and CSF drainage. Further elevations have been shown to potentially cause

**Table 23.1** West Haven criteria for semiquantitative grading of mental state (encephalopathy grades)

Grade 1	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impaired performance of addition
Grade 2	Lethargy or apathy
	Minimal disorientation for time or place
	Subtle personality change
	Inappropriate behaviour
	Impaired performance of subtraction
Grade 3	Somnolence to semistupor, but responsive to verbal stimuli
	Confusion
	Gross disorientation
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

With permission from Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy—definition, nomenclature, diagnosis and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology*. 2002;35:716–21

paradoxical increase in ICP. Surgical tape should be used to secure endotracheal tubes (in a non-circumferential fashion) or tube ties loosened. The head and neck are kept in a neutral position, approximating the midline. Environmental stimulation is kept to a minimum.

## Ventilation

Encephalopathy is usually graded using the West Haven criteria for encephalopathy (Table 23.1). Endotracheal intubation is performed for airway protection in advanced grade III/IV encephalopathy, to facilitate the control of ICP (cerebral blood flow is coupled to cerebral metabolic rate and to  $\text{paO}_2$  and  $\text{paCO}_2$ ) and for the treatment of respiratory failure. Induction of anesthesia should aim to attenuate surges in ICP on laryngoscopy and intubation whilst maintaining CPP within acceptable limits. There is no general consensus regarding the mode of ventilation to be used. Given that acute respiratory distress syndrome (ARDS) may accompany the systemic inflammatory response of FHF (particularly with the development of

raised ICP), a protective ventilatory strategy should be adopted where possible (limiting tidal volumes to ~6 mL/kg and plateau pressure to <30 cm H<sub>2</sub>O). Permissive hypercapnia is poorly tolerated as any rise in paCO<sub>2</sub> will be associated with a concomitant rise in ICP. High levels of positive end-expiratory pressure (PEEP) can diminish venous return and reduce hepatic blood flow; at the same time, PEEP levels up to 15 cm H<sub>2</sub>O have been used safely in patients with TBI and ARDS. A 'best PEEP' strategy (choosing PEEP levels that will provide maximal recruitment whilst avoiding alveolar overdistension to optimise oxygen delivery) is advisable.

Hypoxia and hypercapnia cause CBF (and therefore ICP) to increase. Prophylactic hyperventilation may reduce brain edema and has been shown to delay the onset of brain herniation [29]; however, it can result in unwanted cerebral vasoconstriction which may be detrimental for oxygen delivery to marginal/at-risk areas of brain tissue. The Brain Trauma Foundation recommends the use of hyperventilation as a temporising measure only and suggests that it should be avoided during the first 24 h after TBI. In the setting of ALF, controlled studies have failed to show any benefit, with no reduction in the number of episodes of raised ICP [29]. Hyperventilation should be guided by jugular bulb oximetry or other forms of monitoring of adequacy of cerebral oxygen supply; as with TBI, it should only be used for the emergency rescue of imminent diencephalic herniation.

### Temperature

In general, normothermia should be maintained. Fever needs to be treated aggressively because it stimulates cerebral metabolism and consequently induces vasodilatation. Cooling blankets and paracetamol are both suitable for this purpose. As many patients will require extracorporeal renal replacement therapy, low-temperature control can be easily maintained on extracorporeal circuits.

### Glycemic Control

Hyperglycemia may exacerbate secondary brain injury (Rosner's conjecture) and exacerbate ICH

[30]. A landmark single-centre clinical trial has shown an outcome benefit with tight glycaemic control in critically ill surgical patients [31]. The same group failed to demonstrate a mortality benefit in a medical cohort [32]. In TBI, tight glycaemic control can lead to critical brain tissue hypoxia and has been associated with poor ICP control, higher incidence of bacteremia and worsened survival [33]. ALF is associated with a propensity towards hypoglycemia, and there is no compelling evidence that tight glycaemic control is beneficial in this population. ALF induces a systemic inflammatory response and hypermetabolic state. Catabolism predominates with a negative nitrogen balance and immunodeficiency. The energy expenditure even in the resting state is considerable, and early nutritional support is therefore recommended, although there is little evidence of benefit in this patient population.

### Infection Prophylaxis

Infection is a frequent complication of ALF. In a recent study by the US Acute Liver Failure Study Group (US-ALFSG), the progression of hepatic encephalopathy was associated with sepsis, especially in patients with acetaminophen-induced ALF [34]. Respiratory tract infection, including ventilator-associated pneumonia is most prevalent although line-related sepsis, urinary sepsis, abdominal sepsis secondary to bacterial translocation and de novo septicemia are also common. Gram-positive cocci (*Staphylococci*, *Streptococci*) and enteric Gram-negative bacilli are the most frequently isolated organisms. Fungal infections are also common and may occur in a third of ALF patients [35]. It is routine practice to treat early and aggressively with antifungal therapy. Intravenous catheters should be monitored on a regular basis, changed routinely and removed where possible to avoid infectious complications.

Antibiotic prophylaxis is instituted as a matter of routine in all patients with advanced encephalopathy and when infection seems likely on the basis of clinical and laboratory investigations. US-ALFSG guidelines state that

There are insufficient data to recommend the routine use of antibiotic prophylaxis in all patients with ALF, particularly those with early stage

hepatic encephalopathy....empirical administration of antibiotics is recommended in the following circumstances....

- surveillance cultures reveal significant isolates
- progression of, or advanced stage (III/IV), hepatic encephalopathy
- refractory hypotension
- presence of SIRS

Empirical antibiotics (antibacterial and antifungal agents) also are recommended for patients listed for OLT, because developing infection often results in delisting and immunosuppression is imminent, acknowledging that specific data to support this practice do not exist. It should be recognised that the risk of developing infection with resistant organisms will increase with longer waiting times.

Antimicrobial coverage should encompass commonly responsible organisms given the likely site of infection, the known bacterial flora of the intensive care unit at the time and the results of blood, urine and sputum cultures, chest radiographs and other surveillance modalities. Further details about infections and antibiotic treatment in liver disease and transplantation can be found elsewhere (Chapter 33) in this book.

### **Sedation and Neuromuscular Blockade**

Sedation should be maintained in a continuous manner and be maintained at a depth that will prevent straining or coughing against the ventilator. BIS monitoring to evaluate depth of sedation is not routinely used and recommended. Intravenous anesthetic agents (with the exception of ketamine) decrease cerebral metabolism and reduce CBF via flow-metabolism coupling. Propofol is a widely used agent in this context and may attenuate CBF more effectively than benzodiazepines. Cerebral metabolic rate ( $CMRO_2$ ) is elevated with inadequate anesthesia and will often be reflected by a low  $SjvO_2$ . Infusion of an opiate such as fentanyl is commonplace for synergistic sedative effect, to facilitate endotracheal tube tolerance, as an anti-tussive agent, to attenuate surges in ICP. Opiates themselves have little effect on cerebral metabolism and blood flow. Neuromuscular blockade is rarely required when adequate sedation and analgesia are used. Neuromuscular blocking agents mask seizure activity and may

be associated with the development of critical care polyneuromyopathy. Their routine use cannot be recommended, although practice varies between centres. They are generally used to prevent coughing, straining and ventilator dyssynchrony and associated surges in ICP. Lidocaine can be administered intravenously or via the tracheal tube prior to the application of tracheal suction to attenuate coughing but is not necessarily common practice.

### **Seizure Prophylaxis**

Grade III/IV encephalopathy is associated with a high incidence of non-convulsive seizure activity. Commonly used sedative agents such as propofol and benzodiazepines are well established in the treatment of epilepsy and provide some degree of prophylaxis/protection of the sedated and ventilated ALF patient. The prophylactic use of other anti-epileptics is not recommended. If BIS monitoring is used to assess the depth of sedation, then discordant readings may prompt further evaluation with EEG. The latter should also be considered for neurological deteriorations and to assess burst suppression when barbiturate coma is induced to treat refractory ICH.

### **Ammonia-Reducing Strategies**

Considering the strong correlation between elevated arterial ammonia levels and the development of encephalopathy and ICH, ammonia-reducing strategies may be useful; however, there is no level 1 evidence to support this practice. Many of the agents that are regarded effective in chronic liver disease have no sufficient data to support their use in ALF.

There are no randomised controlled trials of lactulose administration in ALF, and it is often poorly tolerated in critically ill patients receiving high-dose sedation and analgesia, as reduced gut motility frequently leads to worsening gaseous distension. The routine use of lactulose is therefore not recommended. Neomycin, rifaximin and other non-absorbable antibiotics, such as metronidazole, oral vancomycin, paromomycin and oral quinolones, are administered to patients with chronic cirrhosis in an effort to decrease the colonic concentration of ammoniagenic bacteria.



There is also no strong evidence base supporting the use of these non-absorbable antibiotics in ALF.

L-Ornithine-L-aspartate (LOLA) reduces the hyperammonemia of hepatic encephalopathy [36] by increasing ammonia detoxification in the muscle although overall; however, there is no evidence of an outcome benefit. A placebo-controlled blinded study [37] randomised 201 patients with ALF to either placebo or LOLA infusions (30 g daily) for 3 days. Arterial ammonia was measured at baseline and then daily for 6 days. There was no reduction in mortality with LOLA treatment and no difference between the two groups in the improvement in encephalopathy grade, consciousness recovery time, survival time or complications like seizures and renal failure. CVVHD is indicated for acute renal failure, oligo-anuria and acidemia and has been demonstrated to reduce circulating levels of  $\text{NH}_4$ ; part of the effect can be explained by temperature control and reduction in  $\text{NH}_4$  production. There is no evidence that prophylactic use of CVVHD in the absence of other indications for renal replacement therapy improves outcome in patients with ALF and encephalopathy.

### Fluid Management and Osmotherapy

Fluid management should be directed towards the provision of adequate hydration and treatment of hypovolemia. The blood–brain barrier will allow the passage of fluids and electrolytes along their osmotic gradients, and hypotonic fluids should therefore not be used as they have a tendency to exacerbate cerebral edema.

Osmotherapy is effective in attenuating cerebral edema. Mannitol and hypertonic saline are both recommended for this purpose. Mannitol elicits a classically described biphasic response [38]: There is an early fall in ICP as blood rheology improves. The improved blood flow enhances oxygen delivery and, via flow/metabolism coupling, results in cerebral vasoconstriction. A subsequent decrement in ICP is observed approximately 30 min later as mannitol increases plasma osmolality and draws brain water across the blood–brain barrier down its osmotic gradient. Mannitol also acts as an oxygen free-radical

scavenger. Plasma osmolality should not exceed 320 mosmol/kg.

Hypertonic saline includes any concentration  $>0.9\%$  NaCl, but solutions used for osmotherapy in ALF are commonly 2.7–30%. The indications for hypertonic saline are similar to those of mannitol. It also acts by establishing an osmotic gradient across the blood–brain barrier [39] with a subsequent reduction in brain water as water is drawn out of the brain parenchyma down its osmotic gradient. There is a biphasic reduction in ICP, similar to that of mannitol.

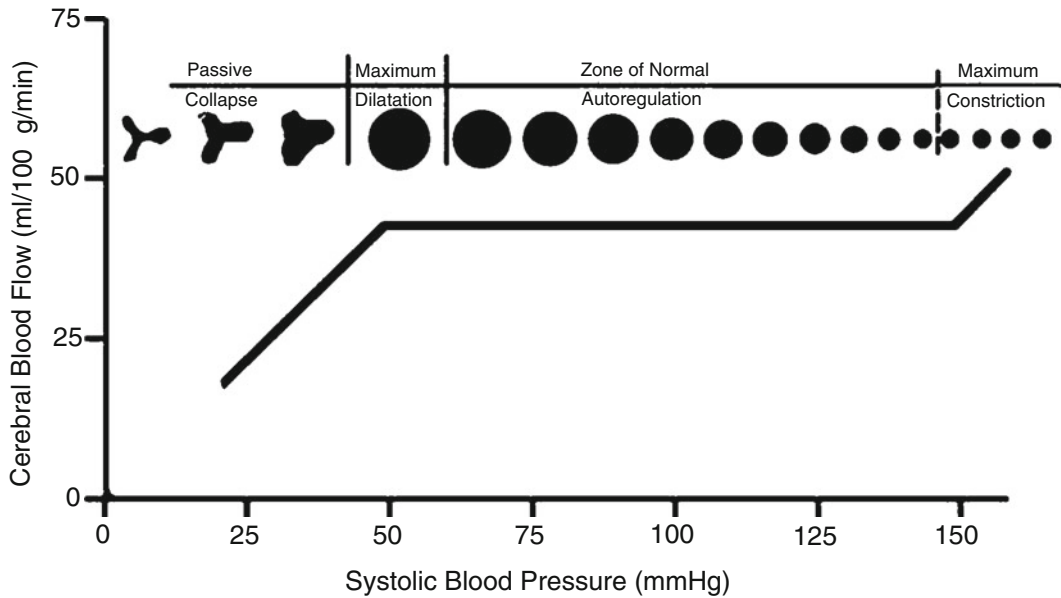
Serum sodium levels of 145–155 mmol/L are commonly used as a target and reduce the incidence of ICP rise above 25 mmHg [40]. In practice, patients with FHF are often anuric and require continuous renal replacement therapy, so serum sodium levels rarely exceed these values even with prolonged infusion.

The osmotic-reflection coefficient across the intact blood–brain barrier is higher (i.e. the BBB is less permeable) for hypertonic saline than for mannitol. It is therefore less likely to accumulate significantly in the brain parenchyma and, in theory, should be a more effective osmotic agent. It has been postulated that rebound ICH may be smaller with hypertonic saline than with mannitol. Hypertonic saline also causes effective volume expansion without a secondary diuresis.

Plasma osmolality is nominally kept below 320 mosmol/L, although this threshold has recently been questioned and poorer outcomes have only been associated with very high serum sodium levels and corresponding plasma osmolalities of 335–345 mosmol/L. Complications of hypertonic saline relate to the administration (tissue necrosis, thrombophlebitis) and metabolic side effects (hyperchloremic acidosis, hypokalemia, hypocalcemia). Osmotic myelinolysis may be precipitated if serum sodium concentrations are corrected too rapidly.

### Therapies targeting cerebral perfusion pressure (CPP)

Under normal conditions, autoregulatory mechanisms ensure that CBF remains constant at approx-



**Fig. 23.3** The relationship between systolic blood pressure (SBP) and cerebral blood flow (CBF) in the uninjured brain. The ability to autoregulate blood flow may be lost

in brain injury, and flow may become pathologically dependent on pressure

imately 50 mL/100 g/min within a CPP range 50–150 mmHg. In the injured brain, the relationship between CPP and CBF changes—the autoregulation curve tends to shift to the right, so that a CPP > 50 mmHg may be required to maintain flow and normal autoregulation may be disrupted, such that CBF becomes proportional to CPP. General principles of fluid management apply, and fluid therapy is perhaps best guided by the appropriate use of cardiac output monitoring that can provide dynamic measures of preload responsiveness and indicate whether or not stroke volume improves in response to filling. Injudicious use of fluids may worsen cerebral edema and associated lung injury. If hemodynamic optimisation with fluid therapy alone fails to achieve adequate mean arterial pressures in the face of systemic vascular resistance, vasopressors may be required to augment the CPP.

Increasing CPP may increase CBF, particularly in injured regions of the brain, but this will only occur if CPP has fallen below the autoregulation threshold or if autoregulatory mechanisms have failed altogether and CBF is proportional to the CPP. This may be desirable, but risks exacerbating ICH through increased cerebral blood flow and blood volume and worsening cerebral edema

(increased hydrostatic pressures). Increasing CPP can also cause cerebral vasoconstriction (thus lowering the ICP) if autoregulation is intact (Fig. 23.3).

The target CPP has been the subject of some controversy. In polytrauma cases at risk of raised ICP, a MAP of 90 mmHg has traditionally been targeted in patients without ICP monitoring. In patients with ICP monitoring, a target CPP of 70 mmHg was originally recommended by the Brain Trauma Foundation in 1995. A contrasting view is that setting a higher CPP target will worsen brain edema by increasing the hydrostatic pressure gradients across tissue beds. There is also some evidence that targeting higher CPPs may promote the development of ARDS [41], although the underlying mechanism is unclear. This led to the Brain Trauma Foundation lowering the target CPP to 60 mmHg in TBI. The brain tissue oxygen partial pressure ( $PbO_2$ ) may plateau at a CPP of 60 mmHg [42].

Whilst continuing to note the dangers of a CPP >70 or <50 mmHg, a recent recommendation is to monitor markers of cerebral oxygenation and metabolism to adopt an individualised approach to therapy within the CPP range of

50–70 mmHg [43]. Autoregulation thresholds vary over time; hence, CPP goals have to be adapted to changing clinical conditions.

The choice of vasopressor has not been subject of controlled clinical trials. Norepinephrine is the first-line agent, and low-dose vasopressin is increasingly used following trial experience in septic shock and TBI patients. Early concerns regarding increase in cerebral hyperemia with use of vasopressin or vasopressin analogues are probably unfounded. Epinephrine is poorly tolerated due to its effect on aerobic glycolysis and associated worsening of lactic acidosis.

## Strategies for Treating Refractory Increases in ICP

### Barbiturate Coma

Barbiturates can be titrated to burst suppression of the EEG and decrease cerebral metabolism (CMRO<sub>2</sub>) and cerebral blood flow by virtue of flow-metabolism coupling. Sodium thiopental can be used as ‘rescue therapy’ to lower ICP refractory to other measures.

A loading dose of 5–10 mg/kg of sodium thiopental is required, followed by a continuous infusion of 3–5 mg/kg/h. EEG monitoring should be used to guide further therapy. Increasing doses above those required for burst suppression causes unwanted side effects such as arterial hypotension through negative inotropy and a lowering of systemic vascular resistance (dose-dependent) without conferring any additional benefit. Other complications of sodium thiopental therapy include immunosuppression, bronchoconstriction, electrolyte disturbances (notably profound hypokalemia), renal impairment (reduced renal blood flow and increased ADH secretion) and ileus.

After prolonged infusion, the metabolism of sodium thiopental becomes ‘zero order’—the hepatic enzyme systems responsible for its metabolism become overwhelmed, and the lipid-soluble drug accumulates in tissues such as fat and muscle. The duration of action is therefore greatly prolonged and ‘washout’ of the drug takes considerable time. In addition, sodium thiopental

is partly metabolised to pentobarbitone, which has a longer half-life than sodium thiopental itself.

### Indomethacin

Indomethacin has been used in the treatment of refractory cerebral hyperemia [44, 45]. Doses of 25 mg iv over 1 min may have a vasoconstrictor effect, although in these circumstances, CBF may actually increase (as measured by transcranial Doppler) as ICP is reduced and CPP is restored. Indomethacin has been used more extensively in traumatic ICH, in patients with space occupying lesions and animal models and its use is not widely reported in ALF.

### Therapeutic Hypothermia

Cooling the patient’s core temperature to as low as 32–33°C reduces otherwise refractory elevation in ICP in patients with ALF [46]. Arterial ammonia levels and cerebral uptake of ammonia are reduced with hypothermia, with a reduction in cerebral edema and hyperemia. CPP improves as a result of diminished ICP. This degree of hypothermia has some deleterious systemic effects, including coagulopathy, immune suppression, insulin resistance and an increased risk in nosocomial infections—particularly ventilator-associated pneumonia. Prolonged hypothermia in patients not progressing to transplantation requires the use of deep sedation and/or paralysis to attenuate shivering. Several animal studies and case series have been published, and a pilot trial was recently completed: *The Hypothermia to Prevent High Intracranial Pressure in Patients with Acute Liver Failure* (Rigshospitalet, Denmark, 2009) is an open, randomised and unblinded study that intends to evaluate the effect of prophylactic hypothermia on preventing high ICP and compromised cerebral oxidative metabolism. It hypothesises that the reduced cerebral metabolic rate and reduced splanchnic ammonia production might contribute to neuroprotection and reduce the risk of cerebral hypertension in patients with ALF. Results from this trial are to be published soon.

Mild to moderate hypothermia, targeting temperatures of 35–36°C, may represent a

reasonable compromise. ICP is reduced, although perhaps not as effectively as with more profound cooling techniques, and ammonia production is less affected, but the deleterious consequences of profound hypothermia are minimized. Allowing a passive decline of core temperature using an extracorporeal circuit is a simple way of inducing and maintaining mild hypothermia.

### Hepatectomy

Refractory increases in ICP have been treated by total hepatectomy as a bridge to OLT. Marked reductions in ICP following removal of the toxic liver supports the postulate that pro-inflammatory cytokines are involved in the pathogenesis of cerebral edema and/or hyperemia in ALF. The procedure may be lifesaving for extreme cases but requires the availability of a transplantable organ within a very short time.

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### Intra-operative Considerations

Patients are at risk of brain herniation intra-operatively as well as during the peri-operative phases. In an analysis of 116 FHF patients, 13 (11.2%) developed brain death during or shortly after OLT [47], and the exact timing of the neurological insult is unclear. Detry et al. [14] observed that of 12 patients transplanted for FHF, the four patients with normal preoperative ICPs maintained normal pressures intra-operatively. Of the 8 patients with preoperative episodes of increased ICP, 4 patients developed 6 episodes of ICH during surgery. The dissection and reperfusion phases were most associated with cerebral insufficiency secondary to surges in ICP and consequent reduction in CPP. The anhepatic phase was associated with a decrease of the ICP. At the end of the anhepatic phase, the ICP was lower than the preoperative ICP in all patients and below 15 mmHg in all but one patient.

This observation is in concordance with a small study of six cases from King's College Hospital which demonstrated higher ICP levels pre-anhepatic and during graft reperfusion and similarly reduced ICP during the anhepatic phase

[48]. Lidofsky et al. [49] noted that thiopental treatment was most frequently required during liver dissection, but ICP invariably normalised within 15 min of caval cross-clamping. This group also noted transient rises in ICP at the time of graft reperfusion.

The use of veno-venous bypass during OLT has been advocated to maintain cerebral perfusion. It has been proposed that the lack of adequate collateral venous circulation leads to hemodynamic instability and volume replacement that can exacerbate cerebral edema is subsequently required to maintain target hemodynamic parameters. Furthermore, the release of CO<sub>2</sub> during reperfusion can exacerbate cerebral vasodilatation and raise ICP. However, there is no consensus regarding the efficacy of VVB to ameliorate these effects.

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### The Neurology of Chronic Liver Disease

Brain edema and ICH are not commonly recognised features of terminal chronic liver failure, although occasional cases have been reported in the literature. Clinical symptoms and cerebral edema are less severe with chronic liver disease compared with ALF since encephalopathy in chronic liver disease progresses more slowly and adaptive responses can develop. The distribution of edema differs in chronic liver disease; excess brain water is mostly intracellular with ALF, whereas with chronic liver disease, it is mostly extracellular. This may result from the loss of organic solute and water from cells with restoration of volume and minimal effect on function.

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### The Patient with Severe Hyponatremia and CNS Dysfunction

Hyponatremia is common, both in patients with cirrhosis and ALF, and morbidity and mortality are increased in patients with lower serum sodium levels listed for transplant and during the peri-operative phase. Exacerbations of

encephalopathy are increased in frequency, duration and severity in hyponatremic cirrhotics [50]. Hyponatremia in combination with hepatic encephalopathy leads to a clinical picture of confusional syndrome and is similar to other metabolic encephalopathies. The severity of neurological symptoms correlates with the speed and severity of the decrease of serum sodium levels. A gradual drop, even to very low levels, may be tolerated well if it occurs over several days or weeks. Serum sodium levels of <120 mmol/L can significantly lower the seizure threshold, and serum sodium concentration is an independent predictor of EEG abnormalities in patients with HE. Lethargy, seizures and coma may be seen with variable frequency with a slower decrease of serum sodium levels to <110 mmol/L. The osmotic disequilibrium resulting from hyponatremia causes astrocyte swelling. The generation of the action potential and synaptic transmission are also dependent on ionic gradients and the movement of sodium down its electrochemical gradient through Na-specific voltage-gated ion channels.

The resolution of hyponatremia in cirrhotics leads to improvement in related neurological symptoms. To avoid hyponatremia, causes such as diuretic use, infusion of hypotonic fluids and gastrointestinal losses due to diarrhea or medication (lactulose, enema) should be considered. It is important to distinguish between hypovolemic and hypervolemic hyponatremia, as this will determine whether saline infusion or fluid restriction is the appropriate treatment. In ALF, osmotherapy with hypertonic saline infusion increases serum sodium to levels of 145–155 mmol/L and is associated with a reduction in the incidence and severity of episodes of ICH. In chronic cirrhotics with hepatic encephalopathy and hyponatremia, saline infusions may be administered if signs of hypovolemia or recent diuretic use are evident. Under these circumstances, paracentesis may be the preferred treatment modality for resistant ascites [51]. Sodium levels should be normalised prior to liver transplantation in hyponatremic patients to avoid rapid sodium shifts during surgery. Occasionally pre- and intra-operative ultrafiltration therapy is

indicated to prevent postoperative neurological complications.

The rapidity of correction of hyponatremia is based on the speed of onset. If the speed is not known, slow rise in serum sodium concentration at a rate of <0.5 mmol/L/h is advisable. Rapid rises in serum sodium concentration can precipitate osmotic myelinolysis that can cause profound and often permanent neurological deficits. Severe damage of the myelin sheath of nerve cells in the corticobulbar and corticospinal tracts of the brainstem may cause quadriplegia, dysphagia, dysarthria, diplopia, loss of consciousness and locked-in syndrome.

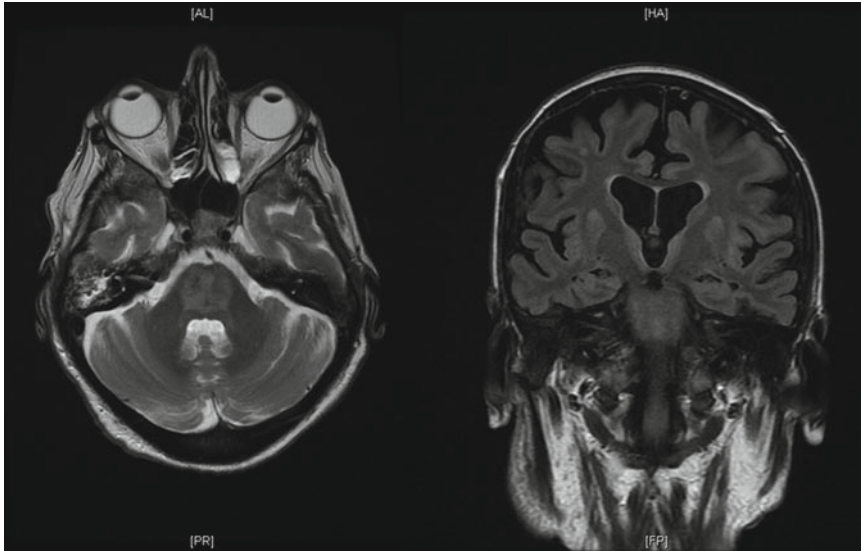
The MRI in Fig. 23.4 is of a patient who went to OLT with serum sodium 128 mmol/L. Subsequent to OLT, the serum sodium rose to 135 mmol/L. The patient extubated successfully but underwent re-laparotomy the following day for ongoing blood loss with consequent infusion of colloid, packed cells and blood products. The day following re-laparotomy, the serum sodium had risen to 142 mmol/L, and there was an associated deterioration in respiratory function and GCS (Fig. 23.4).

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## Neurological Outcomes After Liver Transplantation

Neurological complications are common following liver transplantation (13–43%) [52], in part due to co-morbidities present at the time of surgery (HE, hepatitis C, alcohol, arterial hypertension, etc.). Other factors to consider include effects of calcineurin inhibitors, other drug effects, cerebrovascular accidents (CVA), anxiety, metabolic disorders, CNS infection, rapid shifts of plasma sodium levels, systemic inflammation and infection and persisting porto-systemic shunts.

In those with marked encephalopathy prior to transplantation, neurological outcome is in general favourable, with eventual improvement of cognitive function in the majority of patients; however, resolution of neurological symptoms may be slow in some and persist in a minority. The most tangible radiological evidence for the



**Fig. 23.4** There is a large central area of high T2 signal abnormality in the pons consistent with osmotic pontine myelinolysis

resolution of cerebral edema comes from magnetic resonance imaging that demonstrates an increase in the volume of the ventricles in association with an improvement in neurological and cognitive function after liver transplantation (and is therefore unlikely due to an absolute loss of brain parenchyma). These subtle radiological changes may take months to become evident.

A number of studies have documented an improvement in cognitive function following OLT and an improvement in quality of life index markers. This is not always the case and for a significant number of patients, cognitive deficits persist long into the postoperative period. The etiology for this is likely to be multifactorial but include the presence of hepatic encephalopathy pre-transplant, subsequent neuronal loss, brain atrophy (commonly seen in cirrhosis), presence of cerebral small vessel disease pre-transplant, peri-operative vascular complications, immunosuppression (calcineurin inhibitors) and the persistence of portosystemic collaterals that take time to resolve. Persisting cognitive dysfunction is associated with co-morbidities such as diabetes mellitus, arterial hypertension, hyperlipidemia and increasing age (all associated with other causes of neuronal loss such as small vessel disease).

### **Other Hepatic Diseases with Cerebral Manifestation: Wilson's Disease and Acquired Hepatocerebral Degeneration**

Wilson's disease is an autosomal recessive disorder of chromosome 13 that results in defective biliary copper excretion and copper accumulation in the tissues. It was first described by Dr. Samuel Alexander Kinnier Wilson, a professor of neurology at King's College Hospital. Most of the symptoms are attributable to the deposition of copper through the body. Patients present early with liver disease or late with the neurological syndrome which consists of neuropsychiatric symptoms and movement disorders.

Acquired (non-Wilsonian) hepatocerebral degeneration (AHD) is a chronic progressive neurological syndrome in patients with portosystemic shunts characterised by dementia, dysarthria, ataxia of gait, intention tremor and choreoathetosis (i.e. neuropsychiatric and extrapyramidal symptomatology). AHD and Wilson's disease are often mistaken—the diagnosis depends on age of onset (Wilson's usually presents <30 years), serum caeruloplasmin concentration and the presence of Kayser-Fleischer rings. The disease is associated with multiple metabolic insults and has



been variously linked to the failure of clearance of toxins such as ammonia and manganese. Microscopically, there is patchy cortical necrosis, diffuse proliferation of Alzheimer type II glial cells and neuronal loss.

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**Part III**

**Anesthesiology for Liver Surgery**

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Complex surgical intervention for liver disease is a relatively new addition in medical practice. Early attempts at surgical resection were associated with high rates of total morbidity. Mirroring the experience in cardiac surgery, advances in physiology and anatomy, new technology, standardized surgical techniques, and improvements in perioperative management have all contributed to the current reliability and success associated with hepatic surgery. While hepatic surgery continues to be mostly performed in larger centers, hepatobiliary programs have proliferated so that access to high-quality liver surgical care is now available in virtually all major metropolitan areas in North America. Centers of excellence are generally characterized by a higher volume surgical procedures and a commitment to multidisciplinary specialty care. Hepatology, critical care medicine, interventional radiology, and diagnostic radiology are some of the core disciplines that are required to support a hepatobiliary program.

With modern infrastructure at experienced centers of excellence, total morbidity (mortality + morbidity) associated with hepatic resection overall is approximately 15–25% (2–5%

perioperative mortality and 15–20% morbidity). The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP), a large prospective national database, found a total morbidity associated with all hepatic resections of 19.6%, affected primarily by nutritional status, preoperative liver function, and extent of hepatectomy [1].

Three general factors are known to influence morbidity of hepatic resection:

1. Extent of hepatectomy
2. Extent of underlying liver disease
3. Other comorbidities

The aim of this chapter is to review factors contributing to morbidity of hepatic surgery related to the extent of hepatectomy and underlying liver disease. The influence of other comorbidities (cardiovascular disease, pulmonary disease, chronic kidney disease, etc.) is beyond the scope of this chapter but has been described in numerous surgical and anesthesiology resources.

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## Indications for Nontransplant Hepatobiliary Surgery

Hepatic surgery is performed for both benign and malignant conditions [2–4]. The etiology of mass lesions in the liver is influenced by age and underlying liver disease. Solid mass lesions in older patients are more likely to be malignant than benign, whereas solid lesions in younger patients are more likely to be benign. Benign solid liver tumors include **adenomas**, **focal nodular**

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**hyperplasia**, and **hemangiomas**. Some benign liver tumors may be safely observed, whereas others should be resected; therefore, full evaluation of any solid lesion in the liver by a liver specialist is essential. Indications for resection of benign lesions include risk of malignant degeneration (adenomas, especially those larger than 5 cm), risk of hemorrhage (larger adenomas), compressive symptoms, or functional disability, or because the nature of a mass lesion is uncertain and further surveillance is not considered a reasonable option.

It should be noted that resections for benign lesions are **not** necessarily less morbid than resections for malignant disease, though patients with benign conditions generally do not have underlying liver disease or comorbidities associated with cancer (such as chemotherapy-induced comorbidities). As, for example, the total morbidity of right hepatectomy in healthy live donors still exceeds 30%, the decision to proceed with surgery for benign conditions should be derived from evidence-based indications, thorough risk assessment, and honest appraisal of alternative treatment modalities with the patient. For example, patients with giant hemangiomas generally do not require surgical intervention even with massive tumors, unless there is evidence of growth over time or compressive signs and symptoms. Reassurance and surveillance imaging is often sufficient for the majority of patients.

Other than lymphoma, liver malignancy is only cured by complete surgical resection or equivalent cytoablation, though many patients may benefit from multimodal therapy that is becoming more common. Selected patients may have prolonged survival with palliative surgery, though the decision to perform a high-risk surgery on incurable patients should always be based on multidisciplinary assessment and clear understanding of the goals. For example, debulking surgery is of value in certain pediatric liver tumors to facilitate systemic therapy.

Secondary malignancy (metastatic disease) to the liver is more common than primary malignancy in the United States. Colorectal cancer is the most common primary cause of liver metastases, though all GI tract cancers have the potential

to hematogenously spread to the liver via drainage through the portal circulation. Historically, liver metastases were relative contraindications to resection, but with improvements in systemic therapy for colorectal cancers, disease-free survival and total survival have improved dramatically, leading many surgical oncologists to consider liver resections to prolong life even when curative pathways are unlikely. Previously accepted notions are now shown to be incorrect, including the necessity of 1-cm margin of resection, of disease confined to the liver, and of control of the primary lesion at the same time or prior to liver-based intervention [5].

With multiple surgical options available (resection, ablation, hepatic arterial therapy, etc.), it is possible to individualize surgical therapy as part of a multimodal treatment plan with far more precision than possible in the past. Timing of surgical intervention is especially important in patients with secondary liver malignancy. In fact, current evidence suggests that patients with some stage IV cancers may actually be at greater risk to develop complications related to progression of their liver lesions rather than from the primary tumor, leading surgical oncologists to advocate for treatment of the liver-based disease without resection of the primary cancer when from the primary tumors are asymptomatic and chemosensitive [6]. Meanwhile, in patients undergoing urgent or semiurgent resection of their primary lesions (e.g., due to bleeding or obstruction), many surgical oncologists advocate a wait-and-see approach to liver-based lesions rather than concomitant hepatectomy and colectomy: patients will likely receive stage IV chemotherapy regardless, and the addition of hepatic resection may increase morbidity and delay this therapy. In addition, a staged approach after 6 months of systemic chemotherapy will permit restaging to ensure that disease remains localized to the liver. Patients undergoing hepatic resection after aggressive systemic therapy are at risk for **chemotherapy-associated steatohepatitis** (CASH), an inflammatory liver condition associated with an increased risk of liver failure after resection. Liver transplantation is not a curative option for patients with secondary liver malignancy.

Primary liver cancers include hepatocellular carcinoma, cholangiocarcinoma, and rarely primary cystic neoplasms and sarcomas. **Hepatocellular carcinomas** (HCC) are associated with virtually any chronic liver inflammatory condition, viral hepatitis (B and C) being the most common etiologic factors worldwide. HCC are uniformly fatal without treatment, though the cause of death is more often related to underlying liver disease than tumor progression. Most patients with HCC are not candidates for surgical resection due to the extent of their liver disease, though patients with isolated lesions and well-compensated liver disease are candidates for resection. Resection of early-stage HCC (stage I HCC is defined as solitary lesion less than 5 cm) in low-risk patients is associated with approximately 50% disease-free survival at 5 years, with most late recurrences arising from de novo tumors forming in the remnant liver. Liver transplantation is also a curative option for early-stage (T1 or T2) HCC, though limitations of graft supply and waiting time are an important consideration for candidates. Approximately 20% of liver transplants in the USA are performed for a primary diagnosis of HCC. Patients within T1 or T2 stage criteria are eligible to receive extra priority for waiting time in order to avoid disease progression prior to transplantation. With the development of effective locoregional therapy for HCC (primarily transcatheter embolization), prolongation of survival even for advanced inoperable stages is possible. Locoregional therapy is also utilized routinely as bridge therapy in patients awaiting liver transplantation. Recently the multikinase inhibitor **sorafenib** was approved as a systemic agent for treatment of HCC. Sorafenib has been shown to prolong survival of patients with unresectable HCC and is currently in investigation as an adjuvant agent in combination with locoregional therapy and surgery [7, 8].

Resectional and reconstructive biliary tract surgery is performed for both benign and malignant conditions, including biliary tract cancers (gallbladder and cholangiocarcinoma), benign strictures, cystic disease (choledochal cysts), and complex stone disease, to name a few. Malignant biliary cancers have been associated with very

poor long-term survival, with radical surgery representing the only potential pathway to cure. Adjuvant therapy and neoadjuvant therapy has limited value, and biliary obstruction is usually the presenting symptom. Transplantation is not offered for biliary cancers as a primary diagnosis, though there have been uncontrolled single-center reports of successful posttransplant survival after neoadjuvant therapy of suspected biliary cancer or after discovery of an occult biliary cancer in a liver explant (incidental finding).

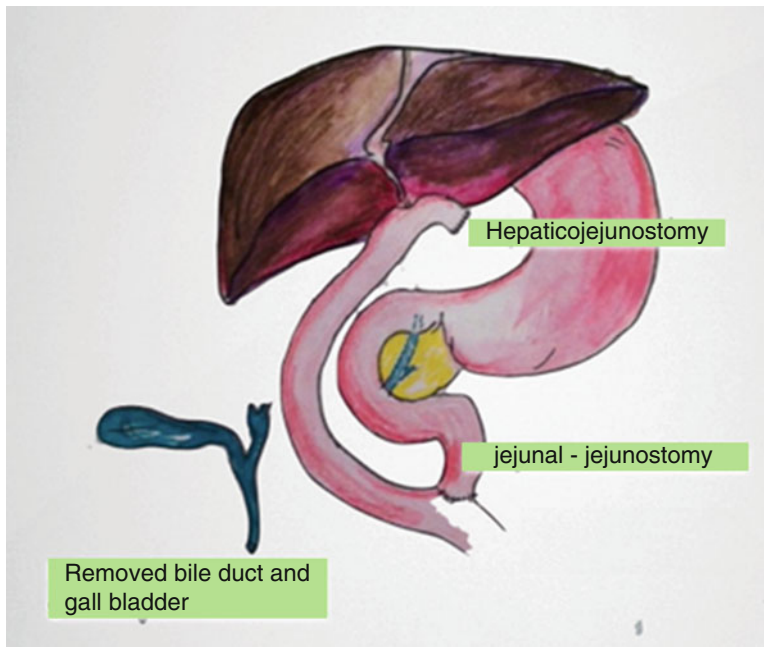
Patients with biliary obstruction may be at higher risk for infectious complications after surgery, especially if the biliary tract has been manipulated preoperatively in order to achieve biliary decompression or if the patient has had prior cholangitis. Biliary decompression can be achieved with either endoscopic means or percutaneously via a transhepatic catheter. Patients with obstructive jaundice who have indications for resection do not necessarily require preoperative biliary decompression unless surgical intervention is delayed. Long-standing biliary obstruction is associated with liver failure and coagulopathy. Resection of the extrahepatic biliary tract requires surgical biliary enteric reconstruction, which is usually accomplished through a Roux-en-Y hepatojejunostomy (“Roux”). The Roux is a defunctionalized limb of jejunum that is constructed with approximately 50 cm of length to avoid reflux of enteric contents into the biliary tract (Fig. 24.1). In some cases, complex reconstruction of multiple segmental bile ducts may be required during biliary reconstruction.

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## Size and Extent of Hepatectomy

Since the publication of **Couinaud’s** classic papers [9], surgeons have utilized the knowledge of segmental anatomy and harnessed the great regenerative capacity of the liver to conceive of and execute anatomic resections ranging from single segmentectomy to extended hepatic resections involving up to 75% of the liver volume. In standard human anatomy, the liver can be divided in eight segments, with four segments accounting for the right lobe (segments V, VI, VII, and VIII, approximately



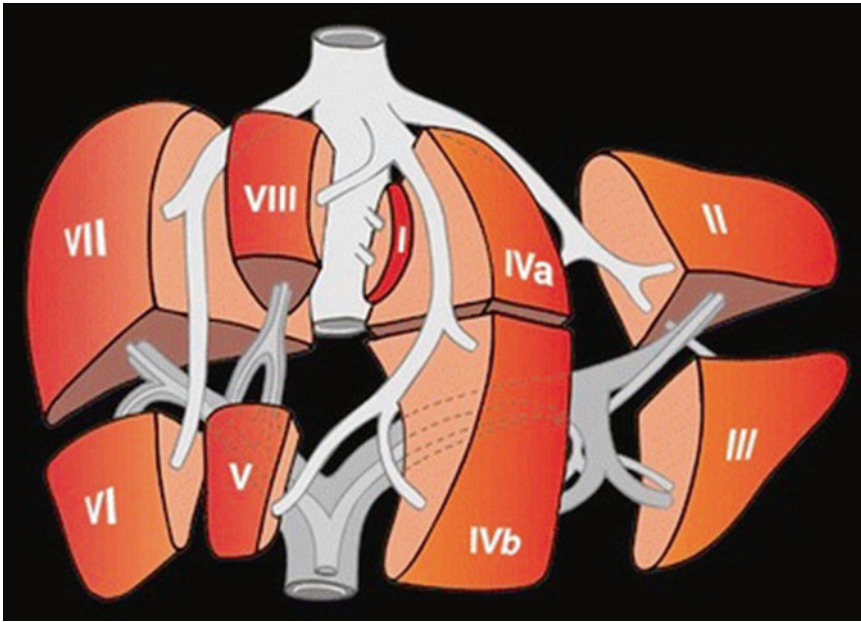


**Fig. 24.1** The Roux-en-Y

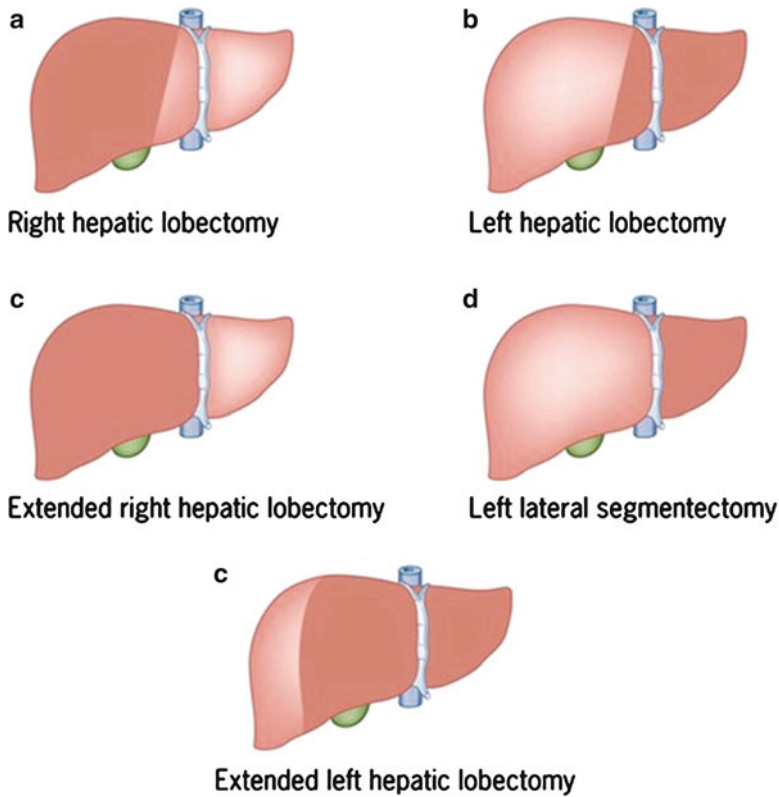
55–60% of liver volume) and three segments accounting for the left lobe (segments II, III, IV, approximately 30–40% of liver volume). Segment 1 is the caudate lobe, located posteriorly surrounding partially the inferior vena cava, which has vascular derivation from both right and left pedicles (Fig. 24.2). Hepatic outflow is dependent on three main hepatic veins in standard anatomy (though there are many variations). The hepatic veins drain into the suprahepatic vena cava just below the diaphragm. The middle hepatic vein defines anatomically the junction between the right and left hepatic lobes. The MHV receives branches from both right and left lobes in varying degrees and patterns. Externally the middle hepatic vein is not visible, so most hepatobiliary surgeons use intraoperative sonography to define the location of the middle hepatic vein during parenchymal transection. The location of the MHV can be estimated with **Cantlie's line** [10], which is a virtual line between the gallbladder fossa inferiorly and the suprahepatic vena cava superiorly. The IHPBA Brisbane 2,000 terminology has been adopted to standardize language of hepatic resections. **Anatomic right hepatectomy** is defined as a parenchymal resection of the four

segments to the right of the MHV. Anatomic right hepatectomy preserves the MHV with the remnant left lobe; thus, the outflow of segment IV (S4) is preserved. **Functional extended right hepatectomy** includes the MHV with the right lobe resection, depriving potentially outflow of a portion of S4. Outflow obstruction in a segment will result in acute congestion of that segment with eventual segmental atrophy if intrahepatic collateral outflow tracts are not present (Fig. 24.3).

**Trisegmentectomy** is a misnomer, though the term is still widely utilized. The actual number of segments being resected in “trisegmentectomy” is five (S4–8); only the lateral segments (S2 and S3) and the left portion of the caudate remains after “trisegmentectomy.” **Nonanatomic resections** are those that are not based on particular segmental vascular pedicles. “Wedge” resections of surface lesions, for example, are often nonanatomic. Whenever possible, surgeons prefer anatomic resections because they permit resection based on pedicle ligation, which may reduce operative time and blood loss. In addition, for cancer operations, anatomic resection removes the entire associated parenchyma based on a



**Fig. 24.2** Couinaud’s anatomy of the liver and division of liver segments



**Fig. 24.3** Types of resections: (a) Right hepatic lobectomy (b) Left hepatic lobectomy (c) Extended right hepatic lobectomy (d) Left lateral segmentectomy (e) Extended left hepatic lobectomy (With permission from: Schilsky, Richard; Posner, Mitchell; Markman, Maurie: Atlas of Cancer, Volume 5, Chapter 39; Springer 2003)

pedicle, which may more fully encompass satellite disease within the vascular distribution of the pedicle. Nonanatomic resections are typically performed for very small surface lesions or when the configuration of a lesion precludes an anatomic resection.

Because the portal circulation is valveless, changes in pressure are transmitted across the entire portal circulation. Normally the large sinusoidal cross sectional area of the liver results in very low resistance across the liver to portal flow. With hepatic resection, a portion of this sinusoidal area is removed, resulting in increased resistance to flow until the liver regenerates. Therefore, all major hepatic resections can be expected to increase portal pressure to some degree, though the changes may be subclinical and of no consequence if the size and health of the remnant liver is sufficient to permit regeneration.

Surgeons estimate the size of the future resected liver and remnant liver using volumetric cross sectional imaging (CT or MRI). Volumetric measurements are labor intensive for the radiologist, though commercially available software exists for calculating volumes and depicting resected segments and remnants based on vascular pedicles in three dimensions. The surgeon should work closely with the diagnostic radiologist when planning a resection and correctly describe the potential resection plan for the radiologist who will help with calculating volumes. Guidelines for remnant volumes are based not only on size but also on the presence of underlying parenchymal disease (hepatitis C or steatosis are common conditions). Suggested size of the remnant liver to avoid small-for-size syndrome is 30% in a healthy liver and at least 40–50% in the presence of liver disease.

When the size and health of the remnant are insufficient, “**small-for-size syndrome**” may occur. Small-for-size remnants are associated with clinical manifestations of portal hypertension, including chronic ascites, hypoalbuminemia, intra-abdominal varices, and bowel wall edema [11, 12]. Cholestasis is a biochemical hallmark of small remnant size. While the

exact mechanisms responsible for cell signaling in regeneration is poorly understood, portal hypertension itself seems to contribute to cellular injury and may inhibit regeneration. It has been demonstrated that portal decompression or attenuation of portal blood flow may facilitate liver regeneration and lessen the sometimes substantial morbidity from small-for-size syndrome. Complications of small-for-size include cachexia, increased susceptibility to infection, and hepatorenal syndrome. Portal decompression options include concomitant creation of a temporary portacaval shunt at the time of operation, which has been primarily utilized during live donor liver transplantation rather than with surgical resection of tumors. Reduction of portal blood flow (and consequently reduction in portal pressure) in resection patients can also be accomplished by splenic artery ligation or postoperative splenic artery embolization.

When hepatic resection is required even in the face of underlying liver disease and/or the expected remnant size is likely to be insufficient, preoperative portal vein embolization (PVE) may reduce morbidity by inducing hyperplasia of the remnant liver and improve the chances of obtaining a complete (R-0) resection (complete removal of all tumor with microscopic examination of margins showing no tumor cells). In most curative cancer surgery, R-0 resection is associated with significant improvement in survival compared to resections that leave gross or microscopic tumor behind. PVE makes use of the observation that interruption of portal blood flow is a signal for the regenerative response. PVE is performed by interventional radiologists who typically access the portal vein either transhepatically or through an internal jugular approach (similar to TIPS). Once accessed, the PV can be embolized on the ipsilateral side of the resection, thus inducing growth of the opposite lobe. Complications of PVE include bleeding and inadvertent occlusion or thrombosis of the main or contralateral portal vein, though these complications are infrequent [13]. After PVE, clinical hyperplasia based on imaging is manifested within approximately 3–4 weeks, though hyperplasia can continue for many weeks after

ward. One limitation of PVE is the delay of a potentially curative surgery while waiting for hyperplasia. This could be an important consideration in tumors exhibiting aggressive behavior, though some centers have begun performing interval “bridge” locoregional tumor therapy, sometimes with systemic therapy in conjunction with PVE. This approach may maximize the potential for an R-0 resection while minimizing morbidity, though the efficacy of this combined preoperative pathway is still unproven in controlled trials of primary or secondary liver cancers. Ultimately the multidisciplinary team with substantial input from the surgeon needs to determine whether there is an advantage to immediate operation vs. delayed operation with PVE +/- locoregional therapy on an individualized basis [14, 15].

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### **Underlying Liver Disease and Estimation of Surgical Risk**

Overall risks associated with hepatic resection have fallen in recent decades: current standards suggest mortality risks of 3–5% for hepatic resection, with total morbidity that is proportional to the extent of hepatectomy (up to 50% or more for extended hepatic resections of four or more segments). Careful selection of candidates and estimation of risk based on medical condition and underlying liver disease is essential to optimize outcomes. All patients undergoing evaluation for hepatic resection should undergo a thorough evaluation for presence and severity of underlying liver disease. Basic evaluation includes a history and physical exam directed at liver-specific signs and symptoms such as ascites, jaundice, gastrointestinal bleeding, thrombocytopenia, and splenomegaly. Past history should focus on known prior liver disease and risk factors for liver disease, including viral hepatitis, alcohol abuse, steatosis/metabolic syndrome, and the type and duration of systemic chemotherapy agents. Some chemotherapeutic regimens, for example, those containing irinotecan, are associated with microsteatosis and inflammation (chemotherapy associated steatohepatitis-CASH). Laboratory profiles should always include base-

line liver function tests including albumin, INR, metabolic panel, and CBC with platelets in addition to serologic testing to exclude viral hepatitis.

In the absence of cirrhosis, elevated liver enzymes (ALT and AST) may suggest inflammatory conditions that could affect the operative risk associated with hepatic resection and determine the feasible extent of the hepatic resection. The most common occult causes of chronic liver enzyme elevation in the general population are steatohepatitis associated with diabetes and obesity, viral hepatitis, and toxins (alcohol or chemotherapy).

