The Critically Ill Cirrhotic Patient

Evaluation and Management

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I wish to express my deepest appreciation to my better half, my wife Asal Shoushtari Rahimi, MD, for her undying support and to our lovely children, Sofia (7) and Kian (6), without whom my life would not be the same.

Furthermore, I owe all my upbringing to my loving parents, Steve and Ziba Rahimi, MD, and my sisters, Susan Khoury Rahimi, MD, and Nina Gutierrez Rahimi, MD.

Preface

This textbook provides a state-of-the-art review in the field of hepatology on the diagnosis, evaluation, and management of the critically ill cirrhotic patient.

It serves as a very useful resource for physicians, healthcare providers, and researchers dealing with a very sick population of chronic liver disease patients. It provides a concise yet comprehensive summary of the current status in the field of transplant hepatology that will help guide patient evaluation and management and stimulate further research investigative efforts. All chapters are written by experts in their respective fields within liver disease and include the most up-to-date scientific and clinical information.

The field of chronic liver disease management of the critically ill cirrhotic patient in the intensive care unit has been transformed by recent changes in management over the past decade. Most importantly, management of hospitalized liver disease patients has evolved towards recognizing and diagnosing infection early, treating life-threatening gastrointestinal bleeding, and potentially (in select cases) offering liver transplantation for acute alcoholic hepatitis prior to the 6-month sobriety period. Furthermore, earlier recognition of acute on chronic liver failure has led to improved outcomes, especially when approached from a multidisciplinary fashion using detailed algorithms now in place to guide management based on prognostic characteristics. Although management of the critically ill cirrhotic patient remains a challenge, improved survival can be attained with the forefront of modern hepatology due to exciting developments discussed in this book.

The etiology of liver disease in the developed world is changing, and background on the epidemiology and natural history of chronic liver disease are presented in the book. Moreover, a great emphasis is placed on obesity and new data regarding frailty/sarcopenia, both of which are related and intertwined, yet at opposite ends of the spectrum, that are equally important in the approach in managing liver disease. Furthermore, critical care management in those with acute chronic liver failure (ACLF) has gained more adoption, and early recognition regarding infection, gastrointestinal bleeding, renal failure, and acute alcoholic hepatitis precipitating ACLF is discussed in detail. Newer therapies regarding management on anticoagulation and portal hypertensive complications, like ascites, acute hepatic encephalopathy

(including portosystemic shunt embolization), and hepatocellular carcinoma updates, are also depicted. Advances in surgical techniques, including living donor liver transplants and gender disparities in liver transplantation, with highlights regarding a new formula to predict which patients might require renal transplant within 5 years after liver transplantation, and recent changes in kidney allocation for liver transplant recipients that require simultaneous liver kidney transplants, are rendered. Finally, the role of palliative care for the critically ill cirrhotic patient is expounded.

Dallas, TX, USA Robert S. Rahimi

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I appreciate and would like to acknowledge all my chronic liver disease patients and their families who have trusted, inspired, and challenged me to become a better teacher, researcher, and transplant hepatologist over the years of service, caring for them.

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Chapter 1
Epidemiology and Natural History of Chronic Liver Disease

Jamil S. Alsahhar and Saleh Elwir

Introduction

Chronic liver disease (CLD) is a leading cause of mortality and morbidity around the world. Alcohol and nonalcoholic fatty liver disease (NAFLD) are leading causes of cirrhosis and CLD in the western world while hepatitis B virus (HBV) is the leading cause in Asian countries [1]. The incidence and prevalence of CLD is increasing and with this there has been an increase in healthcare utilization, hospitalizations, and mortality. Currently cirrhosis is the 12th leading cause of death in the United States and CLD is a leading cause of death in those aged 25–44 years old [2, 3]. In this chapter we will review the epidemiology and natural history of liver disease and review the prognosis associated with various manifestations of decompensated cirrhosis.

Epidemiology of Chronic Liver Disease (CLD)

Over the last two decades there has been an increase in the incidence of CLD. Alcohol, hepatitis C virus (HCV), and NAFLD are the most common causes of CLD in the United States while hepatitis B remains a major cause in China and other Asian countries [1]. The National Health and Nutrition Examination Survey (NHANES) is a nationwide survey collected by the US National Center for Health Statistics of the Centers for Disease Control and Prevention via household interviews, physical examinations, and laboratory data including blood and urine

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samples [4]. Younossi et al. analyzed this data across three different time periods and noted an estimated prevalence of CLD of 11.78% in the period between1988 and 1994. This increased progressively to 15.66% in the period between 1999 and 2004 and 14.78% in the 2005–2008 time period. The rates of hepatitis B and C remained stable across these three time periods. There was a slight increase in the prevalence of alcoholic liver disease initially but this remained stable over the last decade (1.38%+/–0.16% to 2.21%+/–0.18% to 2.05%+/–0.21% in the three study cycles, respectively; $P = 0.014$). The prevalence of NAFLD increased progressively from 5.51% in 1988–1994 to 9.84% in 1999–2004 and 11.01% in 2005–2008. This paralleled an increase in obesity, diabetes, and insulin resistance during the same time periods [4].