Jaundice (hyperbilirubinemia) in the preoperative patient may arise from either obstructive or nonobstructive causes. Nonobstructive causes of jaundice (cholestasis) include synthetic dysfunction related to advanced liver failure (in which case patients will also have associated other findings of liver failure), ischemic injury, acute toxic injury (as in alcoholic hepatitis), and cholestasis associated with sepsis/endotoxemia and parenteral nutrition. Cholestasis unrelated to biliary obstruction will often present with increases of indirect compared to conjugated bilirubin. Cholestasis with enzyme elevation suggestive of acute hepatitis is indicative of underlying parenchymal/hepatocyte derangement, is a risk factor for significant postoperative morbidity, and should therefore be considered a contraindication to major hepatic resection.

Obstructive jaundice is typically seen in patients with common hepatic or common bile duct obstruction, either from benign to malignant causes or in patients with diffuse biliary tract diseases such as sclerosing cholangitis. Obstructive jaundice may not preclude hepatic resection if the intent of resection is to remove the cause of obstruction. Indeed, prospective studies of preoperative biliary decompression prior to major hepatic procedures have not conclusively demonstrated a benefit if immediate surgery can be scheduled. Patients with obstructive jaundice should have cholangiographic imaging, for example, with magnetic resonance cholangiopancreatography as part of the diagnostic evaluation to assist the surgical planning. However, biliary decompression is indicated if delays in surgery

are anticipated to complete the preoperative evaluation or if, for example, preoperative neoadjuvant chemotherapy therapy is planned. Biliary decompression can be accomplished either endoscopically or percutaneously depending on the suspected location of the obstruction.

Patients with cirrhosis have increased risk of morbidity and mortality after major abdominal surgery. Severity of illness associated with cirrhosis has been evaluated using semiquantitative scoring (Childs-Turcotte-Pugh) and quantitative systems (Model for End-Stage Liver Disease or MELD) [16]. Both Child's and MELD score are designed to predict long-term mortality related to liver disease, rather than to predict postoperative risk. ASA (American Society of Anesthesiologists) status and Charlson Index of Morbidity [17] may have greater predictive value after hepatic resection than MELD or Child's Score [18], but a combination of these scoring systems is probably most valuable in clinical practice.

Irrespective of the scoring systems used, advancing cirrhosis dramatically increases surgical risks [19]. MELD score  $>9$  was associated with increased risk of postoperative mortality in a series of patients undergoing resection for hepatocellular carcinoma in a Taiwanese series and in a series from Mayo clinic [20]. Mortality in patients undergoing abdominal surgery ranges from 10% in Child's A patients to 31% and 76%, respectively, for Child's B and C [21]. These rates have improved more recently, but risk of morbidity remains high even in patients with well-compensated cirrhosis. Morbidity is caused by complications of portal hypertension that may not have been present preoperatively such as ascites, renal failure, infection, and liver failure. Consequently, preoperative clinical signs of portal hypertension are a relative contraindication to resection and should be approached with caution based on the patient's indications for surgery and available alternatives. Clinical findings of portal hypertension include thrombocytopenia, splenomegaly, ascites, and/or varices. Subclinical portal hypertension may be present in the absence of these findings, which may be evident on hepatic vein wedge pressure measurement (HVWP). HVWP measurement is indicated in patients with known

cirrhosis that are evaluated for major hepatectomy of three segments or greater. In patients with portal hypertension, preoperative portal decompression using transjugular intrahepatic portosystemic shunt (TIPS) has been suggested as a means of improving postoperative morbidity for nonhepatic abdominal surgery; however, this has not been evaluated in controlled studies, and TIPS itself has associated risks including exacerbation of hepatic encephalopathy. A decision to perform TIPS as a means of facilitating general abdominal surgery should only be made after multidisciplinary evaluation that includes an experienced hepatologist; TIPS is not valuable in facilitating hepatic resection and may in fact increase risk of acute postoperative liver failure because of deprivation of portal flow to the remnant liver.

At our liver center, we utilize multidisciplinary assessment by experienced hepatologists, liver oncologists, as well as hepatobiliary surgeons to perform thorough risk assessment of patients presenting with hepatic malignancies. MELD as well as CTP score and clinical assessment of portal hypertension are utilized for discrimination of operative candidates and to potentially stratify patients for nonoperative interventions. As we also perform liver transplantation, many interventions are performed as bridge therapy for liver transplantation; surgical and nonsurgical cancer therapy is then performed for a different indication than resection for curative intent. For bridge or downstaging therapy, higher MELD or CTP scores may be acceptable provided that there is a consensus that the increased risk of intervention is offset by the desire to achieve transplantation as a curative pathway. These tolerances may be influenced by the regional waiting times for allografts, which differ greatly throughout the United States.

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## Technique of Hepatic Resectional Surgery

Surgical approaches to hepatic parenchymal transection have evolved with time. In general, operative times, blood loss, and injury to the remnant liver have all improved in the past two decades. Blood loss is reduced with the use of



hypovolemic anesthesia during the transection, maintaining a low central venous pressure and reducing back bleeding from the hepatic veins. Reduction of bleeding risk from the inflow vessels is accomplished by pedicle ligation prior to transection. In the classical description of right hepatic lobectomy (segments 5–8), after mobilizing the right lobe, short retrohepatic veins are individually ligated in order to free the retrohepatic vena cava from the liver, the right hepatic vein is encircled and sometimes divided, and the right vascular pedicle (hepatic artery and portal vein) is dissected with their structures individually ligated. After this vascular control is completed, hepatic parenchymal transection is performed along the demarcation line to the right of the middle hepatic vein.

A number of variations have arisen to this basic technique. For example, en mass control of the right hepatic pedicle can be achieved by stapling the right pedicle within the liver parenchyma at the base of the gallbladder fossa, a technique which has been advocated by some surgeons because it avoids the need for hilar dissection. This technique cannot be utilized for donor hepatectomy because the right vascular pedicle is then not usable for graft implantation after stapling.

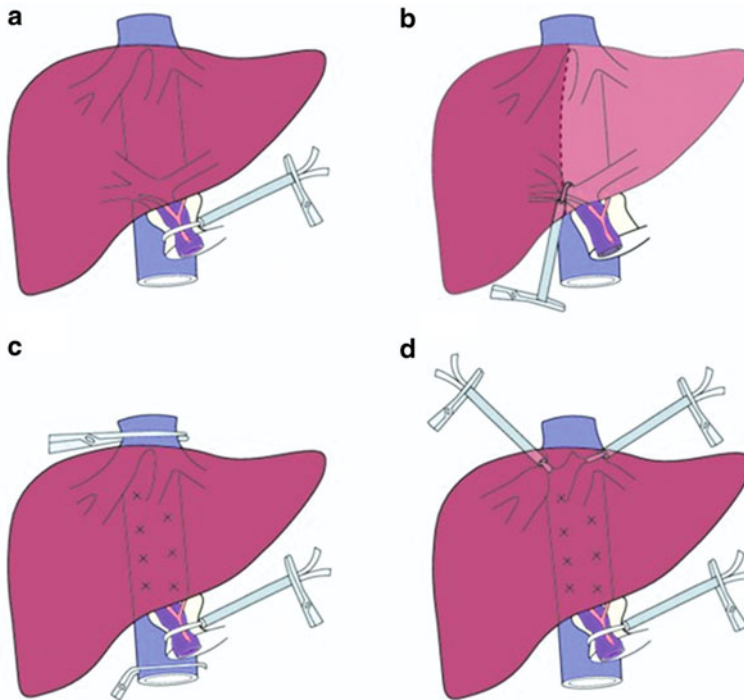
Rather than controlling the entire pedicle, the right pedicle can be controlled during the hepatic parenchymal transection if total inflow occlusion is utilized (Pringle maneuver). Temporary total inflow occlusion can be achieved using a Rummel tourniquet (a piece of tape passed around the porta hepatis and then through a rubber tube) or with careful application of a vascular clamp to the porta hepatis. The normal liver tolerates up to 60 min of warm ischemia, though most surgeons prefer intermittent release of the inflow occlusion every 15 min. Most parenchymal transection can be accomplished in 45 min of total occlusion time or less. Livers with underlying parenchymal disease may not tolerate longer periods of ischemia. With longer inflow occlusion, more substantial ischemia reperfusion injury to the liver can be expected that can increase morbidity especially if the remnant size is small. When possible, avoidance of total inflow occlusion is preferable, but

the decision to proceed with inflow occlusion is based on the relative risk of bleeding vs. ischemic injury. With larger and more complex resections that may involve tumors close to larger vessels, total inflow occlusion may be preferable to minimize bleeding risk.

An extension of total inflow occlusion is total vascular exclusion (TVE), which is derived from the technique utilized for total hepatectomy during liver transplantation (Fig. 24.4). In TVE, inflow occlusion is accomplished in the standard fashion, but the infrahepatic and suprahepatic vena cava is also clamped so that the parenchymal transection can occur in an exsanguinous field. Intermittent unclamping is more difficult during TVE, so in general once TVE is instituted, the surgeon must complete the transection before unclamping. The liver can tolerate up to 60 min of warm ischemia, though in most cases, surgeons would prefer to minimize inflow occlusion to approximately 30 min in order to preserve the remnant liver function. In addition, TVE requires additional mobilization of the liver and retrocaval IVC and ligation of the right adrenal vein in order to accomplish caval vascular occlusion. While TVE unquestionably facilitates rapid parenchymal transection in a bloodless field, it also requires more complex anesthetic management. The return of caval blood flow to the heart is interrupted, and frequently hemodynamic instability can ensue without volume loading and the temporary use of vasopressors. TVE is a useful technique when resection margins are likely to be close to large structures such as the major hepatic veins or IVC, and the surgeon and anesthesiologist are familiar with this method. TVE is not routinely utilized by most hepatobiliary surgeons.

The basic goal of hepatic parenchymal transection is division of the liver parenchymal with identification of blood vessels and bile ducts in advance of transection, so that they may be secured with ligatures or clips prior to transection. There are many different variations and technologies applied to parenchymal transection, though the basic tenet is meticulous, fine technique, and patience in identification and ligation of each small structure. The surgeon must also pay close attention to the plane of transection that





**Fig. 24.4** Types of vascular occlusion: (a) Pringle maneuver (b) “Hemi-Pringle” (c) Total vascular exclusion (TVE) (d) TVE with maintenance of caval blood

flow (with permission from: Lang, H: Technik der Leberresektion; Chirurg 2007 · 78:761–774)

must be identified and planned prior to beginning parenchymal transection using anatomic landmarks and ultrasonography. A well-planned transection plane reduces transection time (important with inflow occlusion), blood loss, risk of involved margins in cancer surgery, and risk of injury to the remnant liver. While this may seem self-evident, transection planes can in fact be quite difficult to maintain when the parenchyma is bulky, the field is bloody, or there are anatomic distortions (e.g., atrophy of a lobe). Consequently, hepatobiliary surgeons often “check” their transection planes constantly during the transection and make adjustments to stay on track. The development of the “hanging technique” [22] has been especially useful in maintaining a straight parenchymal transection line in right or left hepatic lobectomy. In this modification, an umbilical tape is passed around the hepatic vein between the liver and retrohepatic cava and then around the portal vein so that the liver is suspended on the tape. The surgeon

can then use the tape as a target and guide during the transection.

For parenchymal transection, surgeons may divide the liver tissue simply by fracturing it with a clamp or use more complex technologies. The most commonly used device for transection other than clamp fracture is the ultrasonic dissector (Cavitron Ultrasonic Surgical Aspirator - CUSA), originally developed for neurosurgery. The CUSA tip vibrates at a very high frequency, which divides parenchyma but leaves the blood vessels and bile ducts intact (in principle), allowing the surgeon to ligate those structures separately. Another device similar to the CUSA utilizes a high-velocity water jet to divide the liver parenchyma. Other devices are designed to precoagulate liver tissue, allowing the surgeon to divide the tissue with a standard scissors or cautery with less blood loss. There are many precoagulating devices, all of which rely on the transmission of energy (e.g., radiofrequency or microwave energy) to a handheld probe that coagulates liver

parenchyma. Very few controlled studies compared these various techniques of parenchymal division. Most surgeons use a standard reproducible technique with minor modification in every case, but ultimately the art and craft of surgical technique is unique to the individual surgeon and the quality of the liver tissue that is being divided.

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### **Alternatives to Resectional Approaches for Liver Lesions**

While complete resection of a solid lesion with a negative margin (R-0 resection) is considered the goal in cancer surgery for solid tumors, nonresectional cytoablative approaches to tumor control have been applied increasingly when resection is not possible due to underlying liver disease, comorbidities, or anatomic location and pattern of lesions. All the current targeted cytoablative options include localization of a lesion either by direct visualization or intraoperative sonography, followed by insertion of a probe or antenna into the lesion to accomplish transfer of energy to destroy the tissue. Radiofrequency ablation is the most common technique of cytoablation, though chemical ablation (e.g., alcohol), microwave ablation, cryoablation, and other technologies have also been used. Ablative techniques may cause less morbidity than resection while still achieving local tumor control, especially for smaller lesions [23]. With larger lesions and lesions in proximity to vascular structures, complete durable tumor control is less likely because viable tumor may persist at the margins of ablation. Ablation can also be performed sequentially and in combination with other therapies such as transarterial embolization and for control of multiple lesions. Ablation can even be used in combination with resection to achieve R-0 control of bilobar disease. The disadvantage of ablation (compared to resection) is that without complete extirpation and pathologic analysis of the lesion, it is never certain that all of the tissue has been destroyed. Closer surveillance imaging and monitoring with tumor markers (when relevant) is therefore required with any ablative approach. There are no long-term controlled trials that directly compare

ablation with resection for malignant liver lesions, and there is considerable debate about “standards of care” with respect to application of newer ablative techniques compared to conventional resection [24]. Nevertheless, there has been a dramatic increase in ablative procedures for liver tumors. Best practices regarding selection of modalities can be achieved by multidisciplinary evaluation at experienced liver centers.

Ablation is generally associated with lower surgical risk than resection, and many lesions are amenable to a laparoscopic rather than open approach. However, ablation can also be associated with significant morbidity. Morbidity is influenced by underlying liver disease, presence of portal hypertension, and the size, number, and location of lesions undergoing ablation. With larger ablations, massive tissue destruction may cause myoglobin precipitation in the renal tubules [25], so adequate hydration is important. In addition, larger ablation zones may be at risk for superinfection and liver abscess formation, especially in patients at risk for bacterial contamination of the liver parenchyma (e.g., patients with biliary enteric anastomoses). Therefore, many surgeons extend antibiotic prophylaxis for 1 week postoperatively with agents that cover gastrointestinal flora. Finally, thermal injury to close structures is an important consideration that must be factored into decision making before proceeding with an ablation plan. Bystander structures that are adjacent to the liver include the GI tract (stomach, duodenum, and colon especially), right kidney, and diaphragm. Major vascular structures that can be injured include structures close to the liver hilum: gallbladder, main and primary segmental branches of the portal vein, hepatic artery, and bile duct.

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### **Minimally Invasive Hepatic Surgery**

Routine application of minimally invasive techniques in liver surgery was first introduced in conjunction with cytoablation platforms (radiofrequency ablation, especially) in the mid-1990s, though simple wedge resections were also performed in the early 1990s by Gagner, Flowers, and other laparoscopic surgical pioneers [26].

Since then, increasing surgical experience with minimally invasive surgery applied to the liver has led to an expanding array of options for patients undergoing hepatobiliary surgery [27, 28]. Series of multisegmental resections and even donor hepatectomies [29] have been published. At most large liver centers, current practice is to evaluate every patient scheduled to hepatobiliary surgery for possible minimally invasive approaches. This can include initial laparoscopy for staging followed by conversion to open, hand-assisted procedures or complete operations performed entirely via laparoscopy [30, 31]. Specialized tools for liver transection and intraoperative sonography have been developed. Laparoscopic hepatic surgery should only be performed by surgeons with experience in open hepatic surgery. Benefits of laparoscopic surgery compared to open techniques include less incisional pain, better cosmetic results, and earlier return to full functional status.

Some of the lessons learned in laparoscopic liver surgery include the following:

- Hepatic vein back bleeding during transection actually seems to be less of a problem during laparoscopic transection compared to open. This may be related to the pneumoperitoneum that reduces venous bleeding. Goals of fluid management during laparoscopic hepatectomy differ somewhat from open hepatectomy in that targeted hypovolemia (low CVP) may not generally always be required (and often less well tolerated) during laparoscopy because there is less concern for HV back bleeding.
- Laparoscopic argon beam coagulation (ABC) during hepatic surgery has been associated with air embolus, because of the increased intraperitoneal pressure during use of the laparoscopic ABC can cause air to enter open hepatic vein radicles. This can be prevented by judicious application of ABC and venting of gas from the ports during ABC to avoid elevation of abdominal pressure [32].
- Laparoscopic nonanatomic resections, especially those in the posterior sectors (S6 and S7), can be difficult because of the requirement for full mobilization of the right lobe and

the posterior location of the lesions. They require special attention to the transection planes to ensure negative oncologic margins. These transection planes may be more difficult to appreciate through the camera than during open surgery. Larger lesions may also obscure the operative field during laparoscopy. Hand-assisted approaches may facilitate difficult resections or can be performed using hybrid laparoscopic/open technique through smaller incisions (“mini-open” techniques). In all laparoscopic cases, the operative team including the anesthesiologist should be prepared for large-volume transfusion as in any major hepatobiliary case. In addition, a fully open instrument tray and equipment should be available in case conversion to open surgery is required. It is important for the anesthesiologist and surgeon to discuss the operative plan at the start of the case.

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# Liver Resection Surgery: Anesthetic Management, Monitoring, Fluids, and Electrolytes

# 25

Jean Mantz and Catherine Paugam-Burtz

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## Introduction

Liver resection surgery has become a cornerstone of the therapeutic strategies for primary hepatocarcinoma and liver metastases together with systemic chemotherapy, embolization, and radiotherapy. Cancer (either hepatocellular carcinoma or metastases) by far represents the most frequent indication for liver resection surgery. Other common indications are polycystosis, hydatidosis, benign tumors, pheochromocytoma, and trauma. Two major resection subtypes can be distinguished on anatomical bases (Fig. 25.1): right hepatectomy, which includes resection of segments V–VIII, and left hepatectomy, which consists of resection of segments I–IV and sometimes I. Right lobectomy consists of right hepatectomy plus resection of segment IV. Left lobectomy is a left hepatectomy restricted to segments II and III. Liver resection is considered major when more than three segments are involved.

Several studies indicate that survival following liver resection is significantly affected by the

volume of liver resected, preoperative liver function, response to portal vein embolization, and condition of the remnant liver parenchyma, which is a major postoperative prognostic factor. Postoperative 30-day mortality and liver failure after liver resection is on average 3% in patients with noncirrhotic parenchyma, while it may reach 8–10% in patients with chronic liver disease such as cirrhosis [1–9]. Besides the status of the remnant liver, age, and comorbidities such as a compromised cardiovascular function or a metabolic syndrome with nonalcoholic steatohepatitis, the extent of the resection, the preoperative liver function, and the chemotherapy with antiangiogenic factors are well-identified factors that may worsen postoperative prognosis [10, 11]. Increasingly elderly patients with substantial comorbidities present for liver resection surgery and require optimization of the preoperative status and complex intraoperative management. This chapter will review the goals of preoperative risk evaluation, the anesthetic agents and techniques relevant to liver resection, the hemodynamic consequences of vascular cross clamping during liver resection, the intraoperative monitoring with emphasis on recent controversies on hemodynamic issues, and a discussion of the issue of vascular filling, electrolytes, transfusion, and blood saving agents and techniques. We will also briefly discuss the postoperative analgesic techniques available for liver resection and give an insight in the anesthetic management of promising surgical techniques such as laparoscopic hepatectomy [12].

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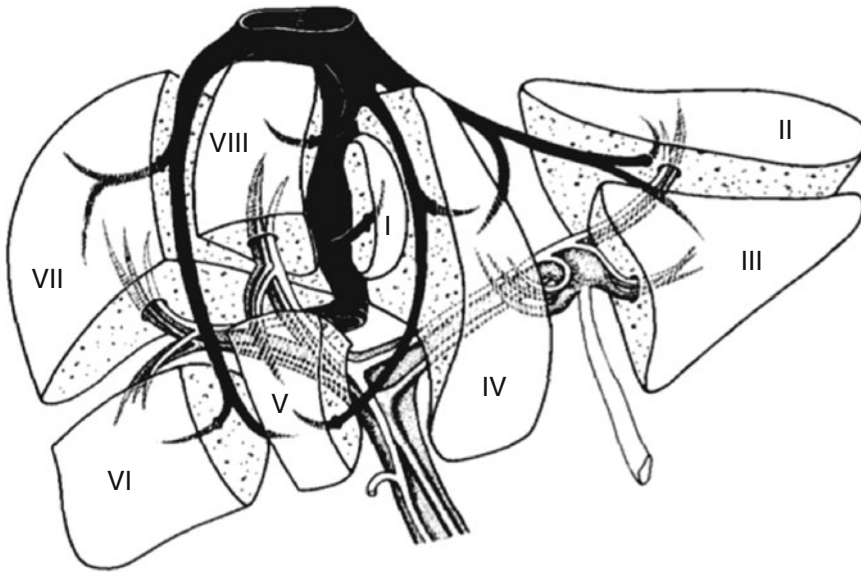
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**Fig. 25.1** Anatomical segmentation of the liver, with kind permission from Springer Science + Business Media

### Preoperative Risk Evaluation

The intraoperative period presents the highest risk for morbidity and mortality for cirrhotic patients. Limited cardiovascular reserve due to possible cardiomyopathy and a low systemic vascular resistance make these patients more prone to develop hemodynamic instability. Cirrhosis also increases the risk for intraoperative hemorrhage, postoperative respiratory, and renal failure, as well as liver failure. The Model of End-Stage Liver Disease (MELD) score predicts nontransplant mortality in patients with cirrhosis [13, 14]. In a retrospective cohort of cirrhotic patients undergoing noncardiac surgery, Ziser et al. identified various preoperative conditions that worsen postoperative mortality, including a Child-Pugh C vs. A or B score, ascites, renal failure, chronic obstructive pulmonary disease, sepsis, gastrointestinal bleeding, ASA physical status 4 or 5, major surgery, and intraoperative hypotension [15]. In cirrhotic patients, the accepted criteria for liver resection in hepatocarcinoma are a Child-Pugh status A (Child B is accepted for small peripheral nodules), a unique nodule <5 cm, the absence of esophageal varices or portal hypertension, and a transhepatic pressure gradient

<10 mmHg [16]. Transaminases should be elevated less than a threefold normal value [17]. A retention of indocyanine green clearance (ICG) <14% at 15 min is considered a cutoff for major hepatectomy (more than three segments) [18]. The incidence of postoperative liver failure after liver resection is low in noncirrhotic patients but markedly increased with cirrhosis. However, regardless postoperative liver failure represents a life-threatening complication of liver resection surgery [2, 3, 5]. Of the different prognostic tools that have been developed for predicting the risk of postoperative liver failure, the most commonly used are INR or prothrombin time and bilirubin. A prothrombin time less than 50% together with a serum bilirubin level greater than 50  $\mu\text{mol/ml}$  (2.9 mg/dL) (the fifty–fifty criteria) as early as on postoperative day 3 is a predictor of postoperative mortality in patients undergoing liver resection [19, 20]. These results are fairly consistent with the study of Mullen et al. that demonstrated that a postoperative INR >2 together with a bilirubin level greater than 7 mg/dL is an accurate predictor of mortality in this context [3]. Response to preoperative portal embolization and ICG are also accurate predictors of postoperative liver failure [21]. Postoperative renal failure is also



associated with significant postoperative morbidity and mortality [22], and preoperative elevations of alanine aminotransferase (ALT), preexisting cardiovascular disease, chronic renal failure, and diabetes were identified as the best predictors of postoperative renal failure following liver resection [23]. An individual probability score of death after liver resection in cirrhotic patients based on age, ASA physical status, bilirubin creatinine, INR, and etiology of cirrhosis has been developed at the Mayo Clinic and is available at <http://www.mayoclinic.org/meld/mayomodel9.html>. Close attention should also be paid to electrolytic disorders and coagulation, infection, and nutritional status during the pre-anesthetic examination, and these should be optimized preoperatively [24].

Careful evaluation of the risk of cardiovascular major adverse events is important in patients with compromised coronary or myocardial function undergoing liver resection surgery. The incidence of major cardiovascular adverse events is approximately 3% in this patient population. Furthermore, the presence of a metabolic syndrome should be carefully examined. The guidelines for preoperative cardiac risk assessment and perioperative cardiac management in noncardiac surgery have been recently updated [25, 26] and should be applied. Several lines of evidence support that systematic coronary angiography and revascularization (by stenting or bypass) prior to surgery are not beneficial to patients undergoing noncardiac surgery [27]. In patients with compromised coronary function, noninvasive exploration of the coronary reserve can be performed by either stress echocardiography or thallium-persantine angioscintigraphy. The decision for coronary revascularization by coronary stenting should also be weighed against the risk of rapid progression of the cancer as the recommended delay of elective surgery after bare-metal stenting (4–6 weeks) may cause a cancer to grow enough to become unresectable. For the same reason the use of drug-eluting stents is unrealistic in these patients. Strict maintenance of cardiovascular medications such as beta-blockers and statins throughout the perioperative period is recommended [28], but initiation of beta-blockade in

patients not on chronic beta-blocker therapy before surgery is not recommended. In patients with chronic beta-blockade therapy, particular caution should be paid to the intraoperative hemodynamic monitoring and optimization, since the reduction of postoperative major cardiovascular adverse events and mortality attributed to beta-blockers can be counterbalanced by an increase incidence of stroke and noncardiac mortality [29]. In patients with chronic antiplatelet therapy for secondary prevention of thrombotic events, a growing body of evidence finds that the risk of discontinuation of antiplatelet therapy before surgery exceeds the risk of maintaining this treatment throughout the perioperative period [30–33], and this consideration may also apply to liver resection surgery.

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## Intraoperative Management

### Anesthetic Agents

The main goals of anesthesia for liver resection surgery are, first, to avoid aspiration of the gastric content during induction, second, to maintain intraoperative hemodynamic stability, particularly in case of massive blood loss and in response to vascular clamping and unclamping, and, third, to minimize blood loss and conduct an appropriate transfusion strategy. The risk of aspiration of the gastric content at induction of anesthesia is high in cirrhotic patients with voluminous ascites, and rapid sequence induction should routinely used. Pharmacokinetics of drugs is highly variable in cirrhotic patients because of major changes in distribution volumes and sodium retention, albumin plasma levels, metabolism, and elimination processes. Therefore, the effect of a bolus is unpredictable. Due to a vasoplegic profile, cirrhotic patients are prone to develop hypotension with induction of anesthesia. Anesthetics for which elimination primarily depends on renal clearance or redistribution (such as propofol, etomidate, fentanyl, sufentanil) are the first-choice drugs, while those depending on hepatic metabolism, for example, using the P450 cytochrome system such as

thiopental and alfentanil should be avoided. Remifentanyl and cisatracurium may be used as they do not accumulate even when administered by continuous infusion. Poorly metabolized volatile anesthetics such as isoflurane or desflurane may be used for maintenance of anesthesia, and they improve hepatic blood flow and splanchnic perfusion [34]. Target-controlled propofol infusion may be an interesting and worthwhile concept since it may help to blunt intraoperative hemodynamic changes [35, 36]. The pharmacology of anesthetic drugs in patients with liver failure is discussed elsewhere (Chapter 3) in this book.

## Vascular Occlusions

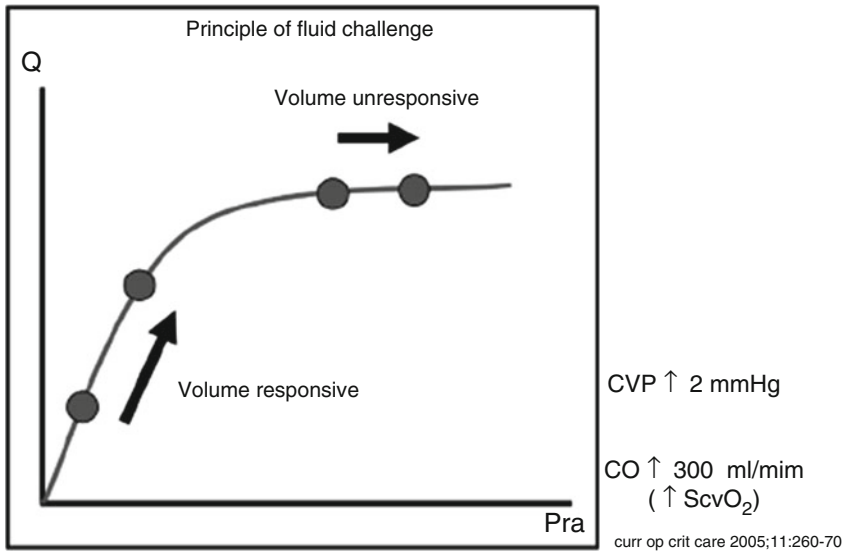
Occlusion of the portal triad (Pringle's maneuver) and total vascular exclusion (simultaneous clamping of the infrahepatic and suprahepatic vena cava) are commonly used occlusion techniques to minimize intraoperative blood loss [37]. The Pringle's maneuver is associated with a 15% decrease in venous return and cardiac output, which is compensated for by an increase in sympathetic tone and usually well tolerated [38–40]. It usually results in a slight increase in mean arterial pressure. These maneuvers unavoidably cause an ischemic insult that may jeopardize liver regeneration after hepatic resection surgery. In case of prolonged duration, the Pringle's maneuvers may cause a reperfusion syndrome with hypotension by unclamping in addition to liver ischemia. Intermittent clamping and ischemic preconditioning are highly and equally effective in minimizing liver injury [41]. Intermittent clamping appears superior, however, for durations of occlusion >75 min. of the triad [42]. Nonsurgical tools for liver protection have been reviewed and include pharmacologic interventions targeting microcirculation, oxidative stress, proteases, and inflammation [37, 43]. Recent data indicate that sevoflurane may also serve as a preconditioning stimulus during liver resection surgery [44]. According to a recent meta-analysis, vascular occlusion of the portal triad is associated with a decrease in blood loss by 800 mL, an increase in postoperative liver injury, and no

impact on red cell transfusion, mortality, or liver failure [45].

Total vascular exclusion of the liver is associated with a substantial decrease (up to 80%) in venous return. Cardiac output and mean arterial pressure are decreased by 40% and 10%, respectively, due to a marked increase in sympathetic tone with an increase in heart rate and systemic vascular resistances [46]. Tolerance to this situation depends on the intravascular volume status, the presence of portosystemic shunts, and possible impairment of ventricular function. These parameters have to be evaluated and optimized before considering to proceed with total vascular exclusion. However, reliable predictors of intolerance to this maneuver remain to be established. Other intraoperative procedures such as the "hanging maneuver" in which the liver is suspended by lifting it up with a tape that is passed behind the liver facilitate resection using the anterior approach for major hepatectomy. Reduction of liver mobility during dissection achieved by this maneuver significantly improves intraoperative hemodynamic stability [47, 48]. Lateral clamping of the inferior vena cava is also at times used to reduce bleeding during particular delicate phases of liver dissection.

## Hemodynamic Monitoring

Maintaining effective intravascular volume to ensure tissue perfusion and cellular oxygenation is the physiologic goal independent of the type of surgery. This consideration also applies to liver resection, with particular emphasis on liver perfusion and oxygenation. This approach involves titration of fluids to physiologically relevant endpoints that can be monitored and responded to in the operating room; however, the question is how to decide which endpoints to choose. For liver resections, the choice of endpoints should result in adequate use of fluid therapy avoiding hypovolemia and inappropriate tissue perfusion. On the other hand, administration of excessive fluids with subsequent risks of pulmonary and peripheral edema should also be avoided. Finally, maintenance of central venous pressure (CVP) at acceptably



**Fig. 25.2** Preload dependence of cardiac output as illustrated by the hemodynamic response to a fluid challenge (with permission from *Curr Opin Crit Care* 2005; 11: 260–70)

low values can contribute to decreased intraoperative bleeding. Therefore, any device that allows direct or indirect evaluation of left ventricular stroke volume and responsiveness to fluid loading will be a good candidate for routine use in liver resection surgery and similar considerations apply to the monitoring of tissue oxygenation.

Hemodynamic monitoring during liver transplantation is discussed in detail elsewhere (Chapter 9 and Chapter 12) in this book

### Invasive Arterial Pressure

A substantial amount of information can be obtained from monitoring invasive arterial blood pressure. Blood pressure does not reflect blood flow, and hypovolemia and hypoperfusion may be present even with normal blood pressure. However, there are clearly thresholds below which some organs, such as the brain, the liver, or the kidney, are not adequately perfused. Therefore, any severe intraoperative hypotensive episodes during liver resection should be promptly corrected by fluid loading and/or short-acting vasopressors. An increase in arterial blood pressure in response to fluid loading reflects an increase in stroke volume and supports appropriate correc-

tion of hypovolemia (Fig. 25.2). Conversely, no change or a decrease in blood pressure with fluid loading indicates that further fluid challenge is inappropriate and can result in overfilling. Intraoperative hypotension has been identified as a predictor of 6-month mortality in cirrhotic patients undergoing surgery [15]. Monitoring of respiratory variations of the arterial pulse pressure ( $\Delta$ PP or pulse pressure variation—PPV) has become increasingly popular also in major hepatic surgery. This index has been initially reported as a reliable predictor of responsiveness to a fluid challenge in mechanically ventilated patients with ARDS. It can be obtained by applying the following formula:

$$\Delta PP(\%) = 100 \times (PP_{\max} - PP_{\min}) / [PP_{\max} + PP_{\min}] / 2$$

The  $\Delta$ PP (or PPV) index has been established as sensitive and specific for predicting fluid responsiveness during major hepatic surgery [49]. Noteworthy,  $\Delta$ PP measured noninvasively by the Finapres plethysmographic device was as effective as that obtained by measurement of arterial pressure variations. A similar index derived from arterial waveform analysis, the stroke volume variation (SVV), has also been validated in patients undergoing liver transplant surgery, as well as ICU mechanically ventilated patients [50, 51]. In a recent study, a modification

of the arterial wave form analysis using an aortic input impedance model [model-simulated cardiac output (MCO)] has also been found an acceptable alternative for reflecting cardiac output during liver transplantation surgery [52].

## Vascular Filling Pressures

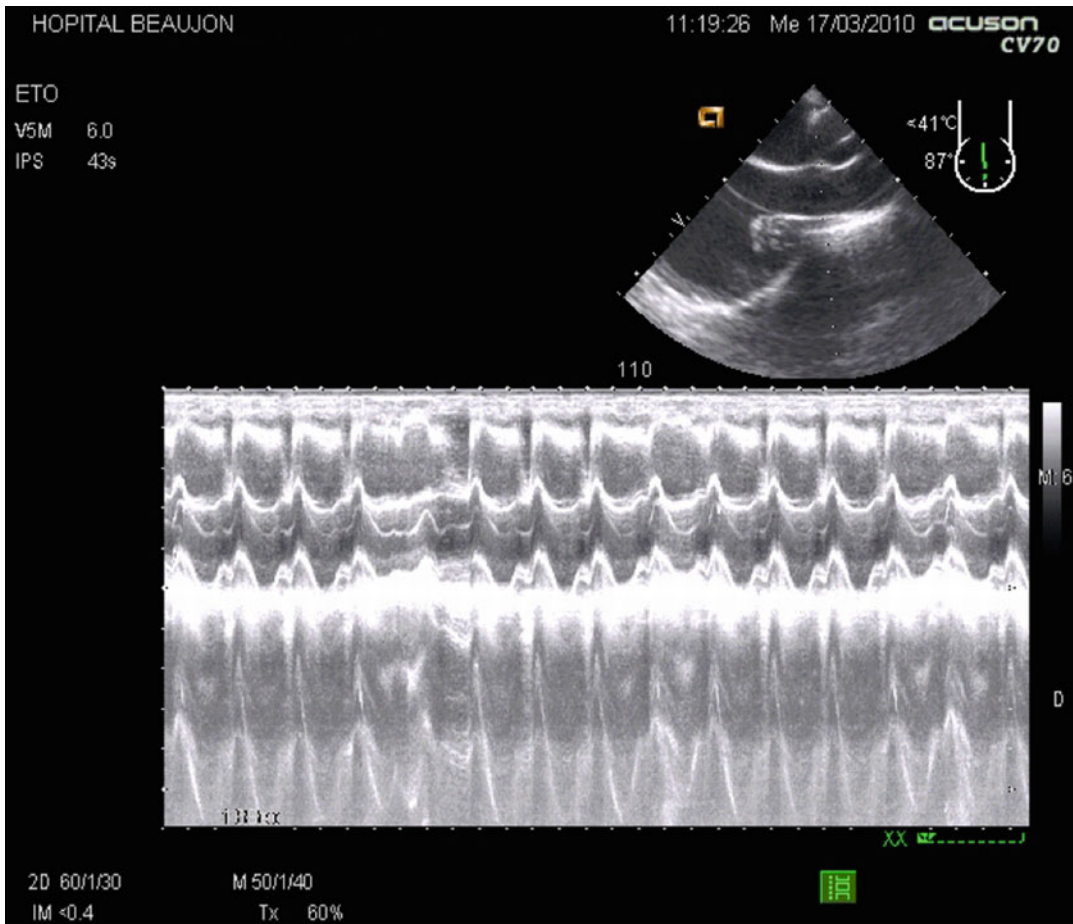
The use of CVP as an index of preload has been popular in hepatic surgery [53]. Although CVP may indirectly reflect volume status, it is not a reliable predictor of the response to fluid loading [54] and associated with many limitations in hepatic surgery. High CVP values (>10 mmHg) favor uncontrollable retrograde bleeding occurring during clamping of the portal triad, but whether CVP can be recommended as a monitor or endpoint to guide the hemodynamic management of patients undergoing major hepatic surgery (liver resection or transplantation) remains a matter of debate [55–58]. Continuous monitoring of CVP has been justified for a long time in liver surgery because of several studies suggested that maintaining a CVP below 5 mmHg was associated with improved outcome and a decreased transfusion requirements during liver resection [59–66] or transplantation [67, 68]. Briefly, reducing CVP can only be obtained by rendering the patient hypovolemic, either by hemorrhage or partial clamping of the inferior vena cava or increasing depth of anesthesia. While possibly feasible in minor or intermediate liver resection, this goal cannot be accepted in major liver resection. Noteworthy, all studies supportive of a low CVP-guided strategy for liver resection and transplantation suffer from major methodological flaws. Most were either retrospective or prospective nonrandomized cohorts with a low number of patients or underpowered randomized controlled trials. Many employed strategies to reduce CVP via pharmacologic interventions (nitroglycerin, diuretics) to decrease cardiac output, and some even rendered patients severely hypovolemic requiring high-dose vasopressors to maintain blood pressure and thereby increasing risk of postoperative renal failure. None of these studies were able to demonstrate an improvement of

postoperative outcome defined by survival or long-term morbidity.

Pulmonary artery (Swan Ganz) catheters represent a useful device to guide optimization of hemodynamics (fluid loading, catecholamines) in patients undergoing liver transplantation, although no outcome benefit has been reported. It provides accurate, continuous, rapid response time, precise, reproducible, operator-independent, and low-cost information on systemic and pulmonary hemodynamics. A major limitation of the pulmonary artery catheter is the poor performance of the pulmonary wedge pressure as a reliable marker of left ventricular filling [51]. It cannot be recommended as a routine hemodynamic monitor for patients undergoing major liver resection. Mixed (or central) venous oxygen saturation obtained with a pulmonary artery catheter may provide useful information on rapid changes occurring in patients with compromised left ventricular failure [69]. Frequent measurement of blood lactate levels provides a useful information on the adequacy of intraoperative oxygen delivery to the tissues and has been used as an endpoint, for example, in sepsis trials.

## Transesophageal Echocardiography

Transesophageal echocardiography (TEE) is a potentially attractive device that offers several advantages if used during major liver surgery (Fig. 25.3). TEE is an increasingly popular imaging tool that provides immediate visual information about the dynamic function of the heart. It delivers accurate, precise, real-time information on ventricular filling, stroke volume, and myocardial dynamics [70]. TEE further visualizes air embolism in the right heart circulation originating from the hepatic veins or inferior vena cava and can help guide percutaneous cannulation of the internal jugular vein for venovenous bypass [71]. Its perioperative use is generally associated with a low incidence of complications, but severe mishaps such as esophageal perforation have been reported during cardiac surgery. The presence of esophageal varices is usually considered a (relative) contraindication to its use. Its use is



**Fig. 25.3** Intraoperative view of the supradiaphragmatic inferior vena cava by transesophageal echocardiography (TEE) illustrating the respiratory variations of the diameter of the inferior vena cava Upper panel: Echographic

view, lower panel: time-motion Doppler recording via an axis corresponding to the dotted line, with (from top to bottom) the right atrium, the superior vena cava, and the left atrium

expensive and dependent on operator experience and cannot be continuously used in the postoperative period. TEE can be helpful to understand a complex, unexpected hemodynamic status any time during surgery. Nevertheless, no data demonstrated the superiority of this monitor over any other device in patients undergoing major liver surgery.

### Esophageal Doppler

The esophageal Doppler monitor (ODM) aims to estimate stroke volume and cardiac output, and a small number of studies performed outside the

frame of liver resection on a restricted number of patients have shown that intraoperative esophageal Doppler monitoring may improve patient recovery [72, 73]; however, none of them were designed to examine mortality or other “hard” outcomes as a primary endpoint. The current level of evidence supporting the use of one device over another for hemodynamic monitoring in patients undergoing major abdominal surgery is weak. A recent meta-analysis including five randomized controlled trials of patients undergoing colorectal surgery found that intraoperative optimization of stroke volume with esophageal Doppler is not superior to routine practice to improve postoperative mortality [73]. Another



study compared the ability to measure cardiac output with the esophageal Doppler device compared to the pulmonary artery catheter during liver transplantation [74] and found a Bland and Altman plot bias near zero, but a broad limit of agreement, indicating that ODM was not an acceptable alternative for measuring cardiac output in this context.

The ultrasound cardiac output monitor (USCOM) measures blood flow across the cardiac valves using continuous wave Doppler ultrasound. When compared with cardiac output determined by pulmonary artery catheter thermodilution technique in patients undergoing liver transplantation, it demonstrated a good agreement and reproducibility of cardiac output measurements between USCOM and the pulmonary artery catheter. One limitation of the USCOM is the inability to measure pulmonary artery pressures.

In summary, the best hemodynamic monitoring for liver transplantation remains to be determined. We do believe that there is insufficient data to support a beneficial effect on outcome of any strategy guided by CVP. The preference should be given to a monitoring device that is able to predict the response to ventricular filling, such as  $\Delta PP$  or SVV or TEE when feasible. Frequent measurements of  $S_vO_2$  or lactate concentrations may be useful to ensure adequate oxygen delivery.

## Fluids and Electrolytes

Maintaining effective intravascular volume to ensure tissue perfusion and cellular oxygenation is the physiological goal independent of the type of surgery. This consideration also applies to major liver surgery (resection, transplantation), with particular emphasis on liver perfusion and oxygenation. Fluid therapy has to be balanced between underuse leading to hypovolemia and inappropriate tissue perfusion and, on the other hand, administration of excessive fluids with subsequent risks of pulmonary and peripheral edema and hepatic congestion. A strategy based on restrictive intraoperative crystalloid therapy (4 mL/kg/h) vs. a liberal protocol has been shown

to reduce the rate of postoperative complications and length of hospital stay following major abdominal surgery [75]. In a randomized controlled trial, Donati et al. have shown that a goal-directed intraoperative therapy based on maintenance of mean blood pressure above 80 mmHg, urine output above 0.5 mL/kg/h, and oxygen extraction ratio less than 27% was associated with a decreased incidence of postoperative organ failures and length of stay after major abdominal surgery [76]. However, hepatic surgeries were excluded from these studies. The choice between crystalloids and colloids to optimize intraoperative vascular filling during liver resection remains open, and comparative data are scarce. A recent study found the use of modern hydroxyethyl starch for fluid replacement in living-donor liver transplantation as safe and effective as albumin [77].

The NICE-SUGAR study conducted in 6,000 ICU patients suggests that tight glycemic control may offer no additional benefit over maintaining blood glucose in the 140–180 mgXdL<sup>-1</sup> in ICU, mechanically ventilated, patients [78]. Are there potential implications of this study in the perioperative context of liver resection surgery? A recent review, accompanied by an editorial published in *Anesthesiology*, reasonably concludes that while avoiding hyperglycemia is clearly beneficial, the appropriate glucose targets and specific subpopulations who might benefit from tight glucose control with intensive insulin therapy remain to be identified [79, 80]. In other words, due to the potential risk of hypoglycemia, it seems premature to advocate strict glycemic control in the OR in any subpopulation of surgical patients including hepatic resections.

## Transfusion

Red cell transfusion is a cornerstone of perioperative care and determinant of outcome after major liver surgery. Five to 20% (up to 60% in some studies) of elective liver resections require red cell transfusions intraoperatively. Massive red cell transfusion is necessary in 1 out of 20–30 patients, while the incidence of transfusion of



plasma and platelets is very low. Risk factors for transfusion are the presence of cirrhosis, the extent of liver resection, and portal hypertension. Recently, scores with good discriminatory ability to predict the necessity of red cell transfusion during liver resection have been developed [81, 82]. Growing evidence supports that red cell transfusion is associated with a significantly worsened outcome and cost after anesthesia and surgery [83]. Operative blood loss during resection of hepatocellular carcinoma was found to be a predictor of recurrence and survival rates [84]. Increasingly attention has focused on the potential risk of cancer progression associated with red cell transfusions. In an experimental study of rats, transfusion of autologous- or allogeneic-aged red cells was responsible for an increased retention of tumoral cells in the lung, and this was clearly related to erythrocytes and not leukocytes or soluble factors contained in the plasma. A possible explanation would be that the transfused erythrocytes impair cellular immunity, particularly natural killer (NK) cells, by decreasing their efficacy to eliminate tumoral cells [85]. These considerations underscore the importance of minimizing perioperative blood loss in patients undergoing liver resection. Although some blood salvage techniques or pharmacologic interventions to reduce blood loss may be safe and effective in patients undergoing liver resection surgery [86, 87], none of these interventions targeting reduction of perioperative bleeding have resulted in a demonstrable decreased mortality or morbidity rate [88, 89]. Without an available alternative therapy, red cell transfusion remains the only way to compensate for severe blood loss or persisting hemorrhage. Delaying transfusions because of underestimation of the severity of hemorrhage undoubtedly causes a significant number of deaths within the 24 first postoperative hours [90, 91]. The decision to transfuse blood products should not be based on the biological or laboratory abnormalities of coagulation only (i.e., increased INR or low platelet count), since these abnormalities poorly predict intraoperative bleeding. Jarnagin et al. showed that in patients undergoing major liver resection, a target hemoglobin level of 8 g/dL resulted in a significant reduction

in red cell requirements compared to standard transfusion strategy. However, no effect of this strategy on the incidence of postoperative complications was found [92]. It should be emphasized that an intraoperative target hemoglobin concentration of 8 g/dL corresponds to the “standard” practice in many institutions, while transfusing patients with hemoglobin levels greater than this was defined as the “standard practice” in this study. A randomized trial by Lodge et al. did not find that recombinant coagulation factor VIIa reduced either the number of patients requiring transfusion or the amount of red cell units administered during liver resection [93]. A reasonable threshold for transfusion in the OR is within a hemoglobin level between 7 and 10 g/dL, depending on whether hemorrhage is under controlled and if the patient is likely going to tolerate further hemorrhage.

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## Postoperative Analgesia and Rehabilitation

Postoperative rehabilitation is highly recommended after major surgery, since it facilitates recovery by decreasing postoperative complications and length of hospital stay [94]. Immediate postoperative removal of the nasogastric tube is associated with a decrease of pulmonary complications after liver resection surgery [95]. Analgesic techniques particularly regional analgesia are effective in decreasing postoperative pain after major abdominal surgery [96], and subgroup analysis of randomized controlled trials suggests a benefit from postoperative epidural analgesia with local anesthetics with a reduction of respiratory complications after major abdominal surgery. However, the most recent meta-analysis on this topic does not show any other advantage than a slight but significant decrease in pain scores with epidural analgesia over opioid patient controlled analgesia. Ketamine is an interesting agent for postoperative analgesia, since it decreases morphine requirements, prevents hyperalgesia, and facilitates epidural analgesia after major abdominal surgery [97], but larger studies of ketamine are lacking. Intra- and

postoperative lidocaine infusion may also improve postoperative analgesia, and rehabilitation after abdominal surgery [98], however, due to hepatic metabolism overdose is possible. Another promising technique, a continuous preperitoneal infusion of ropivacaine has proven efficacy in decreasing pain and accelerating recovery after colonic surgery [99]. This may be due at least in part to an attenuation of postoperative diaphragmatic dysfunction induced by abdominal surgery [100]. Coagulation disorders may limit the safety of epidural analgesia in cirrhotic patients. Therefore, the choice of epidural or spinal regional analgesia after liver resection should be based on a careful risk/benefit analysis including extensive disclosure of the risks of the different techniques to the patient. As coagulation often temporarily worsens in the early postoperative period after liver resection, removal of the epidural catheter prior to discharge of the patient may be delayed or require transfusion of plasma to normalize coagulation. A single-dose intrathecal morphine injection before surgery instead of an epidural catheter will avoid this possible problem. Guidelines for the placement of neuraxial analgesia in patients with coagulation defects as formulated, for example, by the American Society of Regional Anesthesia (ASRA) apply for hepatic resection as well. More detailed information about pain management is found elsewhere (Chapter 35) in this book.

## Laparoscopic Liver Resection

Analysis of the literature suggests that minimally invasive liver resection for colorectal metastasis is safe, feasible with comparable oncologic results to open liver resection for both minor and major liver resections even with prior intra-abdominal operations [101]. Laparoscopic surgery, compared to open surgery for colorectal metastasis, seems to be associated with equal or reduced postoperative morbidity [102]; however, the available data is reported from single-center studies with experienced surgeons in highly selected patients. And these results may not be generalizable. Laparoscopic liver resection does

not appear to be appropriate as a standard procedure in all cases and institutions and may be more feasible in resection of hepatocellular carcinomas than colorectal liver metastases. Left lateral sectionectomy and limited resection of solitary peripheral lesions are particularly suitable while laparoscopic hemihepatectomies remain very challenging [103]. With the appropriate indication and operators, this surgical approach is probably associated with a better postoperative outcome than open laparotomy. However, the experience of very few centers in a high selective patient population does not allow to infer general conclusions to date.

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Navraj Kahlon and Tricia Brentjens

Led by Thomas E. Starzl, the era of liver transplantation began in 1963 at the University of Colorado, and by 1967, the first patient transplanted by this group survived more than a year [1]. However, not until further advances of knowledge, experience, and surgical technique in the field of split-liver technique allowed the transplantation of one donor graft into two recipients [2], was living donor liver transplantation (LDLT) attempted. First successfully performed in 1989 by Broelsch et al. [3] at the University of Chicago, a young girl born with biliary atresia was the recipient of her mother's left lobe of liver. Since that time, experience in the field has grown to include adult-to-adult living liver transplantation.

As the wait list for liver transplants far exceeds the availability of cadaver donors, the use and widespread acceptance of LDLT have increased. However, the need to protect the donor from unacceptable risk is of paramount concern. In one case series, hospital mortality from hepatic resection was 3% [4]. Fortunately, the worldwide experience for LDLT has demonstrated a much lower mortality rate of 0.4–0.6% [5] for living liver donation, yet an order of magnitude higher than the risk for renal donation [6]. It is therefore imperative that a potential liver donor is

thoroughly investigated and screened to optimize the safety of the procedure.

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## Preoperative Evaluation

In 2000, the Live Organ Donor Group published a consensus statement, providing a guideline how to screen prospective liver donors [7]. Variations of this guideline exist from center to center as to which evaluation or procedure is performed during which phase of the screening process.

## First Evaluation Phase

The first evaluation phase involves prescreening the prospective donor, usually performed by a registered nurse to confirm that a potential donor meets the following criteria [8]: The prospective donor should be of legal age and have sufficient intellectual ability to understand the procedure and the associated risks. There should be evidence of an emotional relationship between the prospective donor and recipient, and potential donors who are believed or known to have been coerced into the process must be excluded. It is paramount to safeguard the donor and ensure that their welfare supersedes all other concerns including those of the recipient. The potential donor must also have the ability and willingness to comply with long-term follow-up. ABO incompatible grafts are known to have a poorer long-term outcome, and thus, ABO compatibility is

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**Table 26.1** Laboratory investigations during first phase of evaluation

Laboratory investigations [11]		
Amylase	Serology for	HBV
		HCV
Lipase		HIV
Glucose		CMV
Protein		EBV
Protein electrophoresis		HSV
Triglycerides		
Cholesterol		
TSH		
C-reactive protein		Protein C
Ferritin	Protein S	
Transferring saturation	Antithrombin III	
Alpha-1-antitrypsin	Factor V Leiden mutations	
Ceruloplasmin	Prothrombin mutations	
Antinuclear antibodies	Homocysteine	
Coagulation profile	Factor VIII	
Urinalysis	Cardiolipin	
	Antiphospholipid antibodies	

considered a prerequisite for donation [8]. The donor should be negative for hepatitis B surface antigen and hepatitis C antibody. Some centers may accept hepatitis B core antibody positive. As these donors have been exposed to hepatitis B at some point in the past, it is prudent to perform a liver biopsy if the candidate is to be further considered. About 18–34% of potential candidates are rejected in this first phase without utilizing significant resources or undergoing invasive testing [9, 10].