Similar to the findings observed in the NHANES survey, the rates of obesity and diabetes are increasing globally [1]. The global prevalence of NAFLD is estimated at 25.24% (95% CI, 22.10–28.65) with the highest prevalence in the Middle East and South America and lowest in Africa. Many of these patients have associated obesity, diabetes, and metabolic syndrome [5, 6]. A Markov model to forecast NAFLD disease burden in eight countries (China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States) for the period 2016–2030 projected a modest growth in total NAFLD cases (0–30%). The study projected an increase in NAFLD prevalence, advanced liver disease, and liver-related mortality [7].

Bell et al. evaluated patients newly referred to gastroenterology clinics in three different locations across the USA between 1999 and 2001. About two thirds had hepatitis C and alcohol as causes of their liver disease and about 20% had cirrhosis at the time of evaluation [8]. One of the issues of the NHANES survey is that it includes civilian noninstitutionalized patients. This excludes many high-risk patients such as homeless and incarcerated patients that have higher prevalence of chronic liver disease especially hepatitis C. Gish et al. estimated 3.2 to 4.9 million Americans have chronic hepatitis C virus infection by supplementing NHANES data projections with estimates from incarcerated and homeless patients [9]. Although direct acting antivirals are available and highly effective in the treatment of hepatitis C, many patients are unaware of their diagnosis or have other obstacles that prevent them from obtaining treatment [1]. Recent data has found that the proportion of patients on the liver transplant waitlist or undergoing liver transplantation for chronic HCV infection is decreasing while the percentages of patients on the waitlist or receiving liver transplants for NASH or alcoholic liver disease are increasing [10].

Chronic liver disease is associated with an increase in healthcare utilization. In 2010, chronic liver disease and cirrhosis accounted for 547,955 outpatient and emergency department visits. During the same year 243,170 hospitalizations for CLD and cirrhosis with a total cost of more than 3.3 billion dollars were recorded. The number of hospitalizations was up by 21% compared to 2003 [11]. The rate of hospitalizations for CLD increased by 92% between 2004 and 2013 compared to an increase of 6.7% for congestive heart failure (CHF) and 48.8% for chronic obstructive pulmonary disease (COPD) during the same time [12]. Patients with CLD were younger than patients admitted for CHF or COPD. Patients with CLD had longer

hospital stays (7.3 days vs 6.2 days for CHF and 5.9 days for COPD, $P < 0.01$). A higher proportion of patients with CLD died or were discharged to hospice (14.2% vs 11.5% of patients with CHF and 9.3% of patients with COPD, $P < 0.01$). In addition, a higher proportion of patients with CLD were readmitted to the hospital within 30 days (25% vs 21.9% of patients with CHF and 20.6% with COPD, $P < 0.01$) [12].

Globally, mortality from complications of cirrhosis and CLD is high [1]. In 2010, cirrhosis accounted for over one million deaths worldwide [13]. In the United States CLD and cirrhosis were the 12th leading cause of death in 2016, accounting for more than 40,000 deaths, or 12.5 deaths per 100,000 populations [2]. When evaluating individual ethnic groups, CLD and cirrhosis were the fifth leading cause of death in non-Hispanic American Indian or Alaska Native group and seventh in the Hispanic population [2, 3].

Despite the high reported numbers, it is likely that liver-related mortality rate is underestimated. Analysis of mortality data from the Rochester Epidemiology Project database noted 261 liver-related deaths; of these deaths only 71 (27.2%) would have been recorded in the National Center for Health Statistics database [14]. Based on these findings, the authors concluded that the true liver-related mortality is likely underestimated in the United States [14].

Natural History of Cirrhosis

The advancement of liver disease through various degrees of fibrosis is dependent on many factors including the etiology of the disease and the presence of other cofactors both environmental and genetic (e.g., the combination of alcohol and hepatitis C is associated with increased risk of fibrosis as opposed to either etiology alone). In patients with NAFLD, fibrosis progression by 1 stage takes 14.3 years and 7.1 years for patients with NASH [15].