## Second Evaluation Phase

The second phase requires a thorough medical, laboratory (Table 26.1), and psychological evaluation. The potential donor is presented to the transplant team, and a decision is made whether to proceed to comprehensive donor evaluation. The patient's overall health status is assessed, and specifically, the absence of diabetes, severe or uncontrolled hypertension, and any hepatic, cardiac, renal, or pulmonary disease is confirmed (Table 26.2) [11]. A thorough preoperative anesthetic evaluation should be done at this time as well.

A transplant psychologist and/or a social worker will conduct the psychosocial evaluation. The goal is to educate the potential donor about the psychosocial impact of donor surgery and recovery, identify potential psychological or psychiatric issues that preclude donation, and ensure donor is able to consent without coercion by recipient, recipient's family, or transplant team.

## Third Evaluation Phase: Graft Feasibility Determination

The tests listed in Table 26.3 will aid in determining graft suitability; however, not all of these tests are routinely performed in all centers. It is important to ascertain hepatic volumetric data, delineate hepatic anatomy including hepatic artery, portal vein, hepatic veins, and assess the degree of steatosis [7]. The degree of steatosis can be assessed using imaging techniques [12]. The percentage of steatosis is subtracted from the estimated liver volume, thus yielding a corrected liver volume [13]. If deemed necessary, percutaneous liver biopsy can also be performed. It is center-specific whether a candidate with significant steatosis is accepted.

**Table 26.2** Noninvasive investigations during the second phase of evaluation

Noninvasive investigations [11]	
Electrocardiography	Doppler ultrasound of carotid arteries
Chest roentgenogram	Abdominal ultrasound
Pulmonary function test	Echocardiography

**Table 26.3** Tests to determine graft feasibility during the third phase of evaluation

Volumetric CT or MRI scan of liver
Splanchnic arteriography
Endoscopic retrograde cholangiopancreatography
Liver biopsy

The three phases of the evaluation of the potential liver donor are listed in Table 26.4.

## Ethical Considerations

In 2006, The Transplantation Society issued an ethics statement with respect to the living lung, liver, pancreas, and intestinal (extra-renal) donor. (Care of the live kidney donor was addressed 2 years earlier at the International Forum on the Care of the Live Kidney Donor held in Amsterdam.) The Transplantation Society concluded:

The Ethics Committee of TTS recommends that live lung, liver, pancreas and intestine donation should only be performed when the aggregate benefits to the donor–recipient pair (survival, quality of life, psychological, and social well-being) outweigh the risks to the donor–recipient pair (death, medical, psychological, and social morbidities) [14].

The committee defined essential ethical elements that need to be followed by the transplant center.

The responsibility of the transplant team performing live donation includes:

- Involvement of health-care professionals exclusively responsible to the donor
- Repetition of the information
- Psychosocial evaluation
- Provide a reflection period after medical acceptance and decision to donate
- Assess donor retention of information and understanding

- External review committees

Informed consent needs to include:

- Cognitive capacity
- Voluntary decision
- Donor understanding
- Disclosure, including recipient conditions which may impact the decision to donate with recipient's permission
- Expected transplant outcomes (favorable and unfavorable) for the recipient
- Information on alternative types of treatments for the recipient, including deceased organ transplantation
- Donor registries

Donor autonomy needs to be assured including the freedom to withdraw from the donation process at any time, with reasons for not proceeding kept confidential.

Donor selection should include:

- Legally incompetent or those who lack the capacity for autonomous decision making should be excluded from donation.
- Rarely an independent advocate for the donor needs to be appointed.
- In the event that nondirected or distant acquaintance live organ donation is considered, special considerations to prevent donor exploitation should be made.
- Centers should regard long-term access to health care after the procedure as a prerequisite for donation.
- The donation process and follow-up should be cost neutral for the donor.

## Contraindications to Donation [5]

A calculated remnant liver less than 30% of original liver volume with complete venous drainage puts the donor at risk of too-small-for-size syndrome. Preoperative volumetric imaging may actually overestimate actual liver volume by 10%. Similarly, an estimated graft liver volume to recipient body weight ratio (GWBWR) of <0.8% is a contraindication for donation. Other contraindications are:

- ABO incompatibility except in special circumstances, such as infants <1 year of age

**Table 26.4** Living donor evaluation criteria

Phase I	Phase I	Phase II	Phase II	Phase II	Phase III
Age	Relationship	Psychosocial support	Medical evaluation	Laboratory evaluation	Graft assessment
18–60	Emotionally related to recipient; ABO compatible; negative serology for hepatitis and HIV viruses	Adequate psychosocial support systems as determined by pediatric transplant team, psychiatry, and social services	Comprehensive history and physical examination negative for acute or chronic illness affecting operative risk	Hematologic, serum chemistry, liver, and kidney function normal; normal EKG and CXR*; negative serology for hepatitis and HIV viruses	Volumetric MR* scan excludes occult mass lesions, documents adequate liver volume; graft represents at least 50% of expected recipient liver mass; arteriography documents arterial supply for anticipated graft (for adult LRT* only)

\*EKG electrocardiogram; CXR chest X-ray; MR magnetic resonance; LRT living-related donor transplant. Reprinted with permission from [8]

without presence of isoagglutinins, and in emergencies where a cadaveric transplantation is not possible

- Portal or sinusoidal fibrosis
- Nonalcoholic steatohepatitis (NASH)
- Steatosis >20% (only for right liver)
- Portal inflammation and necrotic-inflammatory changes
- HIV, HCV, or HBV (HBsAg+) positive

A BMI >30 kg/m [2] is a relative contraindication to donation as these candidates usually have hepatic steatosis. Another concern is the presence of patent foramen ovale (PFO) in the donor, as the risk of paradoxical air embolism during the resection is increased [15]. It has even been advocated that the preoperative evaluation should include echocardiography to rule-out PFO [16].

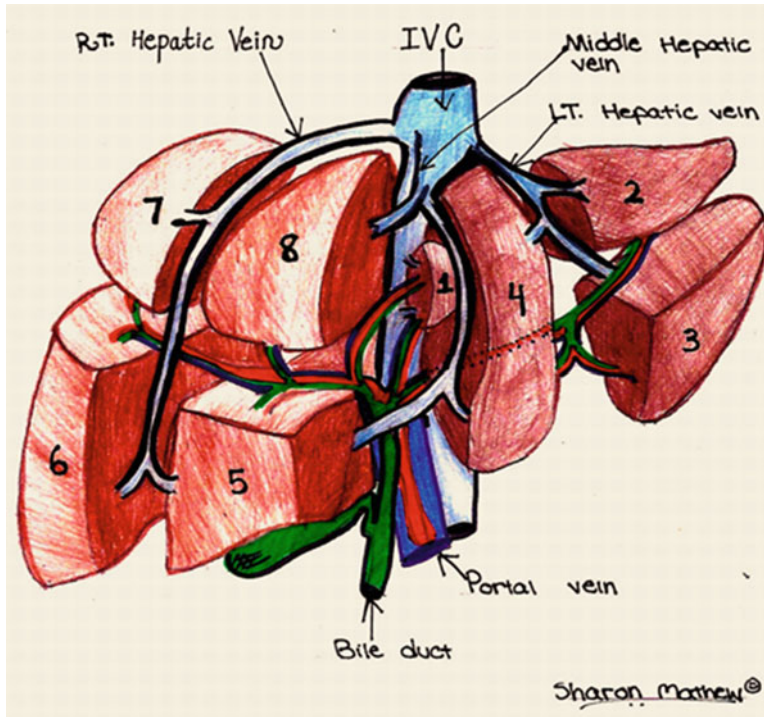
## Surgical Technique

In 1957, Claude Couinaud, a French surgeon, published his seminal work *Le Foie: Études anatomiques et chirurgicales* [17]. By delineating the segmental anatomy of the liver (Fig. 26.1), hepatectomy surgery became possible.

Four anatomic allografts are classically described for LDLT [18, 19]. The entire right

liver lobe (Couinaud segments V–VIII) is most commonly transplanted, comprising more than 60% of the donor's total liver mass. Normal liver volume is 1,294–1,502 mL in women and 1,796–1,956 mL in men [20]. The entire left liver lobe (Couinaud segments II–IV) is approximately 35% of the total liver volume, yielding 300–500 cc allografts that are ideally suited for recipients weighing approximately 50 kg. The left lateral segment (Couinaud segments II–III) yields 20% of total liver volume, a 200–300 cc allograft, and is used in large donor-to-recipient size disparity, and the recipient weight for a left lateral segment graft is usually restricted to less than 40 kg. Extended right liver (Couinaud segments IV–VIII) hepatectomy is the least commonly utilized graft and provides greater than 70% of standard liver volume (SLV) and is suitable for a small donor to large recipient situation. Risks to the donor by removal of such a large portion of the liver make this technique unjustifiable in most situations (Table 26.5).

Options for pediatric LDLT include entire left liver lobe, left lateral segment, and left lateral segment with a part of segment IV [19]. To assess graft size adequacy, a graft weight to recipient body weight ratio (GWBWR) is calculated [21]. Alternately, the percentage of the calculated SLV can be used [22, 23]. The graft size is considered



**Fig. 26.1** Couinaud's segmental anatomy of the liver

**Table 26.5** Extent of liver resection, involved Couinaud's segments and percentage/weight of liver removed.

Allograft	Couinaud's segments	Percentage liver removed (%)	Volume yield (cc)
Entire right lobe	V–VIII	60	600–900
Entire left lobe	II–IV	35	300–500
Left lateral segment	II–III	20	200–300
Extended right liver	IV–VIII	70	800–1,000

adequate if the GWBWR is within 1–3% [19]. A ratio of 0.8% is considered the minimum to prevent small-for-size syndrome in the recipient; however, experience at our center has shown successful grafting with graft ratios of as low as 0.49%. Recipients with severe portal hypertension or decompensated disease will require a larger graft, irrespective of calculated GWBWR. In general, left lobe will be used for recipient with a body weight 20–40 kg and left lateral segment or left lateral segment plus portion of segment IV for recipients with a body weight <40 kg [19]. In instances where a graft larger than left lobe is necessary, left half of caudate lobe can be added [24].

For pediatric LDLT, laparoscopic left lateral segmentectomy to resect segments II and III and

removal through a Pfannenstiel incision has been reported [25]. Laparoscopic right hepatectomy has also been described for adult living donor transplantation and is now routinely employed at our center [26]. However, classically, a right or bilateral subcostal incision with midline extension is performed for live liver organ donation.

## Anesthetic Management

Due to the potential for large volume blood loss during the hepatectomy, central venous catheterization is recommended to allow for rapid volume replacement and monitoring of central venous pressure (CVP). A low CVP (2–4 mmHg) is

desirable in order to minimize blood loss [4]. Pringle's maneuver, the surgical technique of intermittently occluding inflow, is routinely used to minimize blood loss in hepatectomy surgery; however, the risk of ischemic injury to the graft has in the past precluded its use in living donor hepatectomy. Recent evidence shows that this procedure can be safe for the graft, provides a cleaner surgical field, and results in a lower incidence of biliary complications [27, 28]. Techniques utilizing Trendelenburg position, volume restriction, nitroglycerine infusion, and furosemide administration may all be useful maneuvers to reduce CVP [29]. In addition to reducing CVP, Trendelenburg position of 15° is advocated to reduce the risk of venous air embolism.

The anesthesiologist must also be cognizant to minimize possible insult to the resected graft [30]. Firstly, hepatotoxic drugs, such as halothane, should be avoided. Halothane has a rate of metabolism of 20% and a risk of autoimmune hepatitis greater than that any of the other available inhaled anesthetics. Secondly, perfusion to the liver should be optimized. Hepatic blood flow is decreased by the nitrous oxide, by an elevated CVP, and as a consequence of a reflex vasoconstriction of the hepatic arterial and portal venous system in response to elevated pressures in the hepatic sinusoids. Lastly, graft edema must be minimized to reduce the risk of graft thrombosis, and the administration of mannitol to the living donor may aid in reducing graft edema [30]. Ultimately, LDLT has the advantage of minimizing cold ischemic time to 1 h or less as compared to the 4 up to 12 h of cold ischemic time with deceased donor transplantation. As a consequence, inflammatory markers after reperfusion are lower in LDLT and may improve graft survival [17].

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## Postoperative Management

At the conclusion of the operation, muscle relaxation is adequately reversed, and the vast majority of patients can be safely extubated in the operating room. At our institution, intensive care admission is routine and with an uneventful

recovery transferred to the surgical floor on postoperative day 1 and discharged from hospital postoperative days 7 to 10.

As living donors are generally healthy and unacquainted with chronic disease, postoperative complaints of pain are often greater than in patients who underwent hepatic resection of tumor [31, 32]. Preoperative epidural catheter placement may be an excellent option for postoperative analgesia [33] with the additional benefits of a shorter duration of postoperative ileus, attenuated stress response, fewer pulmonary complications, and early ambulation [34]. However, some centers avoid epidural analgesia as significant postoperative derangements of the coagulation profile can occur, and these may complicate the removal of the epidural catheter at a time when the patient is getting ready for discharge home [35].

In addition to the risk of postoperative coagulopathy due to lower hepatic volume, heparin administration to prevent graft thrombosis at the end of liver parenchymal dissection may further prevent anesthesiologists to place an epidural catheter [35, 36]. It is recommended that heparin administration be delayed 1 h after catheter placement and catheter removal delayed 2–4 h after the last dose of heparin and not until the aPTT is checked [37], and fortunately, the average time of heparin administration from epidural catheter placement is usually greater than 4 h [35].

Patient-controlled analgesia (PCA) is another mode of analgesia commonly used in many centers [30, 36]. Our center uses preoperative intrathecal morphine (ITM 0.3–0.5 mg) in combination with postoperative PCA, a regimen that is superior to PCA use alone [38]. A mild self-limiting pruritus is the most common adverse effect of ITM [38]. Preoperative ITM is not inferior to epidural catheter use as determined by the visual analog scale, but intravenous opioid use and incidence of pruritus are greater [39].

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## Complications

The altruistic nature of living donor hepatectomy for transplantation necessitates that all precautions to protect the donor must be taken. Deep



**Table 26.6** Clinical and biological outcome of living liver donation

	RH mean $\pm$ SD	LH mean $\pm$ SD	LL mean $\pm$ SD
<i>Clinical</i>			
Hospital stay (days)	7 $\pm$ 2.5	5.9 $\pm$ 1.3	6.66 $\pm$ 1.5
Anesthesia time (min)	528 $\pm$ 108	453 $\pm$ 73	340 $\pm$ 39
Estimated blood (mL)	583 $\pm$ 277	400 $\pm$ 175	294 $\pm$ 145
<i>Biological</i>			
INR peak	1.75 $\pm$ 0.3	1.37 $\pm$ 0.2	1.27 $\pm$ 0.2
TBili peak (mg/dL)	3.05 $\pm$ 1.4	2.6 $\pm$ 1	1.5 $\pm$ 1.3
AST peak (IU/L)	348 $\pm$ 260	239 $\pm$ 225	289 $\pm$ 226

Reprinted and adapted with permission from [6]. *RH* Right hepatectomy, *LH* Left hepatectomy, *LL* Left lateral hepatectomy, *INR* International normalized ratio, *TBili* Total bilirubin, *AST* Aspartate aminotransferase

vein thrombosis (DVT) leading to pulmonary embolism is a potentially catastrophic postoperative complication that can result in donor morbidity and/or mortality [40]. The use of graduated compression stockings and intermittent pneumatic compression intra- and postoperatively has been well validated in reducing the incidence of DVT [41]. Additionally, the prophylactic administration of subcutaneous heparin can reduce the risk of DVT by 50–70% [42]

Blood loss depends on the hepatectomy performed. A right hepatectomy (RH) is a more lengthy and challenging procedure and, as can be expected, associated with a longer anesthesia time, larger blood loss, greater derangements of the coagulation profile occur and significantly longer hospital stay compared to a left hepatectomy (LH) or left lateral hepatectomy (LL) [6] (Table 26.6). An early report of 100 consecutive hepatic resections reported that 59 of these patients received exogenous blood products [4]. A common strategy to minimize exogenous blood product administration is the use of intraoperative blood salvage, washed in a Cell-Saver™ (Haemonetics Laboratories, Boston, MA), and retransfusion of the red blood cells at the conclusion of the hepatectomy [16]. Preoperative autologous blood donation, erythropoietin administration, and isovolumetric hemodilution are other possible strategies variably employed.

Postoperative recovery and regeneration of the remnant liver begin immediately after resection. Transaminase enzymes peak within 48 h, and bilirubin usually peaks on approximately day 3 [16]. Small-for-size syndrome, usually described

as a transplanted graft that is inadequate in size and function, may also occur in the donor if the remaining volume is too low. A too small liver remnant can present with prolonged cholestasis, transaminitis, and synthetic function derangements [16]. The care for small-for-size syndrome is mainly supportive; however, various strategies have been proposed, including octreotide or vasopressin therapy to reduce portal pressure and intraportal glucose and insulin infusions to hasten remnant liver regeneration [16]. One case of liver failure in the donor requiring liver transplantation has been reported [43].

Biliary leaks are the most common serious complication after donor hepatectomy [43]. One case series reported biliary leaks in 13% of donors. Twenty percent of these cases resolved with external drainage via the original Jackson-Pratt drain, half required additional percutaneous drainage and 30% required endoscopic nasobiliary drainage. The source of the leak is commonly the cut surface, but may also be at the stump of the right hepatic duct [44]. A lower rate of 5–10% biliary leaks was observed with left lateral segmentectomy [19]. Biliary strictures occur less often; the same case series reported this complication in 1.5% of all donors [44]. Biliary strictures will more frequently require invasive interventions with temporary endoscopic retrograde biliary stenting and one donor required hepaticojejunostomy 20 months after surgery.

The most common reason for reoperation in the living donor is to repair an incisional hernia [45]. The occurrence of hernia is more frequent in

the obese population (BMI > 30) [46]; however, obesity is only a relative contraindication and does not necessarily preclude donation. A bilateral incision with midline extension has a higher risk of incisional hernia, as compared to a right subcostal incision with midline extension [19].

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Oliver Panzer and Jennifer Sandadi

Over the years, improvements in the understanding of the functional anatomy of the liver, patient selection, and surgical technique have greatly reduced the rate of complications of hepatic surgery. Consequently, the number of liver resections has greatly increased over the last decade. Nonetheless, intraoperative complications continue to exist. This chapter will discuss the most common complications associated with non-transplant liver surgery and evaluate potential treatment options. We will focus on methods to reduce intraoperative blood loss and ischemia–reperfusion injury after hepatic resections and, lastly, discuss the issue of low remaining hepatic mass in the setting of excessive liver resection.

Evaluation of the surgical risk of patients undergoing elective liver surgery must include the preoperative condition of the patient; the degree of cirrhosis, steatosis, or fibrosis; and the extent of possible liver dysfunction and associated comorbidities such as coagulopathies, renal insufficiency, and portopulmonary hypertension. Furthermore the extent of the liver resection and the estimated remaining hepatic function need to be considered. All of these factors affect perioperative outcome and are required for a complete anesthetic assessment prior to surgery. *More details about the preoperative risk evaluation are discussed elsewhere (Chapter 24) in this book.* Moreover it is well

known that the extent of intraoperative blood loss with subsequent transfusions is related to increased morbidity and mortality [1–6].

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## Blood Loss

The number of resected liver segments and perioperative blood loss is the most important predictors for perioperative morbidity and mortality. In 1977 Foster et al. reported a mortality of over 20% in major hepatic surgery with major hemorrhage, causing 20% of the deaths alone [7]. More recent analysis of more than 1,800 patients undergoing liver resections reported a perioperative mortality of only 5%, with almost 0% in the last 200 cases. The authors ascribed the improvement in perioperative mortality to substantially improve parenchymal-sparing surgical techniques and a decrease in blood loss. The resection of more than three segments or the performance of complex hepatectomies, however, is still associated with increased blood loss and transfusion requirements [8]. Other studies reported en bloc resection, surgeon with low case volume, tumor size, tumor proximity to major hepatic vessels [9], and operative time [10] as independent risk factors for perioperative blood loss during hepatectomies [11]. Poor preoperative liver function, especially with impaired hemostasis, has long been thought to increase intraoperative blood loss, but this has recently been challenged by laboratory studies of patients with cirrhosis [4, 12] and reports of major hepatic surgery in patients with cirrhosis

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**Table 27.1** Hemostatic changes in patients with liver disease that either contribute (A) or counteract (B) bleeding

<i>A. Changes that impair hemostasis</i>
Thrombocytopenia
Reduced hematocrit
Platelet function defects (?)
Enhanced production of nitric oxide and prostacyclin
Low levels of coagulation factors II, V, VII, IX, X, and XI
Vitamin K deficiency
Dysfibrinogenemia
Low levels of plasmin inhibitor, factor XIII, and TAFI
Elevated levels of tPA
<i>B. Changes that promote hemostasis</i>
Elevated levels of VWF
Elevated levels of factor VIII
Decreased levels of protein C, protein S, and antithrombin
Low levels of plasminogen

From: Lisman and Leebeek [14], Table 1, with permission

without the need for transfusion of blood products [4]. Evidence shows that the deficiencies in procoagulant factors are in part compensated by a simultaneous downregulation of anticoagulant function [13, 14] and hemostasis can be preserved in patients with liver disease (Table 27.1). However, this hemostatic equilibrium is easily unbalanced by triggers like sepsis or intraoperative hemorrhage.

## Treatment

### Surgical Techniques

Improvements in surgical techniques such as hepatic inflow and outflow control have greatly reduced the amount of intraoperative blood loss. The Pringle maneuver aims to reduce vascular inflow by occlusion of the portal vein and the hepatic artery. Total vascular occlusion includes the Pringle maneuver and additional clamping of the infrahepatic and suprahepatic vena cava [15]. Both techniques decrease intraoperative blood loss at the expense of hepatic ischemia–reperfusion injury and impairment of liver regeneration

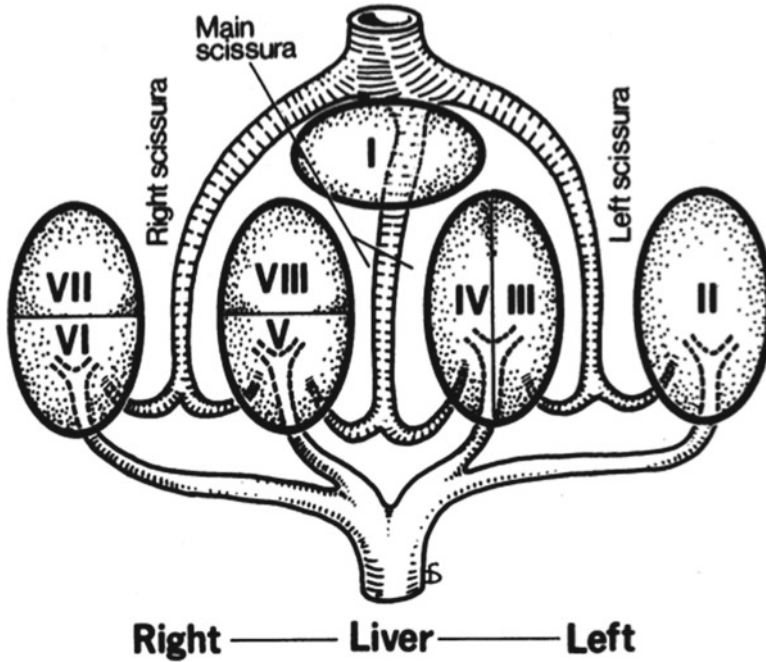
[16, 17]. The quality of the liver tissue and the surgical dissection method utilized will also affect parenchymal bleeding [18]. Better understanding of the liver anatomy and major advances in hepatic imaging led to the development of parenchymal-sparing surgical techniques for liver resection. The advantages of a segmentally oriented resection particularly in patients with pre-existing liver disease include better conservation of functional liver parenchyma and reduced hemorrhagic complications compared to the classic lobar or wedge resection. The anatomical basis for the segmental resection is built on the fact that the three hepatic veins divide the liver into four sectors, where each sector is fed by a distinct portal vein pedicle (Fig. 27.1). A similar division can be found for hepatic arteries and bile ducts. Identification and clamping of one portal pedicle leads to the demarcation of the corresponding liver segments and allows a resection of these segments without affecting the vascular supply of the neighboring tissue (Fig. 27.2).

New dissection devices for the transection of the liver parenchyma such as ultrasonic dissection, hydro-jet dissection, and radiofrequency ablation-based devices have been introduced with varying degrees of success [18]. Although most of these devices have demonstrated decreased blood loss during transection, some performed slowly and the overall benefits cannot be clearly elucidated at this time. Personal preference and the availability of the equipment influence the use of a specific device. Additional prospective studies are required to evaluate the superiority of each method or device. Vascular control is needed to limit the extent of blood loss, but the method of control should be selected based on the location and complexity of the resection and the skill level of the surgical team.

### Fluid Management

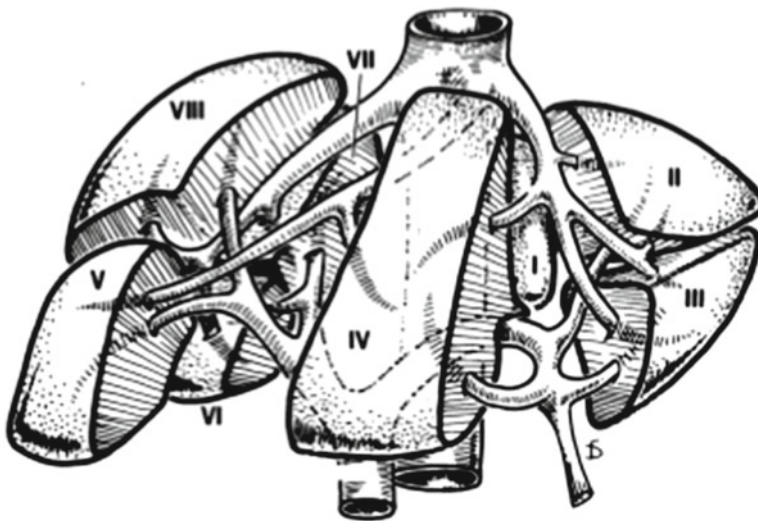
The anesthesiologist's role in reducing intraoperative blood loss and complications cannot be underestimated and includes intraoperative fluid management, transfusion requirements, and pharmacological interventions. Fluid management





**Fig. 27.1** Segmental organization of the liver. The hepatic veins reside in the portal scissurae, which divide the liver into four sectors. Each sector is composed of one or more anatomic segments. The right hemi-liver consists

of segments V, VI, VII, and VIII. The left hemi-liver consists of segments II, III, and IV (From: Blumgart LH, ed. *Surgery of the Liver and Biliary Tract*. 2nd ed. London: Churchill-Livingstone; 1994, with permission)



**Fig. 27.2** Exploded views of the liver demonstrating the liver segments according to Couinaud's nomenclature, as seen in the patient (From: Blumgart LH, ed. *Surgery of*

*the Liver and Biliary Tract*. 2nd ed. London: Churchill-Livingstone; 1994, with permission)



strategies during liver surgery have long been debated with the focus on central venous pressure (CVP) monitoring. While some form of hepatic inflow occlusion is frequently used during liver surgery, intraoperative bleeding is mostly caused by backflow from valveless hepatic veins. Thus, reducing CVP below 5 mmHg has been advocated and reported to improve the surgical field during dissection and reduce transfusion requirements in several studies for liver resection [19–26] or transplantation [27–29]. Methods to achieve a low CVP consist of volume contraction by the restrictive use of fluids, the use of vasodilating agents, and the use of diuretics or even perioperative phlebotomy. Opponents of a low intraoperative CVP state the higher risk for complications, including systemic tissue hypoperfusion and postoperative renal failure [30] which may outweigh the benefits. It is important to note that there are no definitive studies demonstrating an improvement of postoperative outcome, survival, or long-term morbidity using a low intraoperative CVP. Furthermore, it has been argued that pulmonary artery occlusion pressure and CVP fail to predict the ventricular filling volume, cardiac performance, or response to volume infusion in normal subjects [31]. Other intraoperative methods for monitoring preload (transesophageal echocardiography) remain to be tested and are covered in more detail elsewhere (Chapters 9 and 12) in this book.

During major liver resection, transfusion of packed red blood cells, fresh frozen plasma, platelets, and/or cryoprecipitate may be necessary, and specific transfusion goals should be discussed by the anesthesiologist and the surgical teams prior to surgery. (see chapter “Anesthetic Management, Monitoring, Fluids and Electrolytes” for a detailed discussion on intraoperative transfusion.)

## Pharmacological Agents

Pharmacological agents, such as topical hemostatic agents, antifibrinolytic drugs, and procoagulant drugs, are available as complementary measures to reduce intraoperative blood loss.

Topical hemostatic agents act by initiating coagulation cascades at the transected surface of the parenchyma or by creating a matrix for endogenous coagulation, for example, using collagen, gelatin, or cellulose sponges [18, 32]. Fibrin sealants in liver surgery have been tested in a large, randomized, controlled trial of 300 patients undergoing partial liver resection [33]. This study showed no difference in total blood loss, transfusion requirement, or postoperative morbidity between the treatment group (fibrin sealants) and a control group (no fibrin sealants). Future prospective studies are required to further test the efficacy and utility of various topical agents in reducing intraoperative blood loss.

Antifibrinolytic drugs include tranexamic acid, aminocaproic acid, and aprotinin. Tranexamic acid and aminocaproic acid inhibit the proteolytic activity of plasmin and the conversion of plasminogen to plasmin by plasminogen activators. Aprotinin is a serine protease inhibitor derived from bovine lung, which inhibits trypsin, chymotrypsin, plasmin, tissue plasminogen activator, and kallikrein [32]. Aprotinin has been removed from the market due to the association between aprotinin and serious end-organ damage in cardiac surgery [34]. However, aprotinin in liver transplant surgery has not shown increased risk for thromboembolic events or renal failure [35, 36]. Both aprotinin and tranexamic acid significantly reduce blood loss and transfusion requirements by 30–40% during liver transplantation [35]. The use of antifibrinolytics in liver resections has not been extensively studied and warrants future prospective analysis. It is important to note that these drugs are adjuncts to complement surgical technique and proper anesthetic care during liver surgery, and should not be utilized as solitary hemostatic methods.

Recombinant factor VIIa has been studied as a procoagulant drug in several randomized clinical trials of patients undergoing liver resection or transplantation [18, 37–40]. None of the clinical trials assessing the efficacy and safety of factor VIIa in liver surgery and transplant discovered major safety issues; however, they also failed to demonstrate a significant decrease in blood loss or transfusion requirements [18]. Recombinant

factor VIIa is used most often as a last resort in situations of massive hemorrhage and cannot be recommended as a routine pharmacological agent to limit blood loss.

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## Perioperative Hepatic Insufficiency

Overall the incidence of perioperative hepatic insufficiency within 72 h after surgery is approximately 3% in patients undergoing resection for cancer or metastases. Most of these patients, however, have evidence of impaired liver function preoperatively, reflecting a higher risk of perioperative hepatic failure and death [41]. In fact the model for end-stage liver disease (MELD) score correlates well with the incidence of post-liver resection hepatic failure and has been suggested to help select appropriate patients for hepatectomies. In one study, patients undergoing hepatectomy with an MELD score >10 developed liver failure in 37.5% of the cases, whereas none did with an MELD score <9 [42]. Ischemia–reperfusion injury, small-for-size syndrome (SFSS), and major blood loss are the most important etiologies causing postoperative liver failure after hepatectomy [43].

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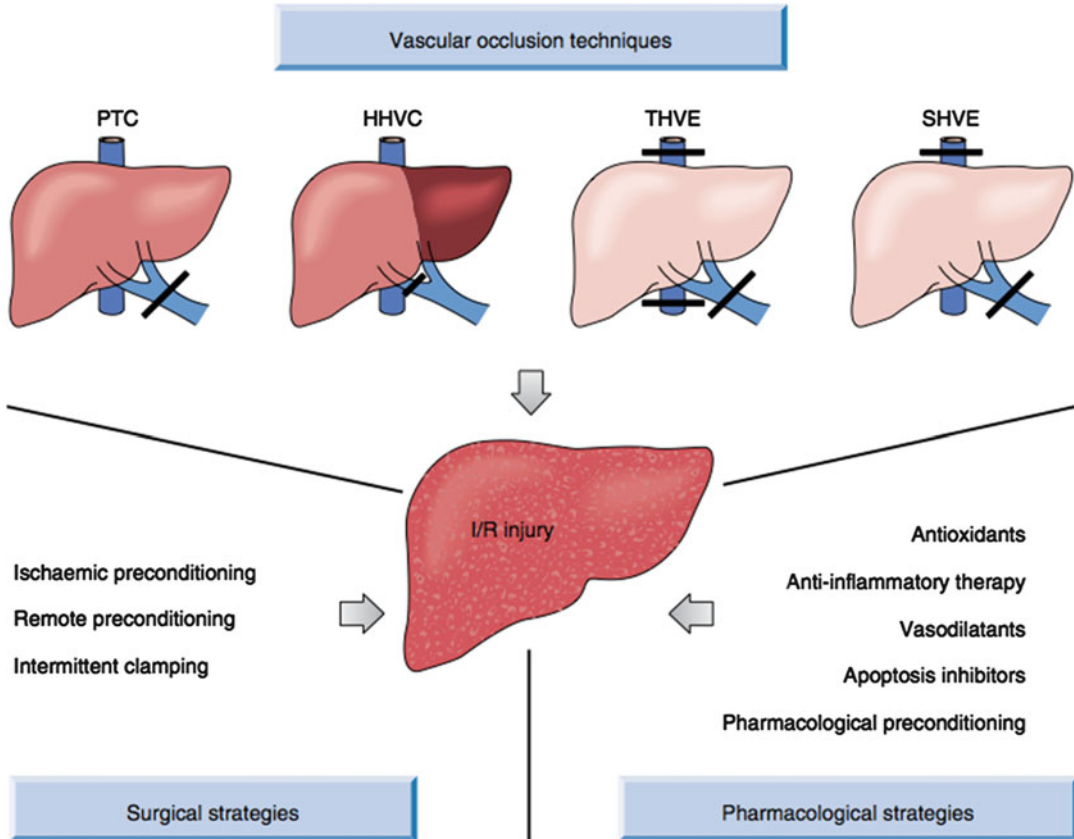
## Ischemia–Reperfusion Injury

Ischemia–reperfusion (IR) injury can lead to liver failure, resulting in coagulopathies, renal failure, severe metabolic acidosis, cerebral edema, and hypothermia. The pathophysiology of IR injury during surgical clamping and liver resection is complex and occurs in two stages. During the initial phase (approximately 2 h after reperfusion), reactive oxygen species are released, and activated Kupffer cells (liver macrophages) may release multiple proinflammatory mediators such as tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) and nitric oxide (NO), triggering a systemic inflammatory response. The oxidative stress ultimately causes necrosis or apoptosis of hepatocytes and endothelial cells [44]. During the late phase (6–48 h after reperfusion), infiltration by activated neutrophils dominates the process. The inflammatory response is

maintained, and impairment of the microcirculation via the release of endothelin-1 (vasoconstriction) and platelet aggregation leads to further hepatocyte damage [44–47]. Steatotic as well as cirrhotic livers are more susceptible to IR injury than a healthy hepatic parenchyma. In fatty liver disease, mitochondrial changes paired with altered receptor expression lead to decreased intracellular ATP levels. The altered anatomy and increased concentrations of endothelin-1 in cirrhotic patients may cause a marginal blood supply, limiting the tolerance of hypoperfusion. Subsequent ischemia during surgery will thus aggravate a preexisting supply–demand mismatch and amplify hepatocyte destruction.

## Treatment

There are currently no proven treatment modalities to ameliorate reperfusion injury, which result in improved clinical outcome; in animal studies, interventions like ischemic preconditioning (IPC) and intermittent vascular clamping (IC) or new pharmacological strategies have shown promising results for liver resections; however, the clinical translation has been disappointing so far (Fig. 27.3). During IPC, the vascular supply to the liver is interrupted intermittently for short periods of time, provoking a conditioning response in order to better tolerate prolonged periods of ischemia. On a molecular basis, adenosine, nitric oxide (NO), and induction of cytoprotective genes seem to play a key role [44, 48]; however, the exact mechanisms are not well understood. The potential beneficial effects of IC are probably based on the same mechanisms as IPC. IC is vascular occlusion during liver surgery with intermittent releasing. Various clamp-release-time regimens have been published, resulting in attenuated liver injury but no difference in clinical outcomes compared to continuous vascular occlusion [49–51]. Based on a Cochrane meta-analysis by Gurusamy et al., it seems that at present, IPC and IC reduce hepatic injury, evidenced by laboratory tests, and reduce transfusion requirements but so far failed to show any clinical benefit [48, 52].



**Fig. 27.3** Synopsis of surgical and pharmacological strategies for hepatic ischemia–reperfusion (IR) injury induced by portal triad clamping (PTC), hemihepatic vas-

cular clamping (HHVC), total hepatic vascular exclusion (THVE), or selective hepatic vascular exclusion (SHVE). (From Bahde and Spiegel [44], with permission)

Experimental studies of pharmacological agents to decrease liver damage caused by the blood supply occlusion have demonstrated some promising results [53]. Amrinone, prostaglandin E1, pentoxifylline, dopexamine, dopamine, ulinastatin, gantaile, sevoflurane, and propofol have all been evaluated. Ulinastatin (a neutrophil-elastase inhibitor experimentally used for the treatment of septic shock, circulatory shock, and adult respiratory distress syndrome) significantly lowered postoperative enzyme markers of liver injury; however, there was no significant difference in mortality, liver failure, or postoperative complications [53–55].

Potential pharmacological hepatoprotective drugs, such as pentoxifylline, have shown promise when used as a pretreatment for a small graft in liver transplantation and may reduce the likeli-

hood of inadequate liver function in the liver remnant [56]. Pentoxifylline is a TNF $\alpha$  synthesis inhibitor found in Kupffer cells, and its usefulness has only been studied in a murine model of partial liver transplant. Acetylcysteine has also been examined for its roll in hepatoprotection [57, 58]. However, clinical trials in the perioperative treatment of patients undergoing liver transplantation have not shown an overt benefit for the patient. Other agents such as cardiotrophin-1 (an interleukin-6 cytokine), somatostatin (a beneficial agent in reducing portal pressure), FK 409 (a low-dose nitric oxide donor), and sirolimus (an immunosuppressive agent) were hepatoprotective and demonstrated improved survival in rat models [59–61]. Although these pharmacological agents are promising, their effectiveness has only been successful in animal models, and further clinical

trials in humans are needed. Other studies evaluated the early use of beta-adrenergic drugs, such as dobutamine, to augment hepatic oxygen supply and uptake in cirrhotic livers [62]. Volatile anesthetics are routinely used in the operating room and have shown additional benefits by induction of anti-inflammatory, anti-apoptotic, and anti-oxidative properties [63]. In a small study in patients undergoing liver resection with continuous inflow occlusion, preconditioning with sevoflurane not only reduced parameters of hepatic injury but also led to fewer perioperative complications. Patients with steatotic livers seemed to benefit even more from the hepatoprotective effect of sevoflurane [64]. However, some authors caution the use of volatile anesthetics as they are implicated in causing hepatic injuries ranging from transaminitis to fulminant hepatic failure [65]. Larger randomized controlled trials are required before any of these pharmacological agents can be recommended for routine clinical practice [66]. For now, adequate perfusion with maintenance of adequate portal vein to CVP gradient to ensure flow remains paramount during the reperfusion phase.

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### Small-for-Size Syndrome

There is no definite test to determine preoperatively how much hepatic tissue can be safely resected. Should the liver remnant volume (LRV) be below a certain threshold, it cannot sustain normal physiological functions and will progress into liver failure in the postoperative period approximately 3–5 days after surgery. “Small-for-size syndrome” is the term used to describe the postoperative course of jaundice, coagulopathy, encephalopathy, cerebral edema, ascites, and renal and pulmonary failure associated with this potential catastrophe [67, 68]. The pathophysiology of the syndrome is related to excessive portal venous inflow, obstructed hepatic venous outflow, metabolic and physical condition of the recipient, graft steatosis, and exposure to gut-derived endotoxin [68, 69]. The increased portal flow can lead to a rise in portal pressure and increased stress in the hepatic parenchyma that may contribute to sinusoidal endothelial cell injury and hepatocellular death [60, 61].

Prediction of liver failure is difficult and not only depends on the extent of hepatic resection but is also affected by the severity of preexisting liver disease, liver function, and patient age. The first step is to assess how much liver tissue needs to be resected in the individual patient. The consensus is that in patients with normal hepatic parenchyma, up to four segments can safely be resected (approximately 50–60%). In healthy individuals with a normal liver, resections of up to 80% have been reported without complications. A recent study questioned, however, suggested that the total remaining LRV measured by CT volumetry is more predictive than the actual number of anatomical segments resected. The analysis of 126 patients undergoing liver resection for colorectal metastases showed that 90% of the patients with less than 25% remaining volume progressed to liver failure, whereas none did with >25% of LRV [70]. Thus, the recommended minimal functional LRV undergoing extended hepatectomies should be >25% in patients with normal livers and >40% in patients with impaired liver function (steatosis, cirrhosis, fibrosis, or following chemotherapy) [71]. Patients considered unresectable, based on a too small predicted LRV (<25% in a normal liver), may benefit from hepatic artery or portal vein embolization (PVE). Selective embolization leads to considerable shrinking of the diseased areas and simultaneous hypertrophy of the LRV. PVE not only increases the volume of the remaining liver but also improves its function and decreases the incidence of postoperative hepatic dysfunction [72, 73].

Other strategies, such as splenectomy or splenic artery ligation, have been devised to decrease portal vein inflow in an attempt to avoid portal hyperperfusion and the resultant SFSS. As mentioned earlier, the use of hepatoprotective surgical techniques and pharmacological agents may prove beneficial in promoting the growth and avoiding postoperative hepatic dysfunction; however, only future clinical trials will determine their ultimate use. Lacking more specific treatment options, it is crucial to maintain adequate perfusion to the remaining liver, avoiding portal vein inflow and/or hepatic vein outflow obstruction.

## Minimal Invasive Resection

Minimally invasive liver resection is gaining popularity; however, its generalized use is limited by the ability to gain sufficient intraoperative control of bleeding and hemostasis. Due to concerns about clean resection margins and technically difficult manipulations, large tumors and tumors near the hilum are generally not considered for laparoscopic surgery. Initial attempts of laparoscopic resections were reserved for peripheral lesions, mainly on the left side [74]. As previously discussed, recent advances in surgical devices to control parenchymal bleeding in open hepatectomies have also led to increased use of laparoscopic techniques for technically more challenging hepatectomies. The Pringle maneuver can be utilized laparoscopically to control vascular inflow and parenchymal bleeding that is encountered during transaction [74, 75]. Major complications continue to be difficult access, physiologic alterations associated with pneumoperitoneum, and complications of the operative procedure necessitating conversion to an open procedure [76]. Restricted access to achieve sufficient hemostasis still limits the widespread use of minimally invasive liver surgery. However, with the use of newer surgical devices and increasing experience of surgical operators, laparoscopic liver surgery represents an effective method of surgery for more advanced liver pathology in the future.

Over the years the number of hepatic transplants and partial resections has increased mostly due to safer surgical techniques and newer pharmacological therapies. While many patients have benefited from this progress, it has also enabled the use of surgery in extremely sick patients previously deemed inoperable, thus increasing the probability of intraoperative complications. Interestingly the perioperative morbidity and mortality are still improving, most likely secondary to development of parenchymal-sparing surgical techniques, reduced blood loss, and potential hepatoprotective strategies. There is and always will be the risk of intraoperative complications, and only the foresight, skill, and cooperation of the surgical and anesthesiological teams will effectively help tackle these complications.

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## Liver Disease and its Implications for Surgery

It has been estimated that approximately 5–10% of all patients with cirrhosis of the liver will undergo surgery other than liver transplantation during the last 2 years of life [1]. These patients pose a substantial perioperative challenge to the anesthesiologist, and careful attention to the pre-operative, intraoperative, and postoperative management is required. The myriad manifestations of liver disease and its high operative risk imply that surgery should never be taken lightly in this group of patients. Alternative nonsurgical therapies should be considered whenever appropriate, and the risks and benefits of all surgical and non-surgical options should be discussed with the patient or their surrogate in depth.

Patients with advanced liver disease undergoing non-transplant surgery are at markedly increased risk of perioperative morbidity and mortality [2–7]. Del Olmo studied 135 patients with cirrhosis of the liver undergoing non-hepatic procedures and found higher blood transfusion requirements, longer

hospital stays, and more complications when compared to 86 matched controls [2]. The mortality rate was 16.3% in patients with cirrhosis compared to 3.5% in the control population.

A retrospective review of 733 patients with cirrhosis who underwent surgery other than liver transplantation by Ziser et al. found a 30-day post-operative mortality and perioperative complication rates of 11.6% and 30.1%, respectively [3]. Complications that occurred in these patients associated with increased mortality included pneumonia, ventilator dependence, infection, new-onset or worsening ascites, and cardiac arrhythmias. Independent predictors of morbidity and mortality that emerged after multivariate analysis are listed in Tables 28.1 and 28.2. This study further demonstrated an almost exponential relationship between the number of independently predictive risk factors and the risk of perioperative complications (Fig. 28.1). The risk of complications increased from 9.3% of patients with one risk factor, to 63% of patients with four or five risk factors, to 100% of patients with seven or eight risk factors.

## Emergency Surgery

The mortality risk increases two- to threefold when cirrhotic patients undergo emergency surgery, particularly when the procedure involves the abdomen or is necessary because of trauma [4, 8–11]. Mansour et al. observed that the mortality rate in emergency vs. elective abdominal surgery in cirrhotics was 50% vs. 18%, respectively [9].

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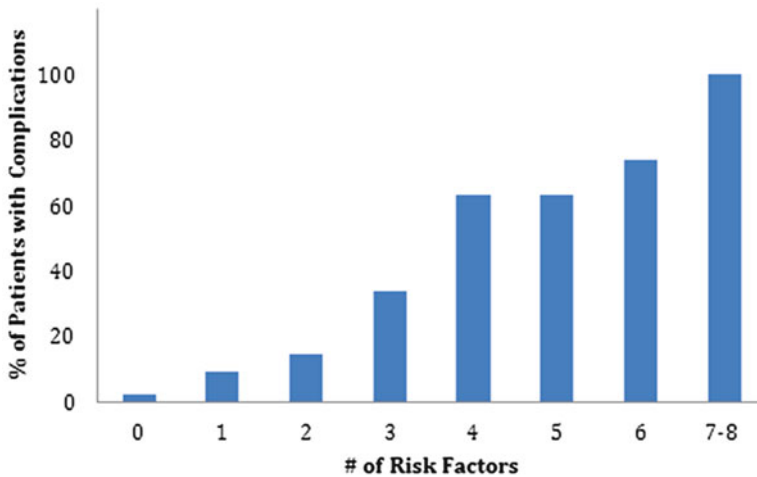
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**Table 28.1** Independent predictors of postoperative complications in cirrhotic patients undergoing surgery [3]

Patient factors
Elevated serum creatinine (SCr)
Preoperative infection
Chronic obstructive pulmonary disease (COPD)
American Society of Anesthesiology (ASA) physical status 4 or 5
Disease factors
Etiology of cirrhosis other than primary biliary cirrhosis (PBC)
Child-Turcotte-Pugh (CTP) class B or C
Preoperative upper gastrointestinal (UGI) bleeding
Ascites
Surgical factors
Invasiveness of procedure
Intraoperative hypotension

**Table 28.2** Independent predictors of postoperative mortality in cirrhotic patients undergoing surgery [3]

Patient factors
Male gender
Preoperative infection
American Society of Anesthesiology (ASA) physical status 4 or 5
Disease factors
Etiology of cirrhosis other than primary biliary cirrhosis (PBC)
Child-Turcotte-Pugh (CTP) class B or C
Ascites
Surgical factors
Thoracic surgery



**Fig. 28.1** Effect of number of risk factors on perioperative complication rate [3]

Teh et al. found that emergency surgery was the only independent predictor of postoperative hospital duration and that 100% of cirrhotic patients who underwent emergency surgery died [4]. Demetriades et al. retrospectively reviewed outcomes in 40 cirrhotic patients undergoing laparotomy after trauma [11]. Complication rates, mean surgical ICU length of stay, mean hospital charges, and overall mortality (45% vs. 24%) were all significantly greater in the cirrhotic patients compared to controls. Both the Model for End-Stage Liver Disease (MELD) score and/or Child-Turcotte-Pugh (CTP) class (see below) are reliable

predictors of increased risk of perioperative morbidity and mortality in cirrhotic patients undergoing emergency surgery [4, 9]. A summary of the data related to postoperative mortality rates by surgical procedures in the patient with cirrhosis is presented in Table 28.3.

### Perioperative Risk Assessment

Assessment of perioperative risk in patients with liver disease is complex. In addition to the urgency and type of surgery planned, consideration must

**Table 28.3** Mortality rates associated with specific types of surgery in patients with cirrhosis

Type of procedure	Overall mortality rate (%)
Appendectomy [12]	9
Bariatric surgery <sup>a</sup> [13]	10
Cardiac surgery [14, 15]	16–25
Cholecystectomy	
Open, CTP class C [16]	23–50
Laparoscopic, CTP class A and B only [17, 76]	0–1
Endoscopic sphincterotomy for common bile duct stones [77]	7
Esophageal surgery [18, 78, 79]	17–26
Herniorrhaphy [18]	
Incisional	6
Umbilical, elective	2
Umbilical, emergency	11
Laparotomy for trauma [11]	45
Total knee arthroplasty [80]	0

<sup>a</sup>Includes perioperative and late deaths from liver failure in 91 patients who continued with bariatric surgery despite the finding of unexpected cirrhosis  
CTP Child-Turcotte-Pugh

be given to the etiology, severity, and chronicity of the patient's disease [19]. Patients with liver disease may also have comorbidity unrelated to their hepatic dysfunction that adversely affects surgical outcome, such as chronic obstructive pulmonary disease (COPD) or diabetes mellitus. The most common postoperative adverse events are bleeding, infection, pneumonia, worsening liver failure, and renal failure [20].

Most studies have examined perioperative risk in the patient with cirrhosis, and little information is available about less severe liver disease or specific liver diseases. However, the etiology of the liver disease appears to be less important than the degree of preoperative hepatocellular dysfunction. Severe liver failure is estimated to be the proximate cause of as many as 50% of postoperative deaths in patients with advanced liver disease undergoing non-hepatic surgery [18].

A number of conditions pose such an increased risk of postoperative morbidity and mortality that they are generally recognized as contraindications to elective surgery (Table 28.4) [5, 21]. The

**Table 28.4** Absolute contraindications to elective surgery in patients with liver disease [5, 21]

Fulminant hepatic failure
Acute viral or alcoholic hepatitis
Child-Turcotte-Pugh class C cirrhosis
Severe coagulopathy
PTT >3 s above control despite treatment
Platelet count <50,000/mm <sup>3</sup>
Severe extrahepatic complications
Hypoxemia
Cardiomyopathy, heart failure
Acute kidney injury

most obvious disease states include acute viral or alcoholic hepatitis, symptomatic active hepatitis, and fulminant liver failure. Cirrhotic patients in CTP class C (see below) should not undergo elective surgery. Severe coagulopathy that is not readily correctable, including a prothrombin time (PT) more than 3 s above control or a platelet count <50,000/mm<sup>3</sup>, also contraindicates elective surgery, as do comorbid conditions such as congestive heart failure, acute renal failure, and hypoxemia.

## Preoperative Screening for Liver Disease

Routine screening laboratory testing for hepatic disease in an otherwise asymptomatic and healthy surgical candidate is neither cost-effective nor helpful. Not only is the prevalence of liver disease low in the general population, but an isolated abnormal laboratory test is of questionable significance and unlikely to change management or outcome. The Mayo Clinic gave up routine preoperative screening in 1988 after only 0.3% of 3,700 healthy, asymptomatic patients presenting for elective surgery were found to have an abnormality in their liver enzymes. Of those laboratory abnormalities, almost 20% were predictable based on history and physical exam, and none were associated with adverse outcome [22].