Once patients develop cirrhosis then they are at risk of liver decompensation. A systemic review suggested that the median survival of patients with compensated cirrhosis is 12 years [16]. This stage is defined by the absence of ascites, hepatic encephalopathy, or bleeding varices. The development of any of these features marks the development of decompensated cirrhosis which has a median survival of approximately 2 years. Transition from a compensated to a decompensated cirrhosis occurs at a rate of 5–7% per year [16]. D'Amico et al. divided cirrhosis into four stages based on the presence or absence of ascites or varices. One-year mortality ranged from 1% in patients with compensated cirrhosis without clinically significant portal hypertension to 57% in patients with decompensated cirrhosis with ascites and esophageal varices (Table 1.1).

The rate of decompensation is variable and depends on the patient population studied and the clinical events that occur in these patients. In patients who present with an isolated variceal hemorrhage, the 5-year mortality is 20%. Morality rate increases to 80% if variceal hemorrhage was accompanied by other decompensat-

Table 1.1 One-year outcomes of patients with liver cirrhosis according to stage

Stage of cirrhosis	Description	Annual mortality
Stage 1	No ascites or varices	1%
Stage 2	Varices but no ascites	3.4%
Stage 3	Ascites +/− varices	20%
Stage 4	Ascites and bleeding varices	57%

Adapted from D'Amico et al. [16]

ing events [17]. The occurrence of ascites and hepatic encephalopathy carry an increased risk of mortality and morbidity. In addition to the mortality from decompensated cirrhosis, hepatocellular carcinoma is a major cause of death from liver disease worldwide [1].

Ascites

Ascites is one of the most common complications of portal hypertension and a leading cause of hospital admissions in patients with cirrhosis [18]. In the developed world, 75% of patients presenting with ascites have cirrhosis as the underlying etiology. In those with compensated cirrhosis, the 10-year rate of developing ascites is up to 50% [18]. Once ascites develops, the 1- and 5-year mortality rate is 15% and 44%, respectively [19]. The development of ascites is associated with further complications including dilutional hyponatremia, refractory ascites, and hepatorenal syndrome. When accounting for these complications, the 5-year mortality rate increases up to 90% [19]. Refractory ascites occurs when the recurrence of ascites cannot be prevented despite adequate medical therapy. The presence of refractory ascites portends a negative prognosis, with a median survival of only 6 months [20]. Refer to Chap. 2 for a more thorough discussion of ascites.

Spontaneous Bacterial Peritonitis (SBP)

One of the complications associated with ascites is the development of spontaneous bacterial peritonitis (SBP). SBP is one of the most common bacterial infections noted in patients with cirrhosis, observed in up to 10% of hospitalized patients [21, 22]. The mortality rate associated with SBP reaches 20%, and the 1-year risk of recurrence is 70% [23]. The proposed mechanism of SBP development is translocation of gut bacteria into circulation and ascites fluid as a result of multiple mechanisms including intestinal bacterial overgrowth, increased intestinal permeability, and decreased immunity. Patients with ascitic fluid protein less than or equal to 1.0 g/dl are at higher risk for development of SBP [24]. The most common organisms noted in SBP are gram-negative bacteria, but the increasing use of wide-spectrum antibiotics has led to a rise in gram-positive and extended-spectrum B-lactamase-producing *Enterobacteriaceae* [21]. The three most common

organisms isolated are *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcal pneumonia* [25]. Up to 50% of patients with SBP are asymptomatic; hence it is recommended that patients presenting with acute decompensation should undergo a diagnostic paracentesis to rule out SBP [25]. The diagnosis of SBP is made when the ascetic fluid polymorphonuclear (PMN) count is >250/mm^3. It is important to distinguish between spontaneous bacterial peritonitis and secondary bacterial peritonitis. Secondary bacterial peritonitis represents 4.5% of cases of peritonitis and is typically seen in the setting of perforation and should be suspected when polymicrobial cultures are isolated and/or lack of improvement of peritonitis despite medical therapy [26].

Refer to Chap. 7 for a more thorough discussion on infections, specifically SBP.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is renal failure that occurs in the setting of CLD without an identifiable cause for renal disease [27]. There are two types of HRS. Type 1 is rapidly progressing renal failure, occurring mainly in the setting of severe alcoholic hepatitis and infections (SBP), while type 2 is more chronic. Up to 30% of patients with SBP develop type 1 HRS [28]. Patients with type 1 HRS have higher MELD scores (equal to or greater than 20) with a median survival of 1 month [29]. Patients with type 2 HRS had a median survival rate that depends on the MELD score. Those with MELD score greater than or equal to 20 have a median survival of 3 months, while MELD less than 20 have a median survival of 11 months [29].

Refer to Chap. 5 for a more thorough discussion on renal failure and HRS.