Patients presenting for preoperative assessment may have known liver disease, or it may be revealed by a careful history and physical exam. When the preoperative evaluation reveals signs

**Table 28.5** Modified Child-Turcotte-Pugh score for cirrhosis

Variable	Point value <sup>a</sup>		
	1	2	3
Ascites	None	Slight	Moderate
Albumin (mg/dL)	<2	2–3	>3
Prothrombin time (PT)			
Seconds >control	<4	4–6	>6
INR	<1.7	1.7–2.3	>2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

<sup>a</sup>Class A=total score 5–6, class B=total score 7–9, class C=total score 10–15. The modified Child-Turcotte-Pugh score utilizes the international normalized ratio (INR) in lieu of the PT. Encephalopathy grades: 1=constructional apraxia; 2=asterixis, confabulation; 3=stupor; 4=coma

or symptoms of significant hepatic dysfunction in a patient without such a diagnosis, additional workup is required before proceeding to elective surgery. This may include liver function tests, hepatitis and drug screening, right upper quadrant ultrasound, complete blood count with platelet count, electrolytes, blood urea nitrogen (BUN), serum creatinine (SCr), coagulation studies, and other tests as indicated.

### Acute Liver Disease

Over the last four decades, the poor outcome after surgery in patients with acute alcoholic and viral hepatitis has been well documented [19, 23, 24]. As most cases of acute hepatitis are self-limited, all but the most emergent procedures should be postponed until the patient has made a full recovery. This implies resolution of active inflammation as measured by transaminase levels or cellular infiltration on liver biopsy. If the decision is made to proceed with surgery after recovery, these patients should be carefully managed preoperatively to medically optimize any coexisting systemic derangements.

### Chronic Liver Disease

In a study of the natural history of compensated cirrhosis, 47% of patients eventually developed at least one major complication, including ascites, jaundice, hepatic encephalopathy, or gastrointestinal hemorrhage. Compared to patients with no

evidence of major complications, the median survival time decreased significantly from 8.9 to 1.6 years [25]. During the preoperative visit, it is essential to elucidate whether the cirrhotic patient has a history of one of these key complications. This provides insight into the patient's overall prognosis as well as the risk of postoperative morbidity and mortality.

### Systems for Assessing the Severity of Liver Disease

Assessment of the risk of postoperative morbidity and mortality is equally important in patients with well-compensated liver disease. There are two disparate but well-established risk assessment systems that may be helpful in decision making for the patient with liver disease undergoing non-hepatic surgery.

#### Child-Turcotte-Pugh Classification

A long-standing and widely used tool for the assessment of disease severity and overall mortality risk in patients with cirrhosis is the CTP classification (Table 28.5). A score of 1, 2 or 3 is assigned based on the degree of abnormality in each of five parameters, including serum bilirubin, serum albumin, PT in seconds above normal, grade of encephalopathy and severity of ascites. On this basis, the minimum score is 5 and the maximum score is 15. A score of 5–6 is assigned to CTP class A, 7–9 to CTP class B, and 10–15 to CTP class C.

Multiple studies dating back to the 1980s and 1990s have shown the usefulness of the CTP

$$\text{MELD} = 3.8[\text{Ln SB}] + 11.2[\text{Ln INR}] + 9.6[\text{Ln SCr}] + 6.4$$

SB = serum bilirubin in mg/dL, INR = International Normalized Ratio of prothrombin time; SCr = serum creatinine in mg/dL

Ln is the natural logarithm of each variable

A number of calculators are available on-line for calculating MELD

**Fig. 28.2** Model for End-Stage Liver Disease (MELD) score

classification in predicting perioperative morbidity and mortality. In these studies, perioperative mortality rates were approximately 10% in CTP class A patients, 30% in CTP class B patients, and as high as 82% in CTP class C patients [9, 26]. However, a more recent retrospective review by Telem et al. published in 2010 found significantly lower postoperative mortality rates of 2, 12, and 12% for CTP class A, B, and C, respectively [27]. It is reasonable to assume that mortality rates have declined because of advances in surgical technique, anesthetic management, and postoperative care, but additional research is warranted to see if these lower rates are reproducible. Until then, general guidelines hold that patients with CTP class A disease have minimal risk in undergoing elective surgery and may proceed assuming no other contraindications. Those with CTP class C disease have significantly increased risk of operative mortality, and as such, elective surgery is contraindicated. Patients with CTP class B disease fall into an intermediate category and must be evaluated on an individual basis; consideration may be given to elective surgery if preoperative medical interventions can improve their status or surgery provides a substantial benefit.

There are a number of risk factors that are not taken into consideration by the CTC classification. For example, even in patients with CTP class A liver disease, preoperative portal hypertension is an independent predictor of postoperative complications such as jaundice, encephalopathy, and ascites [28]. Preoperative placement of a transjugular intrahepatic portosystemic shunt (TIPS) may decrease perioperative complications in these patients [29].

### Model for End-Stage Liver Disease

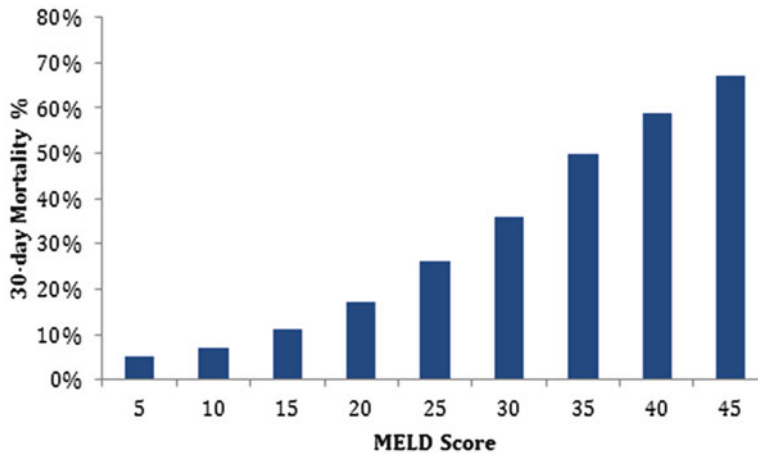
A more recently developed tool, the MELD is based on a complex nomogram that incorporates exponentials of three variables: total bilirubin, SCr, and INR (international normalized ratio of the prothrombin time). Scores start at 6 and are capped at 40 with higher scoring patients at greater risk of 3-month mortality (Fig. 28.2).

Although originally developed to estimate 3-month survival in patients undergoing the TIPS procedure, the MELD score has become the key indicator for priority listing for patients considered for liver transplantation. It has also been validated in assessing prognosis across a broader range of liver diseases and severity, as well as in acute variceal bleeding and acute alcoholic hepatitis [30–33].

More recently, the MELD score has shown promise as a tool to predict perioperative morbidity and mortality in patients with liver disease undergoing abdominal, orthopedic, cardiovascular and other non-transplant surgeries [4, 10, 34, 35]. Northup et al. retrospectively reviewed 140 non-transplant surgeries performed on patients with cirrhosis and found the MELD score to be an independent predictor of 30-day mortality (Fig. 28.3). As the preoperative MELD increases from 5 to 15, 20, 25, and 45, the risk of postoperative 30-day mortality increases from 5 to 11%, 17, 26, and 67%, respectively [36].

Hanje and Patel suggest that patients with a MELD score of <10 pose an acceptable risk and may undergo elective surgery; whereas those with scores >15 are at significantly increased risk and should avoid elective surgery. Patients with a MELD score between 10 and 15 should be evaluated individually with particular attention





**Fig. 28.3** MELD score and risk of 30-day mortality after non-transplant surgery in patients with cirrhosis [36]

paid to the urgency and type of surgery to be performed [37].

The MELD score has been compared with the CTP classification in predicting postsurgical outcome. In general there is good correlation between these two scoring systems in predicting perioperative morbidity and mortality [10, 34, 38]. One study found the MELD score to be superior to the CTP in predicting mortality after intra-abdominal surgery [35], suggesting that the MELD score avoids the CTP score's dependence on subjective criteria such as ascites and encephalopathy.

However, it is important to remember that the risk of perioperative morbidity and mortality increases with increasing severity of liver disease, regardless of which scoring system is used.

### Other Measures of Hepatic Function

Several quantitative tests of liver function have been evaluated as predictors of perioperative morbidity and mortality in patients with liver disease. These include the aminopyrine breath testing, indocyanine green clearance, galactose elimination capacity, and the rate of metabolism of lidocaine to monoethylglycineylidide [5]. While these tests do provide a measure of prediction, their prognostic and practical utility is not necessarily superior to the CTP classification or MELD score and is therefore not clinically used for this purpose.

## The Impact of the Surgical Procedure

### Abdominal Surgery

The postoperative mortality of patients with cirrhosis undergoing non-hepatic abdominal surgery is extraordinarily high with an estimated risk of 30% [8, 26]. Neeff et al. retrospectively analyzed data of 138 cirrhotic patients undergoing non-hepatic intra-abdominal and abdominal wall surgeries and found an overall perioperative mortality rate of 28%. Perioperative mortality was significantly higher after intra-abdominal surgery than those performed on the abdominal wall, (35% vs. 8%, respectively) [8].

### Laparotomy

Laparotomy is known to be associated with a greater reduction in liver blood flow than non-abdominal surgery, perhaps due to retraction on abdominal viscera leading to reflex vasodilation and hypotension [39]. In patients with prior abdominal surgery, vascular adhesions may result in increased intraoperative bleeding, which may further decrease hepatic blood flow and exacerbate ischemic liver injury [5]. The presence of portal hypertension contributes to hepatic venous engorgement and bleeding during intra-abdominal

**Table 28.6** Laparoscopic vs. open cholecystectomy [44]

	Laparoscopic cholecystectomy	Open cholecystectomy	<i>p</i>
Operative times (min)	123.3	150.2	<0.042
Intraoperative blood loss (mL)	113	425.2	<0.015
Hospital length of stay (days)	6	12.2	<0.001

Data compiled from a meta-analysis of four studies comparing laparoscopic with open cholecystectomy in patients with hepatic cirrhosis [44]. For explanation, see text

surgery, and preoperative decompression of portal pressure by a TIPS procedure can decrease the incidence of postoperative complications [35].

## Cholecystectomy

Gallstones are twice as prevalent in patients with cirrhosis than in the general population, and it is not uncommon for these patients to present for cholecystectomy [40]. Open cholecystectomy has long been known to be associated with an unacceptable mortality in patients with cirrhosis, reported as high as 26–50% [16,41]. Laparoscopic cholecystectomy was initially accepted because it was initially believed that bleeding might be more easily controlled by open exposure. There is increasing evidence to support the safety of a laparoscopic approach, particularly in patients with CTP class A or B disease and those with well-compensated cirrhosis and no portal hypertension [17, 42, 43]. In a 2003 meta-analysis, Puggioni and Wong reviewed four articles comparing laparoscopic vs. open cholecystectomy in patients with cirrhosis and found that the laparoscopic approach was associated with significantly shorter operative times, intraoperative blood loss, and hospital length of stay (Table 28.6) [44]. These findings were confirmed in a recent prospective randomized trial of 110 cirrhotic patients. Compared to the open procedure, laparoscopic cholecystectomy was associated with significantly decreased operative time, blood transfusion, postoperative morbidity, and hospital length of stay [45].

Attempts have been made to estimate perioperative risk in patients requiring cholecystectomy.

A retrospective analysis compared patients with cirrhosis undergoing cholecystectomy with case-matched controls. Factors predictive of postoperative morbidity included preoperative elevation of the components of the MELD score (INR, serum bilirubin, and SCr) as well as thrombocytopenia. Patients with a preoperative MELD score higher than 8—a relatively low score—had a significantly greater risk of postoperative morbidity [34].

## Bariatric Surgery

Obesity is associated with an increased incidence of nonalcoholic fatty liver disease (NAFLD). This is a spectrum that may begin as benign fatty liver (steatosis) but in a small fraction of patients progresses to an inflammatory response to fat called nonalcoholic steatohepatitis (NASH), which may lead to scarring and ultimately, in about 20% of cases, frank cirrhosis [46]. The incidence of obesity and its surgical treatment are increasing, and NAFLD (fatty liver, NASH and cirrhosis) is increasingly diagnosed at the time of bariatric surgery.

A recent review of liver histology from 12 studies of 1,620 severely obese patients who underwent bariatric surgery revealed steatosis in 85–98%, NASH in 24–98% and cirrhosis in 1–7% [47]. Data are limited, but mortality in cirrhotic patients who undergo bariatric surgery is thought to be increased [13]. However, there is evidence that successful bariatric surgery and subsequent weight loss may result in significant improvement in NAFLD, including NASH [48–50].

## Cardiothoracic Surgery

### Cardiac Surgery with Cardiopulmonary Bypass

Cardiac surgery with cardiopulmonary bypass (CPB) in cirrhotic patients is associated with substantially higher perioperative morbidity and mortality. Risk factors for hepatic decompensation following cardiac surgery include total CPB time, perioperative pressor requirements, and the use of non-pulsatile vs. pulsatile CPB [5]. Existing coagulopathy is aggravated when CPB induces additional platelet dysfunction, fibrinolysis, and hypocalcemia.

Klemperer et al. studied 13 cirrhotic patients who underwent coronary artery bypass grafting (CABG), valve replacement, or both. Five patients had CTP class B disease, and all these experienced major complications and only one survived. The remaining eight patients had CTP class A disease and fared better: 25% experienced major complications and none died [51]. Postoperative mortality was related to postoperative infection and bleeding rather than cardiac dysfunction.

Both CTP class and MELD score are reliable predictors of perioperative morbidity and mortality after cardiac surgery with CPB. Mortality rates vary between 3.2 and 11% with CTP class A cirrhosis; 18 and 42% with CTP class B; and 67 and 100% with CTP class C disease, which is considered a contraindication to cardiac surgery [38, 52].

### Off-Pump Cardiac Surgery

No randomized controlled trials exist comparing cardiac surgery with CPB to off-pump CABG. There are anecdotal data of successful outcomes in CTP class A and B patients undergoing off-pump CABG. Ben Ari et al. reported a patient with CTP class C cirrhosis who survived off-pump CABG before undergoing liver transplantation [53]. Given these data, it appears prudent to evaluate the patient with advanced cirrhosis and cardiac disease for the least invasive options such as off-pump procedures, angioplasty, and valvuloplasty.

### Thoracic Surgery

There are few data on perioperative morbidity and mortality for patients with cirrhosis

undergoing thoracic surgery. In a small retrospective review of 17 cirrhotic patients who underwent surgery for non-small cell lung cancer, patients with CTP class A disease experienced no morbidity or mortality, whereas those with CTP class B disease had morbidity and mortality rates of 30.8 and 7.6%, respectively [54].

## Preoperative Evaluation and Management

Common complications of liver disease include ascites, hematologic abnormalities, pulmonary disease, and renal and neurologic dysfunction. The most appropriate way to prevent postoperative morbidity is to identify and treat such complications prior to surgery. We will present symptoms and complications of liver disease and their relevance for patients undergoing non-hepatic surgery. The manifestations of liver disease are discussed in more detail elsewhere (Chapter 1) in this book.

### Ascites and Fluid and Electrolyte Imbalance

Ascites elevates the diaphragm and decreases functional residual capacity and is associated with basal atelectasis and sympathetic pleural effusions that further compromise oxygenation and ventilation in the perioperative period.

Tense ascites may also result in increased intra-abdominal and renal vein pressure, which decreases renal blood flow and increases the risk of perioperative renal dysfunction. The presence of ascites also increases the risk of postoperative wound dehiscence or abdominal wall herniation.

In patients without edema or in those for whom there is not enough time for a course of diuretics, it may be helpful to drain tense ascites preoperatively or during laparotomy. Paracentesis must be performed cautiously, however, given the risk of inducing acute intravascular hypovolemia and hypotension which may then lead to further liver injury and renal dysfunction.

Many patients with liver disease are prescribed the aldosterone antagonist, spironolactone, which

is very effective in maintaining a modest potassium-sparing diuresis. However, its onset and offset are slow (2–3 days), and its potassium-sparing effect in acute renal insufficiency may provoke acute hyperkalemia. If possible, spironolactone therapy should be discontinued 3–4 days before surgery.

Hyponatremia is common in patients with severe liver dysfunction, although usually not symptomatic. Treatment including fluid restriction may be warranted preoperatively if the serum sodium concentration is less than 120–125 mmol/L. Excessively rapid serum sodium elevation can rarely result in a devastating neurologic complication, central pontine myelinolysis. There is merit to the adage to correct hyponatremia at a rate similar to that with which it developed.

### **Coagulopathies and Other Hematologic Abnormalities**

The coagulopathy associated with liver disease is multifactorial, but dominated by impaired synthesis of the vitamin K-dependent coagulation factors, factors II, VII, IX, and X. This is exacerbated by malnutrition, cholestasis, and use of antibiotics such as neomycin that eliminate the gut bacteria that produce vitamin K. Inactive forms of the procoagulants are produced, known as proteins induced by vitamin K absence. The severity of hepatocellular disease is directly reflected by the degree of prolongation of the prothrombin time (PT) or INR. The partial thromboplastin time (PTT) is usually preserved until a late stage or unless other processes affect hemostasis, for example, disseminated intravascular coagulation (DIC).

Moderate thrombocytopenia (platelet count 50–75,000 mm<sup>3</sup>) is very common and a consequence of increased breakdown (hypersplenism secondary to portal hypertension), impaired production (low levels of hepatically synthesized thrombopoietin), or acute complications such as gastrointestinal (GI) bleeding or DIC. Patients with coexisting severe renal dysfunction may also have a qualitative platelet defect because of ure-

mic suppression of release of platelet-activating von Willebrand factor–factor VIII complex.

Dysfibrinogenemia occurs in advanced liver failure and implies abnormal fibrinogen function even though plasma levels may be normal or even elevated. The latter is more likely to occur in chronic hepatitis, hepatocellular carcinoma, or cholestasis. About 60–70% of fibrinogen is non-functional, with abnormal alpha chains and a high sialic acid content, similar to that produced by immature hepatocytes.

Anemia is common and may occur via several mechanisms including acute or chronic blood loss, malnutrition, and bone marrow suppression. Chronic alcoholism may be associated with macrocytic anemia.

The liver is the source of the endogenous anticoagulants, the vitamin K-dependent protein C and protein S produced by hepatocytes and the vitamin K-independent antithrombin III produced in the endothelium. Impaired synthesis of any of these proteins may create a prothrombotic state. Hypercoagulability is characteristic of primary biliary cirrhosis, primary sclerosing cholangitis, and hepatocellular carcinoma. It is not uncommon for hypercoagulability and hypocoagulability to coexist. The former is often intrahepatic, predisposing to portal or hepatic vein thrombosis, whereas the latter is usually extrahepatic with increased GI and surgical bleeding.

Fibrinolysis becomes disordered because of impaired synthesis of both fibrinolysins (notably plasminogen) and antifibrinolysins (histidine-rich glycoprotein, thrombin-activatable fibrinolysis inhibitor). However, the most important fibrinolysin, tissue plasminogen activator (tPA), is synthesized in the endothelium independently of liver function.

### **Preoperative Correction of Coagulopathy**

An attempt to correct a prolonged preoperative PT or INR may be made using parenteral vitamin K and/or fresh frozen plasma (FFP). Vitamin K administration takes 12–18 h to become fully effective in restoring factor VII levels, and the administration of several units of FFP represents a substantial volume load that may induce acute pulmonary congestion or even right heart failure.

Patients with severe liver disease may become refractory to vitamin K or FFP transfusion.

Prothrombin complex concentrates contain factors II, VII, IX, and X as well as small quantities of protein C and protein S to provide “hemostatic balance.” They are advocated for the rapid (10 min) reversal of a prolonged prothrombin time induced by coumadin. In a German study, 22 patients with severe liver disease were given a virus-inactivated PCC to achieve rapid hemostasis for bleeding [55]. What was described as “very good” hemostasis was achieved in 75% of patients without adverse effects or evidence of viral disease transmission. Further studies are clearly needed.

Cryoprecipitate may also be useful as it contains a significant amount of fibrinogen and von Willebrand factor in addition to clotting factors but with minimal volume.

Several studies have demonstrated that administration of recombinant factor VIIa is a safe and effective method of correcting coagulopathy in patients with cirrhosis [56–58]. However, the drug is very costly, and recombinant factor VIIa did not show a benefit in reducing the requirement for blood transfusion in a study of patients undergoing partial hepatectomy [59].

Patients with a quantitative platelet deficiency should receive preoperative platelet transfusion to raise counts to 100,000/mm<sup>3</sup> or as appropriate for the procedure type and risk of blood loss.

8-Desamino-D-arginine vasopressin (DDAVP, desmopressin) stimulates the release of von Willebrand factor VII complex from endothelium and is useful to correct coexistent uremic platelet dysfunction.

## Pulmonary Disease

Preoperative assessment of pulmonary function may be beneficial, particularly in patients with advanced liver disease. Such assessment might reasonably start with simple spirometry and an arterial blood gas analysis. Dyspnea and hypoxemia are common in advanced liver disease and may be caused by a number of pulmonary processes including hepatopulmonary syndrome

(HPS), portopulmonary hypertension (PPH), and hepatic hydrothorax. Pulmonary complications of liver disease are discussed in more detail elsewhere (Chapter 22) in this book.

### Hepatopulmonary Syndrome

HPS is defined as an increased alveolar-arterial (A-a) gradient and widespread intrapulmonary arteriovenous vasodilation in the setting of chronic liver disease. It may occur in as few as 4% or as many as 47% of patients with end-stage liver disease [60, 61]. Unique manifestations of HPS include upright dyspnea (platypnea) and hypoxemia relieved by lying flat (orthodeoxia).

Type I or minimal pattern HPS has a very finely dispersed radiographic pattern and is generally responsive to an increase in supplemental oxygen. Type II HPS is characterized by discrete arteriovenous malformations, responds poorly to supplemental oxygen, and represents a very high risk for surgery.

The only recourse for severe HPS of either type is liver transplantation.

### Portopulmonary Hypertension

PPH is defined as a mean pulmonary artery pressure greater than 25 mmHg in a patient with coexisting portal hypertension and no other cause of pulmonary hypertension. It is rare, occurring in 2–4% of patients with end-stage liver disease [62].

A number of therapeutic options exist for modulating elevated pulmonary artery pressure in the perioperative period. These include inhalation of nitric oxide (a potent, selective pulmonary vasodilator that activates cyclic GMP) or iloprost (a prostacyclin analog that activates cyclic AMP), or systemic administration of epoprostenol (prostacyclin), sildenafil (a phosphodiesterase V inhibitor that delays cyclic GMP breakdown), or bosentan (an endothelin antagonist). These drugs may be used individually but are additive in effect when used simultaneously.

### Hepatic Hydrothorax

Hepatic hydrothorax is estimated to occur in approximately 5% of patients with end-stage liver disease. Preoperative drainage is generally not recommended as the associated hypoxemia is

mild, and the effusion tends to re-accumulate quickly [63]. Chest tube placement may be helpful during the postoperative period if a large pleural effusion impairs ventilator weaning.

## Renal Dysfunction

### Pathways to Acute Kidney Injury

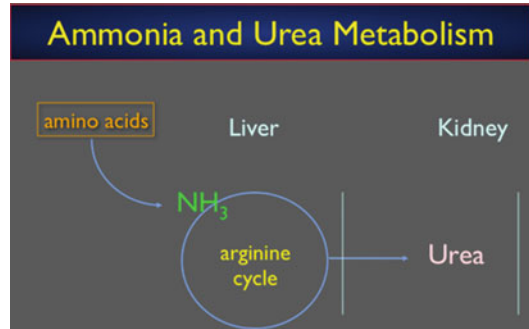
Patients with liver disease are at risk of perioperative acute kidney injury (AKI) by at least five distinct pathways, although these often coexist and overlap in a complex fashion. There is a constant risk of superimposed acute ischemic or nephrotoxic renal injury with resultant classic acute tubular necrosis. Patients may develop hepatorenal syndrome (HRS), which manifests as a refractory prerenal syndrome. Severe tense ascites may itself be associated with a form of HRS or can lead to a true compartment syndrome with renal compression. Severe obstructive jaundice is associated with a high risk of concomitant renal injury. Finally, chronic kidney disease increases the renal risk of perioperative AKI.

### Evaluation of Renal Function

In patients with advanced liver disease, traditional laboratory tests such as BUN and SCr may be misleading as markers of severity of renal dysfunction or AKI. Normally, amino acids are deaminated in the liver, producing ammonia, which is converted to urea in the arginine cycle (Fig. 28.4). With liver disease, this conversion is depressed, ammonia accumulates, and urea production is markedly decreased. BUN therefore markedly underestimates prerenal states caused by hypovolemia or gastrointestinal (GI) bleed. With AKI, even moderate elevations of BUN indicate severe injury. Similarly, SCr may be low because of depleted muscle mass and/or increased total body water.

### Superimposed Acute Kidney Injury

The hemodynamic derangements associated with anesthesia and surgery may increase the risk of renal hypoperfusion and exacerbate new or existing renal dysfunction. Nephrotoxic medications,

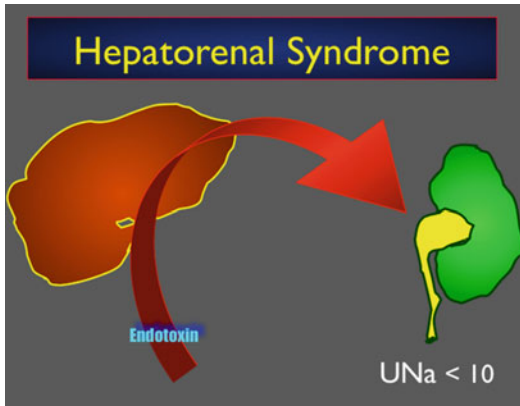


**Fig. 28.4** Schematic of ammonia and urea metabolism. All amino acids undergo deamination in the liver, whereby the  $-NH_2$  group is split off and converted into ammonia ( $NH_3$ ). Ammonia enters the arginine cycle and is converted to urea, which is excreted in the urine. In acute kidney injury (AKI), urea accumulates and the blood urea nitrogen (BUN) rises. With an acute gastrointestinal bleed (e.g. variceal bleed), blood protein is absorbed and urea production increases. In acute liver injury, the arginine cycle is impaired and ammonia is not converted to urea. Ammonia accumulates and BUN remains very low, even in the face of AKI or variceal bleeding

diuretics, large-volume paracentesis, gastrointestinal bleeding, or infection may increase this risk further. When planning the anesthetic management for these patients, it is important to minimize potential insults and maintain adequate intravascular volume during the perioperative period.

There is evidence that preoperative administration of human albumin may provide some renal protection in high-risk patients. Sort et al. randomized 126 patients with cirrhosis and spontaneous bacterial peritonitis to treatment with an intravenous antibiotic (cefotaxime) alone or antibiotic plus human albumin (1–1.5 g/kg) on days 1 and 3 [64]. The incidence of AKI decreased significantly from 33 to 10%, hospital mortality from 29 to 10%, and 3-month mortality from 41 to 22% with the use of albumin. Plasma renin activity was decreased in the albumin group, suggesting that it achieved a more effective arterial blood volume. A small, randomized control trial by Singh et al. found that midodrine (an oral alpha-adrenergic agonist) may be as effective as albumin in preventing paracentesis-induced circulatory dysfunction, and actually increased urine flow and natriuresis [65].





**Fig. 28.5** One of the proposed mechanisms of hepatorenal syndrome (HRS). Porto-systemic shunting facilitates the absorption of endotoxin that bypasses the hepatic reticulo-endothelial filter and enters into the systemic circulation. Kupffer cell function is impaired so that any endotoxin is not eliminated. Endotoxin makes its way to the renal circulation, where it causes disruption of circulatory homeostasis, as well as direct cellular toxicity. The kidney reacts by avidly conserving sodium, so that urine sodium (UNa) is typically  $< 10$  mEq/L

### Hepatorenal Syndrome

HRS is a poorly understood, complex, multifactorial disorder that is often precipitated by complications in a patient with advanced liver disease. One proposed mechanism is the absorption of endotoxin into the systemic circulation via porta-systemic shunts, exacerbated by Kupffer cell and hepatic reticuloendothelial dysfunction (Fig. 28.5). Endotoxin is directly nephrotoxic to the tubular epithelium and also induces disordered renal perfusion.

Whatever the triggering factor, progressive splanchnic vasodilation occurs [66], ultimately with reflex renal vasoconstriction and sodium retention so that the patient develops oliguria with a very low urine sodium (characteristically,  $< 10$  mEq/L). The oliguria is unresponsive to aggressive hydration, akin to a resistant prerenal syndrome. It is noteworthy that the pathogenesis is related to the milieu and kidney anatomy is unchanged. It was noted many years ago that normal kidney function is restored when a kidney is donated from a patient dying of liver failure into a recipient with normal liver function.

There are two descriptive forms of HRS (Table 28.7). Type 1 HRS is associated with shock or spontaneous bacterial peritonitis and rapidly progressive. Within a couple of weeks, the SCr increases to more than 2.5 mg/dL, and mortality is 50% within a month of onset. There has been some success in Europe in reversing HRS 1 with the combination of the vasoconstrictor terlipressin (a vasopressin analog) and albumin [67], but the definitive therapy is liver transplantation [68].

Type 2 HRS is associated with refractory ascites (see below), SCr increases slowly to about 1.5 mg/dL, and the median survival is about 6 months. These patients respond very well to the TIPS procedure, which should be considered as a preoperative intervention for non-transplant surgery.

### Ascites

Severe, tense ascites may result in a compartment syndrome when abdominal pressure is elevated  $> 25$  cmH<sub>2</sub>O. This impairs cardiac output and renal blood flow, and by inducing renal compression and venous hypertension results in progressive impairment of renal function.

Restoring cardiac output does not reverse the situation, and only decompressing the elevated intra-abdominal pressure relieves it. A preoperative TIPS procedure may be very helpful.

### Obstructive Jaundice

Bile salts detoxify gut bacterial endotoxin. When obstructive jaundice develops, bile salt excretion is impaired and endotoxin may enter the portal system. Because of portosystemic shunting and Kupffer cell dysfunction, endotoxin gains entry into the systemic circulation including the kidneys where it acts as a direct tubular toxin and impairs renal blood flow. Preoperative bile salt administration with sodium deoxycholate has been demonstrated not only to decrease endotoxemia occurring in obstructive jaundice [69] but also to provide perioperative renal protection [70].

**Table 28.7** Characteristics of types of hepatorenal syndrome (HRS)

Type	HRS 1	HRS 2
Time course	Rapidly progressive	Slowly progressive
Serum creatinine (SCr)	SCr >2.5 mg/dL in 2 weeks	SCr >1.5 mg/dL
Complicates	Shock, SBP	Refractory ascites
Outcome	Mortality 50% in 1 month	Median survival 6 months
Treatment	Terlipressin + albumin Liver transplantation	TIPS

SBP spontaneous bacterial peritonitis; TIPS Transjugular intrahepatic portosystemic shunt Terlipressin is a vasopressin analog not available in the United States

## Neurologic Dysfunction

### Hepatic Encephalopathy

Hepatic encephalopathy is the most important neurologic complication of severe liver disease and may range from mild confusion to deep coma. Elevated arterial ammonia is commonly associated with abnormal central nervous system (CNS) function, but it is a marker of disordered protein metabolism rather than a primary etiologic factor. Acute encephalopathy may be precipitated by any number of additional factors that are likely to occur in the perioperative period, including hypovolemia, hypoglycemia, gastrointestinal bleeding, renal failure, active infection and sedatives, or opioids used perioperatively [21].

One important phenomenon is nonionic diffusion trapping of ammonia. In an acidic milieu, ammonia gains a hydrogen ion to become ionized ammonium ( $\text{NH}_4^+$ ) that cannot cross lipid membranes. In an alkalotic milieu, ammonium loses the hydrogen ion to become ammonia, which, as it is nonionized, freely crosses lipid membranes and enters the CNS. Whether or not this is the precise mechanism, encephalopathy worsens in the presence of alkalosis. Many patients with advanced liver disease have secondary hyperaldosteronism, characterized by hypokalemic alkalosis that can exacerbate hepatic encephalopathy.

Patients with acute encephalopathy should have elective procedures postponed until their mental status returns to baseline. Precipitating

factors of encephalopathy should be identified and corrected. Metabolic alkalosis associated with hypokalemia should be treated by careful correction with potassium chloride; in severe situations, dilute (0.1 N) hydrochloric acid has been infused via a central line [71]. Additional treatment options include efforts to decrease absorption of gut protein by oral lactulose, titrated to 3–4 soft stools per day or oral rifaximin in patients that are intolerant of lactulose [72]. Protein restriction, although used in the management of encephalopathy, is not supported by clinical evidence and may complicate wound healing in the already malnourished patient.

### Alcohol Encephalopathy

It has been estimated that 20% of heavy drinkers develop alcoholic hepatitis and 25% develop cirrhosis [73]. The National Institute on Alcohol Abuse and Alcoholism has estimated that 44% of all deaths from liver disease in 2003 were attributable to alcohol [74]. When the patient with alcoholic liver disease presents for surgery, a history of current or recent alcohol abuse indicates a very high risk of acute withdrawal and delirium tremens in the perioperative period. Patients with acute alcoholic intoxication should not be subjected to elective surgery because of sensitivity to all sedative agents, risk of aspiration, and impaired platelet aggregation [1]. Wernicke's encephalopathy (dementia, ataxia, ophthalmoplegia) is a complication of chronic alcoholism induced by thiamine deficiency and may benefit from its preoperative supplementation.

## Specific Disease Entities

### Hereditary Hemochromatosis

Hereditary hemochromatosis is an autosomal recessive disorder in which mutations of the HFE or other genes cause increased intestinal iron absorption and its subsequent deposition in tissues such as the liver, heart, pancreas, and pituitary. In addition to liver disease, a number of additional clinical manifestations affect morbidity and mortality in the perioperative period, including dilated cardiomyopathy, heart failure and conduction disturbances, diabetes mellitus, and an increased risk of certain infections. Patients should be carefully screened for the presence of these manifestations and medically optimized prior to undergoing elective surgery.

### Wilson's Disease

Wilson's disease is an autosomal recessive disorder caused by a defect in the gene that codes for copper binding. This defect leads to defective biliary excretion of copper and its subsequent accumulation in multiple organs, potentially leading to hepatic, neuropsychiatric, renal, and other dysfunction.

First-line treatment is a copper-chelating agent such as D-penicillamine, which however can suppress collagen production and impair postoperative wound healing [75]. Discontinuation of the medication is not recommended because this may result in prompt hepatic decompensation and liver failure. The American Association for the Study of Liver Diseases suggests that the D-penicillamine dose be decreased by 25–50% in the third trimester of pregnancy to promote wound healing in women undergoing cesarean section [12]. This guideline may be reasonably extended to other types of surgery as well, and it is recommended that a dose adjustment occurs 2 weeks before and after surgery. Neuropsychiatric involvement in Wilson's disease may preclude a patient from providing informed consent.

### Autoimmune Hepatitis

First described in the 1950s, autoimmune hepatitis is a chronic hepatitis of unknown etiology that occurs in all ages. Glucocorticoids are the main-

stay of treatment, and those patients taking more than prednisone 5 mg daily (or the equivalent) should be considered for perioperative stress dosing depending on the surgical stress associated with the planned procedure.

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## Anesthetic Management

### Choosing the Right Drugs

#### Pharmacologic Considerations

No specific anesthetic drugs or techniques have been shown to be superior in managing the patient with significant liver disease. Obviously it is prudent to avoid any agent with known hepatotoxic or nephrotoxic effects. All anesthetic techniques have the potential to decrease cardiac output and blood pressure and thereby decrease hepatic blood flow. This may be exacerbated if splanchnic vasoconstriction is induced by hypovolemia, stress, or shock.

Regional anesthesia may be safely used in the absence of thrombocytopenia and if coagulation studies (INR, PTT) are within normal limits. Local anesthesia may help to preserve hepatic blood flow if blood pressure and cardiac output are maintained. The common presence of coagulopathy, ascites, and encephalopathy unfortunately limits its application in this population.

Pharmacokinetic and pharmacodynamic abnormalities are prominent in liver disease as discussed in more detail elsewhere (Chapter 3) in this book, and all sedative and anesthetic medications must be carefully titrated to the desired effect. The liver plays a central role in drug metabolism by converting fat-soluble active moieties to water-soluble metabolites that can be excreted in the bile or urine. It does so through two distinct pathways: biotransformation via the CP450 enzyme system, which is highly susceptible to liver injury; and simple glucuronide conjugation, which is more robust. For example, the elimination of midazolam, a benzodiazepine dependent on biotransformation, is more readily affected by liver dysfunction than its cogener, lorazepam, which is rendered water soluble through simple glucuronide conjugation.

Liver disease alters drug pharmacokinetics not only because of impaired hepatic biotransformation or conjugation but also because of an increased volume of distribution. Thus, loading dose requirements for certain drugs may be high, but emergence may be substantially delayed. This applies particularly to neuromuscular-blocking agents such as vecuronium and rocuronium, whose initial dosing is increased and onset of action is delayed in patients with severe liver disease due to an increased volume of distribution, but whose recovery time may be prolonged by impaired hepatic clearance.

### Neuromuscular-Blocking Agents

The effects of succinylcholine may be slightly prolonged in the patient with severe liver dysfunction because of low levels of plasma cholinesterase. However, the prolongation is seldom clinically important and should not preclude the use of succinylcholine for rapid sequence induction (see below).

Atracurium and cisatracurium are intermediate neuromuscular-blocking agents that undergo spontaneous pH-mediated breakdown in the blood (Hoffman elimination) or nonspecific ester hydrolysis. Their elimination is independent of liver function, and they are logical and safe agents in a patient with liver disease. A metabolite of both drugs, laudanosine, may accumulate after high doses of continuous infusions and is associated in dogs with neurotoxicity including seizure activity. This effect has not been encountered in humans or reported in patients [21], and there is evidence that laudanosine may actually be neuroprotective in patients undergoing neurosurgery [14]. As discussed above, neuromuscular-blocking agents that are dependent on hepatic biotransformation such as vecuronium or rocuronium should be used if at all sparingly and with caution.

### Volatile Anesthetics

All the currently used volatile anesthetic agents (sevoflurane, isoflurane, desflurane) decrease hepatic blood flow due to their effects on the central circulation, but this can usually be overcome with appropriate hemodynamic management. Of

perhaps historic significance in countries with advanced medical system is the so-called halothane hepatitis. This is a highly fatal condition of centrilobular necrosis associated with reexposure to halothane, which is still in widespread use in less-developed countries. Of all the volatile anesthetics, halothane undergoes the greatest degree of metabolism: about 20%, compared with sevoflurane (5%), enflurane (2%), and isoflurane and desflurane (both 0.2%). Mild halothane hepatotoxicity (type 1) is very common and induced by reductive metabolites. It is of little clinical consequence and usually missed unless laboratory evidence of mild transaminitis is looked for and found. Fulminant hepatotoxicity (type 2) is thought to be an immunologic hepatitis whose mechanism is immune sensitization of oxidative trifluoroacetate metabolites produced by the CP-450 2E1 system [15]. There is a genetic predisposition and it is more common in obese middle-aged women, but the most important precipitating factor is halothane reexposure, especially within 1–2 weeks after the first exposure. The coexistent use of drugs like acetaminophen that stimulate mixed function oxidases increases the risk by increasing production of oxidative metabolites. The incidence has been estimated to be 1:35,000 cases of halothane exposure, but there have been very rare reports of hepatitis occurring when the reexposure has been to newer volatile agents.

### Opioids

All opioids, including fentanyl, morphine, hydromorphone, and methadone, undergo hepatic biotransformation and/or glucuronide conjugation in the liver and may accumulate in patients with significant liver dysfunction. Delayed emergence should be anticipated if they are used at standard doses. Opioids will have an enhanced pharmacodynamic effect with even latent hepatic encephalopathy and should be dosed with great caution, especially in patients with an unprotected airway.

Remifentanyl is a potent opioid that undergoes rapid hydrolysis by esterases in the blood, and has an elimination half-life of 8 min. As such, its pharmacokinetic properties are independent of

liver function, and remifentanyl is ideally suited for administration by continuous infusion in patients with severe liver disease. However, the same caveat regarding its pharmacodynamic effects applies, and it should be titrated to effect very cautiously.

### **Propofol**

Propofol is a potent induction and maintenance agent that is rapidly cleared from the CNS because of its high lipid solubility. This is the most important determinant of its duration of action, even if its hepatic metabolism is slowed, and it remains relatively short-acting in patients with advanced cirrhosis. Nonetheless, propofol must be used with caution as it depresses the circulation through inhibition of reflex tachycardia and vasodilation. These effects may be particularly detrimental in a patient who is already hypotensive at baseline.

### **Immediate Preoperative Preparation**

Patients with severe liver disease are very sensitive to the depressant effects of all sedatives, and premedication is best omitted except for aspiration prophylaxis. Small doses of IV sedation can be given in the induction room or operating room under direct observation in patients without significant ascites or encephalopathy. Proper monitoring of vital signs and the ability to take over ventilation at any time must be assured. Because these patients are so susceptible to infection, special attention must be given to universal precautions and scrupulous aseptic technique. At the same time, all staff should be aware of the possible danger to themselves of viral transmission, and as a precaution uniform staff, hepatitis B vaccination is recommended.

### **Anesthetic Induction**

Hepatic encephalopathy places patients at risk to hiccoughs, nausea, and vomiting. Gastric emptying is delayed in patients with severe liver disease and increases the risk of regurgitation and aspira-

tion during anesthetic induction. This risk is exacerbated by severe ascites with increased abdominal pressure. Management of anesthetic induction should incorporate thorough preoxygenation, generous fluid loading, and aspiration precautions. If the patient has an easy airway, rapid sequence induction and intubation is recommended. If the airway is difficult, awake fiberoptic intubation may be facilitated by low doses of a drug that does not depress ventilation such as dexmedetomidine should be considered.

### **Intraoperative Monitoring and Management**

Intraoperative liver injury may occur secondary to a diverse number of insults. These include hypotension, hypoxemia, medications, blood loss and transfusion, infection, and the stress response to surgery. Delivery of blood and oxygen to the liver may be impaired by hemodynamic instability, surgical retraction of the abdomen, manipulation of the liver, endogenous and exogenous vasoconstrictors, and anesthetic agents. Hypocarbica and hypercarbica decrease portal blood flow. The anesthesiologist should anticipate, attempt to prevent, and vigorously treat these factors. Intraoperative complications that may occur as a consequence of severe liver disease include hypoxemia (ascites, HPS), bleeding (coagulopathy), oliguria (HRS), and hypoglycemia. These complications should be anticipated and minimized by careful maintenance of intraoperative systemic, hepatic, and renal hemodynamics. Blood glucose levels should be checked frequently throughout the perioperative period, with intravenous infusion of a glucose-containing fluid to prevent hypoglycemia and appropriate insulin dosing as needed.

The severity of the patient's liver disease and the complexity of the planned surgical procedure should dictate the extent of invasive monitoring and vascular access. Given the constant specter of coagulopathy and surgical bleeding, it is prudent to place large bore intravenous access for all but the least invasive procedures. Similar consideration should be given to arterial cannulation and monitoring.



Central venous cannulation with or without pulmonary artery catheterization can be helpful when substantial fluid shifts are anticipated in the patient with cardiovascular and/or pulmonary morbidity or large-volume transfusion is anticipated. Transthoracic and transesophageal echocardiography are excellent tools for monitoring cardiac filling and function intraoperatively, although the former may be limited by the location of the surgical field and the latter by the presence of esophageal varices and coagulopathy.

## Emergence and Postoperative Care

Anesthetic emergence may be delayed and complicated by vomiting, aspiration, hypotension, respiratory depression, and acute respiratory failure. To reduce the risk of aspiration, patients should have their trachea extubated only when they are fully awake. A short period of postoperative mechanical ventilation should always be considered to allow controlled emergence, avoid reversal agents, and facilitate the evaluation of neurologic and ventilatory function prior to tracheal extubation. Potential postoperative complications include bleeding, oliguria, encephalopathy, acute respiratory failure, sepsis, wound dehiscence, and acute hepatic failure. The detailed postoperative management of patients with liver disease is addressed elsewhere (Chapter 29) in this book.

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## **Part IV**

# **Critical Care Medicine for Liver Transplantation**

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## Introduction

The liver transplant recipient is admitted to the intensive care unit (ICU) immediately after surgery for monitoring, resuscitation and stabilization of organ systems, management of intraoperative complications and hemodynamic perturbations, correction of coagulopathy, evaluation of graft function, and initiation of immunosuppression (Fig. 29.1). Physiological perturbations in the perioperative period affect the duration of ICU stay and may precipitate further complications and potentially multisystem organ failure (Fig. 29.2).

A multidisciplinary team that includes intensivists, hepatologists, and transplant surgeons should care for the liver transplant patient. Consultations may be requested with specialists in cardiology, pulmonary medicine, infectious diseases, and nephrology (especially if renal replacement therapy is considered) for patients with comorbidities or when complications arise. This chapter reviews the current state of knowledge of routine management of the liver transplantation patient in the ICU.

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## Initial Organ Response to Liver Transplantation

### Cardiovascular Response

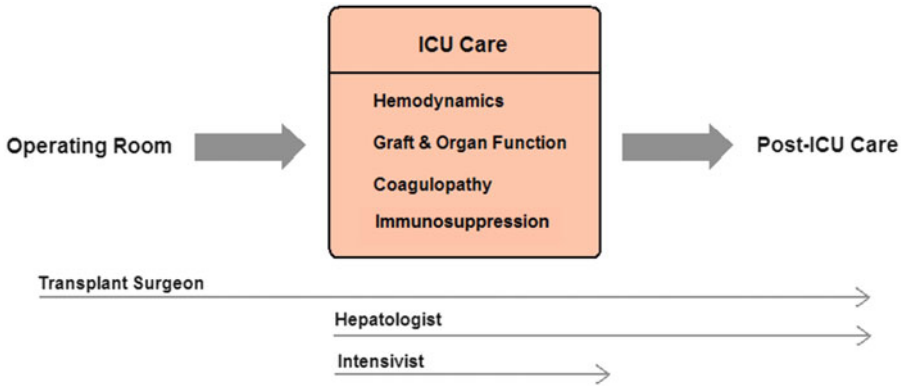
Liver transplantation has been reported in patients with coronary artery disease, cardiomyopathies secondary to alcoholic liver disease, amyloidosis, or hemochromatosis. The cardiovascular system of patients with end-stage liver disease mimics the hyperdynamic circulatory changes of patients with sepsis. Tachycardia, elevated cardiac output, low arterial blood pressure, and low systemic vascular resistance are characteristic [1]. Hypotension after liver transplantation has multiple etiologies (Fig. 29.3).

Vasodilation is commonly seen after liver transplantation. After unclamping of the portal vein desaturated blood from the obstructed portal circulation, potassium, protons, cold components, and inflammatory mediators such as interleukin-6 and tumor necrosis factor alpha are released into the systemic circulation, decreasing systemic vascular resistance and myocardial contractility. A sustained 30% decrease in mean arterial blood pressure for more than 1 min during the first 5 min after reperfusion is commonly defined as postreperfusion syndrome [2]. Other causes of vasodilation in the ICU include liver failure, infection, and inflammatory response to surgery.

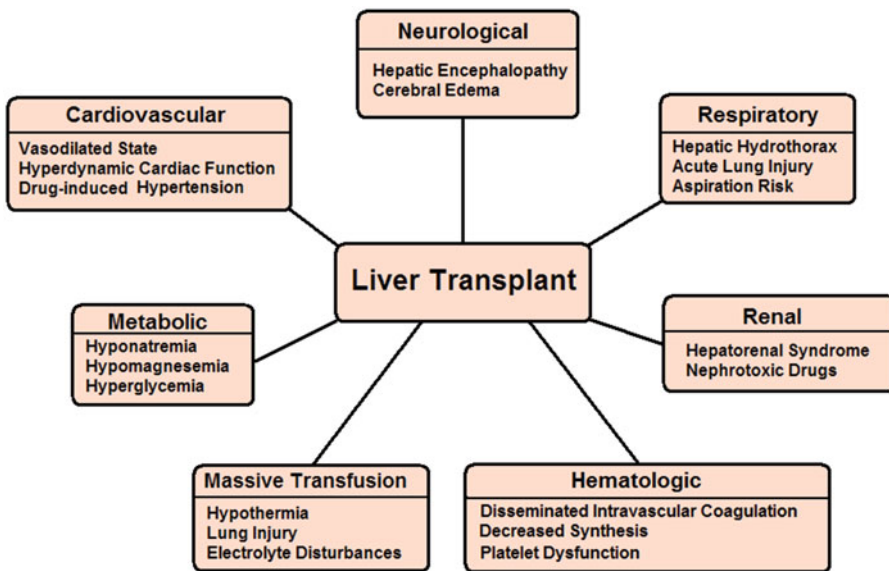
Management of vasodilatory hypotension focuses on expanding the intravenous volume, administering vasoconstricting agents such as

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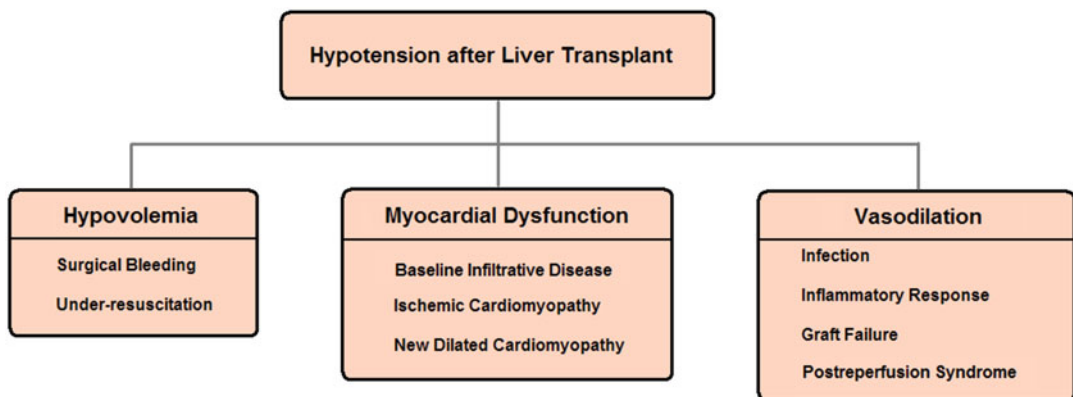
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**Fig. 29.1** Postoperative care of the liver transplant recipient



**Fig. 29.2** Organ systems and how they are affected by liver disease



**Fig. 29.3** Differential diagnosis of hypotension after liver transplantation

norepinephrine or vasopressin, and determining the underlying cause of vasodilation. Aggressive fluid resuscitation without assessment of fluid responsiveness should be avoided. Administration of excessive intravascular fluid to a non-fluid-responsive patient increases cardiac filling pressures, which can cause hepatic congestion and pulmonary edema and may require reintubation.

Significantly decreased peripheral vascular resistance in cirrhotic patients may lead to supra-normal cardiac output at baseline. In the postoperative period when the patient's circulatory system is challenged with increased afterload secondary to increased vascular resistance, ejection fraction and cardiac output may subsequently decrease. In this setting, echocardiography may show impairment of myocardial function similar to that found in septic patients. Consequently, dilated cardiomyopathy may develop after transplantation [3]. This myocardial depression may require inotropic and diuretic support but is often reversible. Inadequate management of impaired contractility will cause elevations of central venous pressures and hepatic congestion. Portal venous pressures may then increase and reduce enteral perfusion pressures, which in turn causes bacterial translocation, inflammation, and hypotension.

Postoperative hypertension occurs with chronic hypertension, inadequate pain control, volume overload, hypoglycemia, immunosuppression, and the onset of cerebral edema. Calcium channel blockers such as amlodipine are often used to manage cyclosporine- or tacrolimus-induced hypertension.

After liver transplantation, abnormal potassium and magnesium levels, poorly placed central venous catheters, and right atrial stretch from fluid shifts may cause postoperative arrhythmias, most commonly atrial fibrillation. Immediate biphasic synchronized cardioversion is performed in patients with hemodynamically unstable atrial fibrillation and beta-blockers and calcium channel blockers can be used to manage atrial fibrillation in the stable patient. Administration of non-dihydropyridine calcium channel blockers such as diltiazem or verapamil may increase levels of calcineurin inhibitor immunosuppression

via inhibition of the cytochrome P450 system. Amiodarone may be useful in treating atrial fibrillation; however, the potential for hepatic toxicity has limited its long-term use in patients after liver transplantation.

## **Pulmonary Response**

Potential causes of postoperative hypoxemia and respiratory failure in patients after liver transplantation include atelectasis from the compressive effects of ascites, hepatic hydrothorax, hepatopulmonary syndrome, underlying chronic pulmonary disease, and occasionally acute respiratory distress syndrome [4, 5]. Ascitic fluid can enter the pleural space through small channels in the diaphragm to cause a hepatic hydrothorax, which usually predominates on the right side. Muscle wasting and intra-abdominal hypertension from ascites increase the work of breathing. Resolution of hepatopulmonary syndrome after transplant is possible but may take months.

Postoperative ARDS may be a result of direct surgical insult, generalized inflammatory processes, intraoperative aspiration, or transfusion of blood products. These conditions can increase the permeability of the alveolar capillary membrane, creating a capillary leak syndrome with exudation of fluid and protein into the alveolar space, to cause noncardiogenic pulmonary edema. In its most dramatic form, it presents as the acute onset of a massive outpouring of proteinaceous fluid from the endotracheal tube. Noncardiogenic pulmonary edema is distinguished from cardiac failure by normal or low left atrial or pulmonary artery wedge pressures and a high protein concentration in the edema fluid (albumin concentration 90% or greater than that of serum albumin concentration).

## **Renal Response**

Patients with acute kidney injury (AKI) and cirrhosis have a higher incidence of complications and increased risk of mortality after liver transplantation than those without renal failure.



Preoperative gastrointestinal bleeding, diarrhea from infection or lactulose administration and diuretic medications change circulatory function and cause hypovolemia that may result in kidney injury. As cirrhosis progresses, a reduction in systemic vascular resistance causes compensatory activation of the renin-angiotensin and sympathetic nervous systems, which leads to ascites, edema, intrarenal vasoconstriction, and renal hypoperfusion. Hepatorenal syndrome (HRS) is caused by functional renal vasoconstriction in response to splanchnic arterial vasodilation [6].

Postoperative renal function correlates with preoperative glomerular filtration rates [6]; however, in patients with cirrhosis and HRS resistant to diuretics, renal function may improve after transplantation. Postoperatively, sepsis and nephrotoxic calcineurin inhibitors such as cyclosporin A and FK506 (tacrolimus) may contribute to renal dysfunction. Chronic allograft nephropathy in patients who have received liver, heart, lung, or kidney transplants is now the third most common reason for placing patients on the waiting list for a kidney transplant.

Managing liver transplantation patients with low urine output, renal dysfunction, or postoperative hyperkalemia is challenging and continuous renal replacement therapy may be used to manage volume shifts, acid–base balance, and electrolyte disturbances.

## Neurological Response

Hepatic encephalopathy is a neuropsychiatric complication of acute liver disease that ranges from mild confusion to cerebral edema with intracranial hypertension. Patients have disturbances in consciousness, cognitive abilities, behavior, neuromuscular function, concentration, reaction time, memory, and/or electroencephalogram readings. The pathogenesis of hepatic encephalopathy is poorly understood, but most theories implicate elevated levels of ammonia, a gut-derived neurotoxin, which is shunted to the systemic circulation from the portal system. Bacteria in the intestinal tract produce ammonia, which crosses the blood–brain barrier into astro-

cytes that detoxify it to glutamine. An increased concentration of intracellular glutamine causes swelling of astrocytes, which reduces their ability to regulate neurotransmission. High serum ammonia levels characterize patients with hepatic encephalopathy but ammonia levels do not correlate with the severity of neurological symptoms. This observation suggests that other factors, such as hyponatremia, gastrointestinal bleeding, and infection, contribute to the development of hepatic encephalopathy [7–9]. Left untreated, cerebral edema can progress to intracranial hypertension and herniation of the brain. Hepatic encephalopathy typically improves in patients who receive a well-functioning graft. By contrast, graft dysfunction may lead to persistence or new onset of altered mental status which should prompt further investigations.

## Sodium and Electrolyte Response

Preoperatively, patients with advanced cirrhosis develop decreased effective blood volume followed by circulatory dysfunction. Hypervolemic hyponatremia is common due to impaired excretion of solute-free water resulting in expanded extracellular volume, ascites, and edema. Patients with hypovolemic hyponatremia due to renal loss of extracellular fluid (overdiuresis) or loss from the gastrointestinal tract rarely have ascites or edema but present with prerenal azotemia from low circulating volume or hepatic encephalopathy from a rapid reduction in serum osmolality [6, 10].

Hyponatremia is associated with HRS, ascites, increased risk of death from liver disease and postoperative mortality after transplantation. Patients who undergo liver transplantation are at risk for perioperative central pontine myelinolysis (CPM), a neurological condition characterized by symmetric noninflammatory demyelinating lesions in the basis pontis. The etiology of CPM is uncertain, but osmotic stress on central nervous system cells is theorized, and CPM correlates with rapid correction of hyponatremia [10].

Hypomagnesemia may be worsened by calcineurin inhibitors, loop diuretics, and significant

blood loss. Total serum calcium is often low because liver transplant patients commonly have low serum albumin with reduced calcium binding. Therefore, ionized calcium levels should be followed routinely and corrected as indicated. Another possible cause of hypocalcemia is citrate chelation after the administration of a significant volume of packed red blood cells. Malnutrition and vitamin D deficiency may also lead to perioperative hypocalcemia.

### **Glycemic Response**

Elevated blood glucose is often a result of the stress response and its presence can provide the practitioner with insight into the severity of a patient's illness. After liver surgery, the metabolic and endocrine function of transplant patients can range from mild hyperglycemia with no clinical consequence to the severely altered neuroendocrine responses associated with chronic critical illness. Acute hyperglycemia has emerged as a marker of outcome after liver transplantation surgery and acute hypoglycemia is associated with poor graft function and sepsis [11, 12]. Immediate postoperative glucose control can be challenging because multiple factors affect glucose levels, including inflammatory response to transplantation surgery, steroid administration, hepatic dysfunction, altered glycogen stores, and insulin resistance of liver failure.

### **Coagulation Response**

Patients with liver disease have hemostatic changes that promote both bleeding and thrombosis. Inadequate synthesis of most coagulation factors (except for von Willebrand factor), thrombocytopenia, platelet function defects, dysfibrinogenemia, and elevated tissue plasminogen activator levels cause bleeding. Elevations of von Willebrand factor and factor VIII, as well as decreased levels of ADAMTS-13, protein C, protein S, antithrombin, alpha 2-macroglobulin, plasminogen, and heparin cofactor II, favor thrombosis. Thrombin generation is often normal

in cirrhosis. Thrombin generation is considered a function of procoagulant factors, and anticoagulant factors that inhibit thrombin are not considered [13–16].

Levels of fibrinogen, an acute phase reactant, are normal or increased in liver disease. Patients with severe hepatic dysfunction, however, may synthesize fibrinogen poorly, which increases the risk for bleeding. Although high concentrations of fibrinogen are found in patients with chronic hepatitis, cholestatic jaundice, and hepatocellular carcinoma, clot formation is not enhanced because fibrinogen is dysfunctional. Patients may have an abnormal thrombin time with normal prothrombin time [17] and activated partial thromboplastin time values. Typically, heparin effects, disseminated intravascular coagulation or hyperfibrinolysis have been resolved in the operating room. However, dilutional coagulopathy, ongoing platelet, and factor consumption in the early postoperative phase and poor graft function may contribute to clinical bleeding in the postoperative period. Even a functioning transplanted liver may not produce sufficient levels of coagulation factors for several days, and so plasma, cryoprecipitate, or platelet transfusions may be required.

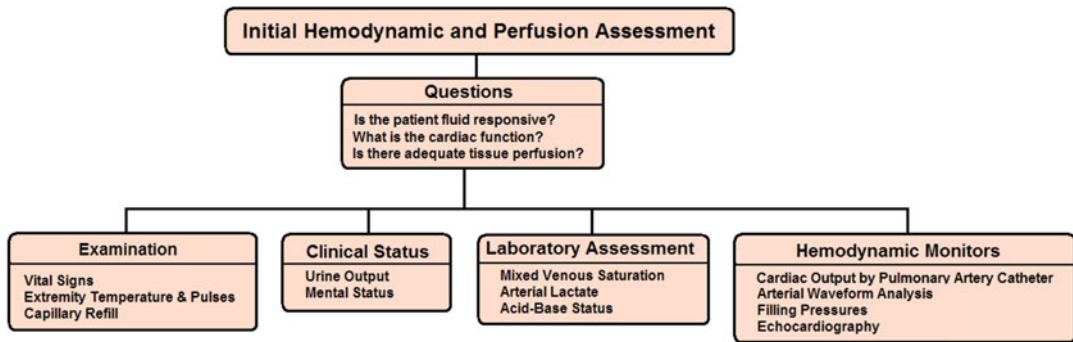
Uncontrolled hemorrhage and massive transfusion in the operating room or the ICU may cause the lethal triad of acidosis, coagulopathy, and hypothermia. Left uncorrected, each of these abnormalities can exacerbate the others, creating a “bloody vicious cycle.” Early complications of massive transfusion that may become apparent in the ICU include (a) acute hemolytic transfusion reactions, (b) febrile nonhemolytic transfusion reactions, (c) transfusion-related acute lung injury, (d) transfusion-associated circulatory overload, (e) allergic reactions, (f) bacterial sepsis, (g) hypocalcemia, and (h) hyperkalemia [18].

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## **Initial Care After Liver Transplantation**

### **Hemodynamic Monitoring**

Liver transplant patients will arrive in the ICU with several invasive hemodynamic monitors.



**Fig. 29.4** Algorithm to assess the hemodynamic and perfusion state of the liver transplant recipient

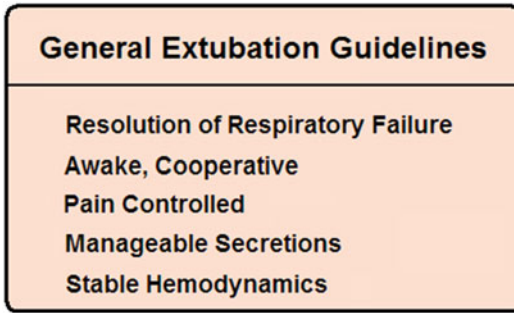
The intensivist needs to assess fluid responsiveness, the degree of vasodilation, the presence of myocardial dysfunction, and the adequacy of tissue oxygen delivery and organ perfusion immediately after arrival (Fig. 29.4). A radial arterial catheter is used for beat-to-beat blood pressure monitoring and frequent sampling of blood. Pulse pressure variation, calculated from the invasive arterial tracing help in the assessment of fluid responsiveness. Peripheral arterial pressure measurements may not be reliable in patients with severe vasoconstriction or vasodilation and second arterial catheter is often placed in the femoral artery to measure central aortic blood pressure. Central venous access is established to measure right atrial pressure and to administer vasoactive drugs and blood products. Central venous pressure monitoring does not reliably measure blood volume or change in blood volume [19]. The use of a pulmonary artery catheter depends on local practice and the physiological state of the patient. Mixed venous oxygen saturation values are measured to assess cardiac output and adequacy of global oxygen delivery, but these measurements are also affected by changes in oxygen-carrying capacity and oxygen consumption. Echocardiography assesses ventricular filling, contractility, and function. Diagnoses such as myocardial ischemia, pulmonary embolism, pleural effusions, and technical complications of the inferior vena cava anastomosis can be detected with transesophageal echocardiography (TEE) and the risk of rupture of esophageal varices with TEE is rare. Bladder pressures should be measured routinely to evaluate intra-abdominal

hypertension, especially when elevated intra-abdominal pressure is suspected, as with bleeding or ascites.

## Mechanical Ventilation

Although many patients can be extubated in the operating room or within 6 h after the operation, mechanical ventilation is frequently required for 24–48 h after transplantation. Physical examination, assessment of arterial blood gas values, ventilator mechanics, and chest radiography guide management of mechanical ventilation. Reasonable initial ventilation settings include a mode of assisted control volume control ventilation with a tidal volume of 8–10 cc/kg ideal body weight (determined by the patient's height); a respiratory rate of 10–15 breaths per minute, and an  $\text{FIO}_2$  titrated to maintain an oxygen saturation >95%. Respiratory alkalosis may be observed in patients with a high respiratory drive from liver dysfunction.

The use of positive-pressure mechanical ventilation and positive end-expiratory pressure (PEEP) is of concern in the liver transplant patients as they lead to increased intrathoracic pressure, and decreased venous return from the inferior vena cava and hepatic veins. This may lead to congestion of the graft. However, the clinical relevance remains controversial, as studies with PEEP of up to 10 cm  $\text{H}_2\text{O}$  have shown no adverse effects on hepatic arterial, portal venous, or hepatic venous flow [7]. Ventilator management in ARDS should focus on limiting lung



**Fig. 29.5** Extubation guidelines

stretch via low tidal volumes (4–6 cc/kg) and permitting hypercapnia.

Daily assessment of liver transplantation patients for ventilator weaning with a reduction in sedation should be performed by assessing hemodynamic stability, respiratory strength, and oxygenation. Mechanical ventilation should be discontinued when the following conditions are met: the underlying reason for respiratory failure has resolved, the graft is functioning, the patient is awake and cooperative, the patient’s pain is well controlled, tracheobronchial secretions are manageable, and vasopressor requirements are stable (Fig. 29.5).

## Sedation

A sedation scale can facilitate the appropriate level of sedation to promote comfort, facilitate mechanical ventilation, and prevent hypotension. Two commonly used sedation scales are listed in Table 29.1. The Ramsay Sedation Scale is a simple 6-point scale that has been in regular use since it was first described in 1974 [20]. It incorporates four levels of increasing sedation but only one level of agitation, and for this reason has been criticized as imbalanced. The Richmond Agitation-Sedation Scale (RASS) has recently achieved prominence because it is more balanced across levels of sedation and agitation, correlates better with electroencephalographic assessment, and has been integrated with an assessment of delirium called the Confusion Assessment Method for the ICU (CAM-ICU) (Fig. 29.6). Several other instruments for assessment of seda-

tion focus on agitation and physiological parameters. The Riker Sedation-Agitation Scale (SAS), the Motor Activity Assessment Scale (MAAS), the Adaptation to the Intensive Care Environment (ATICE), and the AVRIPAS scale, which incorporates heart rate and respiration have all been utilized to guide sedation [21–25]. It is important to note that these scales assess the level of sedation only and not pain, anxiety, or level of cognition; they cannot be used in the presence of neuromuscular blockade; and none of them have been exclusively validated in patients with neurological injury such as cerebral edema.

Sedation can be considered as a combination of three components: anxiolysis (which is indicated for every ICU patient), hypnosis (i.e., the induction of sleep, which may be indicated in sicker and/or ventilated patients), and amnesia (loss or lack of recall). Sedation is distinct from analgesia (the relief of pain) and sedative agents such as propofol and the benzodiazepines (lorazepam and midazolam) have no analgesic effects. Sedating a patient for agitation induced by pain may further disinhibit their control functions and lead to a paradoxical increase in agitation. Also, although amnesia is essential during general anesthesia in the operating room, the potent anterograde amnesia induced by benzodiazepines, even at subhypnotic doses, results in confusion and disorientation on awakening, and may predispose toward ICU delirium. In contrast, propofol provides amnesia only during sleep and emergence is therefore likely smoother.

The intensivist should consider an “analgesia first” or “A-1” approach to relieve the patient’s pain before administration of sedation [26]. This approach will avoid disinhibiting a patient whose agitation is due to pain as discussed above. There is evidence that an A-1 approach decreases sedation requirements and time on the ventilator [27–31]. In addition to pain from incisions and drains ICU patients experience pain and discomfort with procedures such as tracheal intubation, endotracheal tube suctioning, and repositioning. Failure to treat pain exacerbates endogenous catecholamine activity, which predisposes to myocardial ischemia, hypercoagulability, hypermetabolic states, sleep deprivation, and delirium [32, 33].

**Table 29.1** Sedation scales

Modified Ramsay sedation scale		
1	Awake	Anxious, agitated, restless
2	Awake	Cooperative, orientated, serene
3	Awake	Responding only to commands
4	Asleep	Brisk response to stimulation <sup>a</sup>
5	Asleep	Sluggish response to stimulation <sup>a</sup>
6	Asleep	No response to stimulation <sup>a</sup>

Score	Assessment	Description
Richmond Agitation-Sedation Scale (RASS)		
+4	Combative	Overtly combative, violent, danger to staff with observation
+3	Very agitated	Pulls or removes tube(s) or catheters, aggressive with observation
+2	Agitated	Frequent nonpurposeful movement with observation or dyssynchrony with ventilator
+1	Restless	Anxious, apprehensive, but not aggressive
0	Alert and calm upon observation	
-1	Drowsy	With loud speaking voice awakens >10 s, not fully alert
-2	Light sedation	With loud speaking voice briefly awakens to voice <10 s
-3	Moderate sedation	With loud speaking voice has movement or eye opening without eye contact
-4	Deep sedation	Movement to physical stimulation
-5	Unarousable	No response to physical stimulation

<sup>a</sup>Stimulation = glabellar tap or loud noise

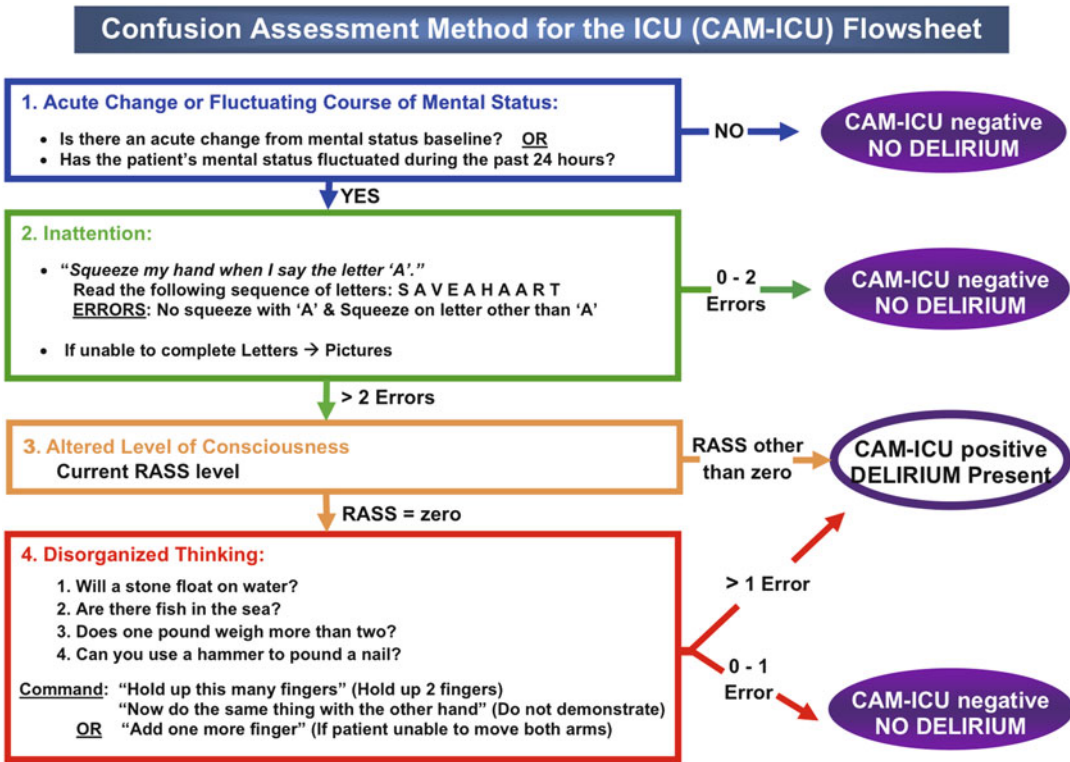
Opioids are the mainstay of pain management in the ICU (Table 29.2) and synthetic analgesics such as fentanyl and remifentanyl are commonly used. These agents are administered as a bolus or as an infusion to manage pain and facilitate synchronous mechanical ventilation. Fentanyl has a high hepatic extraction ratio and its metabolism is slowed in patients with liver disease (e.g., cirrhosis) or hepatic dysfunction (e.g., congestive heart failure and shock) [34].

Benzodiazepines such as midazolam and lorazepam are lipid soluble, and because they accumulate in fat stores, prolonged infusions result in markedly delayed emergence. Patients with hepatic dysfunction may be sensitive to benzodiazepines. Conversely, patients who have a history of alcohol abuse may require increased doses of benzodiazepines. Lorazepam is diluted in propylene glycol, which has been associated with AKI and metabolic acidosis and the osmolar anion gap

should be calculated in patients receiving lorazepam doses greater than 1 mg/kg/day.

Propofol is a potent sedative that decreases catecholamine levels, induces vasodilation, and limits baroreflex cardiovascular responses. Although propofol sedation may promptly lower intracranial pressure (ICP) in the liver transplant patient with cerebral edema [35–37], it may also induce hypotension, especially in hypovolemic patients, and thus decrease cerebral perfusion pressure [36, 38]. Because propofol is so highly lipid soluble, it is suspended in a 20% fat emulsion that may predispose the patient to infection, hypertriglyceridemia, and pancreatitis [39–43]. High-dose propofol (>50 µg/kg/min) infusions for prolonged time in the setting of shock, high endogenous or exogenous catecholamines, and corticosteroids is associated with the rare but potentially fatal propofol infusion syndrome that appears to result from an intracellular block in fat





**Fig. 29.6** The Confusion Assessment Method for the ICU. “Copyright © 2002, E. Wesley Ely, MD, MPH and Vanderbilt University, all rights reserved”

oxidation, resulting in intractable lactate acidosis, myocardial depression, and death [44].

In contrast to gamma-aminobutyric acid agonists, dexmedetomidine sedates without changes in respiratory rate, oxygen saturation, or arterial carbon dioxide tension [45]. Unlike benzodiazepines, clinical doses of dexmedetomidine are not associated with anterograde amnesia; patients are easily aroused from light levels of sedation and emerge without confusion or disorientation. When left undisturbed, they go back to their previous level of sedation. Thus, dexmedetomidine produces interactive or cooperative sedation and facilitates neurological examination [46–48]. Although dexmedetomidine may decrease the incidence of delirium in the ICU, this effect has not been extensively studied in liver transplantation patients who may have a pretransplant encephalopathy. Dexmedetomidine is dependent on hepatic elimination.

In the postoperative period, early weaning of sedation allows for assessment of mental status.

Medical history, chart review, and discussion with family and other medical providers allow a reasonable comparison to preoperative mental function. Altered mental status should prompt thorough evaluation, excluding common causes such as residual anesthetic agents, electrolyte and glucose abnormalities, infection, inadequate gas exchange, and intracranial pathology. Failing to find a specific cause may suggest graft dysfunction.

### Immunosuppression

Immunosuppressive regimens are discussed in detail elsewhere (Chapter 30) in this book. However it should be mentioned that often latest on postoperative day 1 immunosuppression needs to be started. Frequently, however, the degree of intraoperative renal injury may not be apparent so soon, and early aggressive immunosuppression at this time may add further injury, even



**Table 29.2** Intravenous analgesics and sedatives

Medication	Intermittent (Bolus) dose	Infusion dose	Onset of action	Half-life	Active metabolites	Unique adverse effects
Fentanyl	25–50 µg	10–400 µg/h	2 min	1.5–6 h	N	Accumulation of parent compound
Remifentanyl	Not recommended	0.05–0.2 µg/kg/min		3–10 min	N	Hyperalgesia
Hydromorphone	0.25–0.5 mg	0.5–1 mg/h	15 min	2–3 h	N	
Morphine	0.5–10 mg	1–10 mg/h	15 min	3–7 h	Y	Histamine release Accumulation of metabolite in renal failure
Midazolam	1–2 mg	1–10 mg/h	2–5 min	3–11 h	Y	Accumulation of parent compound
Lorazepam	0.5–1 mg	1–10 mg/h	5–20 min	8–15 h	N	Accumulation of metabolite in renal failure High-dose PG-related acidosis or renal failure
Propofol	Not recommended	5–70 µg/kg/min	Immediate	26–32 h	N	PRIS Infection risk
Dexmedetomidine	Not recommended	0.2–1.5 µg/kg/h	30 min	2–5 h	N	Elevated triglycerides Bradycardia

PG propylene glycol; µg micrograms; mg milligrams; PRIS propofol infusion syndrome

precipitating AKI. The decisions of when and how to start immunosuppression in the liver transplant recipient should therefore involve the hepatologists, transplant surgeons, and intensivists.

## Hepatic Encephalopathy

Initial management of hepatic encephalopathy should include the identification and treatment of reversible triggers of this neuropsychiatric syndrome, such as gastrointestinal bleeding and infection. Nonabsorbable disaccharides such as lactulose decrease absorption of ammonia from the intestinal tract via catharsis. Excessive dosing of lactulose causes dehydration. Oral antibiotics (rifaximin, neomycin, vancomycin, paromomycin, or metronidazole) reduce ammonia-producing enteric bacteria. Rifaximin, in combination with lactulose, may prevent episodes of hepatic encephalopathy [7, 9, 49].

Patients who develop fulminant hepatic failure are at risk for hepatic encephalopathy, cerebral edema with increased ICP, and the possibility of herniation. ICP monitoring should be strongly considered for patients with fulminant hepatic failure and encephalopathy. Historically, many clinicians avoided ICP monitoring as it carries the risk of intracranial bleeding. More details of ICP monitoring are discussed elsewhere (Chapter 23) in this book.

ICP elevations to greater than 25 mmHg should be treated with mannitol to increase serum osmolarity and reduce cerebral edema. Preoperative hyperventilation has not been shown to improve outcome, and corticosteroids are not indicated. Pentobarbital coma may be indicated for patients who are unresponsive to mannitol, but coma may worsen cerebral perfusion by causing systemic hypotension. Many centers consider sustained cerebral hypoperfusion (cerebral perfusion pressure <40 mmHg) as a contraindication to transplant because of the high risk for brain death. In the future, transcranial Doppler ultrasonography may offer a noninvasive means of monitoring elevated ICP in these patients. Drugs or conditions that exacerbate elevations in ICP should be avoided. Other neurological complica-

tions include stroke, seizures, and coma. A focal deficit diagnosed in the ICU should prompt consideration for stroke or bleed and trigger immediate head CT.

## Sodium and Electrolyte Management

Distinguishing between hypervolemic and hypovolemic hyponatremia is essential to guide treatment. Hypervolemic hyponatremia is managed with fluid restriction (1–1.5 L/day) and withholding of diuretics. Vaptans, medications that block the vasopressin-2 receptor, increase solute-free water excretion by blocking renal vasopressin 2 receptors and may preclude water restriction so that diuretics can be continued. Patients with hypovolemic hyponatremia are not given diuretics; instead, saline is administered to increase plasma volume and sodium [10].

Rapid changes in the concentration of serum sodium cannot be predicted, and a “safe” rate of correction of hyponatremia has not been definitively established; sodium correction at a rate of less than 12 mEq/L/day is considered safe by some experts. Preoperative correction of hyponatremia may prevent a rapid rise in serum sodium intraoperatively and postoperatively. Due to intraoperative fluid replacement, high sodium loads may cause rapid swings in serum sodium, or even hypernatremia at the end of surgery. Sodium bicarbonate should be administered cautiously because it has a high concentration of sodium.

Potassium, magnesium, and calcium levels should be monitored frequently and abnormal levels corrected. Metabolic acidosis is managed by improving hemodynamic parameters and adjusting minute ventilation. Severe metabolic acidosis may require slow administration sodium bicarbonate or tromethamine (THAM) in combination with hyperventilation.

## Glycemic Control

Although the role of “tight glycemic” control has not been adequately studied immediately after liver transplantation, the results of the

Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) investigation, a large multicenter, multinational, randomized, and non-blinded trial of medical and surgical patients, suggest that intensive insulin therapy does not improve outcomes [50]. Maintaining glucose levels between 140 and 180 mg/dL is a reasonable goal in most situations. Insulin should preferably be administered by intravenous infusion, and glucose should be monitored continually.

### **Management of Coagulopathy and Bleeding**

Warming the room, applying forced warming systems on the patient's body, administering blood products and fluids through a fluid warmer and heating and humidifying inspired gases reduce the risk of hypothermia. Dilutional coagulopathy and thrombocytopenia may be prevented by transfusing packed red blood cells, fresh frozen plasma, and platelets in a 1:1:1 ratio [18]. The risk of transfusion-related acute lung injury may be reduced by minimizing transfusions. When transfusions are required, packed red blood cells with a short storage time and fresh frozen plasma from men or nulliparous women may also decrease this risk. Overaggressive transfusion can elevate central venous pressures and cause acute engorgement and ischemia of the transplanted liver.

### **Evaluating Graft Function**

Assessment of graft function begins in the operating room. Good texture and color of the graft, evidence of bile production, hemodynamic stability, and decreasing lactate levels are signs of a well-functioning graft. Hypocalcemia often resolves quickly as the graft metabolizes citrate during the final phases of the procedure. Metabolic alkalemia can develop as a result of citrate metabolism. Potassium levels tend to normalize with the onset of hepatocyte function. A number of recipients exhibit hyperglycemia resistant to insulin.

In the ICU, clearance of lactic acid (conversion to pyruvate), production of glucose (gluconeogenesis and glycogenolysis), resolution of encephalopathy, emergence from anesthesia (biotransformation of agents), normothermia (metabolic activity), normalization of coagulopathy, decreasing total bilirubin levels, production of bile (visible if a biliary tube was placed), resolution of HRS (resolving endotoxemia), and adequate urine output suggest a functioning graft. Preservation and reperfusion injury causes transaminases to rise immediately after surgery, but enzyme levels usually fall within 24–48 h. Even high levels of transaminases are not necessarily a reason for major concern as they are an indicator of past injury and not present function. New synthesis of coagulation factors will not correct factor depletion for hours to days after the transplant. As the transplanted liver begins to function, other organ systems will generally improve.

If postoperative graft dysfunction or failure occurs, other organ systems may fail as well. Graft dysfunction is characterized by lactic acidosis, hypoglycemia, and altered mental status or persistent encephalopathy. Severe dysfunction should prompt the clinician to exclude surgical complications such as anastomotic problems and may require reexploration. In addition, a general and gradual worsening of the patient's clinical status days after transplant may be due to allograft rejection and require a diagnostic liver biopsy. In contrast to past practices, routine biopsies are seldom performed.

### **Assessment of Vascular and Biliary Complications**

Vascular complications include anastomotic bleeding and stenosis or occlusion from thrombosis or kinking of vessels. Thrombosis of the portal vein or hepatic artery compromises viability of the graft. Abdominal Doppler ultrasound is used to assess the hepatic vessels. Hepatic artery thrombosis, which is more common than portal vein thrombosis, may cause hepatic necrosis leading to liver failure. Portal vein thrombosis

may cause liver dysfunction, tense ascites, and variceal bleeding. Patients with bile leaks experience fever, abdominal pain, and peritoneal irritation. Bile leaks develop early in the postoperative course and may be identified by bilous fluid in drains. Ultrasonography that shows abdominal fluid collections or cholangiography can confirm the diagnosis. Bile leaks are managed with endoscopic placement of a biliary stent or relaparotomy.

Anastomotic complications occur relatively early after liver transplant. Poor vascular flow may also compromise the integrity of ductal structures, leading to an increase of alkaline phosphatase and gamma-glutamyl transpeptidase. These problems may be amenable to radiological intervention, or require reexploration.

## Prevention of ICU Complications

### Gastrointestinal Stress Ulcers

ICU patients are at risk for developing gastrointestinal stress ulcers because hypovolemia, hypoperfusion, sympathetic nervous system activation, and inflammation impair protective mechanisms. Coagulopathy and mechanical ventilation are independent risk factors for stress ulceration and pharmacological ulcer prophylaxis with H<sub>2</sub>-receptor blockers, proton-pump inhibitors, or sucralfate should be initiated after transplantation [51]. Enteral nutrition alone is not sufficient to prevent stress ulceration. Theoretically, an increase in gastric pH via gastric acid suppression promotes bacterial colonization of the gastrointestinal tract and may increase the risk for nosocomial pneumonia and *Clostridium difficile* infections [17, 52–54].

### Venous Thromboembolism

Contrary to conventional belief, patients who undergo liver transplantation may be hypercoagulable and are not protected against venous thromboembolism. Liver transplant patients are not “autoanticoagulated.” Imbalances in the clot-

ting cascade toward hypercoagulability, as well as immobility, surgery, and system inflammation, increase the risk of venous thromboembolism and pulmonary embolism [14–16, 55, 56]. Thromboembolic prophylaxis includes graduated compression stockings and/or intermittent pneumatic compression and low-dose unfractionated heparin or low-molecular-weight heparin. If there is no evidence of active bleeding, pharmacological thromboembolic prophylaxis should be initiated on postoperative day 1.

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Amit Gera and Kosh Agarwal

The aims of this chapter are to provide an overview of the processes involved in immunological rejection after liver transplantation, explain the pharmacotherapy required to treat and prevent graft rejection and discuss alternative immunosuppressive strategies

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## Immune Rejection

The liver has a lower incidence of rejection compared to other organs and does not require HLA matching of donor and recipient prior to transplantation. However a substantial number of recipients still develop graft rejection. Early acute rejection usually does not affect long-term graft survival and has conversely been associated with increased patient and graft survival. One study found that patients who had at least one episode of acute rejection had improved 4-year patient (82.8% vs. 75.9%) and graft survival (76.5% vs. 71.7%) [1].

There are three main types of organ rejection:

- *Hyperacute rejection*. This is rare and occurs within minutes to hours of restoration of the

hepatic circulation during transplantation. It is characterized by endothelial injury and fibrin deposition resulting in intravascular thrombosis. There is no lymphocytic infiltration or bile duct injury. It results from pre-sensitization to donor antigens.

- *Acute cellular rejection*. Characterized by portal inflammation, bile duct damage and endothelitis [2] (Fig. 30.1).
- *Chronic rejection*. Characterized by ductopenia and obliterative vasculopathy affecting large and medium-sized arteries and the portal microcirculation (Fig. 30.2). It has an incidence of less than 4% and requires augmentation of immunosuppression [3]. Severe cases can require re-transplantation and impact upon long-term graft survival.

The incidence of acute liver rejection was 60% in the 1990s [4] and decreased to 15% since 2000 [5] due to the introduction of new drugs and better management of immunosuppression. Most cases occur within 90 days of surgery and respond to high-dose corticosteroids [6]. In both acute and chronic rejection there is T-cell-mediated damage of donor-derived bile ducts and vascular endothelium.

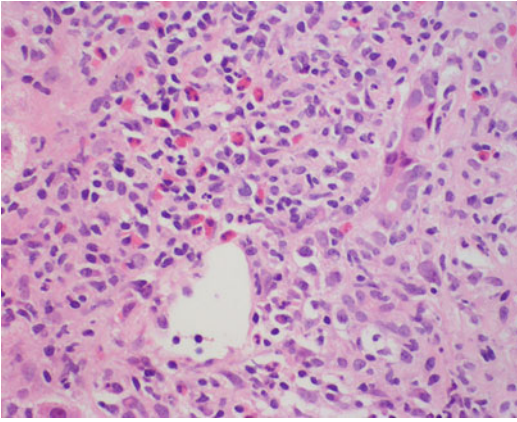
Steps in the development of acute cellular rejection include (Fig. 30.3):

1. *Allograft recognition*—foreign antigens are presented to lymphocytes by antigen presenting cells (dendritic cells, macrophages, B lymphocytes) in lymphoid organs, e.g. spleen, regional nodes. These are loaded onto the major histocompatibility complex (MHC) by

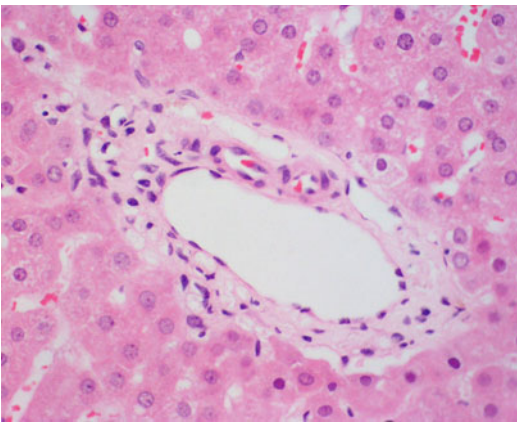
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**Fig. 30.1** Histological features of acute rejection. There is portal inflammation with cholangitis and endotheliitis



**Fig. 30.2** Histological features of chronic rejection. Branches of portal vein and artery with bile ductopenia

the antigen presenting cell which are recognized by CD3 (and also CD4/CD8). The T-cell receptor on CD3 interacts with the MHC of the antigen presenting cell—this is stabilized by CD4/CD8 resulting in “SIGNAL 1” a calcium-dependent pathway.

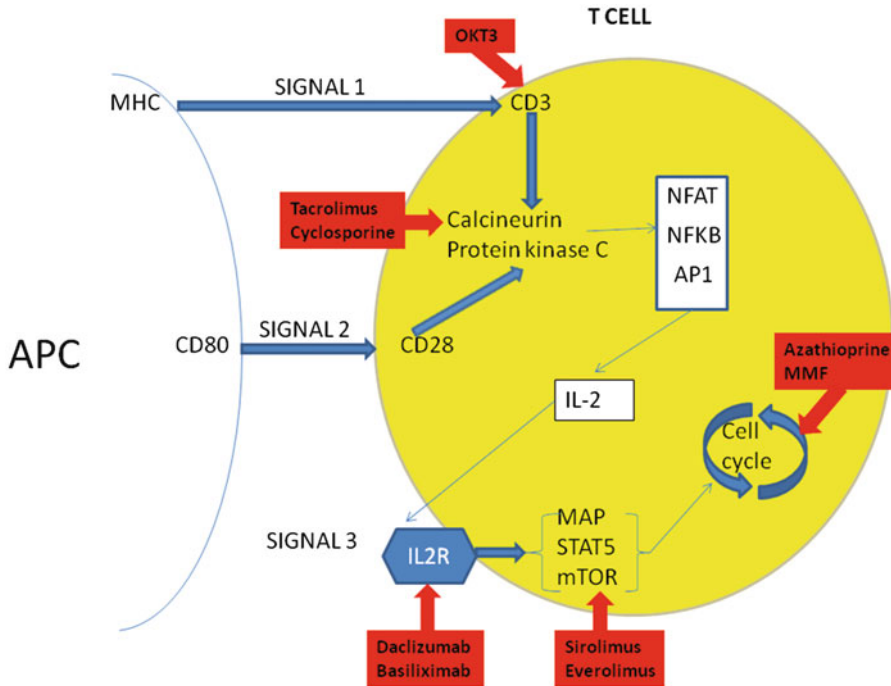
2. *T-cell activation*—this is achieved by binding of co-stimulatory molecules (CD28, CD 40, PD1) on T-cells with ligands on the antigen presenting cell—“SIGNAL 2”, a  $\text{Ca}^{2+}$ -independent process. Both signals are required for naïve T-cell activation and are mediated by calcineurin and Protein Kinase C activation of NF-AT, NF-KB and AP-1. These bind to gene promoters associated with T-cell activation and proliferation, i.e. promotes IL2 production

which initiates G0 to G1 transition of the cell cycle [7]. Inhibition of this pathway has been the predominant site of action in immunosuppression therapies utilizing calcineurin inhibitors (CNIs) such as cyclosporin and tacrolimus.

3. *Clonal expansion*—“SIGNAL3”: auto/paracrine activation of T-cells. Receptor of the IL2 family activate JAK 1/3 in T-cells [8]—which activates mammalian target of rapamycin (mTOR), STAT5, Ras-Raf MAP kinase [9] resulting in cell proliferation, DNA synthesis and cell division. Sirolimus and everolimus inhibit signal 3. Other molecules are produced which inhibit SIGNAL 2 (e.g. CD152) and decrease T-cell receptor signalling [10]. Azathioprine and mycophenolate mofetil (MMF) inhibit purine and DNA synthesis.
4. *Inflammation*—activated T-cells result in release of cytokines that recruit cytotoxic T-cells, B-cells, activated macrophages and adhesion molecules. Further activated T-cells are attracted by these leading to the release of  $\text{TNF } \alpha/\beta$  perforin, granzymes. Corticosteroids and anti-lymphocyte antibody act via this route.

## Immunosuppressive Agents

Immunosuppressive medication can be classified in several different ways: biologic vs. pharmacologic, induction therapy vs. maintenance therapy and by site or mechanism of action. Most regimens use a combination of drugs with different sites of action on the T-cell response pathway. This enables variable dosage and treatment adjustment according to response and adverse effects. The current mainstay of treatment involves the use of CNIs in combination with steroids. There is an increasing use of tailor-made protocols individualized to the patient and etiology to stratify risk of rejection and protect long-term graft function while minimizing adverse effects. For example, in cases with renal impairment, induction therapy with renal sparing agents are often given to enable a lower dose of nephrotoxic CNIs to be used in the early post-transplant



**Fig. 30.3** Mechanisms of allograft rejection and of immunosuppressive drugs

phase. See Table 30.1 for an overview of currently used immunosuppressive agents and their adverse effects.

### Calcineurin Inhibitors: Cyclosporine and Tacrolimus

Cyclosporine was the first CNI to be routinely used for post-transplantation. It was derived from the fungus *Tolypocladium inflatum* in 1972 and was evaluated for use as an immunosuppressive agent in 1976 [11]. Its use has now often been superseded by Tacrolimus (FK506) which is approximately 100 times more potent on a molar level [12]. Tacrolimus is a macrolide antibiotic similar to erythromycin that was derived from the fungus *Streptomyces tsukubaensis* in 1984 [13].

### Method of Action

Cyclosporine binds to cyclophilin which causes inhibition of calcineurin, a calcium/

**Table 30.1** Side effects of the most commonly used immunosuppressive drugs

Drug	Common adverse effects
Tacrolimus	Nephrotoxicity, neurotoxicity, hypertension, diabetes, metabolic acidosis
Cyclosporine	Nephrotoxicity, neurotoxicity, hypertension, diabetes, metabolic acidosis, hyperlipidemia, gingival hyperplasia, hypertrichosis
Corticosteroids	Hypertension, diabetes, osteoporosis, obesity, cataracts, poor wound healing
Mycophenolate mofetil	Myelosuppression, diarrhea, viral infections
Sirolimus	Poor wound healing, hyperlipidemia, myelosuppression, pneumonitis, rash

**Table 30.2** Drugs that increase and decrease CNI and sirolimus levels

Increase levels	Decrease levels
Calcium antagonists Verapamil, nifedipine, diltiazem	Anticonvulsants Phenytoin, carbamazepine, phenobarbital
Antifungals Fluconazole, itraconazole, ketoconazole, voriconazole, clotrimazole	Antibiotics Rifampicin, rifabutin
Macrolides Azithromycin, erythromycin, clarithromycin	St. John's wort
Protease inhibitors E.g. ritonavir, darunavir, saquinavir	
Metoclopramide	
Amiodarone	

calmodulin-dependent phosphatase. This prevents the dephosphorylation of activated T-cells which inhibits their nuclear entry and thus upregulation of pro-inflammatory cytokines including IL-2 (Signal 2 pathway) [14].

Tacrolimus inhibits calcineurin by binding to FK-binding protein-12. This in turn binds to a separate site to cyclosporine/cyclophilin on calcineurin resulting in a similar inhibitory pathway for IL-2 production. These two drugs cannot be used simultaneously as they compete with other for immunosuppressive action.

### Pharmacokinetics and Metabolism

The original formulation of cyclosporine was as Sandimmune, a corn oil-based agent with a highly variable absorption and only an average of 30% bioavailability. Absorption was dependent on the presence of bile salt availability. The use of T-tubes which interrupted enterohepatic circulation after transplantation necessitated intravenous administration. A microemulsion form, Neoral, was subsequently developed and adopted into regular practice. This formulation is less dependent on bile acids for absorption resulting in improved overall bioavailability. Distribution is concentration dependent and is predominantly in

adipose, adrenal, hepatic, pancreatic and renal tissue. In blood it is primarily bound to lipoproteins in plasma. The half-life is 18 h and it is mainly excreted into bile [15].

Tacrolimus is well absorbed from the gastrointestinal tract with a bioavailability in liver transplant patients of approximately 22%. The rate of absorption is best under fasting conditions. It is 95% bound to erythrocytes, with 99% of the remaining 5% bound to plasma proteins. Less than 0.1% is unbound, and it is this fraction that exerts the pharmacological activity [16]. The half-life varies from 31 to 48 h.

CNIs are metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme in the gastrointestinal epithelium (approximately 50%) and the liver where first pass hepatic metabolism accounts for a further 10%. The metabolites have minimal immunosuppressive effects. Drugs that interact with CYP3A4 will affect the concentration of CNIs (Table 30.2).

### Adverse Effects

Major long-term adverse effects are related to the kidneys. CNIs cause a reduction in renal blood flow and GFR by vasoconstriction of the afferent renal arteriole [17]. Longitudinal studies of liver transplant patients with chronic renal insufficiency demonstrate that CNI toxicity is the most common clinical and histologic diagnosis in patients who progress to end stage renal failure [18]. Both cumulative dose and duration of CNI exposure are related to the degree of renal damage [19]. These changes are reversible in the short term. Nearly 20% of liver transplant recipients go on to develop renal failure within 5 years [20]. This is a major clinical issue in post-transplant care and the concern about renal toxicity has led to CNI sparing regimes in patients with pre-existing renal dysfunction.

Hypertension is commonly seen, often due to the renal changes [21] and amlodipine is the drug of choice used to treat CNI-induced hypertension. Neurotoxicity is potentiated by low magnesium levels and often improves with magnesium supplementation [22]. Tremor, headache and

insomnia are the other adverse effects. Less common are convulsions, confusion, psychosis and reduced consciousness.

Metabolic effects: Diabetes, hyperlipidemia, hyperkalemia and metabolic acidosis are frequently observed. Gingival hyperplasia and hypertrichosis are specific to cyclosporine [23].

## Clinical Use

Tacrolimus (Prograf<sup>TM</sup>) has mostly superseded cyclosporine as the first-line drug in liver transplantation. Several studies have demonstrated a lower incidence of acute cellular rejection with tacrolimus compared to cyclosporine with similar patient and graft survival, and tacrolimus is usually the first choice CNI in de novo transplants [24–26].

In the immediate post-operative period tacrolimus can be administered orally or via an oro- or nasogastric tube if the patient remains intubated, usually at a starting dose of 1–2 mg twice daily. It is given in combination with intravenous steroid. Levels are checked and the dose is adjusted accordingly.

## Therapeutic Drug Monitoring

The immunosuppressive effects of CNIs are related to the total drug exposure that is represented by the area under the drug-concentration-time curve (AUC). Both drugs have a narrow therapeutic window. For tacrolimus, the 12-h trough concentration is a good estimation of the AUC: and blood samples taken 10–14 h after dosage are predictive of exposure [27]. There is no clear consensus as to the optimal dosing regimen in transplantation. One recommendation is to aim for trough concentrations of 10–20 ng/mL in the first post-transplant month provided good graft function and the absence of toxicity; 5–15 ng/mL in the next 2 months; and then 5–10 ng/mL [28]. Levels are adjusted according to renal function and the presence or absence of rejection.

A new once daily formulation of tacrolimus (Advagraf<sup>TM</sup>) has recently been introduced.

Once-daily dosing may improve compliance while allowing the same total daily dose and monitoring strategies [29]. Other generic formulations of tacrolimus will become available.

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## Corticosteroids

Corticosteroids are the most frequently used non-CNI drug immunosuppressants in liver transplantation and pulse dose methylprednisolone remains the first-line treatment for acute cellular rejection. Corticosteroids were initially used in high doses in the early era of transplantation and resulted in inevitable high morbidity. The current practice is based upon their use as induction therapy with early dose reduction over 6–8 weeks and possible withdrawal due to the myriad adverse effects.

## Method of Action

Corticosteroids have a wide variety of immunomodulatory and anti-inflammatory actions. They bind to glucocorticoid receptors resulting in inhibition of gene transcription of pro-inflammatory cytokines including IL-2, IL-6, TNF- $\alpha$  and IFN- $\gamma$ . These cytokines are required for the macrophage and lymphocyte response to allograft antigens. In addition, there is direct suppression of complement and antibody binding, stabilization of lysosomal enzymes, suppression of prostaglandin synthesis and reduction of histamine and bradykinin release.

## Adverse Effects

These are well known and summarized in Table 30.1.

## Clinical Use

Typical regimens use methylprednisolone 10–50 mg intravenously in the immediate post-operative period after a bolus of 500 mg



methylprednisolone in the operating room. Methylprednisolone is continued until enteral administration is possible and the dose is then converted to prednisolone 20 mg. The aim is to taper the dose gradually depending on the overall response to immunosuppression and etiology of the underlying liver disease. Withdrawal within 3–6 months in those with no evidence of rejection or autoimmune disease is often successful [30]. High-dose pulsed steroids are used to treat acute cellular rejection. Typically hydrocortisone 100 mg daily for 3 days or methylprednisolone 500 mg daily for 2 days is administered in conjunction with an increased dose of tacrolimus.

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### **Antimetabolites: Azathioprine and Mycophenolate Mofetil**

Antimetabolites were not initially used in liver transplantation, and they were used as part of strategies to reduce the frequency of CNIs related renal failure and to treat refractory rejection.

Azathioprine is the pro-drug form of 6-mercaptopurine that is then converted to 6-thioguanine, 6-methyl-MP and 6-thiouric acid. These active compounds interfere with DNA replication. Thiopurine methyltransferase (TPMT) is the enzyme required in the conversion of azathioprine to 6-MP. Polymorphisms of TPMT exist which cause decreased activity and allow toxic level of azathioprine to build up resulting in acute myelosuppression [31]. It is therefore essential to check TPMT activity prior to commencing therapy. Further metabolism is via xanthine oxidase and therefore it must not be used with allopurinol, a xanthine oxidase inhibitor, as toxicity will be potentiated.

Usage in liver transplantation has been limited due to adverse effects including liver toxicity, cholestatic jaundice, hepatic veno-occlusive disease, hypersensitivity, pancreatitis and bone marrow suppression, particularly in patients with portal hypertension. It is currently used primarily as adjunctive therapy.

MMF is derived from *Penicillium* and was first discovered in 1893 [32]; however, its evaluation as an immunosuppressant was not until the 1990s [33]. Two forms are available: MMF

(CellCept, Roche) and enteric coated mycophenolate sodium (Myfortic, Novartis).

### **Method of Action**

The active compound is mycophenolate acid (MPA). MPA inhibits the action of inosine monophosphate dehydrogenase (IMDPH), the rate limiting enzyme in the synthesis of guanosine nucleotides which are essential for DNA synthesis. Most cell types have a second pathway for nucleotide synthesis; however, lymphocytes do not possess such activity. There are also two isoforms of the IMDPH enzyme. The second isoform is more prominent in lymphocytes, and has preferential selectivity for MMF [34].

### **Pharmacokinetics and Metabolism**

MMF is well absorbed from the gastrointestinal tract and undergoes immediate hepatic first-pass metabolism to MPA. The half-life is approximately 18 h with bioavailability estimated at 90%. Food decreases MPA concentration so MMF should be administered at least 1 h before or 2 h after eating. MPA is 97% protein bound, with free MPA as the active fraction. MPA is further metabolized by the liver to mycophenolic acid glucuronide which has 93% urinary elimination. Liver disease impairs MPA conjugation, thus increasing its half-life. MPAG is also excreted into bile. Further hydrolysis back to MPA by gut organisms leads to enterohepatic recirculation of MPA and a second peak concentration 6–12 h post-ingestion [35].

### **Adverse Effects**

The most common dose related adverse effect is diarrhea. Other gastrointestinal adverse effects include nausea, vomiting and abdominal pain [36]. Bone marrow suppression can also occur. If these adverse effects do not improve with dose reduction, MMF should be stopped. There is also an increased incidence of viral and fungal



infections including CMV, HSV and candida with the use of MMF. Its use is not recommended in pregnancy due to the increased risk of congenital malformation and spontaneous abortion.

## Clinical Use

Predominant use is as a CNI-sparing agent as MMF is not nephrotoxic. It is more frequently used in patients requiring additional long-term immunosuppression, e.g. following documented previous rejection [37]. MMF has replaced azathioprine as it is associated with a lower incidence of biopsy proven rejection in combination with CNI [38]. There is no role of MMF as monotherapy due to the high incidence of ACR, steroid-resistant rejection and chronic rejection requiring re-transplantation [39].

## Therapeutic Drug Monitoring

The data to support monitoring is of limited quality as drug levels and effects are affected by a variety of factors including serum protein levels, other immunosuppressive agents and renal function leading to significant inter-patient variability [40].

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## mTOR Inhibitors: Sirolimus and Everolimus

The two mTOR inhibitors licenced for use in transplantation are sirolimus and everolimus. Sirolimus was discovered in soil samples from Easter Island (Rapa Nui) in 1964 and initially developed as an anti-fungal [41]. It is structurally similar to tacrolimus and is a naturally occurring product of *Streptomyces hygroscopicus*. Everolimus is a chemically modified form of sirolimus to improve absorption.

## Method of Action

Sirolimus and everolimus bind to the FK-binding protein-12 but do not inhibit calcineurin. Instead

they inhibit mTOR that is required for mRNA translation necessary for cell cycle progression, (which is halted in the G1 phase), IL-2 production and cellular proliferation. T-cell activation occurs, but IL-2-induced proliferation does not occur.

## Pharmacokinetics and Metabolism

Sirolimus is a highly lipophilic compound that is readily absorbed when in oily solution or micro-emulsion (bioavailability 14–18%). It has a half-life of 62 h and reaches steady state in 5–7 days. The long half-life necessitates regular drug monitoring. It is extensively bound to plasma proteins and metabolized by CYP3A4 (see Table 30.1) in the intestine and liver. Most of the metabolites are excreted in feces via a P-glycoprotein pump.

## Adverse Effects

Hyperlipidemia, thrombocytopenia, anemia and leucopenia are commonly seen. Rarer adverse effects include aphthous ulceration, acne, arthralgia and interstitial pneumonitis (resolves on withdrawal) [42]. Specifically in liver transplantation, an increased incidence of hepatic artery thrombosis and wound dehiscence in the first month post-transplant has been reported [43].

## Clinical Use

Studies of mTOR inhibitors as monotherapy have demonstrated the possibility of an increased risk of hepatic artery thrombosis and poor wound healing. There is also a higher incidence of rejection. Current practice is for introduction as combination therapy with tacrolimus in patients requiring broader immunosuppression or as a replacement monotherapy for patients intolerant of CNIs. In particular, early introduction of sirolimus may be most beneficial to prevent progression of renal complications of CNI.

Sirolimus has a potential anti-tumour effect: patients transplanted with HCC have been found to have a prolonged survival with sirolimus compared to CNI [44] but further confirmatory studies are required.

### Therapeutic Drug Monitoring

Sirolimus levels are estimated by either immunoassay or chromatography. It is essential that the same method is consistently used. Trough levels <6 ng/mL are associated with an increased incidence of rejection; levels >15 ng/mL have an increased risk of hyperlipidemia and thrombocytopenia [45]. Trough levels obtained 5–7 days after dose adjustment are sufficient due to the long half-life of sirolimus.

### Antibody-Based Therapies

These are generally utilized as induction of immunosuppression or as salvage for steroid refractory rejection.

#### Polyclonal Antibodies: Anti-thymocyte and Anti-lymphocyte Globulin

These agents are prepared by inoculation of rabbits with human lymphocytes or thymocytes. A purified gamma globulin fraction of antisera is used to prevent serum sickness. They were first used in the early era of transplantation with steroids and azathioprine prior to the introduction of CNI. Their action is on multiple T-cell antigens, B-cell antigens, HLA class 1 and 2, macrophages and NK cells causing lymphocyte depletion [46].

Adverse effects include fever, hypotension, headache, aseptic meningitis, ARDS, pulmonary edema and graft thrombosis. Steroids, antihistamines and acetaminophen are given as pretreatment to counteract these adverse effects. Polyclonal antibodies are currently used as an induction agent, a steroid-sparing agent or as the treatment of steroid-resistant rejection.

### Monoclonal Antibodies

*Anti IL-2 (CD 25) receptor antibodies* such as daclizumab or basiliximab are used as induction therapy to prevent rejection, especially in cases with renal dysfunction peri-transplantation as they allow lower or later start of nephrotoxic CNI [47]. Various protocols are in use. Typically the anti IL-2 (CD 25) receptor antibodies are administered on the first post-operative day and then 4–7 days post-transplant and they remain in circulation for several weeks. There are few adverse effects and they are generally very well tolerated.

*OKT3 (muromonab-CD3)*: binds to the CD3 receptor on mature T-cells, preventing signal 1 activation and depletion of lymphocytes by T-cell lysis and cytokine release [48]. Adverse effects are similar to ATG, but OKT3 is less well tolerated with a higher incidence of post-transplant lymphoproliferative disease (PTLD). Administration is by intravenous infusion and onset of action is within minutes, lasting 1 week. It is commonly used to treat steroid-resistant acute rejection and requires premedication antibodies with steroids, antihistamines and acetaminophen similar to polyclonal antibodies.

*Campath (Alemtuzumab)* is a humanized anti-CD52 monoclonal antibody that causes lymphocyte depletion from the circulation and peripheral nodes. Its role in immunosuppressive regimens is not yet identified, but it can be used as induction therapy to facilitate lower doses of CNI and in conjunction with sirolimus.

### Special Situations

As individualized therapy becomes more common, immunosuppression for patients with hepatitis C infection and with renal failure are of particular relevance.

*Hepatitis C*: this is now the single most common reason for transplantation in industrialized countries. Re-infection of the graft is almost universal [49] and occurs in the immediate post-transplant period [50]. High-dose steroid therapy for acute rejection causes an increase in viremia

and more rapid progression of disease recurrence [51]. Strategies used include early steroid withdrawal and the combination of induction therapy with IL-2 blockade [52]. Some in vitro studies suggest that cyclosporine instead of tacrolimus has an inhibitory effect on replication [53] but the concentrations used in these replication studies were greater than 1,000 times of physiological concentration. Novel cyclophilin inhibitors (e.g. Debio 025) have demonstrated anti-HCV activity and are undergoing clinical trials as the treatment for HCV [54]. Therefore there may be a role for either cyclophilin inhibitors or cyclosporine in the post-transplant HCV. Furthermore cyclosporine is less diabetogenic than tacrolimus and diabetes is considered a risk factor for fibrosis progression post-transplant for HCV [55].

*Renal failure:* Renal dysfunction and acute kidney injury after liver transplantation is common and has important implications for subsequent patient morbidity and survival. Ten to 60% of LT recipients develop post-operative acute kidney injury and 10–25% require post-operative renal replacement therapy [56]. The need for post-operative renal replacement is associated with a two to six-fold increased risk of 1-year mortality [57]. Longitudinal studies of liver transplant patients with chronic renal insufficiency demonstrate that CNI toxicity is clinically and histologically the most common cause in patients who progress to end stage renal disease [58]. A number of strategies have been employed to minimize the dose of CNI in the immediate post-transplant period in patients at risk of developing renal injury, principally those with pre-existing renal dysfunction. Minimizing early acute CNI-induced renal injury will reduce the incidence of acute and chronic renal disease later after transplant. Induction of immunosuppression with IL-2 receptor blockers or ATG and delayed or reduced dose start of CNI is commonly part of renal-protective protocols. Some centre will also convert CNI to mTOR inhibitors in patient with acute kidney injury.

A wide range of different immunosuppressive agents are now available with varying degrees of potency and toxicity. Newer agents are in

development that will enable more tailored regimens depending on the etiology of the underlying liver disease and to prevent renal toxicity. In an era of organ shortage that results in sicker patients with significant co-morbidities and the use of marginal, extended criteria grafts individualized immunosuppressive protocols are of increasing importance. The long-term aims are to develop agents and protocols that immunological tolerance and potentially immunosuppression withdrawal.

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The incidence of postoperative renal insufficiency and acute kidney injury (AKI) in patients undergoing liver transplantation ranges from 20% up to 90% [1] and more than 80% of these episodes occur within the first 2 postoperative days. Earlier studies found that mortality at 30 days was 50% in patients who developed AKI and 29% in non-AKI patients [2]. AKI necessitating renal replacement therapy has been associated with mortality rates from 55 to 90% [3]. Risk factors for the development of AKI in these patients include preoperative renal dysfunction represented with a higher preoperative serum creatinine (SCrea), greater requirements for intraoperative blood transfusion, more frequent episodes of intraoperative hypotension, and other preexisting comorbidities [2].

AKI was traditionally defined as an acute reduction in glomerular filtration rate (GFR) sufficient to cause azotemia and multiple at times conflicting definitions existed in the literature

that made comparisons of studies difficult. In 2004 the second international consensus conference of the Acute Dialysis Quality Initiative (ADQI) Group proposed a new classification scheme for AKI that includes separate criteria for SCrea/GFR and urine output [4]. These RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease) criteria define AKI either by SCrea/GFR (increase of SCrea  $\geq 3$  times of the baseline or GFR decrease of 75% of the baseline, or SCrea  $\geq 4$  mg/dL) or by urine output (urine output  $< 0.3$  mL/h  $\times 24$  h or anuria  $\times 12$  h). A more recent definition by the Acute Kidney Injury Network (AKIN) proposes “An abrupt (within 48 h) reduction in kidney function currently defined as an absolute increase in SCrea of more than or equal to 0.3 mg/dL ( $\geq 26.4$   $\mu$ mol/L), a percentage increase in SCrea of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg/h for more than 6 h)” [5] as a definition of AKI, reflecting the fact that even small changes of SCrea affect outcome for example after cardiac surgery.

Post-transplant AKI can be attributed to several causes (Table 31.1). Acute tubular necrosis (ATN) appears to be the major cause of AKI. Fraley et al. divided ATN into ischemic and nephrotoxic causes and attributed 52% of ATN to ischemia and 18% of ATN to nephrotoxic causes [6]. Other significant causes of postoperative ATN include contrast nephropathy, sepsis, and rarely rhabdomyolysis.

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Early diagnosis of AKI is of critical importance as only early intervention can potentially affect outcome. However SCrea is a very slow and insensitive marker that reflects renal function but not injury. It may take days after a renal injury for SCrea to increase and any intervention at this time would be too late. Furthermore, the decision when and how to start immunosuppression with nephrotoxic immunosuppressive often needs to be made before an increase of SCrea reveals substantial renal injury.

Recently novel biomarkers of renal injury have been discovered and tested as predictors of renal injury after liver transplantation. Of these neutrophil gelatinase-associated lipocalin (NGAL) is one of the most promising. NGAL is a 23 kD protein that can be detected in urine and blood within hours after renal injury and is a sensitive marker in multiple scenarios of kidney

injury. After liver transplantation NGAL increases rapidly in blood and urine and can predict AKI with good sensitivity and specificity [7–9]. Further studies are required to confirm the clinical utility of this and other biomarkers.

In patients with ATN, muddy-brown casts are usually seen in the urinary sediment and an increased fractional excretion of sodium is evident. Treatment of ATN is usually supportive and there is no intervention that is able to prevent or ameliorate AKI [10]. However it is important to avoid further renal insults by maintaining blood pressure and renal perfusion and minimizing nephrotoxic drugs. Pharmacologic agents that may cause AKI are listed in Table 31.2.

AKI can usually not be attributed to a single cause and multiple renal insults are required to cause clinically overt AKI. Pre-existing renal insufficiency and hepato-renal syndrome, intra- and postoperative hypotension, hypovolemia, and vasopressor requirements possibly in conjunction with caval crossclamp (and renal venous obstruction) and the use of nephrotoxic drugs such as calcineurin inhibitors all contribute to renal injury and may precipitate AKI. Common postoperative causes of AKI are explained in more detail below.

**Table 31.1** Causes of postoperative renal failure in liver transplantation

Acute tubular necrosis	Calcineurin inhibitor toxicity	Other
Ischemic	Tacrolimus	Abdominal compartment syndrome
Nephrotoxicity	Cyclosporine A	Hemolytic uremic syndrome
Nephropathy		Thrombotic thrombocytopenic purpura
Sepsis		Infection
Rhabdomyolysis		

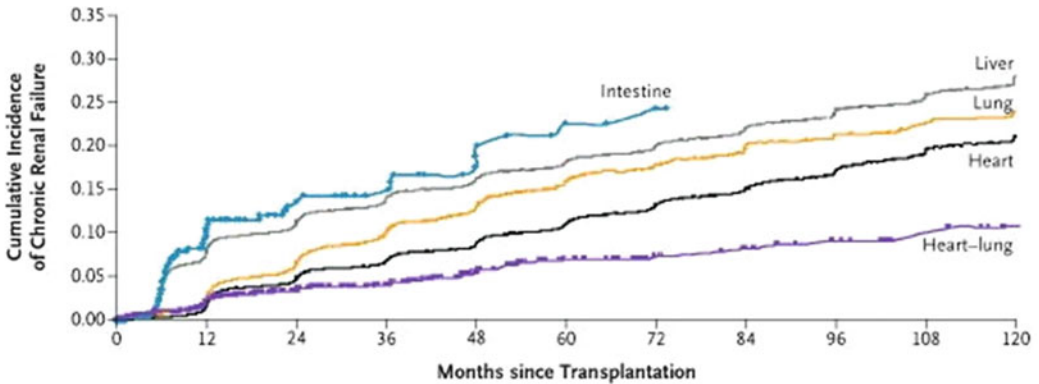
### Calcineurin Inhibitors

Both tacrolimus and cyclosporine A contribute to the development of chronic renal failure in the post-transplant period in liver transplantation patients and the use of both tacrolimus or

**Table 31.2** Agents associated with renal failure

Pre-renal hemodynamic changes	Acute tubular necrosis	Acute interstitial nephritis
Cyclosporin	Aminoglycosides	Penicillins
Tacrolimus	Amphotericin B	Cephalosporins
Radiocontrast agents	Cisplatin	Sulfonamides
Amphotericin B	Cephalosporins	Rifampin
ACE inhibitors	Radiocontrast agents	NSAIDs
ACE receptor blockers		COX-2 inhibitors
NSAIDs		Interferon
COX-2 inhibitors		Interleukin-2

From Coffman TM. Renal failure caused by therapeutic agents. In: Greenberg A, editor. Primer on kidney diseases. San Diego: Academic; 1998. p. 260–5



No. at Risk	0	12	24	36	48	60	72	84	96	108	120
Heart-lung	576	375	295	219	194	156	133	107	72	46	30
Heart	24,024	19,885	17,238	14,687	12,341	10,022	7997	6104	4526	3096	1991
Intestine	228	152	110	84	57	33	23	13	8	5	5
Liver	36,849	28,495	24,041	19,508	15,724	12,564	9844	7345	5292	3614	2261
Lung	7,643	5,633	4,316	3,184	2,327	1,629	1136	745	468	258	133

**Fig. 31.1** Cumulative incidence of chronic renal failure among 69,321 persons who received nonrenal organ transplants in the United States between January 1, 1990,

and December 31, 2000. (with permission: [17] Ojo AO et al. *N Engl J Med* 2003;349:931–940)

cyclosporine has been associated with acute increases in creatinine due to changes in renal hemodynamics [11]. Nonprogressive and dose-dependent renal dysfunction may be observed with elevations in SCrea levels paralleling the elevations of serum levels of the calcineurin inhibitor. Lowering the dose of calcineurin inhibitors may ameliorate deteriorating renal function. In addition, there have been a number of studies suggesting that chronic nephrotoxicity may be alleviated by the use of rapamycin as the primary immunosuppressive agent instead of calcineurin inhibitors [11, 12]. Late changes of calcineurin inhibitor use include renal tubular atrophy and renal interstitial fibrosis [13, 14] that may lead to irreversible renal failure requiring hemodialysis. Strategies to reduce the dose of calcineurin inhibitors by using alternate forms of immunosuppression have been attempted. Induction of tolerance in liver transplantation where calcineurin inhibitors are slowly weaned to very low doses may significantly diminish or eliminate the renal toxicity related to these agents while still providing adequate immunosuppression [15].

Careful monitoring of calcineurin inhibitor levels is essential to avoid major toxicity. And decreasing doses when supra-therapeutic levels are observed may lessen the incidence of chronic

renal failure. Other supportive treatments include strict control of blood pressure, control of hyperlipidemia, and control of post-transplant diabetes mellitus [16]. Often, however, renal failure is unrelenting and renal replacement therapy is necessary. Liver transplantation has the second highest incidence of renal failure requiring renal replacement therapy of solid non-renal transplants (after intestinal transplants). Twelve, 36 and 60 months after liver transplantations 8.0%, 13.9%, and 18.1%, respectively, developed chronic renal failure (Fig. 31.1). Chronic renal failure after non-renal solid organ transplantation is associated with a 4.55 times higher risk of death compared to patients with no chronic renal failure [17]. Therefore preventing chronic renal failure by reducing calcineurin inhibitors to the lowest possible dose and avoiding other injuries is paramount to ensure long-term success of the transplant.

### Thrombotic Thrombocytopenic Purpura: Hemolytic Uremic Syndrome

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) have been described in patients after liver transplantation

and are often attributed to immunosuppressive drugs. Both cyclosporine A and tacrolimus have been associated with TTP-HUS [18–22]. HUS is characterized by fever, microangiopathic hemolytic anemia and thrombocytopenia. In TTP, these symptoms are accompanied by neurologic changes and acute renal failure. TTP-HUS may be associated with malignant hypertension and subsequent arteriolar injury. The diagnosis is usually made on clinical grounds alone but may be confirmed by renal biopsy. Plasmapheresis has been successfully used with or without holding the toxic drug however usually changing immunosuppression is required to treat this condition.

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## Abdominal Compartment Syndrome

Increased intra-abdominal pressure is a contributing factor to AKI after liver transplantation. Progressive and abrupt increases in intra-abdominal pressure reduce cardiac output, contribute increased inspiratory pressures when ventilated and decreases in splanchnic, hepatic, and renal perfusion. These changes are collectively referred to as “abdominal compartment syndrome” [23–25]. Biancofiore et al. [26], using urinary bladder manometry, has shown that up to 32% of patients undergoing liver transplantation have intra-abdominal pressures greater than 25 mmHg. This elevation in intra-abdominal pressure was associated with renal failure, lower filtration gradient, and prolonged ventilation in the post-transplant period and may exacerbate renal injury to a degree that renal replacement therapy is necessary. Increased intra-abdominal pressure may also impede blood flow to the liver and graft function [27]. Frequent measurements of intra-abdominal pressure and possibly re-exploration if the intra-abdominal pressure is sustained high may help alleviate this problem.

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## Infectious Complications

Postoperative infections can progress to sepsis and septic shock and cause substantial renal injury that may progress to renal failure requiring

renal replacement therapy. Specific infection that cause direct renal injury are often caused by viruses. Epstein-Barr virus (EBV) has been reported to cause renal failure in patients after liver transplantation [28]. If detected, appropriate antiviral therapy should be initiated. Post-transplant lymphoproliferative disorder (PTLD) may occur secondary to EBV and has been shown in autopsy studies to infiltrate the kidney [29]. Although there has not been a clear correlation between renal infiltration in PTLD and renal failure, this should be considered in the differential diagnosis of AKI.

There have been case reports of JC and BK polyoma viruses causing hemorrhagic cystitis and renal failure in bone marrow transplant recipients [30] and renal allograft recipients [31–33]. No reports of these viruses causing renal failure in liver transplant patients have been cited, however, these viruses have been found in the urine of liver transplant patients [34] and should be considered when other causes are not found.

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## Summary

Renal failure after liver transplantation is a serious and life-threatening complication. Early identification of high-risk patients is essential to minimize the development of this problem. Early diagnosis of renal dysfunction and optimal medical management postoperatively in the intensive care unit is required to ameliorate further renal injury. If irreversible renal failure develops, renal replacement therapy with hemodialysis may be required and possible renal transplantation should also be considered if ARF is not reversible.

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Srinath Chinnakotla and James F. Trotter

The increasing organ donor shortage in recent years has forced the use of liver allografts with more expanded criteria for selection which are allocated to sicker and more decompensated recipients, resulting in an increase of the number of transplants. Furthermore advances in surgical technique have allowed the use of partial liver grafts both split and living donor in order to increase to the donor pool. However, this has resulted in novel challenges and particularly graft dysfunction, graft failure, and small for size syndrome (SFSS) have become more important than ever. Clinically, post-liver transplant graft failure is a continuum ranging from an ambiguous and easily reversible graft dysfunction to a complete absence of function and primary non-function. The incidence of graft dysfunction varies from 13 to 27% and the incidence of primary non-function affects 4–7% of the deceased donor liver grafts [1–3]. With living donor liver transplantation, cold and warm ischemia times are minimal and donor quality typically excellent and primary non-function is less common with a 3% incidence reported in the A2ALL study [4]. However,

recipients of living donor liver transplants have a higher incidence of SFSS as cause of early graft failure. Early graft failure in both deceased donor and living donor liver transplant recipients has a major impact on the prognosis and clinical outcome after liver transplantation (LT). This chapter will outline the risk factors for early allograft dysfunction and provide a guide to early diagnosis and management strategies of graft failure and SFSS.

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### Assessment of Liver Graft Function

#### Operating Room

Signs of graft function are apparent in the operating room after reperfusion of the liver allograft. Very soon after completion of the portal vein and hepatic artery anastomosis, the liver should pink up uniformly, start producing bile, metabolic acidosis should correct itself, and coagulation abnormalities should improve. Bile production during the transplant procedure itself is an excellent prognostic sign and the bile flow rate was one of the most useful predictors of postoperative function in many studies. Bile production may reflect the recovery of adenosine triphosphate synthesis in the graft. Anecdotally, the color of the bile may be equally important, with golden brown color considered ideal. Signs and symptoms of graft failure can be recognized very early during surgery: Unusual or discolored appearance of the liver, worsening coagulopathy after reperfusion

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of the liver graft, abnormal CO<sub>2</sub> production, persistent lactic acidosis, inadequate urine output, inability of patients to raise the core body temperature, hemodynamic instability, abnormalities in glucose, and hyperkalemia are all indicators that should alert the anesthesiologist to the possibility of early graft failure.

### Early Postoperative Period

Postoperatively the diagnosis of early graft failure and primary non-function can be made on the basis of clinical findings and laboratory values.

Good postoperative mental status and good urine output and renal function are indicative of satisfactory allograft function. Progressively increasing encephalopathy, low urine output, worsening metabolic acidosis, and hypotension should alert to the possibility of graft failure. Liver function tests obtained immediately after surgery are more reflective of the blood products and coagulation factors the patient has received in the operating room; however, after 12-h post-transplant these may be more indicative of the function of the new liver allograft. Prothrombin time and therefore also international normalized ratio (INR) are good indicators of the synthetic function of the new liver because the biological half-life of factor VII is only 4–6 h and, without adequate liver synthesis, plasma concentrations rapidly fall [5]. The serum transaminases reflect the degree of preservation injury and usually peak 24 h post-transplant and then decrease by approximately 30% every 24 h post-transplant for the first few postoperative days. Serum transaminases less than 2,000 U/L are indicative of minimal preservation injury and serum transaminases in ten of thousands or levels that are steadily increasing imply severe organ damage and unlikely recovery. In one study, serum AST level of >5,000 U/L resulted in a primary non-function rate of 41% as opposed to a rate of 10% in those with peak AST levels of 2,000–5,000 U/L [6]. Elevated prothrombin time and alanine transaminase levels may have similar predictive value. Persistent lactic acidosis, hypoglycemia, hyperkalemia, increasing hyperbilirubinemia and

persistent hypoprothrombinemia are all prominent signs of poor function however rather than the absolute value of any of these tests the trend is of even greater importance.

Multiorgan system failure is the inevitable result in the absence of a functioning liver and poor outcome is not necessarily associated with any particular individual organ system but rather the number of organ systems involved.

In some patients the graft failure may be more insidious in presentation especially well-compensated patients with low preoperative Model for End Stage Liver disease (MELD) score.

Multiple different definitions of early allograft dysfunction using various laboratory cut-off values have been described. Recently Olthoff et al. defined early allograft dysfunction as an elevated serum bilirubin >10 mg/dL and an INR >1.6 on postoperative day 7 or AST levels >2,000 U/L within the first 7 days and found that patients with early allograft dysfunction using this definition have a tenfold higher chance of death within 6 months [7].

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### Management of Early Graft Failure

It is imperative that vascular (hepatic artery, portal vein, hepatic vein outflow) or other technical complications are expeditiously excluded. Vascular patency can be quickly evaluated by a Doppler ultrasound by an experienced radiologist. Doppler ultrasound often reveals a low resistive index in the hepatic artery. Often, a surgical re-exploration is the most expeditious way to exclude a wide variety of vascular and mechanical complications and allow “hands on” assessment and a safe biopsy of the graft. If there is a technical problem, it can be rectified at the time of re-exploration. In the case of mechanical compression of the liver due to a size mismatch (large liver in a small recipient), the abdominal cavity should be expanded leaving the fascia open or by closing the abdomen with a synthetic mesh.

The best treatment of graft failure is avoiding the use of grafts that carry a significant risk of primary non-function (Table 32.1), careful selection of recipients, and a good technical,



**Table 32.1** Risk factors for early graft failure

Donor	Procurement-related factors	Recipient
Age >60 years	Non-heart beating donors	Hemodynamically unstable patient on multiple pressors
Steatosis >30%	Prolonged cold ischemia time >16 h	
Hypernatremia >165		
Multiple high-dose pressors of the donor		
Prolonged hospitalization of the donor		

logistical, and anesthesiologic technique during the liver transplant operation. Once the diagnosis of graft failure is established, the critical question is, if the graft failure is reversible or not. In general if there is increasing serum transaminases (in the thousands), poor synthetic function with elevated prothrombin time and INR despite continuous administration of fresh frozen plasma, persistent metabolic acidosis, renal failure, and worsening encephalopathy, it is very unlikely that the graft will improve and the only remaining treatment is urgent re-transplantation [8]. Once the patient is listed for urgent re-transplantation (status Ia in the USA), our practice has been to maintain adequate cardiac output and perfusion to the liver and initiate continuous venovenous hemodialysis (CVVHD). Primary non-function will almost always precipitate acute renal failure and fluid overload from large volume blood transfusions to correct aberrant coagulation that will necessitate CVVHD. There are several additional advantages of initiating CVVHD including lowering ammonia levels, correcting acid-base and fluid-electrolyte disturbances, lowering the CVP and albeit reducing the congestion of the liver graft, improving pulmonary congestion and clearing lactic acidosis. This will often stabilize the patient until a new liver graft becomes available. Prostaglandin E1 and Prostacyclin infusion may be helpful to increase hepatic blood flow although this potential benefit has not been demonstrated in large randomized trials [9]. In cases of severe hemodynamic or pulmonary instability due to toxic metabolites released from the necrotic liver graft, a hepatectomy and/or temporary portocaval shunt may be required [10]. This is obviously a drastic step but can result in temporary stabiliza-

tion in a patient on the verge of cardiopulmonary collapse. The authors' experience has shown that although patients with primary non-function are very sick and in multiorgan failure excellent outcomes can be achieved if they are carefully stabilized and then re-transplanted [8].

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### Small for Size Syndrome

If a partial liver graft (living donor or split) is unable to meet the functional demands of the recipient; liver graft failure may ensue manifesting itself as coagulopathy, ascites, prolonged cholestasis, and encephalopathy, often associated with renal and respiratory failure. These patients are further at increased risk for sepsis and gastrointestinal bleeding. This ill-defined clinical picture is considered to be primarily linked to insufficient graft size and is hence termed "small for size syndrome." A liver biopsy performed on such grafts often shows cholestasis with bile plugs, and areas of regeneration and ischemia with patchy necrosis [11]. The etiology of SFSS is likely to be multifactorial. Donor factors associated with an increased risk of SFSS after liver transplantation include graft to recipient weight ratio (GRWR) of <0.8% and preexisting steatosis of the donor graft [12]. The recipient factors include a decompensated recipient with a high MELD score and very severe portal hypertension. The exact pathogenic mechanisms of SFSS are still unclear; critical graft size and function, graft injury, regeneration, and recovery may all contribute to SFSS [12]. Recent clinical studies have focused on the reduction of portal venous inflow to the small graft to prevent development of

SFSS, thereby implicating portal hyperperfusion as a cause of SFSS [12]. Spontaneous improvement of liver function may occur over time but approximately 50% of recipients with SFSS will die of sepsis or other complication within 4–6 weeks after transplantation [13]. Therefore prevention of SFSS after transplantation is key. Once SFSS is established after partial liver graft transplantation and technical complications such as bile leak or vascular thrombosis have been excluded by imaging studies further treatment is supportive. If the patient has evidence of a large spleen or severe portal hypertension, splenic artery ligation to reduce portal vein blood flow has been reported in one study of seven patients. If there is no response to intervention, the prudent course would be to retransplant the patient before sepsis or multiorgan failure develops [14].

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Fuat Hakan Saner

When Thomas Starzl reported the results of the first liver transplant program in 1976 [1] only 29% of the transplanted patients survived 1 year after transplantation and the main cause of death at that time was uncontrolled bleeding due to severe coagulopathy and acute and chronic rejection. Infection was considered less common. Only when cyclosporine was introduced as an immunosuppressant drug to avoid acute and chronic rejection, the reported 1-year survival increased to 80–90%. But with improved survival infectious complications after liver transplantation became more common.

The incidence of sepsis and septic shock increased substantially in the last three decades [2] and due to the extensive and prolonged use of third-generation cephalosporines and chinolones there was a shift towards gram-positive bacteriae, particular to methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) [3]. Furthermore the extended use of third-generation cephalosporins and imipenem/cilastatin induced the growth of *Acinetobacter*, yeast, and VRE [4] (Fig. 33.1).

Infection is now one of the leading causes of morbidity and mortality in liver transplant patients. More than 50% of liver transplant patients develop infections during the first year

after transplantation [5] with the majority of bacterial infections occurring within the first 2 months after transplantation.

Pulmonary complications such as pneumonia are a major cause of death in liver transplant patients [6] and the majority of pneumoniae is caused by bacteria (50–70%) [7–10] especially gram-negative rods. *Aspergillus* species are the most common nonbacterial organisms causing pneumonia in the first month after transplantation.

In the early post-transplant setting the ICU physician is mainly confronted with bacterial and fungal infections and this review will therefore focus on these microbes.

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## Risk Factors for Infections

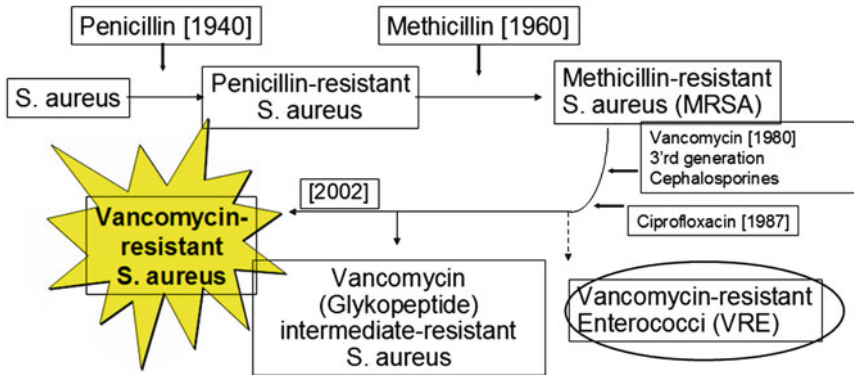
### Risk Factors for Bacterial Infections

After liver transplantation, bacteremia has been documented in 20–40% of patients [8, 11–13] with a reported mortality of 15–36% [8, 12]. Early after liver transplantation it is difficult to estimate the likelihood of infection in a setting of fever and/or altered laboratory general markers of infection and inflammation such as C-reactive protein (CRP) or procalcitonin (PCT). Markers that are able to reliably predict the probability of bacteremia in febrile patients would allow a more judicious and appropriate use of antibiotic while culture results are pending.

Singh et al. [14] evaluated the risk factors for bacterial infections in 59 liver transplant patients

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**Fig. 33.1** Development of resistance in gram positive cocci: In 1940 Chain et al published a report about penicillin as a chemotherapeutic agent (Lancet 1940; 236, 226–228). Already that same year this group described an enzyme from bacteria that is able to destroy penicillin (Nature 1940; 146, 837–837). Methicillin was the first

penicillinase-resistant antibiotic, however in 1963 Methicillin-resistant staphylococcus aureus (MRSA) evolved. With the extended use of cephalosporines, chinolones, and vancomycin, vancomycin resistant enterococci (VRE) and Vancomycin resistant s.aureus occurred.

with clinical signs of infection. When comparing patients with post-transplant bacteremia to patients with non-bacteremic systemic inflammation, bacteremic patients were significantly more likely to have renal dysfunction, diabetes mellitus, higher APACHE II scores, lower serum albumin levels, and were more like in the ICU at the time of onset of symptoms. White blood cell count, bilirubine, or prothrombin time was not significantly different as was temperature, which was previously assumed to be an early and nonspecific marker for infection in surgical patients.

PCT is a prognostic marker for infection in non-transplant patients and it is suggested that guiding antibiotic treatment to the level of PCT may reduce the antibiotic exposure with a comparable cure rate [15–17]. There is little data supporting the use of PCT as a marker of infection after liver transplantation. Van den Broek et al. evaluated PCT and CRP as a prognostic markers for infectious complications in liver transplant patients with life-threatening infections [18]. In a univariate analysis peak PCT and peak CRP were significantly higher in patients with infections compared to patients without infections. Using multivariate analysis male sex, BMI < 20 kg/m<sup>2</sup> (vs. BMI > 25 kg/m<sup>2</sup>), acute liver failure as an indication for liver transplantation and prolonged cold ischemia time (>420 min)

but not peak PCT were independent risk factors for infection.

Furthermore anti-thymocyte globulin (ATG) can markedly increase PCT in patients [19] and when ATG is part of an immunosuppressive protocol, symptoms can be very similar to sepsis (fever, elevated liver enzymes, low-dose catecholamine requirement) and the diagnosis of infection becomes very difficult.

### Risk Factors for Fungal Infection

Invasive fungal infections have been reported in 5–42% of liver transplant recipients with an associated mortality of 25–71% [20–23]. The unique susceptibility of liver transplant patients to invasive fungal infection is well recognized; the main cause of fungal infections is candidemias [24].

Pre- and intra-operative risk factors for invasive fungal infections in liver transplant patients include previous liver transplantation particular within 30 days, renal failure, specifically when dialysis is required, extended use of antibiotic prophylaxis, reoperation due to bleeding or bile leak, and treatment of rejection with pulsed dose of steroids [8, 25, 26]. In the recent years more and more non-albicans strains are evident and azole-resistant albicans are frequently isolated [26].

## The Role of Selective Digestive Decontamination (SDD), Antibiotic Prophylaxis, and Antimycotic Prophylaxis

Most centers currently use perioperative antibiotic prophylaxis for 2 or 3 days, however, there is no evidence to support this approach. Antibiotic prophylaxis is only able to prevent wound infections, not pneumonia, bile leak, or abscess and extended use of antibiotics will increase multi-drug-resistant (MDR) bacteriae [3] and is a risk factor for fungal infection [26].

In 1983 Stoutenbeek described the use of selective digestive tract decontamination (SDD) [27] to prevent nosocomial infections and since then multiple studies have evaluated the use of SDD after liver transplantation. There were four prospective randomized trials with conflicting results [28–31]. Safdar et al. [32] undertook a systematic review and meta-analysis of randomized trials of SDD vs. placebo after liver transplantation and found SDD to be effective in reducing gram-negative infections. However, due to more frequent gram-positive infections, the effect on the overall rate of infection was limited. The relative risk of infection with SDD was 0.88 (95% CI, 0.7–1.1) indicating no statistically significant reduction of infections with the use of SDD.

There are two important studies of antimycotic prophylaxis after liver transplantation: Winston et al. [33] evaluated the efficacy and safety of prophylactic fluconazole in liver transplant recipients in a randomized, double-blind, placebo-controlled trial. More than 200 liver transplant recipients received fluconazole (400 mg/day) or placebo up to 10 weeks after transplantation. Fungal colonization increased in patients who received placebo (from 60 to 90%) and the incidence of fungal colonization in patients who received fluconazole (from 70 to 28%) was decreased. Confirmed fungal infections occurred in 45 of 104 placebo recipients (43%) but only in 10 of 108 fluconazole recipients (9%,  $P < 0.001$ ). Fluconazole prevented both superficial infection (29 of 104 patients receiving placebo recipients (28%) compared to 4 of 108 patients receiving fluconazole (4%);  $P < 0.001$ ) and invasive infection (24 of 104

patients receiving placebo (23%) compared to 6 of 108 patients receiving fluconazole (6%);  $P < 0.001$ ).

Singh et al. evaluated the efficacy of liposomal amphotericin B as prophylaxis for invasive fungal infections in high-risk liver transplant patients requiring hemodialysis. They compared this cohort with a historical control group without antifungal prophylaxis [34]. Antifungal prophylaxis with liposomal amphotericin B reduced the incidence of fungal infections from 36% in the historical control group to 0% in the treatment group. Moreover antifungal prophylaxis with liposomal amphotericin B protected against fungal infections independent of covariates. However, both studies failed to demonstrate a difference in outcome after liver transplantation with antifungal prophylaxis. These results were confirmed by a meta-analysis [35]: Prophylaxis reduced colonization and confirmed fungal infections and mortality attributable to fungal infection but did not affect the overall mortality or empiric treatment for suspected fungal infection. The beneficial effect of antifungal prophylaxis was predominantly associated with a reduction of *Candida albicans* infections and of mortality attributable to *C. albicans*. Compared to controls however, patients receiving antifungal prophylaxis experienced a higher number of episodes of non-albicans candidae infections, especially *Candida glabrata* and no beneficial effect on invasive aspergillus infection was observed.

In conclusion, although antifungal prophylaxis has been widely studied and practiced, no consensus exists on which patients should receive prophylaxis, with which agent and for what duration. Depending on the local epidemiology and incidence of fungal infection transplant centers with fungal infection rate  $< 8\%$  does not require prophylaxis. Concerns about selection of triazole-resistant *Candida* strains are real and a potential disadvantage of prophylaxis. It may be more reasonable to identify patients at risk for fungal infections and treat assumed fungal infections early and preemptively instead of using general antifungal prophylaxis on all transplant recipients. Due to a shift towards non-albicans strains, use of echinocandin instead of fluconazole [36] may be indicated.

## Multiple Resistant Gram-Positive and Gram-Negative Bacteria

### *Staphylococcus aureus* (MRSA)

MRSA is an important cause of infection in liver transplant patients. The incidence of MRSA is continuously increasing and a significant cause of blood stream infections (BSI). In some intensive care units in the USA, MRSA has a prevalence of >64% [37]. However in Europe even after liver transplantations the MRSA rate for BSI was only 13% [8]. In the absence of transplantation, risk factors associated with MRSA infection are prolonged illness, co-morbidities, especially diabetes mellitus and renal failure requiring dialysis, longer ICU and hospital stay, and extended exposure to third-generation cephalosporines and chinolones [3, 38]. Colonization with MRSA increases the risk of later infection usually by the colonizing strain [39]. Liver transplant recipients who are colonized with MRSA have a higher incidence of MRSA infections, ranging from 31 to 78% [40, 41]. Carriage of MRSA does not increase the mortality rate [40]; however, once MRSA infection is evident the mortality risk is clearly increased [40].

Vancomycin is the drug of choice for infections caused by sensitive MRSA [42] and should be given to obtain adequate trough levels of at least 10 µg/mL. Trough levels above 10 µg/mL when the minimum inhibitory concentration (MIC) is 1 µg/mL [43] and 15–20 µg/mL, if MIC is ≥2 µg/mL [44] are required to prevent the development of resistance. In critically ill patients a loading dose of 25–30 mg/kg should be considered [45]. However there is an incremental risk of nephrotoxicity from 12 to 42.7% associated with higher vancomycin doses. The risk increases with higher vancomycin trough levels, longer duration of vancomycin use, concomitant use of other nephrotoxic agents, and in patients who are critically ill or with sepsis or previously compromised renal function [46–51]. Data on the degree of renal recovery are scarce and the mechanisms of vancomycin toxicity have only partially been evaluated. Liver transplant patients at an increased

risk for kidney injury (for example due to the use of calcineurin inhibitors or preoperative impaired kidney function) should be treated with alternative drugs without nephrotoxic side effects.

*Linezolid* is bacteriostatic and approved for skin and soft tissue infections (SSTI) and nosocomial pneumonia but not approved for the treatment of MRSA sepsis or endocarditis. With long-term use (>28 days) thrombocytopenia and/or peripheral and optic neuropathy may occur. There is no interaction with the cytochrome P450 enzymatic system. Interestingly, a recent trial of 46 liver transplant patients at risk for thrombocytopenia with proven gram-positive infection indicated that the use of linezolid was not associated with thrombocytopenia but conversely a significant increase of the platelet count during treatment with linezolid was observed [52].

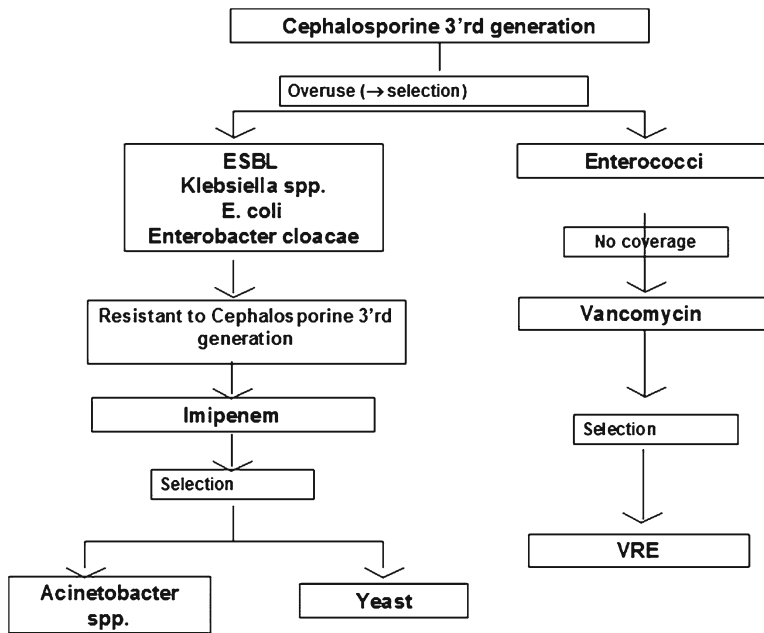
*Daptomycin* is bactericidal and used to treat SSSI, MRSA bacteremia, and right-heart endocarditis but should not be used to treat MRSA pneumonia, because it is inactivated by lung surfactant.

*Tigecycline* is bacteriostatic and approved for SSSI and intraabdominal infections (IAIs). There is no data about treating of bacteremia or endocarditis with *tigecycline*. Caution should be used in the presence of confirmed bacteremia because serum concentrations can rapidly decrease between doses [53].

### Prevention and Infection of MRSA in Liver Transplant Patients

Several guidelines have been proposed to reduce the rate of MRSA colonization and infections [54, 55]. These guidelines were not evaluated for liver transplant patients; however, due to the absence of data in liver transplant patients, we suggest to use these recommendations issued for general ICU populations. Liver transplant candidates with MRSA should be identified by routine nasal swab and MRSA in colonized patients should be eradicated using local mupirocin ointment. The use of antibiotics should be judicious and appropriate. We recommend to limit the empirical use of antibiotics and avoid long





Modified to Bernstein Chest 1999 .

**Fig. 33.2** Extended use of cephalosporines emerges resistant bugs. The overuse of third-generation cephalosporines induces the growth of bacteria which are not covered by cephalosporines. First of all the growth of enterococci is increased, which were treated initially with Vancomycin, which induces the growth of Vancomycin-resistant entero-

cocci (VRE). On the other hand the overuse of third-generation cephalosporines stimulates in bacteria the enzyme extended-spectrum beta-lactamase (ESBL), which is able to destroy all amino- and ureidopenicillins. The use of imipenem/cilastatin stimulates the growth of *Acinetobacter* and increases the risk of yeast infections

perioperative prophylaxis therapy, adopt the narrowest spectrum therapy for documented infections, limit the use of antibiotics to 7 days and avoid treating contaminations [56, 57].

### Vancomycin-Resistant Enterococcus

VRE have emerged as a relevant pathogen in liver transplant recipients. VRE colonization and infection was first described at the Mayo Clinic in 1995 [58]. The rate of colonization is center-dependent and more common in the USA than in Europe. Most common infections caused by VRE in liver transplant patients are blood stream, intraabdominal, biliary tract, and wound infections [59–61]. VRE infections in liver transplant

patients are often severe and associated with prolonged ICU and hospital stay [62] and increased mortality [63]. One of the main risk factors for VRE colonization is the extended and inappropriate use of Vancomycin and second- or third-generation cephalosporin (Fig. 33.2) [64].

### Treatment of VRE

*Linezolid* has become the drug of choice for many types of VRE infection. Linezolid has been used in the treatment of serious VRE infections, including VRE bacteremia, VRE endocarditis, and SSTI [65–67].

*Daptomycin*, a lipopeptide, has in vitro bactericidal activity against the most relevant gram-positive

organisms, including VRE. Six mg/kg daptomycin is approved for patients with MRSA bacteremia and right-heart endocarditis and studies evaluating higher doses (8–12 mg/kg) are ongoing. During daptomycin treatment, creatininkinase and myoglobin should daily be monitored because of the risk of daptomycin-induced rhabdomyolysis [68].

*Tigecycline*, a glycopeptide, is a broad-spectrum antibiotic with high in vitro activity against VRE. There is little clinical data about the use of tigecycline for VRE. A retrospective study of ICU patients after major abdominal surgery with a mean APACHE II score of 27 found that 16% of the patients were infected with MRSA and 27% with VRE. Tigecycline was used in combination in 76% of these cases and alone in 24%. The mortality rate was 30%, significantly lower than the expected mortality of 55% considering the high mean APACHE II score in this group [69]. Due to rapidly declining serum levels tigecycline cannot be recommended as the first-line treatment for enterococcal sepsis. However, a case report demonstrated clinical cure in a patient with severe enterococcal sepsis treated with tigecycline alone [70].

Prevention and infection control for VRE can be achieved by using antibiotics selectively only for a clear indication, especially vancomycin and third-generation cephalosporines. If infection is suspected, a thorough search for a focus should be initiated, for example by CT scan of the chest and abdomen or transesophageal echocardiography to exclude endocarditis (very rare in liver transplant patients) and by the use of viral surveillance.

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### Multidrug-Resistant Gram-Negative Bacteria in Liver Transplant Patients

In the recent two decades the rate of MDR gram-negative bacteria has increased [71]. These are extended-spectrum beta-lactamase (ESBL)-producing bacteria, carbapenem-resistant *Klebsiella* and *Escherichia coli* and MDR *Acinetobacter baumannii*. The risk factors associated with infections with MDR bacteria is similar to gram-positive bacteria. Prolonged ICU stay, higher APACHE II score, extended and prolonged antibiotic exposure are the main

risk factors for MDR gram-negative bacteria. Prompt recognition and adequate treatment are critical for a successful outcome.

### ESBL and Carbapenase-Producing Enterobacteriaceae

Treatment of choice for *ESBL-producing Enterobacteriaceae* is carbapenems [72]; however, it should be guided by antimicrobial susceptibility testing. Treatment options include colistin alone [73] or in combination with tigecycline [74]. *A. baumannii* is susceptible to carbapenems (exceptionertapenem)[75] and *Stenotrophomonas* infections can often be treated with trimethoprim/sulfamethoxazole [76].

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### Fungal Infections in Liver Transplant Patients

*Candida species* are the most common cause for fungal infections in liver transplant patients [7] and frequently occur within the first 3 months following transplantation [77]. In recent years earlier occurrence (within the first 4 weeks) has been reported. *C. albicans* is a dominant pathogen which is responsible for about 65% of *Candida* infections, followed by *C. glabrata* with 21% [26]. *Candida krusei* which is common in stem cell transplant patients is far less common in liver transplant patients [78]. The risk of candidemia is discussed in detail above. The diagnosis of invasive candidiasis is dependent on recovery of an organism from a sterile body site, such as the bloodstream, intra-abdominal fluid, or abscess material. *Candida* detected in the bronchoalveolar lavage (BAL) must be considered a contamination and should not be treated, even after liver transplantation [79]. Liver transplant patients with fever of unknown origin (negative CT Scan of chest and abdomen, endocarditis, and viral infections have been ruled out and treatment with broad spectrum antibiotics, e.g., imipenem+Linezolid has been unsuccessful) should be treated preemptively [80].

Immunosuppressed patients such as liver transplant recipients can initially receive an

**Table 33.1** General susceptibility patterns of *Candida* spp.

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	L-Ampho B	Echinocandin
<i>C. albicans</i>	S	S	S	S	S	S
<i>C. tropicalis</i>	S	S	S	S	S	S
<i>C. parapsilosis</i>	S	S	S	S	S	S-R
<i>C. glabrata</i>	S-DD to R	S-DD to R	S-DD to R	S	S	S
<i>C. krusei</i>	R	R	S	S	S	S
<i>C. lusitania</i>	S	S	S	S	S	S

R resistant; S susceptible; SDD susceptible dose-dependent [1]. *C. parapsilosis* isolates resistant to echinocandins are uncommon

echinocandin for 14 days (weak evidence level of II C-benefits and risks closely balanced and/or uncertain). Fluconazole should only be used for patients, who are not critically ill and only for superficial candidiasis. Treatment of invasive candidiasis in liver transplant recipients should follow the same principles as other patients and is extensively discussed in the “Clinical practice guidelines for the management of candidiasis” [80]. Table 33.1 gives a general overview of susceptibility of *Candida* species.

## Amphotericin B

Amphotericin B is a polyene antifungal drug. It was originally extracted from *Streptomyces nodosus*, a filamentous bacterium, in 1955 from cultures of streptomycete. Amphotericin B interacts with ergosterol, the main component of fungal cell membranes, forming a transmembrane channel that leads to monovalent ion ( $K^+$ ,  $Na^+$ ,  $H^+$ ,  $Cl^-$ ) leakage causing fungal cell death. Amphotericin B use has serious adverse effects. Very often a serious acute reaction occurs 1–3 h after the infusion consisting of fever, shaking chills, and headache. Nephrotoxicity is a frequently reported adverse effect and can be severe and irreversible. Liposomal amphotericin B exhibits fewer adverse effects and particular is less nephrotoxic [81].

## Triazoles

Most *Candida* species are susceptible against fluconazole, itraconazole, voriconazole, and posaconazole [82]. Posaconazole demonstrates

excellent in vitro activity against most *Candida* species but requires oral administration, which can be difficult in critically ill patients. Fluconazole, itraconazole, and voriconazole demonstrate significant drug–drug interactions and special attention must be given to dosing adjustments of co-administered drugs, especially calcineurin inhibitors [83]. Daily drug level monitoring is required to avoid unexpected high trough levels.

## Echinocandin

Caspofungin, micafungin, and anidulafungin are only available as parenteral preparations and they have excellent in vitro activity against most *Candida* species including *C. glabrata* and *C. krusei* [84]. *C. parapsilosis* and *C. guilliermondii* demonstrate less in vitro susceptibility to the echinocandins [85]. The echinocandins have few side effects, do not require dose adjustment for renal insufficiency or dialysis and are rarely associated with drug–drug interactions [84]. It is recommended to reduce the dose of caspofungin to 35 mg in patients with liver failure. However, in a retrospective study with liver transplant patients and poor graft function the use of 50 mg caspofungin demonstrated no adverse effects of caspofungin [86] and there have been no reports of hepatotoxicity with the use of caspofungin.

A black-box warning for micafungin has been issued in Europe, based on an increased number of liver tumors observed in animal (rat) models. No such black-box warning has been included in the US label or Japan. In a prospective randomized, double-blind study, where safety and

efficacy of micafungin was evaluated against amphotericin B, 202 patients were treated with micafungin. In none of these patients a liver tumor was diagnosed [87]. In Japan the drug has been used for nearly 10 years, with no reported increased incidence of liver tumors.

## Invasive Aspergillosis

Invasive *aspergillosis* occurs in 1–10% in liver transplant patients [8, 88]. Most invasive fungal infections in these high-risk patients occur within the first-month post-transplant; the median time to onset of invasive aspergillosis after renal replacement therapy and retransplantation was 13 and 28 days, respectively, in one study [89, 90]. Mortality rate in liver transplant recipients with invasive aspergillosis has ranged from 88 to 100% [8, 91].

A substantial delay in establishing an early diagnosis remains a major impediment to the successful treatment of invasive aspergillosis. Isolation of aspergillosis from the respiratory tract in liver transplant patients is rare (1.5%), however with a high predictive value ranging from 41 to 72% for developing invasive aspergillosis [92].

The detection of galactomannan, a component of the aspergillus cell wall, as a predictor of invasive aspergillosis was assessed in a prospective study of 154 liver transplant patients [93]. The documented specificity was 98% and false-positive galactomannan tests were found in up to 13%. Liver transplant patients undergoing transplantation for autoimmune liver disease and those requiring dialysis were significantly more likely to have false-positive galactomannan tests. The galactomannan antigen test may be a useful adjunct in the diagnosis of invasive aspergillosis.

## Treatment of Invasive Aspergillosis

In the last 10 years liposomal amphotericin B replaced the classic amphotericin B as the main treatment of invasive aspergillosis, because it exhibits fewer side effects, in particular less nephrotoxicity [94, 95]. Newer azols and

echinocandins with anti-aspergillus activity and a better tolerance profile further expanded the pool of available anti-aspergillus drugs.

In a prospective randomized trial the successful treatment and survival rate with voriconazole was significantly higher compared to amphotericin B deoxycholate. Voriconazole-treated patients had fewer adverse effects, except transient visual disturbances [96]. Voriconazole is now regarded as the drug of choice for the primary treatment of invasive aspergillosis [97]. Caspofungin is currently the only echinocandin that is approved by the FDA for the treatment of aspergillosis. Caspofungin was successfully used as first-line therapy in heart–lung transplant patients [98] and as salvage therapy in invasive aspergillosis as single agent [99]. In a non-comparative study micafungin could also safely be used as a primary and salvage drug in the treatment of aspergillosis [100].

There are no clinical data about the use of anidulafungin for the treatment of aspergillosis. Posaconazole, a new extended-spectrum triazole has been successfully used in bone marrow transplant patients with graft-versus-host disease and in neutropenic hemato-oncologic as prophylaxis to avoid invasive aspergillosis [101, 102]. In a prospective open-label study posaconazole was successful as rescue treatment for patients refractory or intolerant to conventional therapy [103].

There are only a few data about combined aspergillus treatment. The new IDSA guidelines [97] recommend the combination as salvage treatment. In a prospective study of solid organ transplant recipients that included liver transplant patients, the combination therapy consisting of caspofungin and voriconazole was prospectively assessed in patients with confirmed invasive aspergillosis and compared to a historical control group treated with liposomal amphotericin B only [90]. The overall 90-day survival rate was not different in both groups; however, patients with renal failure infected with aspergillus fumigatus showed a significant better 90-day survival with the combination therapy of caspofungin and voriconazole. Although definitive clinical trials that evaluate the benefits of combined therapy are pending, it should be considered as a rescue treatment in selected cases.

## Conclusion

Liver transplant recipients need meticulous attention for signs of infections and prompt treatment. The use of antibiotics should be restrictive; an extended and inappropriate use confers the risk of MDR bacterial and fungal infections. Antimycotic prophylaxis is recommended in high-risk patients but does not necessarily improve overall hospital mortality. An early and preemptive antifungal treatment with echinocandins in patients suspected of candidemia or voriconazole when aspergillosis is suspected to be favored over using general antifungal prophylaxis.

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## Introduction

Pulmonary complications are common in the period immediately after liver transplantation (LT) to the point that they are almost an expected consequence of the procedure. Approximately one-fifth of patients with end-stage liver disease are hypoxemic prior to transplantation and the hypoxemia may worsen in the post-operative period due to alterations of respiratory mechanics. The published prevalence of pleural effusion, atelectasis and interstitial pulmonary edema is up to 87% [1, 2]. Fortunately the majority of cases are of little clinical consequence as resolution occurs rapidly without the need for complex intervention and without adversely affecting outcome [1].

In some cases however, more serious pulmonary complications such as pneumonia, persistent or late pulmonary edema and acute respiratory distress syndrome (ARDS) develop. These may require prolonged intensive care unit (ICU) management and mechanical ventilation with consequence increases in patient hospital stay, cost, and mortality [3].

This chapter will address the etiologies of peri-operative respiratory failure, management strategies for short-term and prolonged mechanical

ventilatory support, approaches to ventilator weaning and care of the patient with specific causes of respiratory failure including ARDS.

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## Hepatic Hydrothorax and Alteration in Respiratory Mechanics

Hepatic hydrothorax occurs in approximately 5% of patients with severe liver disease, more frequently on the right side more often than the left. Pleural effusions may impair a patient's ability to wean from mechanical ventilation and require post-operative drainage [4]. Although ascitic fluid in the abdomen is usually drained during the surgical procedure, residual or persistent ascitic fluid can reduce functional residual capacity and vital capacity. Implantation of a new liver in the upper part of the right abdomen to take the place of a shrunken cirrhotic liver may also lead to a reduction in vital capacity as the right diaphragm is pushed upwards. Furthermore, LT leads to disruption of diaphragmatic function and, as in any major upper abdominal procedure, post-operative atelectasis can develop.

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## Weaning from Mechanical Ventilatory Support After "Routine" Liver Transplantation

There has been considerable discussion and controversy regarding the time of extubation after LT [5, 6]. Progressive improvement in surgical and

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anesthetic techniques, coupled with increased experience mean that prolonged mechanical ventilation following LT is no longer necessary in the majority of patients [7]. Multiple surgical practices (e.g. cardiac, thoracic) have embraced the “fast-track” concept that targets early extubation with subsequent reduction in costs but without compromising safety [8, 9]. In the majority of centers efforts are made to achieve extubation of most LT recipients within 8 h after the surgical procedure. The intraoperative use of short acting medications and lower dosing of opiates has facilitated rapid post-operative ventilator weaning. For example, Findlay et al. have demonstrated that intraoperative use of midazolam, propofol, cisatracurium and up to 20 µg/kg of fentanyl facilitates early post-operative weaning of ventilatory support [10].

Numerous studies have demonstrated the benefit of the involvement of nurses and respiratory therapists in implementation of ventilator weaning protocols that allow the assessment of weaning readiness and progression along a ventilator-weaning pathway independent of physician involvement. These protocols have been shown to be safe and decrease the duration of mechanical ventilation. Ventilatory support is incrementally reduced to the point of readiness for extubation with the final decision to extubate made by a physician. Figure 34.1 illustrates the post-operative weaning protocol used at our institution. Early liberation from mechanical ventilation in the ICU may or may not decrease ICU length of stay, depending on ICU workflow and established protocols [10]. Involvement of bedside paramedical staff and use of protocols are also useful in the management of longer-term ventilation (see below).

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### Immediate Postoperative Extubation

Immediate post-operative extubation after LT in the operating room for a majority of cases is advocated by some clinicians. In addition to reducing the risk of ventilator-associated pneumonia (VAP) it has been suggested that early extubation might have beneficial effects on

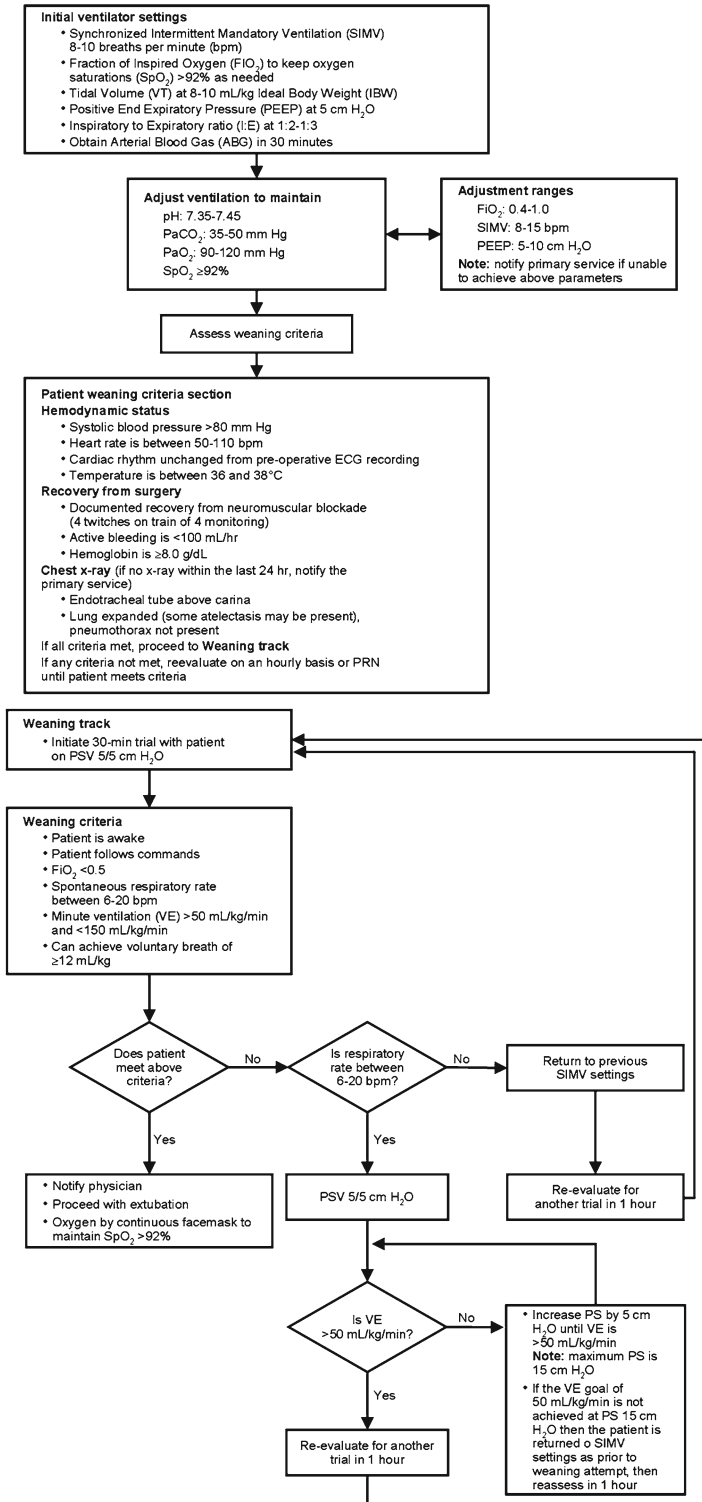
splanchnic and liver blood flow. Immediate post-operative extubation is often performed to avoid ICU admission and subsequently eliminate ICU-associated costs and reduce hospital length of stay [7, 11]. Arguments against immediate post-operative extubation include the contention that a period of post-operative ventilation allows graft function to be consolidated with less sympathetic activation and protects the recipient from the risks of atelectasis, aspiration, or reintubation for surgical re-exploration if required [6, 7, 12]. Once hemodynamic stability, hemostasis and good graft function have been ascertained, extubation can proceed. A short delay in extubation may also allow for better treatment of early post-operative pain that might otherwise be compromised for fear of hypoventilation or airway compromise. In a multi-center US and European study, 391 patients were extubated within 1 h of completion of surgery [13]. Adverse events occurred in 7.7% of them within 72 h of surgery, although most of these adverse events were relatively minor. There was considerable inter-center variability. In some centers early extubation was performed in 60–70% of LT cases with avoidance of ICU admission in many of those cases, and a resultant reduction in costs [11, 14, 15]. To date, there has not been a randomized trial of immediate vs. early vs. delayed extubation after LT.

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### Patients Who Require Prolonged Ventilatory Support

A significant number of patients will not be suitable candidates for early extubation after LT. The introduction of the Model for End Stage Liver Disease (MELD) system for organ allocation was designed to prioritize patients of higher illness severity or need for the allocation of donor organs. The result has been an increase in the acuity of illness of recipients. Such individuals may be poorer candidates for immediate extubation and even their eligibility for “fast-track” protocols may be questionable. Furthermore, in cases of intra-operative difficulties such as large transfusion requirements, early extubation may be unwise due to ongoing bleeding, significant

**Fig. 34.1** Post liver transplantation ventilator weaning protocol used at the authors' institution



acidosis, volume overload, and airway edema. Once hemodynamic stability has been achieved, such patients may require diuresis before extubation can be considered. Citrate used as a preservative in packed red blood cells is metabolized to bicarbonate by the newly-functioning liver and the resulting metabolic alkalosis may impair respiratory drive. Acetazolamide causes diuresis and bicarbonate loss and may ameliorate the situation [16, 17].

When pre-transplant encephalopathy exists, patients often require longer to awaken, causing a delay in extubation. Underlying lung disease (e.g. alpha-1-antitrypsin deficiency), pre-operative sepsis, malnourishment and debilitation may require pre-operative ventilation, potentially prolonging the post-operative duration of ventilatory support. Faenza et al. have identified the presence of early post-operative impairment indicated by a low  $\text{PaO}_2/\text{FiO}_2$  ratio as a predictor of prolonged post-operative ventilation [18].

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## Approach to the Difficult to Wean Patient

Weaning from ventilatory support may take days or even weeks in some cases. In general ICUs weaning from the ventilator may account for more than half of total ventilator time. Based on a large body of literature concerning the methodology and best practices for ventilator weaning, the critical care community has refined the approach to liberating patients from the ventilator and guidelines for ventilator weaning have been published by a United States collaborative group [19]. An International Consensus Conference was convened in 2005 and subsequently a number of recommendations for ventilator weaning were published [20]. Patients may be categorized into three groups based on the difficulty and duration of the weaning process: patients who pass the initial spontaneous breathing trial (SBT) and are extubated at the first attempt, those who require up to three SBTs or up to 7 days of weaning after the first attempt, and patients who require longer than 7 days of weaning. Weaning should be considered as part of daily ventilator

management with early consideration given to a weaning plan. SBTs have been demonstrated to be useful to assess for weaning readiness [21] and a 30-min T-piece or low pressure support trial is advocated. Suitable modes of ventilation for weaning remain somewhat controversial, but pressure support or assist control modes are probably superior to synchronized intermittent mandatory ventilation [22–28]. Furthermore, non-invasive ventilatory support (NIV) may be very useful in selected patients. In addition to the use of protocols for extubation of the “routine” LT recipient, many ICUs empower respiratory therapists or nurses to initiate a daily T-piece trial to assess suitability for weaning. Such an approach decreases the duration of mechanical ventilation [29].

Some patients will require tracheostomy. The timing of tracheotomy has been a subject of investigation, and in modern critical care practice, early tracheostomy is advocated when it appears that a ventilated patient will be difficult to wean [30, 31]. The vast majority of LT recipients do not require tracheostomy and there is a certain reluctance to introduce another potential source of infection in an immunosuppressed patient. If required, tracheostomy in this patient population is usually delayed until 2 or 3 weeks of mechanical ventilation have been required. Percutaneous tracheostomy is gaining acceptance among the ICU community, and there is some experience in transplant recipients [32].

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## Protocols

In addition to the involvement of paramedical staff in ventilator weaning, other aspects of ventilatory management may be protocolized. The use of “Ventilator bundles” has been shown to decrease complications—including VAP—and improve outcomes. The most widely studied (and probably implemented) ventilator bundle consists of four items: peptic ulcer prophylaxis, deep venous thrombosis prophylaxis, elevation of the head of the bed to at least 30° and the use of daily sedation “holidays” [33, 34]. The individual components of the bundle have been criticized on



evidence-based grounds and a more “evidence supported” bundle have been suggested (no unnecessary ventilator tubing changes, alcohol based hand hygiene, staff training, sedation and weaning protocols and oral care) [35]. However the general message is that a protocol that addresses VAP prophylaxis (see below) and allows for the early identification of the patient who can be weaned should be used in every ventilated patient and assessed every day.

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### Sedation During Mechanical Ventilation

The appropriate management of sedation is worth particular comment. The use of pharmacologic sedation should not be a default in a ventilated patient. Sedation should be employed only if required to allow appropriate ventilation and then in the minimum dose necessary. The Society of Critical Care Medicine has published guidelines for sedation in the ICU [36]. However, the drug recommended for prolonged sedation, namely lorazepam, may be an unwise choice in patients with hepatic dysfunction. Infusions of propofol or dexmedetomidine and/or fentanyl may be used if sedation is required, with benzodiazepines used sparingly, if at all. Periodic—at least daily—interruptions of sedation allow for the evaluation of the continuing need for sedation and also evaluation of the patient’s neurological status. These “sedation holidays” decrease both ventilator time and ICU stay [37]. Interruption of sedation does not lead to a clinically important incidence of post-traumatic stress disorder or myocardial ischemia [38, 39]. A combination of daily spontaneous awakening trials and daily SBTs was shown to be superior than daily SBTs alone [40]. Postoperative sedation is discussed in detail elsewhere (Chapter 29) in this book.

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### Non-invasive Ventilation

The development of ventilators and masks capable of providing non-invasive mechanical ventilation has added to the armamentarium of the

modern intensivists and the use of NIV has considerably increased over the past two decades [41]. Continuous positive airway pressure (CPAP) improves oxygenation and decreases work of breathing, especially in patients with pulmonary edema and/or left ventricular dysfunction. Biphasic positive airway pressure (BiPAP) is a non-invasive technique of ventilatory support in which a flow and pressure generator applies both an expiratory positive airway pressure (EPAP) and an inspiratory positive airway pressure (IPAP). BiPAP can improve both oxygenation and ventilation. It is unusual to initiate NIV in LT recipients early in the post-operative period. However, difficult-to-wean patients who are not yet ready for complete withdrawal of ventilatory support may be extubated to BiPAP to limit the duration of invasive mechanical ventilation [42]. Furthermore, NIV may be useful when intubation or re-intubation should be avoided while a reversible problem (e.g. pulmonary edema due to volume overload, or opiate-induced hypoventilation) is treated [43]. Patient with a history of obstructive sleep apnea will also benefit from the use of BiPAP after endotracheal extubation especially if they had used BiPAP at home prior to the liver transplant.

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### Ventilator-Associated Pneumonia

VAP is a common nosocomial complication and a major cause of ICU morbidity [44]. It occurs in 8–28% of patients receiving invasive mechanical ventilation and is related to the duration of ventilation. Associated mortality is high. The predominant organisms responsible for infection are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*, but etiologic agents can vary widely depending on the population. VAP is unlikely to develop in the immediate post-operative period in patients who are rapidly weaned from the ventilator but the risk is much higher in patients who are ventilated for longer periods of time, especially in the setting of immunosuppression.

Investigation of suspected VAP should proceed along established guidelines [44]. Bronchoscopy and bronchoalveolar lavage (BAL)

may be required to guide antimicrobial therapy. Consultation with a transplant infectious disease specialist should be considered. Diagnosis and treatment of postoperative pneumonia are discussed in more detail elsewhere (Chapter 33) in this book.

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## Pulmonary Edema

Pulmonary edema is common in the early post-transplant period. In one series of 300 patients X-ray findings consistent with pulmonary edema were seen in 45% of patients. The majority of this pulmonary edema was interstitial and associated with other signs of fluid overload. Resolution occurred within 3–4 days with fluid restriction and diuretic use and there was no adverse effect on outcome [1]. Aduen et al. reported the occurrence and outcomes of pulmonary edema resulting in a  $\text{PaO}_2/\text{FiO}_2$  ratio of less than 300 in a series of 100 consecutive liver transplants and reported a prevalence of 52% [45]. Further analysis of the patients with pulmonary edema revealed that those with immediate pulmonary edema (present immediately post-operatively and resolving within 24 h) had outcomes that were no different from those without pulmonary edema, whilst patients who had persistent pulmonary edema (18%) or who developed pulmonary edema in the post-operative period (9%) had increased duration of mechanical ventilation and longer lengths of ICU stay. A higher pre-operative MELD score was associated with persistent or late pulmonary edema. Regarding the etiology of the pulmonary edema they further reported that half of the persistent group and most of the late group had a pulmonary capillary wedge pressure (PCWP) < 18 mmHg implying altered pulmonary capillary permeability rather than a hydrostatic mechanism as a cause of pulmonary edema. This is supported by findings in a smaller series of patients that found that late onset pulmonary edema was not related to fluid volume administered whilst early onset pulmonary edema was [46]. When pulmonary edema fluid from liver transplant patients was analyzed it was found to be consistent with permeability edema

[47]. Suggestions for the precipitant for the capillary injury include the cytokine release associated with reperfusion of the liver graft and transfusion related lung injury (TRALI) [45, 47, 48] but other mechanisms may also be responsible in different patients.

Once pulmonary edema is found to be non-hydrostatic no specific therapy is indicated and the usual supportive management should be pursued. If TRALI is suspected as a main cause of pulmonary edema the current practice limiting the use of blood and blood products during liver transplantation may be helpful in preventing further injury. Likewise measures to reduce the extent of reperfusion injury should reduce the occurrence of pulmonary edema.

Cardiogenic pulmonary edema secondary to post-transplant dilated cardiomyopathy is seen in a small number of patients and usually presents a few days after transplantation, often when the patient has already left the ICU [49]. A decrease in left ventricular ejection fraction leads to hydrostatic pulmonary edema and respiratory failure requiring readmission to the ICU and the need for non-invasive or invasive mechanical ventilation. This entity is usually reversible; supportive treatment includes inotropes, pressors and diuretics.

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## Hepatopulmonary Syndrome

Liver transplantation is the only successful treatment for patients with hepatopulmonary syndrome. These patients may require preoperative oxygen therapy to maintain satisfactory oxygenation and are at risk of deterioration in the perioperative period. In a review of older case series Krowka et al. identified a pre-transplant resting  $\text{PaO}_2$  of less than 50 mmHg as a risk factor for poor post-transplant outcome [50]. In a recent series of 21 patients with hepatopulmonary syndrome, 11 with baseline  $\text{PaO}_2 < 50$  mmHg, Gupta et al. reported a 100% 6 month survival suggesting improved outcomes with current management techniques [51]. The median time for post-transplant mechanical ventilation was 1 day, however 23% of patients developed hypoxemic respiratory failure requiring ventilatory support for up to

60 days. Techniques used to achieve satisfactory oxygenation included Trendelenburg positioning (to counteract orthodeoxia), the use of inhaled nitric oxide and high frequency oscillatory ventilation. The use of intravenous methylene blue to improve post-transplant oxygenation has also been reported [52]. Prolonged post-transplant oxygen therapy (up to almost 2 years) may be required in these patients and a higher degree of shunting assessed by pre-transplant albumin macro-aggregate scanning was predictive of a slower rate of post-transplant improvement [51]. With this and other reports of improved transplant outcomes for severe hepatopulmonary syndrome [53, 54] more of these patients will likely be transplanted in the future.

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### Portopulmonary Hypertension

As discussed elsewhere (Chapter 22), the management and candidacy of patients with portopulmonary hypertension for liver transplantation is controversial. However most clinicians will agree that these patients can be suitable transplant candidates if acceptable hemodynamic parameters are present [55]. In the immediate post-transplantation period these patients may be at a higher risk of pulmonary complications as well as right ventricular failure and have longer ICU stays [56]. Initial management should include the continuation of pre-transplant therapy for pulmonary hypertension and aggressive prevention and management of conditions that worsen pulmonary vasoconstriction. Pulmonary hemodynamics and right ventricular function should be closely monitored. If pulmonary artery pressures rise or right heart failure occurs treatment should be advanced. Inhaled nitric oxide may be useful in the acute phase [57].

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### Acute Respiratory Distress Syndrome and Acute Lung Injury

ARDS and acute lung injury (ALI) represent an inflammatory response in the lungs due to either a primary lung insult or secondary to a systemic

insult [58, 59]. Either may be seen in patients with liver disease. ALI and ARDS are part of a continuum of lung injury and were defined by an American-European consensus definition conference. They are common ICU problems and have an associated mortality of 25–40%. Both require the presence of diffuse, bilateral pulmonary infiltrates of acute onset due to a non-cardiogenic etiology. The  $\text{PaO}_2/\text{FiO}_2$  (P/F) ratio is then used to differentiate between the two. ALI is a less severe entity with a P/F ratio between 200 and 300. ARDS is present when the P/F ratio is less than 200. ARDS and ALI may develop prior to transplantation in the setting of sepsis or acute liver failure. Perioperatively, ALI or ARDS may develop due to the inflammatory stimulus of the surgical insult or allograft reperfusion. In addition, transfusion related ALI may develop and cause ARD or ALI [60]. Aspiration pneumonitis may develop pre-operatively or (less likely) at induction of anesthesia, giving rise to ARDS or ALI [47]. Months or years after transplantation the immunocompromised recipient may present with pneumonia or septic shock and ARDS may develop. Graft failure, whether caused by primary non-function, acute rejection or vascular occlusion, may also lead to the development of ALI or ARDS. Furthermore, treatment of rejection using monoclonal antibody therapy (e.g. OKT3) may cause an inflammatory lung insult leading to diffuse alveolar hemorrhage and/or ARDS [61].

The frequency of ARDS and ALI in the ICU has prompted much investigation into the causes, prevention and treatment of these life-threatening syndromes. The National Institutes of Health in the United States has funded the multi-center ARDSNet group through the National Heart Lung and Blood Institute. This group performed a landmark clinical trial that demonstrated that ventilation with low tidal volumes (6 mL/kg ideal body weight) was associated with decreased morbidity and mortality compared with ventilation using tidal volumes of 12 mL/kg ideal body weight [62, 63]. Patients with severe liver disease were excluded from this study. Positive end-expiratory pressure (PEEP) is routinely used to prevent de-recruitment and atelectasis and to improve oxygenation in patients with ARDS.

By keeping the lungs “open,” PEEP decreases shear stresses which could otherwise lead to a worsening of lung injury. Despite a number of well-designed studies, the optimum level of PEEP remains to be elucidated [64, 65].

There are theoretical concerns regarding the use of PEEP—especially at high levels—in patients with liver disease. Increased intrathoracic pressure as a result of PEEP causes a decrease in venous return and can lead to hepatic venous engorgement. This may cause ischemic liver damage, to which the newly engrafted liver is especially vulnerable. However, Saner and colleagues have demonstrated that although application of PEEP to mechanically ventilated LT recipients increased central venous and PCWPs, hepatic inflow and outflow of the transplanted livers (both cadaveric and living donor) were not impaired by PEEP levels up to about 10 cm H<sub>2</sub>O [66–68].

It is unknown whether higher levels of applied PEEP cause ischemic hepatic damage. When PEEP is required to achieve acceptable oxygenation in patients with ALI or ARDS, it should be applied, recognizing that adequate systemic oxygenation is essential for optimum hepatic function. In addition, lungs that have been injured demonstrate a reduction in compliance that will offset transmission of pressure to the liver.

The use of recruitment maneuvers in ARDS is controversial. Fan et al. performed a systematic review of the available data [69]. Although unable to definitively advise for or against recruitment maneuvers they suggested consideration of recruitment maneuvers for life-threatening hypoxemia in ALI. They did not specifically address the impact of recruitment maneuvers on hepatic perfusion.

When tidal volumes are limited as a lung protective strategy, the respiratory rate may be increased to compensate and maintain adequate minute ventilation. With respiratory rates in the high 20s and 30s, dynamic hyperinflation (“auto-PEEP”) can develop. Such high respiratory rates also increase the shear stresses on the lungs due to the high frequency of opening and closing of lung units. Accordingly, the technique of permissive hypercapnia may be used [70]. The elevation in carbon dioxide levels may also have

implications for the liver graft, although the available data is limited. Other techniques that may be used in the management of ARDS include high frequency oscillation, airway pressure release ventilation, and prone positioning [71–73]. Experience with such techniques in the LT recipient is minimal, although Sykes et al. describe a patient with critical hypoxemia after LT in whom use of the prone position and application of 15 cm H<sub>2</sub>O of PEEP were lifesaving [74].

“Rescue” therapies for critical hypoxemia in ARDS include the use of inhaled nitric oxide and inhaled prostaglandins. These therapies have not been proven in randomized clinical trials to improve outcome, though they may be life-saving in selected cases [75, 76]. Both agents selectively vasodilate pulmonary arterioles in aerated lung units, thus improving ventilation/perfusion matching and potentially improving oxygenation.

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## Conclusion

Although pulmonary complications are common in the immediate post-liver transplant period the majority of these do not lead to significant morbidity. However there are patients who will develop post transplant respiratory failure secondary to either pre-existing conditions or as a consequence of the procedure. Whilst there is little literature specific to the management of the liver transplant patient with respiratory failure, a considerable body of evidence relating to the ventilatory and ICU management of respiratory failure exists. Clinicians caring for these patients should follow current best practices for the ICU management of respiratory failure, integrating approaches specific to liver transplant patients as and when sufficient evidence is available.

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Liver transplantation is a complex surgical procedure requiring comprehensive and intensive multidisciplinary involvement in the perioperative period. Over the years there has been significant evolution of the surgical technique and the perioperative management that resulted in improved outcomes. The anesthesiologist and intensivist play a crucial role throughout the perioperative period and adequate analgesic delivery is of outmost importance during this period. Providing adequate pain control may prove to be challenging and there are unique considerations in patients undergoing liver transplantations. In addition to relieving mental suffering associated with pain, appropriate pain control is essential to prevent the profound physiologic consequences of inadequate analgesia. This chapter aims to address and discuss in detail the analgesic issues in liver transplantation and liver resection.

The goals of analgesia during liver transplantation are similar to other types of surgery, but unique considerations found in patients with end-stage liver disease impact the overall approach to pain management. Altered physiologic parameters including the pharmacokinetics and pharmacodynamics of commonly used analgesics,

decreased coagulation factors, abnormal platelet function, and altered mental status are some of these important considerations. Many patients with end-stage liver disease also have a history of alcohol or drug abuse, as 10–12% of patients undergoing liver transplantation have alcoholic liver disease [1]. These patients often require multiple hospitalizations during which they receive opioids and develop different opioid requirements than healthy patients undergoing similarly extensive operations. It is no surprise then that perioperative pain management in patients undergoing liver transplantation involves a multifaceted approach that includes medical optimization of the patient followed by the development of an analgesic plan that extends from the preoperative setting and continues into the extended postoperative period.

While this chapter will focus on pain management after liver transplantation and living liver donation, many of its conclusions can be applied for the treatment and prevention of pain after hepatic resection as well.

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## Metabolism and Clearance

Biotransformation is the process through which drugs are broken down into metabolites that more easily eliminated by the body [2, 3]. The liver plays a key role in this intricate process such that small changes in liver function or blood flow can dramatically change the concentrations of drugs and their metabolites.

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Cirrhotic end-stage liver disease is characterized by the histological presence of hepatocellular fibrosis. These histological changes, clinically termed cirrhosis, result in decreased hepatic blood flow, porto-systemic shunting, sinusoidal capillarization, and an overall reduction in the activity and quantity of hepatocytes. Consequently these physiologic aberrations alter drug absorption, distribution, and elimination [4]. These changes manifest as increased oral bioavailability, decreased protein binding, prolonged duration of action, and an overall reduction in drug metabolism [3, 4].

Drugs used for both the acute and chronic pain management are primarily lipid soluble and must undergo enzymatic metabolism into more soluble forms before being excreted by the kidneys [2, 4–6]. These enzymatic reactions are categorized as phase I or phase II reactions depending on how the liver alters them. In the case of phase I reactions the drugs undergo chemical modifications including hydrolysis, oxidation, dealkylation, and reduction. In the case of phase II reactions the drugs undergo conjugation, which renders them water soluble [2, 4–6]. Phase I reactions involve the cytochrome P-450 family of enzymes and occur in the smooth endoplasmic reticulum of hepatocytes [5]. More specifically, the isoenzymes primarily involved in phase I metabolism of most drugs, including the opioids, involve the CYP3A4 and CYP2D6 subgroups [2, 6]. Phase II reactions involve conjugation of the parent drug by transferases, such as uridine diphosphate-glucuronosyltransferases (UGTs) whereby methylation, acetylation, and sulfation renders the drugs more water soluble and thus easily excreted [2, 6, 7]. Phase I reactions are more impaired in patients with cirrhosis as compared to phase II reactions. Sellers et al. have shown that the half lives of drugs undergoing phase I metabolism are significantly prolonged when compared to drugs metabolized through phase II reactions in patients with cirrhosis [4, 7] confirming the commonly accepted belief that phase I reactions are greatly impaired in patients with chronic liver disease while phase II are essentially preserved [8].

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## Pharmacokinetics in Liver Disease

Drug metabolism in liver failure is discussed extensively elsewhere (Chapter 3) in this book. We will therefore focus the discussion here on the pharmacokinetics of commonly used analgesics. Opioids have long been the foundation of pain management in anesthesiology. The WHO analgesic ladder recommends the use of opioid analgesics in the treatment of moderate to severe pain. A multimodal approach is essential in tailoring an analgesic regimen that is specific to the individual patient with distinct comorbidities. To avoid under or over treatment, it is imperative to understand the medication classes at our disposal. Opioids remain the gold standard for the treatment of moderate to severe pain in the acute setting, but the use of opioids in the long-term setting of nonmalignant pain continues to be controversial.

### Morphine

Morphine is the prototypic phenanthrene alkaloid derived from opium. It undergoes significant first pass metabolism in the liver, resulting in an oral bioavailability of 30–40% [6, 8]. While the liver accounts for 60–70% of its metabolism, significant extrahepatic metabolism through the kidneys has also been described [9, 10]. In the liver, morphine is metabolized through glucuronidation forming morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G) and to a lesser extent demethylation to normorphine [6, 8]. M3G is the main metabolite of morphine and while it is generally thought to be an inactive metabolite, some studies have suggested that M3G may act as an anti-analgesic [6, 9]. M6G, however, remains pharmacologically active and while it is produced at much smaller amounts can accumulate in patients with renal dysfunction [6, 8]. The metabolism of morphine varies depending on the degree of cirrhosis; however, many studies involving patients with severe cirrhosis (Child-Pugh class C) have demonstrated an increased oral bioavailability due to decreased first pass metabolism,

lower plasma clearance, and prolonged elimination half-lives due to a decrease in total body clearance [2, 6, 8, 11–13]. Using hepatic vein catheterization to directly measure morphine hepatic extraction in cirrhotic patients, Crotty et al. showed that hepatic extraction ratios were decreased by 25% in cirrhotic patients compared to healthy controls [12]. Given the higher free plasma concentrations of morphine combined with the reduced metabolism, many physicians not only decrease the total dose of morphine given but also increase the time interval between doses [6].

## Methadone

Methadone is a synthetic opioid agonist used most commonly as a treatment for chronic pain as well as in the detoxification treatment from heroin. While methadone maintenance therapy (MMT) is a controversial topic in the setting of liver transplantation, it is nonetheless imperative that the anesthesiologist understands its role in the context of end-stage liver disease. Unlike morphine and many of the other opioids, methadone exhibits low hepatic extraction, resulting in a high oral bioavailability [14]. Methadone is highly bound to plasma proteins, with some studies suggesting that 90% of the plasma concentration of methadone is protein bound [6]. This translates to a prolonged elimination half-life of about 30 h (reports ranged from 8.5 to 58 h) [6]. Interestingly the analgesic half-life of methadone may be quite short (4–6 h). Therefore methadone must be used very judiciously in the treatment of acute pain. Methadone undergoes extensive hepatic metabolism through phase I, or oxidative reactions via demethylation to inactive metabolites that are excreted in the urine and bile [6, 15, 16]. The remainder of the drug that escapes hepatic metabolism is excreted unchanged by both the kidneys and through the biliary system. In the context of liver disease, one can infer that methadone metabolism would be slowed due to the impairment of phase I reactions in patients with cirrhosis. Interestingly, studies utilizing mass spectrometry illustrated that the total 24 h

urinary excretion of methadone and its inactive metabolites was drastically reduced in patients with liver disease (32.6%) compared to matched healthy controls (48.3%) [17]. Additionally, Novick et al. found similar findings in alcoholic patients with cirrhosis in which peak plasma levels were lower in the cirrhotic group compared to alcoholic patients without cirrhosis [16]. It seems counterintuitive that peak plasma levels are lower in cirrhotic patients when many studies have demonstrated a prolonged elimination half-life in cirrhotic patients compared to controls. This may be due to a combination of both an increase in the volume of distribution of methadone and intra- and extrahepatic storage of methadone that is independent of reduced enzymatic capacity [6, 16]. Interestingly cirrhotic patients in these studies did not exhibit any signs or symptoms of methadone overdose due to increased biliary excretion of methadone and its metabolites into the gastrointestinal tract [16]. Nonetheless, many anesthesiologists recommend to use methadone cautiously in patients with liver dysfunction [15].

## Hydromorphone

Hydromorphone, a semi-synthetic opioid, is a phenanthrene opioid similar to morphine [18]. Acting primarily at the  $\mu$ -opioid receptor, hydromorphone has a half-life of 1–3 h and is 7–10 times more potent at these receptors than morphine [18, 19]. Hydromorphone also undergoes first pass metabolism in the liver through glucuronidation to form hydromorphone-3-glucuronide (H3G), a neuroexcitatory metabolite that lacks analgesic effects [2, 19, 20]. Studies involving rats, whose lateral ventricles were directly injected with synthetic H3G, have illustrated that the metabolite induces myoclonic jerks, allodynia, and seizures in a dose-dependent manner similar to the neuroexcitatory effects seen with M3G [19]. While both metabolites are too polar to cross the blood–brain barrier (BBB) in large quantities, a clinically significant portion can cross the BBB to elicit the aforementioned effects in patients with impaired elimination [20].

The neuroexcitatory effects of the hydromorphone metabolite are seen clinically in patients with renal failure but less so than with morphine metabolites [15]. Retrospective studies of palliative care patients with renal dysfunction who were switched from morphine to hydromorphone demonstrated an 80% decrease in cognitive impairment, drowsiness, and nausea [21]. While there are limited studies of hydromorphone in either liver transplant recipients or in patients with cirrhosis, data from models using morphine are commonly extrapolated to hydromorphone as they share a common metabolic pathway. As with morphine, many pain physicians recommend using a decreased dose in patients with hepatic impairment [13].

## Fentanyl

The phenylpiperidine class of opioids includes fentanyl, alfentanil, sufentanil, remifentanil, and meperidine. Fentanyl, the most commonly used of these, is a highly potent lipid soluble synthetic opioid agonist [6, 13, 18]. Fentanyl is highly selective for the  $\mu$ -opioid receptor, 80–100 times more potent than morphine [6, 18, 22]. Intravenous fentanyl has a half-life of 1–3 h compared to the transdermal form with a 17-h half-life [13, 23]. The majority of fentanyl (85%) exists in the plasma as the protein bound form with 60% being bound to albumin and the remainder bound to alpha-1 acid glycoprotein [24]. As it is highly lipid soluble, fentanyl must first undergo reuptake from its lipid storage sites before undergoing phase I (CYP3A4) hepatic biotransformation via de-alkylation and hydroxylation to inactive metabolites with less than 10% being excreted in the kidneys unchanged [6, 18, 25]. The major inactive metabolite produced by human hepatic enzymes is norfentanyl while animal enzyme studies have found both norfentanyl and despropionfentanyl as metabolites [25]. An initial study of fentanyl in eight patients with mild-to-moderate hepatic insufficiency failed to demonstrate a significant prolongation in half-life. Haberer et al. showed that the half-life of fentanyl in cirrhotic patients was minimally prolonged to

304 min compared to 263 min in healthy controls [6, 18, 26]. Interestingly, the elimination half time of fentanyl in patients undergoing abdominal aortic surgery with aortic cross clamping was significantly prolonged (8.7 h [27]) possibly due to decreased hepatic blood flow. Unfortunately, there are very few and limited studies analyzing the context-sensitive half time of fentanyl in cirrhotic patients. Many clinicians will administer fentanyl to cirrhotic patients without any dosing reductions, given its lack of active or toxic metabolites.

## Buprenorphine

Buprenorphine, another member of the phenanthrene opioid family, is a highly lipophilic opioid combined agonist–antagonist. While buprenorphine is predominately excreted unchanged in the bile, one-third undergoes hepatic metabolism via both phase I and phase II reactions to form buprenorphine-3-glucuronide and nor-buprenorphine which are inactive and active metabolites, respectively [6, 28, 29]. There is also evidence for entero-hepatic circulation with a small percentage of both buprenorphine and nor-buprenorphine being excreted in the feces [28, 29]. In comparing oral to sublingual and parenteral routes, oral buprenorphine has poor bioavailability due to extensive first pass kinetics while sublingual regimens maintain a bioavailability of 60–70% of the parenteral dose due to its high lipid solubility [30]. Buprenorphine is 30–40 times more potent than morphine. Its metabolite nor-buprenorphine has analgesic effects that are 15–40 times less than buprenorphine [6]. While the drug maintains a high affinity for the  $\mu$ -opioid receptor, buprenorphine produces only partial agonistic effects (at doses <0.5 mg/kg), namely supraspinal analgesia, respiratory depression, and meiosis [30, 31]. Interestingly, studies involving nociceptive stimuli in mice showed that a 5–10% receptor occupancy produced effective analgesia [32]. However, unlike the aforementioned morphine derivatives, buprenorphine has the capacity to antagonize the  $\kappa$ - and  $\delta$ -opioid receptors (at doses >0.5 mg/kg) resulting in limited spinal analgesia, dysphoria,

**Table 35.1** Opioids and equipotent doses

Generic name	Equipotent dose parenteral (mg)	Duration of action (h)
Morphine	10	4–5
Hydromorphone	1.5	4–5
Oxymorphone	1.0–1.5	4–5
Codeine <sup>a</sup>	120 (10–30)	(4–6)
Hydrocodone	(5–10)	(4–8)
Oxycodone	10–15	4–5
Methadone	7.5–10	3–5
Meperidine	80–100	2–4
Fentanyl	100 µg	0.5
Sufentanil	15 µg	0.5
Alfentanil	750 µg	0.25
Buprenorphine	0.4	4–6
Butorphanol	2–3	4–5
Nalbuphine	10	4–5

Adapted from Wood and Wood. *Drugs and anesthesia: pharmacology for anesthesiologists*. 2nd edn.; 1982

<sup>a</sup>Numbers in parentheses, doses and duration of action for oral doses

hallucinations, and delusions [30, 31]. Another important aspect of buprenorphine is the ceiling effect for both analgesic and respiratory depression [18, 30, 33]. Increasing the dose of buprenorphine beyond the analgesic level will produce more dysphoria and other unwanted side effects. Buprenorphine exhibits very slow receptor dissociation from both the  $\mu$  and  $\kappa$  receptors with a half-life of 2–5 h [30, 33, 34]. Clinically, slow receptor dissociation produces fewer withdrawal signs and symptoms of withdrawal upon completion of buprenorphine treatment. This slow dissociation combined with a high receptor affinity also produces a competitive displacement effect when buprenorphine is combined with other opioids [18, 30]. Studies comparing receptor assays of fentanyl and buprenorphine showed that buprenorphine is only displaced from the opioid receptors once very high plasma concentrations of the other opioids are achieved [34]. Additionally, this opioid blocking effect has been observed to last as long as 24 h [30]. These findings led many clinicians to use buprenorphine in addiction medicine where once daily dosing could be used for the treatment of opioid withdrawal.

With the growing clinical use of buprenorphine and other partial agonists, it is important that the anesthesiologist understands how this drug pertains to the liver transplant patient. While there are lim-

ited studies available, based on known decreases in phase I metabolism in the cirrhotic patient, many experts recommend to lower the initial doses of buprenorphine with slow and monitored titration [6, 29]. In the perioperative setting, patients on stable sublingual doses of buprenorphine can be managed with a divided dose of their maintenance regimen. Breakthrough pain is best treated with highly potent opioids, such as fentanyl due to the opioid blocking effects of buprenorphine [29, 30, 33, 34]. As with all opioid regimens in the transplant patient, patients must be closely monitored as changes in hepatic function and perfusion during the perioperative period will affect opioid dosing.

Table 35.1 lists equipotent doses and duration of action of commonly used opioids.

## Dexmedetomidine

Dexmedetomidine, an enantiomer of medetomidine, is a highly selective alpha-2 agonist that is 1,600 times more selective for the alpha-2 receptor than the alpha-1 receptor [35]. Compared to clonidine, dexmedetomidine is 7–8 times more potent at the alpha-2 receptor [35–37]. Being an alpha-2 agonist, dexmedetomidine binds to both central and peripheral alpha-2 receptors. Postsynaptic alpha-2 receptors are located within



the central nervous system with the highest concentration of receptors found in the locus coeruleus [38]. Presynaptic alpha-2 receptors are located within the peripheral nervous system and various organ tissues [35, 37, 38]. Upon activation, presynaptic alpha-2 receptors inhibit the release of norepinephrine from the nerve endings [38, 39]. While dexmedetomidine does have a supraspinal mechanism for analgesia, the primary analgesic response occurs at the level of the spinal cord by inhibition of nociceptive pathways in the dorsal horn [40–43]. Dexmedetomidine undergoes extensive hepatic biotransformation with 95% of the parent drug being metabolized by both phase I and phase II reactions [44] to form inactive and nontoxic metabolites that are excreted in the urine and feces [44]. In healthy patients, dexmedetomidine has an elimination half-life of 2–2.5 h [44]. In patients with severe hepatic impairment, there is a decrease in plasma protein binding and clearance values while the elimination half-life was increased to 3.9–7.4 h [44]. While there are limited studies of dexmedetomidine in liver transplant recipients, one case report described the successful use of a dexmedetomidine infusion for 5 weeks postoperatively without any adverse side effects or signs/symptoms of withdrawal upon termination of the infusion [45]. Similarly, studies evaluating the prolonged use of dexmedetomidine in adult ICU patients suggests that adverse events, such as bradycardia, occur only during drug loading while withdrawal effects such as rebound tachycardia and hypertension were absent [46]. Perioperatively, some anesthesiologists take advantage of the (weak) analgesic effects of dexmedetomidine to decrease the intraoperative MAC of anesthetic agents and the postoperative opioid requirements [38, 47, 48].

## Gabapentin

Originally developed as an antiepileptic drug, gabapentin has become a widely used drug in the treatment of pain syndromes, including post-therapeutic neuralgia, neuropathic pain, diabetic peripheral neuropathy, and to treat acute pain. The FDA originally approved its use in 1994 as an

adjuvant for seizure prophylaxis [49]. Chemically similar to the neurotransmitter GABA [50], multiple studies attempted to elucidate gabapentin's mechanism of action. It likely inhibits specific high voltage activated calcium channels therefore reducing neurotransmitter release [49]. Gabapentin is only available as an oral preparation and its bioavailability is inversely proportional to the dose given [50]. There is no hepatic metabolism and gabapentin is eliminated unchanged in the urine. Its elimination half-life is 5–8 h and as such is often dosed in three times daily regimen [49]. The most common side effects from the drug are somnolence and dizziness. Multiple studies have found an opioid sparing effect of preemptive analgesia with preoperative oral gabapentin. Doses ranged anywhere from 300 to 1,200 mg in these studies. A total of seven meta-analyses have concluded that gabapentin is effective in reducing postoperative pain and has an opioid sparing effect [49]. There are no studies to date looking at the efficacy and safety of gabapentin dosing in end-stage liver disease patients undergoing liver transplantation. However given the lack of hepatic metabolism and opioid sparing effect preoperative administration of gabapentin in carefully selected patients with relatively normal renal function can be considered.

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## Perioperative Pain Management

The recognition that patients with end-stage liver disease suffer from a multitude of symptoms, including nausea, dyspnea, and severe pain, is important but often underappreciated [51]. According to a prospective cohort study by Roth et al., approximately one-third of patients with end-stage liver disease have at least moderate pain, with pain scores very similar to patients suffering from end-stage colon or lung cancer. The study further found that two-thirds of these patients are low-income men with multiple comorbidities including alcoholism and drug abuse. These patients often rate their quality of life as poor to fair [51]. Often patients with a history of substance abuse have undertreated pain due to the notion that these are unreliable patients.

These physician biases in combination with concern of altered hepatic synthetic functions make it understandable why pain in patients with end-stage liver disease is often undertreated.

Ideally analgesic regimens should be continued with modifications as needed through the course of disease progression and the perioperative period. The anesthesiologist's role in analgesic management starts with a thorough history that includes the patient's baseline analgesic regimen. Knowing the patient's preoperative analgesic requirement and response to current therapy will allow the anesthesiologist to better predict the analgesic needs throughout the operative and postoperative period.

### **Methadone Maintenance Therapy**

It is not unusual to encounter patients with end-stage liver disease on methadone maintenance therapy (MMT) for opioid abuse considering that over 80% of these patients are infected with hepatitis C [52]. To date there have been at least four retrospective studies with a total 52 patients on MMT who have received liver transplants [52–55]. Weinrieb et al. found that patients on MMT had much higher opioid requirements both intraoperatively and postoperatively compared to a matched group of patients undergoing liver transplantation not on MMT [52]. Methadone therapy has become a controversial topic in the field of liver transplantation. Some transplant centers require cessation of methadone before a patient is allowed on the waiting list [52]. However the aforementioned studies have demonstrated that in patients on MMT who receive liver transplants substance relapse is rare and survival similar to patients not receiving MMT [53, 56]. We therefore think that patients receiving MMT should not be excluded from transplant eligibility solely based on the fact they are on MMT.

### **Intraoperative Analgesia**

Perioperative analgesia is important to alleviate suffering as well as decrease potentially harmful physiologic consequences. Numerous studies

have assessed the physiologic benefits of analgesia include decreased risk of DVT, decreased risk of developing chronic pain, and decreased length of hospital stay. Although controversies exist regarding the utility of preemptive analgesia, more recent systematic reviews suggest that there may be some benefit from preemptive analgesia as long as appropriate attention is paid to intraoperative and postoperative analgesia as well [57, 58].

The use of opioids including fentanyl, hydromorphone, methadone, and remifentanyl is appropriate during liver transplantation and the intraoperative analgesic management is similar to other major abdominal surgeries. However there are considerations unique to liver transplantation patients. Multiple studies have shown that liver transplantation patients require less morphine than other major abdominal surgeries [59–62]. Eisenach et al. who first demonstrated this difference in 1989, proposed that the decreased morphine use was due to elevated endogenous opioids and not due to altered metabolism [61]. Donovan et al. found higher levels of met-enkephalin in patients with end-stage liver disease both before surgery and postoperatively days 1–3 further evidence that decreased morphine requirements were likely due to increased levels of endogenous opioids [60]. Moretti et al. postulated that the decreased opioid requirements may in part be due to the denervation of the transplanted organ [62]. Regardless of the exact mechanism the anesthesiologist should be aware of this difference in opioid requirements when prescribing patient controlled analgesia for liver transplant patients. To date there have been no studies evaluating patient controlled analgesia dosing regimens in liver transplant patients.

### **Epidural Analgesia**

An area of substantial controversy in liver transplant anesthesia is the perioperative placement and use of thoracic epidural catheters. Decreased synthetic function in the liver leads to decreased coagulation factors and coexisting renal disease may cause platelet dysfunction both affecting

hemostasis and bleeding. Several studies have been published that argue for and against placement of epidurals for liver transplant recipients. Trzebicki et al. recounted the use of thoracic epidurals in liver transplant recipients over the course of 10 years. Only patients with INR < 1.5, aPTT < 45, and platelets > 70 were included. During the 10-year time period 24% or 67 patients undergoing liver transplantation received a thoracic epidural. The authors concluded that placement of preoperative thoracic epidural allowed early extubation: 84% of patients who had an epidural were extubated in the operating room. The epidurals were removed on postoperative day 5 in most patients after normalization of coagulation studies and platelet levels [63]. However Fazakas et al. suggest that although complications are rare, when they do occur they exceed the benefits provided by analgesia [64]. The most challenging piece to the puzzle is the unpredictability of normalization of the coagulation factors and platelets in patients following transplantation. At this time there is not enough evidence to recommend the routine use of thoracic epidurals for perioperative liver transplantation analgesia; however, it is certainly reasonable to consider a thoracic epidural for intraoperative and postoperative analgesia in carefully selected patients.

### Local Infiltration

Infiltration of the wound with subcutaneous local anesthetic has been used for a long time to provide postoperative analgesia in large abdominal incisions. This is potentially beneficial in liver transplant recipients who have large and potentially very painful incisions. Various combinations of injection of surgical incisions with local anesthetics have been studied [65–71] and the data has been conflicting regarding the efficacy of this intervention. Some studies demonstrated a clear benefit while others showed no effect [70, 71]. Local infiltration has not yet been studied in liver transplant patients, however given the minimal cost, lack of significant side effects [72], and the possibility of an opioid sparing effect with the potential for preemptive analgesia, it is reason-

able to infiltrate the wound using a long acting local anesthetic such as bupivacaine 0.25–0.5%.

### Postoperative Analgesia

One of the key goals of providing adequate postoperative analgesia is to minimize physiologic complications while maximizing patient comfort. Multimodal approaches to pain management are an attractive option to reduce the side effects accompanied by pharmacologic interventions but also to decrease the metabolic demand on the newly transplanted liver. Thus, even though parenteral opioids continue to be the mainstay of acute postoperative pain management, ideally analgesia should include a three-pronged approach:

- Pharmacotherapeutic: Opioids and non-opioid adjuvants
- Non-pharmacotherapeutic: Behavioral approaches and physical modalities
- Invasive interventions: Peripheral nerve blocks, trigger point injections, acupuncture

### Pharmacotherapeutic

To date there are no adequate postoperative analgesia studies in liver transplantation to elucidate the most effective analgesic modality. As mentioned earlier this population has decreased opioid requirements. Though there is no consensus statement, the standard practice is to administer opioids via patient-controlled analgesia. NSAIDs are generally avoided in this population due to platelet dysfunction and defunct renal function in patients with end-stage liver disease. Anticonvulsants like gabapentin and pregabalin can be used as adjuvants and even though these agents have not been studied effectively in this population, their use can be considered on an individual basis. Acetaminophen is generally avoided in the immediate post-transplant period, although once graft function is established and hepatic metabolism normalizes acetaminophen is probably safe and should be considered [73].

## Behavioral Approaches

Studies have shown that high preoperative anxiety scores correlate with postoperative dissatisfaction with patient-controlled analgesia [74]. Keeping this in mind, psychosocial counseling including teaching the patient coping skills and anxiety management through distraction, bio-feedback, mindfulness therapy, and deep breathing techniques are ideally started in the preoperative setting. According to UNOS bylaws all patients undergoing liver transplantation must have a psychosocial evaluation before transplantation and this evaluation can be an opportunity to include coping mechanisms to provide insight into perioperative analgesic needs.

## Physical Modalities

Rehabilitative techniques focus on early functional restoration and generally improve the patient's global sense of well-being. Among others, one of the easily used modalities includes simple neuromodulation techniques such as transcutaneous electrical nerve stimulation (TENS). The opioid sparing effect of TENS therapy is of particular importance to patients with opioid intolerance or in patient populations in whom opioid therapy is complicated due to impaired metabolism. There are no controlled studies evaluating the efficacy of TENS therapy in liver transplant patients in the perioperative phase. TENS therapy is a noninvasive, non-pharmacological tool used in the management of acute and chronic pain [75, 76]. It utilizes electrical currents through surface electrodes to modulate central and peripheral pain pathways that ultimately result in decreased pain perception [75, 76]. It was introduced to the medical community in the late 1960s by Wall and Sweet in their sentinel article on TENS for pain management [77, 78]. An interesting finding in this paper which has since been replicated in clinical trials is that TENS analgesia ranges minutes to an hour after termination of electrical stimulation in patients with pain [78]. The main mechanisms involved in TENS modulation of the pain

pathways is the gate control theory and the release of endogenous opioids [77]. Though an intricate description of this process is beyond the scope of this chapter, it is important to note that primary sensory afferents synapse in the dorsal root ganglion at each spinal level and send projections to the substantia gelatinosa of the dorsal horn. The substantia gelatinosa acts as the gate keeper between the periphery and the higher processing pathways [79, 80]. The electrical stimulation of large diameter afferent fibers competes with smaller diameter afferent pain fibers and inhibits transmission of noxious stimuli from the first order to second order neurons [79–81]. Activation of large afferent fibers also leads to the release of GABA and glycine which bind to receptor sites that inhibit second order neurons [81–83]. TENS analgesia is also partly due to the release of endogenous opioids in response to electrical stimulation [76]. Cerebral spinal fluid concentrations of beta-endorphins, methionine, enkephalin, and dynorphin A are elevated in healthy patients after both high and low frequency electrical stimulation [77, 84–86]. Activation of opioid receptors in the dorsal root ganglion inhibits voltage gated calcium channels and opens potassium channels, decreasing neuronal excitability [81]. Clinical studies have shown a reduction in postoperative opioid requirement in patients receiving TENS therapy compared to placebo TENS [87]. Studies looking at postoperative TENS with PCA compared to PCA alone in patients undergoing lower abdominal surgery found a 53% reduction of morphine requirements in patients receiving mixed frequency TENS at 2 and 100 Hz compared to PCA only group [76]. These findings confirmed the opioid sparing effect of TENS therapy and showed a superior effect of mixed frequency TENS (2 and 100 Hz) over low (2 Hz) or high (100 Hz) frequency TENS in reducing postoperative opioid requirements [76, 77]. Not surprisingly, patients who received the TENS therapy also exhibited less nausea, dizziness, and pruritis as compared to the PCA group [76]. None of the patients in the studies mentioned above experienced any side effects from the TENS treatments [76, 87].

## Invasive Pain Interventions

The use of invasive pain interventions in the postoperative phase should start in the preoperative period by considering preoperative epidural placement or spinal duramorph administration in carefully selected patients. Since there is no consensus in this regard, institutional practices and individualization of therapy is key. As mentioned earlier injecting the incision site with a long acting anesthetic may have a role in preemptive analgesia with minimal adverse effects.

Postoperative, if the pain is in a specific distribution, perineural injection of local anesthetic can often provide relief. Blocks to consider include intercostal blocks or transverse abdominis plane (TAP) injections using ultrasound guidance for correct visualization. TAP block provides analgesia for the skin, subcutaneous tissue and peritoneum, while additional analgesia is required for visceral pain. TAP block should therefore be used as a component of multimodal pain treatment. To minimize complications TAP blocks should only be performed by experienced practitioners using ultrasonography. The aim of a TAP block is to deposit local anesthetic in the plane between the internal oblique and transverse abdominis muscles targeting the spinal nerves in this plane. Sensory innervation to the abdominal wall skin and muscles up to the parietal peritoneum will be interrupted. This plane contains the thoracolumbar nerves originating from T6 to L1 spinal roots that supply sensation to the anterolateral abdominal wall. These multiple mixed segmental nerves branch and communicate as they run through the lateral abdominal wall between internal oblique and transverse abdominal (TA) muscles, within the TA fascial plane. The analgesic efficacy of the TAP block compared to placebo has been demonstrated in prospective randomized trials of different surgical procedures such as abdominal surgery [88], hysterectomy [89], or retropubic prostatectomy [90]. All the studies have found a superiority of the TAP block and a reduction of visual analogue scale scores and morphine consumption. More recently a case report was published describing the utility of TAP blocks with a

continuous catheter in two civilian trauma patients, describing multiple perioperative benefits of the TAP block including excellent analgesia, rapid extubation, early hospital discharge, as well as an alternative technique to central neuraxial anesthesia when coagulopathy is present [91]. Though it increasingly used in patients undergoing renal transplantation, the TAP block has yet to gain popularity in the post-liver transplantation patient and it must be used with caution. Risks associated with the TAP nerve block technique should be considered prior to performing the procedure including block failure, infection, inadvertent intravascular local anesthetic injection, and bowel perforation. Farooq and Carey describe a case report of liver trauma with a blunt needle while performing the TAP block [92]. In an attempt to minimize these risks, ultrasound-guided placement by a skilled operator is essential. There number of studies and included patients is still insufficient to reliably guide clinical practice. However TAP blocks may become a valuable tool to optimize analgesia if used judiciously in select patients. Trigger point injections and acupuncture may also be considered in amenable patients with corrected coagulation states.

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## Living Donor Hepatectomy

Pain control for living donor hepatectomy is in some ways more complex than that for the recipient. Living liver donors are healthy and have only very few comorbidities. Since the first living donor hepatectomy was performed in the United States in 1989, the numbers gradually increased during the 1990s with just over 500 being done in 2001. However since 2001 that number has decreased in half likely due to several donor deaths [93]. Given the elective nature of the procedure every precaution must be taken to minimize morbidity, mortality, and also pain and suffering. A small retrospective study found that patients who underwent a right lobe donor hepatectomy had significantly higher pain scores than patients who underwent major hepatic tumor resection [94]. It was postulated that pain



scores were higher due to length of procedure as well as the fact that these patients had no pain before surgery. Preoperatively living donors have normal coagulation factors and platelet function. Therefore placement of thoracic epidurals for postoperative pain control is practiced in many centers. A study by Siniscalchi et al. described a series of 30 donors who received thoracic epidurals. The coagulation status and platelet counts of all patients in this study returned to acceptable levels by postoperative day number 4 allowing the removal of epidural catheters without any complications [95]. Choi et al. describe a similar experience with epidural placement in living donors. Of 360 living donors, 242 received epidural catheters preoperatively. Catheters were removed in 177 of these patients by postoperative day 3–4. None of the patients in this series experienced epidural hematomas [96]. The most common adverse effects in all these studies were pruritis and nausea associated with epidural opioids. Ozkardesler et al., reported a series of 100 living donor patients receiving thoracic epidurals. One of their patients suffered from a postdural puncture headache [97]. Based on these studies it can be concluded that as long as coagulation status is followed closely postoperatively, placement of thoracic epidurals for living donor hepatectomy appears to be a safe and effective method of perioperative analgesia.

Another commonly used mode of analgesia for this patient population is the use intrathecal morphine. A prospective double-blinded study of 40 donor hepatectomy patients compared postoperative morphine consumption in patients who received intrathecal morphine and fentanyl to patients receiving a placebo injection. Patients who received intrathecal opioids used significantly less morphine postoperatively [98]. Another randomized prospective study of donor hepatectomy patients found similar results: patients who received preoperative intrathecal morphine used significantly less postoperative fentanyl via a patient-controlled analgesia delivery system. Both groups have similar side effect profiles with slightly more pruritis found in the intrathecal morphine group [99].

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## Pediatric Liver Transplantation

Pediatric pain management is particularly challenging as pediatric patients are often unable to verbalize their pain or discomfort. While very few analgesic studies have been conducted in this population, many authors believe that in pediatric transplant similar to adult patients a combination of elevated endogenous met-enkephalins and other neuropeptides combined with attenuated sensory input from the denervated liver leads to a decreased need for opioids postoperatively [100]. Not surprising, despite this decreased need for postoperative narcotics, cohort studies have shown that physicians are often undertreating postoperative pain in pediatric patients [101]. Communication barriers, fears of oversedation, and prolonged intubations and pediatric ICU stays are believed to be the main reasons causing ineffective pain control for the pediatric patient [102]. A cohort study by Sharek et al. illustrated that a multidisciplinary and multifaceted approach combining preoperative education of child and parents, immediate postoperative consultations with pain medicine, certified child life specialists, and child psychiatry services combined with intravenous morphine significantly decreases pain scores in pediatric liver transplant patients [102]. While randomized control studies are lacking, case reports have described the use of caudal morphine for acute intraoperative and postoperative pain control in pediatric liver transplant patients. As with all types of neuraxial anesthesia, coagulopathy is a major concern. If clotting factors, platelet levels and coagulation studies are normal, caudal morphine can be an excellent option for perioperative pain control in these patients [100]. As in adults, neuraxial anesthesia in pediatric transplant patients not only blunts the neuroendocrine response to pain that decreases the risk of vascular thrombosis but also minimizes the amount of intraoperative and postoperative opioids and other analgesics presented to the newly transplanted liver [100].



## Chronic Pain

Studies evaluating the quality of life after liver transplantation show improvement of functional status. Belle et al. showed that patient's quality of life improved dramatically after transplantation [103]. Management of chronic pain in patients who have undergone liver transplantation is similar to management of other patients with chronic pain. Pain management physicians use a multimodal approach taking into account the patient's liver function, coexisting medical and psychological comorbidities.

An area of specific interest for the chronic pain specialist is neuropathic pain. Management of these chronic pain patients is particularly difficult during the perioperative transplant period as they are often on stable regimens of opioids, antidepressants, and anticonvulsants to control their pain. Both the tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs) undergo extensive hepatic biotransformation via phase I reactions into metabolites excreted in the urine [104, 105]. While specific randomized control trials of liver transplant recipients are lacking, studies in patients with varying degree of hepatic impairment have suggested that the dose of TCAs and venlafaxine are to be decreased up to 50% [105]. Duloxetine should be avoided altogether given numerous case reports associated with hepatotoxicity and fulminant hepatic failure. As previously stated, gabapentin appears to be safe without any need for dose reductions if the patients has normal renal function. Nonetheless, despite normal postoperative graft function, many pain physicians will still avoid the use of antidepressants as a treatment for neuropathic pain in liver transplant recipients.

## Conclusions

Management of pain in patients with liver disease raises special concerns. The choice of appropriate analgesic agents requires a thorough understanding of their pharmacokinetic and side effect

profiles. Hepatic metabolism complicates the use of intravenous and oral analgesics while the coagulopathy seen with liver disease limits the use of regional techniques in many patients. However a multimodal pain therapy should aim to minimize the pain associated with liver transplantation or resection and ideally renders the patient pain free.

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**Part V**

**Critical Care Medicine for Liver  
Surgery**

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# Postoperative Care of Living Donor for Liver Transplant

# 36

Subramanian Sathishkumar and Tadahiro Uemura

Liver transplantation is a standard treatment modality for patients with end-stage liver disease but the scarcity of cadaveric donors has led to long waiting times for transplant procedures in this severely ill group of patients and many, unfortunately, die before they ever receive a transplant. Current UNOS (United Network for Organ Sharing) data highlights this problem. About 16,000 patients are waiting for a liver transplant in the United States [1] and in 2010 1,467 liver patients died while waiting for a transplant. To overcome the lack of deceased donors, living donor liver transplantation (LDLT) is becoming increasingly common since it was introduced into clinical practice in 1989.

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## Epidemiology

Six thousand three hundred and twenty liver transplants were performed in the USA in 2009. Of these, only 219 were LDLT. The number of LDLT performed reached a peak in 2001 and then decreased dramatically after case reports of donor deaths (Fig. 36.1) [1, 2].

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## Current Surgical Technique

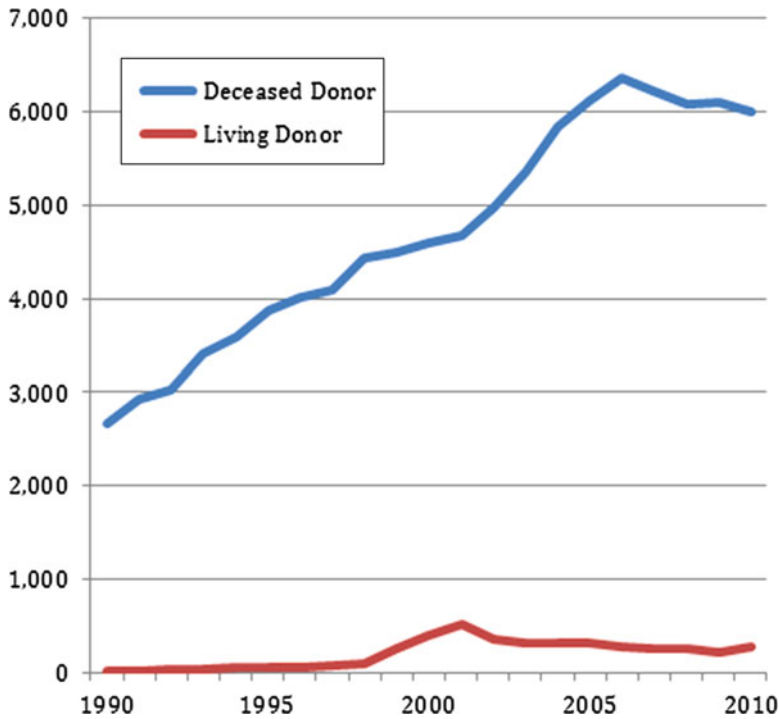
An adult-to-adult living donor liver transplantation (A2ALL) recipient requires about 30–60% of the donor total liver mass, necessitating an entire right or left donor lobe resection [3]. To provide sufficient liver mass to the recipient, resection of one of either left lateral lobe, entire right or left lobe of the liver is required. Early during the development of A2ALL, it became evident that the left lateral lobe was insufficient to provide adequate liver mass and hence an entire right or left lobe resection was required for A2ALL [4]. The decision to use a right or left lobe is often based on Computed Tomography (CT) volumetry (Fig. 36.2) and the donor remnant liver volume. Based on graft volume and remnant liver volume, right or left lobe graft is determined. The remnant liver volume generally should be more than 35% of the whole volume [5]. A recent study reported that right or extended right lobe donation was associated with more frequent and severe complications than non-right lobe resections [6]. Postoperative complications in donors are discussed in detail in the later part of the chapter.

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## Ethical Issues

One of the most important tenets of medicine is nonmaleficence or “First, do no harm.” In order to properly weigh the ethical issues, a precise understanding of risks and benefits to the donor *and*





**Fig. 36.1** Liver transplantation from 1990 to 2010 in the USA comparing deceased and living donor liver transplant (UNOS data)

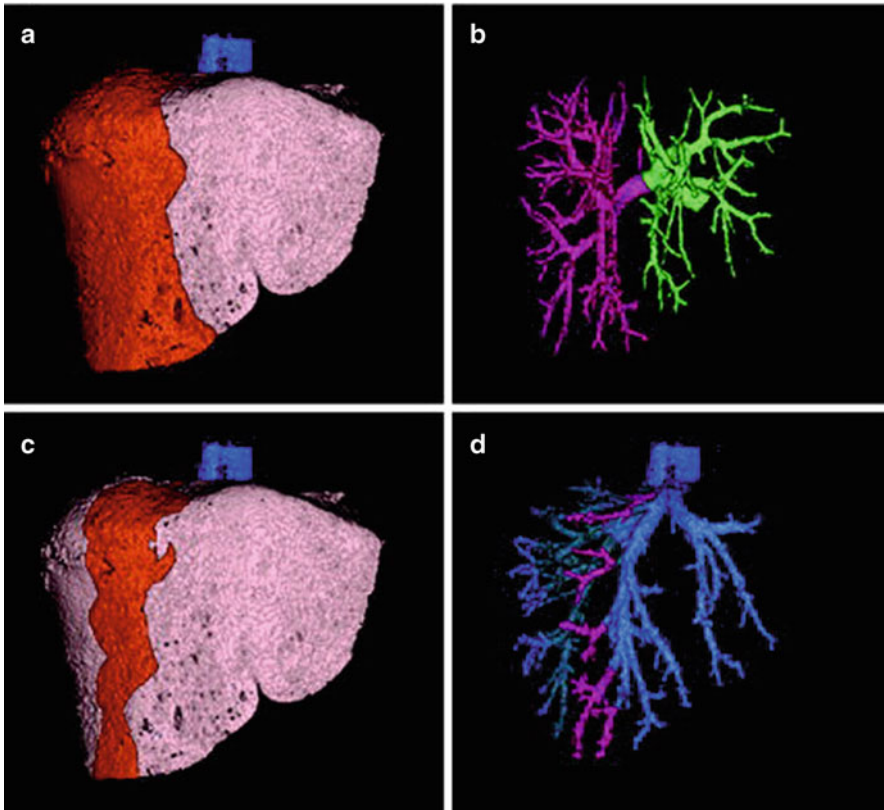
recipient are needed. The ethical challenge in LDLT is that a healthy individual undergoes a lengthy major operation with no *personal* health benefit [7, 8]. The transplant team must consider both the recipient and the donor perspective before proceeding with LDLT. Recipients of LDLT should meet the same listing criteria required for deceased donor liver transplantation (DDLTL). MELD scores (Model for End-stage Liver Disease) are used along with approval of the multidisciplinary transplant team. Preserving the health of the donor and excluding a donor if they are not a optimal candidate are crucial and should supersede any other concerns for the transplant team [7].

### Risk Factors for Postoperative Complication in Living Donors

Several independent risk factors have been associated with an increased incidence of post-operative complications such as biliary leaks,

bacterial infections, incisional hernias, pleural effusions, wound infections, and intra-abdominal abscesses [3]. In particular the following risk factors had a significant association with biliary complications such as [6],

- (a) Donor age: Older donors are more likely to suffer from complications such as delayed liver regeneration and poor long-term survival of the graft. Delayed regenerative capacity can predispose to risk of liver failure [9].
- (b) Surgical technique: Right and extended right lobe resection has been associated with more frequent complications [6].
- (c) Intraoperative blood transfusion: There is higher incidence of biliary complications and infections in donors who received blood transfusion [3]. However a causative relationship is difficult to prove as this could possibly be related to complex surgical dissection leading to more than usual blood loss necessitating blood transfusion.



**Fig. 36.2** 3D-CT image of a liver. Using software, the volume of each vessel branch can be automatically calculated before an operation using the software. (a, b) Construction of a 3-dimensional image shows the perfusion area (red color in panel (a)) of the right portal vein

(purple (b)). (c, d) The construction of a 3-dimensional image shows the drainage area (red in (c)) of the middle hepatic vein (MHV) tributaries (V5, V8; purple in (d)). Adapted with permission from Yonemura et.al Liver Transplantation 2005; 11:1556 [5].

## Postoperative Care

In an effort to minimize postoperative complications, close surveillance of the donor is essential. Optimal management will ensure early ambulation and discharge. Even though these patients are healthy when they enter the operating room, they need careful and intensive monitoring for the first 24 h postoperatively. Experience with this specific patient population is necessary to allow rapid diagnosis and treatment of postoperative problems and prevent morbidity. To ensure close surveillance, most centers admit donors to an intensive care unit (ICU) for overnight monitoring [4, 10, 11] but a step down unit,

intermediary care unit or postanesthesia care unit (PACU) [13] are acceptable alternatives.

## Routine Postoperative Management

### Surveillance for Deep Vein Thrombosis

The risk of thromboembolic complications is increased after major surgery and prophylaxis is indicated [12]. Early mobilization is the key to prevent these complications. Loss of significant liver volume in the donor can lead to decreased synthetic capacity and may cause a subclinical or insidious coagulopathy but also hypercoagulability due to decreased anticoagulant factors (for example, protein C, protein S, or antithrombin).

Prior to starting anticoagulation the potential for coagulopathy should be taken into consideration.

Deep vein thrombosis (DVT) prophylaxis is usually accomplished pharmacologically with either subcutaneous low molecular weight (LMWH) [11, 13] or unfractionated heparin. Unfractionated heparin allows the greatest flexibility with regards to the removal of epidural catheters if these are used for postoperative pain management [14]. LMWH offers the ease of once or twice daily administration. Non-pharmacological measures include sequential compression device (SCD) or thromboembolic stockings.

### Antibiotic Prophylaxis

Single dose broad-spectrum antibiotic prophylaxis is given prior to surgical skin incision. Routine antibiotic prophylaxis is not generally required postoperatively unless specifically indicated. Although infrequent, donors may develop wound infections, intra-abdominal abscess and pneumonia. Prevention of these complications is multimodal including strict barrier precautions, avoidance of perioperative hypothermia and prolonged, prophylactic antibiotics will not prevent these complications.

### Intravenous Fluids and Nutrition

Intravenous (IV) fluid is titrated to urine output and balanced against oral intake. The goal is to maintain adequate tissue perfusion and oxygenation. To avoid remnant liver congestion, IV fluids are judiciously used to avoid high central venous pressures. Generally crystalloids are used. If there is evidence of hypovolemia or blood loss not necessitating blood transfusion, colloids are frequently used but there is no evidence of superiority of colloids in this situation. Blood or blood products are not generally required unless there is hemodynamic instability due to bleeding. IV fluids are continued until full enteral feeding is commenced. Fan et al. reported the use of parenteral nutritional support in the immediate postoperative period to enhance liver remnant regeneration, although this is not a common practice in most centers [15].

### Laboratory Testing

Major hepatic resection causes a measurable decrease in coagulation factors due to transient synthetic insufficiency [16]. It is not uncommon to see a decrement in liver synthetic functions (increased transaminases and bilirubin) and an abnormal coagulation profile that begins to improve as liver regeneration occurs. Complete liver regeneration usually occurs between 1 week and 2 months after resection [17].

Postoperative laboratory surveillance usually includes a complete blood count (CBC), electrolyte and metabolic panel, coagulation profile, and liver function tests (LFTs). These laboratory studies are recommended every day for first 3 postoperative days (PODs), followed by testing on alternate days until discharge [14]. If discharge occurs within 7 days of surgery, these tests can be performed on an outpatient basis if necessary.

### Radiological Evaluation

A postoperative Chest X-ray is usually obtained to check the position of the central venous catheter (CVC) and to rule out CVC-related complications such as misplacement or pneumothorax if a CVC was placed intraoperatively. Ultrasound or duplex imaging of remnant liver is not routinely performed [6] unless abnormal LFTs or the clinical course raise concerns for vascular complications such as portal vein thrombosis (PVT) and hepatic artery thrombosis (HAT).

In the normal course of events, the arterial line, CVC and nasogastric tube (NG) tube (if placed) can be removed on the first POD. If an epidural is used for postoperative pain management, the urinary catheter is removed coincident with discontinuation of the epidural analgesia. If oxygenation is adequate on trials of room air, oxygen supplementation can also be discontinued. The patient is expected to be out of bed on POD 1. On POD 2, clear liquids are often started and if tolerated and bowel sounds are normal, a soft diet can be then introduced on POD 3.

### Postoperative Analgesia

Adequate analgesia along with chest physiotherapy and incentive spirometry is vital to prevent respiratory complication in the postoperative

period. Epidural analgesia is a safe and effective option. After a major hepatic resections the potential for a postoperative coagulopathy exists and should warrant frequent neurological exams until the coagulation profile (prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and platelet count) is normal. The coagulation profile should be normal before the removal of epidural catheter and this may delay mobilization and/or discharge. Therefore many clinicians will preoperatively place a single dose of intrathecal morphine that will provide pain relief for 18–24 h after surgery instead of epidural analgesia [18]. If an epidural is used, analgesia can be transitioned to parenteral and oral analgesics before removal on POD 3 or 4. Intravenous patient-controlled analgesia (IVPCA) is also an acceptable alternative. More details about postoperative pain management can be found elsewhere (Chapter 35) in this book.

### Long-Term Follow Up

Based on retrospective studies, most centers follow patients up at 1, 4, and 12 months after donation [11]. This includes clinical evaluation, liver functions tests, and radiological evaluation if needed.

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## Postoperative Complications

Postoperative complications can be broadly classified as surgical and medical. Unfortunately, complications in living donors are probably underreported due to lack of a global database or registry and possibly a reluctance to report complications. Based on the current literature, the complication rate of donors from single center analysis varies widely from as low as 9% to as high as 67% [19–28]. The European Liver Transplant Registry has reported 0.5% mortality and 21% postoperative morbidity [29]. The Japanese Liver Transplant Society reported no mortality and 12% postoperative morbidity [30]. The variability in morbidity and mortality is likely due to the lack of a standardized system for classifying complications. In an effort

to overcome this classification shortfall, Clavien's classification of complications of surgery, which has been used for general surgery, has also been applied to transplantation (Table 36.1) [31, 32]. Using this classification, the NIH funded A2ALL Cohort Study reported an overall complication rate of 38% in nine transplant centers [3]. Using the same system, Patel et al. reported an overall complication rate of 29.1% [33] and Yi et al. reported a complication rate as high as 78.3% [10]. The reason for these differences, despite using the Clavien system, could be due to transplant center surgical experience as well as the use of retrospective data [3]. The A2ALL study concluded that although most living donors for liver transplants had, in general, low-grade severity complications, a substantial number had severe or life-threatening complications. Quantification of complications would improve postoperative care of these patients and improve the informed consent process [3] and may lead to improved care and long-term outcome of LDLT.

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## Postoperative Complications of the Living Liver Donor

### Bile Leakage

Bile leak is one of the most common complications in living donors and has been called the “achilles heel” of LDLT [8]. Its incidence ranges from 4.7 to 10.6% [3, 6]. The right donor hepatectomy tends to have higher incidence of bile leakage because the biliary system in the right lobe has more anatomical variation than the left lobe. Biliary complications are due to bile leak from stumps and due to biliary ischemia. Unrecognized anatomical variations can predispose to these complications. Preoperative CT cholangiography or intraoperative cholangiograms are helpful in assessing the anatomy of bile ducts. After reporting a decreased incidence of biliary complication with left lobe grafts, Taketomi et al. recommended that the left lobe should be considered first in choosing segments for A2ALL [34].

**Table 36.1** Modified Clavien system for classification of negative outcomes in general surgery and solid organ transplantation

Grade 1	Any alteration from the ideal postoperative course, with complete recovery or complications which can be easily controlled and which fulfills the following general characteristics
	Not life threatening
	Not requiring use of drugs other than immunosuppressants; analgesics; antipyretics; anti-inflammatory agents; antiemetics; drugs required for urinary retention or lower urinary tract infection, arterial hypertension, hyperlipidemia, or transient hyperglycemia
	Requiring only therapeutic procedures that can be performed at the bedside
	Postoperative bleeding requiring $\leq 3$ units of blood transfusion
	Never associated with a prolongation of intensive care unit stay or total hospital stay to more than twice the median stay for the procedure in the population of the study
Grade 2	Any complication that is potentially life threatening or results in intensive care unit stay >5 days, hospital stay >4 weeks for the recipient, but which does not result in residual disability or persistent disease
Grade 3	Any complication with residual or lasting functional disability or development of malignant disease
Grade 4	Complications that lead to retransplantation (grade 4a) or death (grade 4b)

Adapted from Ghobrial et al. [3], with permission

## Surgical Technique and Bile Leakage

Because most bile leakage occurs from bile duct stumps secondary to ischemia, it has been recommended to minimize the use of electrocautery around the bile ducts during liver resection. Some authors suggest that a biliary decompression tube is effective in reducing bile leakage [6] but it is not routinely placed in many centers. Bile leakage from the caudate lobe is problematic and can be refractory to conservative treatment. Careful attention should be paid to the bile ducts in these lobes and may require continuous suture or ligation [33].

## Signs, Symptoms, and Management of Bile Leakage

When bile leakage occurs, patients can present with fever, abdominal or shoulder pain, and bilious drainage from drains and the incision. Bile leakage can be diagnosed by physical exam, ultrasound, CT scan, diagnostic paracentesis, or endoscopic retrograde cholangiopancreatography (ERCP). Bile leakage may resolve after conservative treatment or may require interventional therapy such as continuous drainage, endoscopic retrograde bile drainage, percutaneous drainage, or surgical repair [6].

## Infection

Despite careful surveillance and meticulous operative techniques the incidence of postoperative infection rate ranges from 5.0 to 12.5% [3, 6]. These include pneumonia, urinary tract infection, cellulitis, sepsis, *Clostridium difficile colitis*, wound infection, and intra-abdominal abscess [6, 33]. Infectious complications are often secondary to other complication such as respiratory failure, delayed graft function, or bile leak.

## Hemorrhage

Yi et al. reported 3.8% of donors experienced transient bleeding from surgical drains that improved without blood transfusion [10]. Patel et al. reported one case out of 433 (0.23%) that returned to the operating room for hemorrhage [33]. The A2ALL study did not report any bleeding complications. The overall risks of bleeding complications reported in these studies were very low.

## Pulmonary Embolism

The risk of thromboembolic complications following LDLT has been highlighted in many papers [35, 36]. The incidence of pulmonary embolism has been reported to be between 0.2 and 0.8% [3, 6, 30]. It has been shown that the hypercoagula-

bility observed in living donors is a result of an increase in thrombin–antithrombin complexes and P selectin following surgery. This has also been observed in patients undergoing hepatic resection for benign tumors [37]. Bustelos et al. screened 188 potential donors for bleeding or procoagulant and found that about 20% of them have at least one abnormality. The donors in this study were screened for factor V Leiden, prothrombin mutation, deficiencies of protein C, S, and antithrombin [38]. They recommend preoperative screening of all potential donors for bleeding and hypercoagulable states. Taking into account the potential risk to donor and recipient, screening should be considered even though the cost-effectiveness of performing these tests is yet to be determined. DVT prophylaxis and early ambulation are the cornerstones in preventing rare but life-threatening thromboembolic complications.

### Vascular Complications

The incidences of PVT, HAT, and reversal of portal venous flow are rare but possibly catastrophic complications of the donors. Although the overall risk of PVT is low, it can be life threatening for a healthy donor who may then end up needing a liver transplant. There have been two case reports of PVT and inferior vena cava thrombosis reported by the A2ALL study [3, 6].

### Liver Failure Post-donation

Postoperative liver failure in the donor is often due to inadequate remnant liver volume. To avoid this catastrophic complication, preoperative evaluation is critical. Three-dimensional computed tomography (3D-CT) volumetry is used preoperatively to estimate liver graft volume as well as the donor's remnant liver volume (Fig. 36.2). Donor remnant liver volume needs to be at least 30–35% of total preoperative liver volumes. Two unusual cases of donor hepatic failure have been reported, attributed to nonalcoholic steatohepatitis in one and to Berardinell-Seip syndrome (lipodystrophy syndrome) in the other [29, 39, 40].

**Table 36.2** Donor mortality rates (3, 6, and 39)

European liver transplant registry	0.5%
Taku Iida et al. (Kyoto group)	0.08%
Survey of liver transplantation in living donors in the United States [41]	0.2%

These complications were due to unrecognized pathology in the donor liver. To avoid these problems, some centers routinely perform a liver biopsy as a part of routine preoperative work-up for donors.

### Donor Mortality

Living-related liver donation can be performed with relatively low risk of significant perioperative morbidity and mortality [33]. The overall mortality based on the current literature is between 0.08 and 0.5% (Table 36.2). Trotter et al., in a comprehensive review of the medical and lay literature, reported 19 deaths of live liver donors of which 13 were related to surgery [2]. The causes of death were sepsis (5 cases), liver failure (2 cases), myocardial infarction, cerebral hemorrhage, pulmonary embolism, peptic ulcer disease, and unknown cause (2 cases). As experience in performing these complex procedures increases, improved outcomes and decreased mortality and morbidity should be seen.

### Conclusion

LDLT decreases wait lists for transplants, and is a feasible and potentially lifesaving alternative for select patients. LDLT has become the most effective alternative to DDLT. As this technique continues to evolve, steps to improve perioperative outcomes are required including strategies categorize and standardize the definitions of surgical complications and report them in centralized registries. The development of a valid and useful prognostic scoring system to improve



donor safety will undoubtedly improve perioperative outcomes and facilitate the selection of suitable donors. Minimizing the risk for the donor will continue to be of paramount importance as the use of LDLT expands.

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Albert C.Y. Chan and Sheung Tat Fan

Liver resection remains to be the curative treatment of choice for both malignant and benign liver tumors. With advances in hepatic surgery and operative technique, liver resection has evolved from a rough and hasty procedure to a fine and delicate operation. Such surgical advances have resulted in a dramatic reduction of operative mortality, from over 50% in early series [1] to less than 10% in recent decades [2–4], and targeting “zero” mortality has even become a realistic goal to achieve [5]. However, the postoperative complication rate remains largely unchanged over the years despite a reduction in operative mortality and is in the range of 20–30%. Liver failure, bile leakage, and sepsis are serious complications that can lead to a fatal outcome. In this chapter, we will present our approach for prevention, diagnosis, and management of these complications.

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## Liver Failure

Even with adequate remnant liver volume and absence of comorbid illness, liver failure is the most common cause of mortality after major hepatectomy. Early signs of liver failure include hypotension, respiratory depression, oliguria,

jaundice, hepatic encephalopathy, and coagulopathy. Patients may improve during the initial postoperative period but can deteriorate again afterwards with an onset of drowsiness, jaundice, flapping tremor, ascites, pleural effusion, and oliguria. Early recognition of these symptoms allows for prompt treatment before the patient becomes unsalvageable. On the other hand, many patients with borderline liver function still undergo major hepatectomy and make a full recovery. A comprehensive preoperative assessment is critical in selecting the appropriate patients for partial hepatectomy.

## Preoperative Assessment for Hepatectomy

### Patient Selection

The presence of comorbid illness such as cardiovascular disease [6] and renal impairment [7] increases the risk of hepatectomy. Biological age is not a contraindication for hepatectomy but surgery in elderly patients can be challenging because exposure of the liver is limited by rigidity of the rib cage and lowering the central venous pressure (CVP) may be more difficult and less well tolerated. Severe comorbid illness such as congestive heart failure and chronic renal failure should be considered a contraindication for major hepatectomy. The American Society of Anesthesiologist (ASA) score is frequently used to assess the postoperative risk and is a reliable predictor of morbidity after hepatectomy [8].

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With increasing sophistication of liver function assessment, the presence of comorbid illness has become a more important factor in predicting postoperative outcomes of hepatectomy.

### **Preoperative Assessment of Liver Function Reserve**

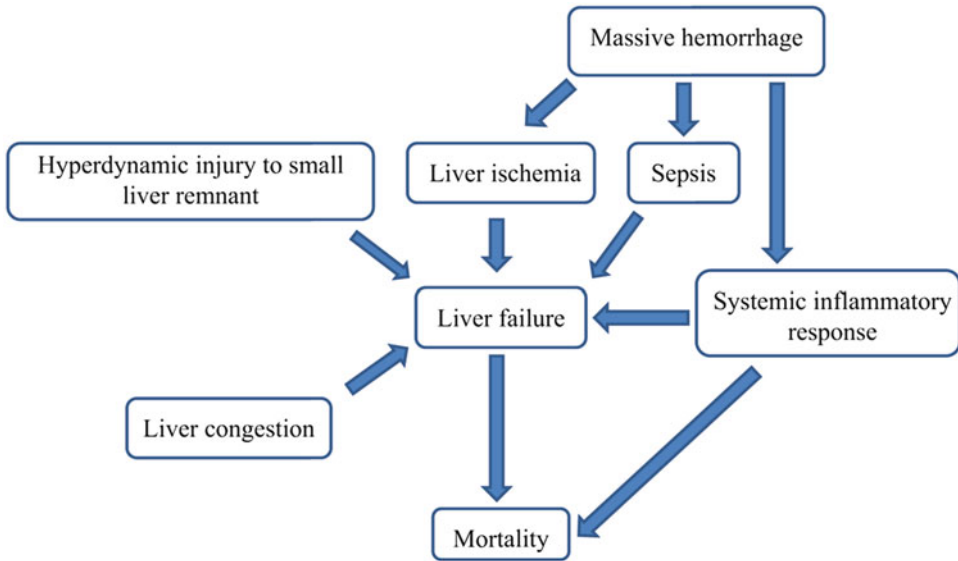
Liver function can be readily assessed by laboratory blood tests. Serum bilirubin and albumin are reflections of excretory and synthetic functions. White cell count and platelets count are surrogate markers for portal hypertension. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are elevated when hepatocytes undergo apoptosis. Raised serum ammonia levels are observed when hepatic encephalopathy sets in and hypoglycemia is an indication of fulminant hepatic failure. The Child-Pugh classification (A, B, C) is commonly used to categorize liver function reserve. Patients with Child-Pugh class A liver function are considered suitable for major hepatectomy, whereas those with Child-Pugh class B liver function are only eligible for minor hepatic resection in selected cases. Nonetheless, the accuracy of this scoring system is confounded by the fact that subjective clinical parameters, i.e., ascites and encephalopathy, are included in the assessment, rendering it susceptible to interobserver variation. To solve this problem, the ALT/platelet count ratio index, which is a biochemical surrogate for histological fibrogenesis in cirrhosis, may be an alternative [9]. Another approach that has been recently adopted in some centers is the use of the model for end-stage liver disease (MELD) score, which includes the international normalized ratio (INR), serum creatinine, and serum bilirubin in its calculation. However, given that most of the patients selected for major hepatectomy have normal renal function and INR, the resultant MELD score is expected to be low, rendering it impractical for clinical application.

The indocyanine green (ICG) clearance test is a sophisticated quantitative test for functional assessment of the hepatocytes. ICG is a nontoxic dye and only occasionally causes allergic reactions in some patients. After intravenous administration, it binds to albumin and  $\beta$ -lipoprotein

and is exclusively metabolized by the liver and excreted unchanged in bile without any enterohepatic circulation. Its clearance is a measurement of liver blood flow and reflects intrahepatic portovenous shunting and sinusoidal capillarization. In a healthy subject, the ICG retention value at 15 min (ICGR-15) after intravenous administration of the dye is about 10%. The ICG clearance test can be used alone or in combination with other clinical parameters for preoperative assessment of liver function. The higher the ICGR-15 value, the higher is the hospital mortality rate after hepatectomy. Our experience indicated that the cut-off value for a safe major hepatectomy of ICGR-15 is 14% and for minor hepatectomy 22% [10]. With experience, the limit could be extended to 17% for major hepatectomy. More importantly, the ICG clearance test is a more sensitive test than the Child-Pugh score in preoperative assessment of liver function and a wide range of ICGR-15 values exist among patients with Child A and B cirrhosis, indicating that liver function is quite variable among patients with Child A or B cirrhosis. ICGR-15 value should be interpreted with caution as falsely high values can be observed with portal vein obstruction, bile duct obstruction, and significant intrahepatic arteriovenous shunting or Gilbert syndrome.

### **CT Volumetry**

The volume of liver remnant after hepatectomy is an important factor in determining postoperative complications and mortality. In view of this, evaluation of the size of future liver remnant by computed tomography (CT) volumetry is a crucial part of the preoperative assessment of liver function. In living donor liver transplantation, a minimum of 25% of graft weight/estimated size of liver volume using the Urata formula (liver volume =  $706.2 \times \text{body surface area} + 2.4$ ) is required to ensure the graft and overall patient survival [11]. In cirrhotic livers, a future liver remnant  $\geq 40\%$  is needed to ensure a safe major hepatectomy. When the future liver remnant is  $< 40\%$ , portal vein embolization (PVE) can be employed to induce hypertrophy of the liver remnant in 3–6 weeks' time. PVE blocks blood flow to the liver



**Fig. 37.1** Operative causes of liver failure

ipsilateral to the tumor so as to divert all the portal inflow into the contralateral lobe and induce clonal expansion and hypertrophy of the hepatocytes [12]. PVE has been shown to reduce the incidence of liver failure after hepatectomy [13]. However, randomized control trials to show the benefit of PVE in terms of reduction in hospital mortality and prolongation of the overall survival of cancer patients are pending.

### Liver Protective Strategy During Hepatectomy

Meticulous surgical technique is an important factor to prevent liver injury due to bleeding and ischemia. Excessive bleeding induces organ ischemia that in turn predisposes to sepsis and systemic inflammatory reaction, resulting in multi-organ failure and, finally, death. Hyperdynamic injury to small remnant liver and liver congestion as a result of inadvertent damage to major hepatic veins are other factors that can lead to liver failure (Fig. 37.1). As a result, surgeons play an important role in liver protection during major hepatectomy. From a technical point of view, the operation should begin with a generous skin incision, for example, bilateral

subcostal incision with midline sternal extension. Adequate exposure is the key to facilitate mobilization of the right liver and dissection along the plane between the anterior surface of inferior vena cava (IVC) and the posterior surface of the caudate lobe. It also provides more space to allow for rotation of the liver to the left side and reduces the chance of avulsion of the right hepatic vein when a right hepatectomy is performed. Thoracotomy for better exposure should be considered when a large tumor is located in segment 7 or 8 of the liver. It is important to remove all packs and gauzes in the liver hilum before excessive rotation of the right liver as this could potentially cause extrinsic compression on the inflow vessels. Excessive rotation of the right liver can also cause compression of the left lateral segment against the left subcostal wound, leading to pressure ischemia. For large tumors, using the anterior approach avoids excessive rotation of the liver as the hepatic transection commences down towards the anterior surface of the IVC once the inflow vessels are divided and ligated. Bleeding volume, blood transfusion requirement, and oncologic outcomes were all shown to improve after adoption of the anterior approach [14]. However, control of hemorrhage deep in the parenchyma can sometimes be difficult with this

approach. To resolve this problem, the use of a hanging maneuver may allow exposure of the deep parenchyma better and hence reduces the difficulty in hemostasis. Hanging maneuver entails blind passage of a long instrument with a tape into the space between the anterior surface of the IVC and the posterior surface of the caudate lobe. Not surprisingly, inadvertent puncture of the IVC upon blind passage of the instrument can occur and cause profuse hemorrhage. Another pitfall of this maneuver is that the plane of transection can be deviated from the original plane guided by the middle hepatic vein if this is adopted right at the beginning of parenchymal transection. Therefore, we recommend that the hanging maneuver should be applied to provide direction for transection only when the middle hepatic vein is exposed and passed by.

Maintaining a low CVP helps to minimize blood loss during hepatic resection [15] as it facilitates venous drainage from the hepatic sinusoids and thus reduces venous backflow and hepatic congestion. A CVP in the range of 3–5 cm H<sub>2</sub>O is preferable though the risk of air embolism becomes a concern if CVP drops below this range. Simple physical measures such as stopping intravenous fluid and tilting the operative table into a reverse Trendelenburg position may help to decrease the CVP. If these measures fail, a bolus of low-dose furosemide can occasionally be administered. A recent report suggested that the use of Milrinone, a phosphodiesterase 3 inhibitor, is effective in reducing the CVP during donor hepatectomy by causing diastolic relaxation of the heart, which in turn improves venous return from the IVC and reduces venous backflow into the liver [16]. Apart from keeping a low CVP, control of inflow vessels, i.e., Pringle maneuver, is another effective way to minimize blood loss during hepatectomy as blood supply from the hepatic arterial and portal circulation is temporarily occluded. Intermittent Pringle maneuver was shown to be effective in reducing blood loss from the transection surface in a randomized control trial [17]. It has also been shown in various clinical studies to be protective against ischemic injury to the liver. However, it does not guarantee a bloodless operative field as bleeding

from hepatic veins can still occur. In this situation, total vascular occlusion, i.e., clamping of both inflow and outflow vessels, can be employed but substantial hemodynamic disturbance can be expected. The ultrasonic dissector is our preferred device for parenchymal transection. It is effective in reducing perioperative blood loss and facilitates exposure of the middle hepatic vein so as to guide the direction of transection. With judicious use of the ultrasonic dissector, perioperative blood loss has been reduced year by year in our center [18].

### Postoperative Management After Hepatectomy

All patients should be admitted to the intensive care unit after hepatectomy with continuous monitoring of hemodynamics, body temperature, and urine output.

Postoperative parenteral nutrition (PN) use is not widespread but has been used at our center to facilitate liver regeneration and is administered through a central venous catheter soon after the operation. PN forms an important aspect in our postoperative management, particularly for cirrhotic patients undergoing major hepatectomy, as it reduces the body net catabolic response to surgery and enhances protein synthesis, which is essential to maintain immunological and metabolic functions. The choice of PN in our center is a solution enriched with branched-chain amino acids as it is anti-catabolic and promotes protein synthesis in cirrhotic patients. Medium-chain triglycerides form part of the PN regimen as it depends less than long-chain triglycerides on binding to serum albumin which is advantageous for cirrhotic patients. No other intravenous fluid other than PN is given in order to avoid fluid overload and liver congestion. The use of PN in the form of branched-chain amino acids reduces postoperative septic complications, ascites formation and, more importantly, quicker recovery of liver function [19]. Early oral intake is encouraged as soon as bowel sounds resume since it maintains intestinal integrity, avoids bacterial translocation, stimulates production of hepatocytes growth fac-



tors, and enhances portal blood flow, which are all important elements for liver regeneration.

### Management of Liver Failure After Hepatectomy

Early referral to a tertiary center with availability of liver supporting devices and liver transplant service is crucial to improve the chance of survival in these patients. Early listing for liver transplantation with high urgency should be considered if there is little sign of hepatic regeneration and there is no clinical improvement or deterioration of clinical symptoms of liver failure. The concept of a liver supporting device is to remove accumulated toxic substance from the body that cannot be metabolized by the failing liver using an extracorporeal circulation system. There are mainly two types of liver supporting devices: bio-artificial and artificial livers. While the development of a bio-artificial liver is still in its infancy, various forms of artificial livers, such as the molecular adsorbent recirculating system (MARS), liver dialysis unit, and the Prometheus<sup>®</sup> device, a combination of albumin adsorption with high-flow hemodialysis, have been approved for clinical use in liver failure. The results of randomized trials of these devices are mixed [20]; in our cohort of 74 patients with liver failure, MARS treatment has been shown to be effective in reducing serum bilirubin and ammonia levels. Though the 30-day mortality rate remains over 70%, about a fifth of the patients were able to receive transplantation [21].

### Bile Leakage

Despite a reduction in operative mortality, the incidence of biliary complications has not changed over the years with an incidence ranging from 4.0 to 8.1% in various large series [22–24]. Therefore, it is of paramount importance to implement measures that allow early detection of bile leakage in order to reduce the adverse effects of biliary complications on postoperative morbidity and mortality.

### Pathophysiology of Bile Leakage, Sepsis, and Liver Failure

The presence of bile and blood clots in the dead space after hepatectomy provides a good medium to harbor bacterial growth. Infection provokes a systemic inflammatory response that is characterized by the release of various cytokines including tumor necrosis factor- $\alpha$ , interleukin-1, and interleukin-6 [25–28]. These cytokines in turn cause dysfunction of the host defense immune system and subsequently multi-organ failure. Patients with loss of liver mass after hepatectomy are certainly more susceptible to the development of liver failure once this cascade of inflammatory reactions is triggered by biliary complications.

### Preventing Bile Leakage: The Role of Surgical Technique

In contrast to blood that has the ability to form clots, bile does not form precipitation and can leak through tiny defects in a divided bile duct or from suture lines in the bile duct stump. Therefore, meticulous surgical technique is the key to prevent bile leakage. In order to appreciate how bile leakage is detected and to be prevented, one has to gain some insight into the operative technique of hepatectomy. The following paragraph describes the technique of hepatectomy adopted by our center.

### Specifics of Surgical Technique of Hepatectomy for Liver Tumors

\*The operation begins with a bilateral subcostal incision with sternal midline extension for optimal exposure and access to the liver. An intraoperative liver ultrasonography is then performed to identify the location of the tumor and its anatomical relationship with the middle hepatic vein so as to define the parenchymal transection line. The gallbladder is then removed and the cystic duct is cannulated by an Fr 3.5 Argyle catheter. An intraoperative cholangiogram is obtained to detect anatomical variation of the biliary system. Hilar dissection is performed to isolate the ipsilateral hepatic artery and portal vein, and is subsequently divided and suture-ligated. By this time, the liver parenchyma that is supplied by the ipsilateral inflow vessels will become discolored and the

transection line will be demarcated. For parenchymal transection, we use the Cavitron® Ultrasonic Tissue Aspirator (CUSA; Valley Lab, Boulder, CO), an ultrasonically powered aspirator that selectively destroys and aspirates parenchyma while sparing vascular and ductal structures. The CUSA allows good exposure of blood vessels and bile duct inside the liver parenchyma and reduces devitalization of liver tissues, especially around the bile ducts. After completion of liver transection, hemostasis is ensured and a bile leakage test is performed. Ten milliliters of diluted methylene blue solution is injected slowly via the cystic duct into the common bile duct. If there is leakage in the raw surface of the liver, it will be shown by extravasation of the methylene blue solution that is then plicated by fine absorbable sutures. Common sites of bile leakage include the bile duct stump, minor ducts over the transection surface, and the caudate lobe. The methylene blue test is a sensitive method to rule out bile leakage. In our previous retrospective analysis of 304 patients who had a methylene blue test, 60 patients had a positive test and 3.6% a confirmed bile leakage [29]. The leakage site was sutured intraoperatively, but 10% of these patients still developed postoperative bile leakage. Among those who had a negative bile leakage test, only 2% developed postoperative bile leakage. In other words, a negative methylene blue test can rule out bile leakage with good sensitivity. However, a randomized control trial that used only normal saline instead of methylene blue solution did not show any advantage of an intraoperative bile leakage test [20].

### Clinical Presentation of Bile Leakage

Advancing age is a risk factor for postoperative biliary complications [22]. Although the causative association between age and bile leak is less clear, it has been shown that intra-abdominal sepsis is more common in elderly patients after hepatectomy [30]. There is a close interaction between infection and bile leakage. Infection may induce tissue devitalization around the bile duct and hence predispose to bile leakage. Alternatively, collection of bile in the dead-space forms a favorable environment for microorgan-

isms to grow. The clinical presentation of bile leakage includes an onset of fever on postoperative day 4–7. For immunocompromised patients, persistent tachycardia after hepatectomy can be the only sign of occult bile leakage. Other possible clinical symptoms include chills and rigors, abdominal distension, malaise, nausea, and vomiting. A bilocutaneous fistula is manifested as bile drainage from the main wound. If left untreated, a continuous bile leakage can lead to bacterial peritonitis and even reactionary hemoperitoneum secondary to intra-abdominal sepsis.

Laboratory blood tests show leucocytosis and an abnormal liver enzymes profile with predominant elevation of serum bilirubin and alkaline phosphatase. Serum gamma-glutamyl transpeptidase ( $\gamma$ -GT) is often high but this is nonspecific as it can also signal a hepatocyte damage on the liver transection surface. A high-resolution CT scan of the abdomen will detect fluid accumulation in the dead space or adjacent to the raw surface of the liver. The source of bile leakage is confirmed by a cholangiogram obtained either by endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC). Any active contrast extravasation can confirm the location of bile leakage. However, it is noteworthy to highlight that the cholangiogram may not be able to detect leakages arising from damage to a segregated bile duct that is not communicating with the main biliary system. It is important to look for any fluid accumulation adjacent to the caudate lobe as this is a common site for leakage from transected bile ducts in the caudate lobe segregated from the main biliary system. In this situation, a cholangiogram via ERCP or percutaneous transhepatic biliary drainage cannot necessarily detect the site of leakage and its diagnosis and treatment depend on image-guided percutaneous drainage. The aspirated bile should then be sent for bacteriological culture. The common causative microorganisms are *staphylococcus aureus*, *Escherichia coli*, and *candida* species. Other microorganisms involved are *streptococcus*, *pseudomonas*, *morganella*, and *bacillus*. When patients present with generalized peritonitis or when nonoperative treatment fails, a reoperation is indicated.

## Management of Bile Leakage

Adequate fluid resuscitation and the use of broad-spectrum antibiotics follow the basic principle for treatment of intra-abdominal sepsis. A patient should be fasted for a sufficient period of time before further intervention is implemented. Any sizeable intra-abdominal bile collection should be drained either percutaneously or by laparotomy. If there is persistent drainage of bile, endoscopic papillotomy and stenting are necessitated. Reoperation is indicated when there are signs of generalized peritonitis or hemoperitoneum. The mortality rate due to biliary complications is high and ranges from 20 to 30%.

## Conclusion

With the use of methylene blue test after parenchymal transection, the incidence of biliary complications has declined from 9.8 to 3.5% in recent years. Meticulous surgical technique is required to repair the site of bile leakage. Avoidance of excessive dissection at the hilar plate and denudation of the bile duct are key factors to prevent postoperative bile leakage.

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