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is one of the most debilitating complications of cirrhosis and signifies a decompensation of cirrhosis. It leads to increased morbidity, mortality, and healthcare utilization, with an annual admission rate of 115,000 [30, 31]. HE is divided into two groups, covert and overt HE. When cirrhosis is diagnosed, up to 14% of patients will have overt HE [32]. The cumulative incidence of overt HE is 45%, while covert HE is reported in 60% of patients with cirrhosis [33]. In patients with cirrhosis without HE, the risk of developing overt HE is up to 25% within 5 years [34]. Risk factors for an HE admission include recent diuretic use and a prior admission for HE [35]. HE is the most frequent cause of readmission in those with decompensated cirrhosis [36]. Patients admitted for HE have a higher in-hospital mortality rate when compared to those with cirrhosis admitted for other causes (OR = 3.90), likely due to underlying infection [35]. Once HE develops, the 1-year survival rate is 42%, while the 3-year survival rate is 23% [34]. In the setting of transjugular intrahepatic portosystemic shunt (TIPS), the 1-year incidence of overt HE post TIPS is about 50% [37].

Prognostic Models

Multiple prognostic models have been developed to determine disease severity and survival in patients with cirrhosis. The most commonly used models include the Child-Turcotte-Pugh score (CTP) and the Model for End-Stage Liver Disease (MELD) score. CTP was initially developed to assess the surgical risk in patients with cirrhosis. It includes both objective measures (serum bilirubin, international normalized ratio (INR), and albumin) and subjective measures (presence of ascites and HE) [38]. According to the presence or absence of these factors, patients are divided into three classes (CTP A patients have a score of 5–6, CTP B have a score of 7–9, and CTP C have a score of 10–15) [39]. As the components that make up the score are known to be associated with increased mortality, the score and CTP class itself gives a good reflection of patient mortality and can be estimated, with CTP A having a ~10% mortality, CTP B ~30% mortality, and CTP C ~80% mortality prior to surgical intervention [16, 40]. CPT score is often easy to calculate and studies throughout the years have confirmed its prognostic value; however the subjective nature limits its use in organ allocation.

Another commonly used tool is the MELD score. The MELD score, which is calculated from serum bilirubin, INR or prothrombin time, and serum creatinine, offers an objective score that accurately predicts the risk of short-term mortality from CLD [41]. It was initially developed to determine the three-month mortality post TIPS, but given its utility and validation in patients with CLD, specifically cirrhosis, its use was broadened to transplant waitlist prioritization and organ allocation as adapted by the United Network for Organ Sharing (UNOS) in 2002 [41, 42]. The MELD score provides a better objective assessment when compared to the CTP score. The score ranges from 6 to 40, with higher scores correlating with greater degree of hepatic dysfunction and greater risk of mortality. The adoption of the MELD score for organ allocation led to a decrease in waitlist mortality and a 10% increase in the number of deceased donor liver transplantations [43]. Furthermore, hyponatremia has been shown in several studies to be an independent predictor of mortality in patients with cirrhosis [44–46]. This effect is most pronounced in patients with low MELD scores and has led to the development of the MELD-Na score, which has been shown to predict waitlist mortality more accurately than MELD score. This score has been used by the United Network for Organ Sharing (UNOS) for prioritization of organs since January 2016 [41].

As the natural history of cirrhosis is being further understood, new factors contributing to worse outcomes have been identified. The presence of bacterial infections has been shown to increase the risk of mortality, regardless of the stage of cirrhosis [47]. Patients with bacterial infections were noted to have a median survival rate of 16.8 months compared to 25.5 months for those without infection. Those with infection and MELD <15 had a similar survival rate to those with MELD >15 without infection [47].

Conclusion

Chronic liver disease not only is prevalent worldwide; it results in chronic liver inflammation and progression to cirrhosis and portal hypertension complications over different timeframes regardless of race, age, or gender; however, depending on the underlying etiology and if the insulting factor(s) for CLD has been removed or treated, CLD and fibrosis could potentially be reversible. Progression of portal hypertensive complications resulting in ascites and hepatic encephalopathy takes years to develop in compensated cirrhotics, so it is imperative to counsel patients on the natural history of cirrhosis so expectations can be managed appropriately and warning signs can be given to family members. The overall morbidity and mortality associated with CLD and cirrhosis varies; therefore early recognition and management of underlying CLD etiologies are paramount, which could decrease the time to progression of cirrhosis complication and decrease hospital readmission rates, which ultimately could improve overall prognosis in this high-risk patient population.

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Chapter 2
Management of Ascites

Florence Wong

Ascites is a common complication of liver cirrhosis, being the most frequent mode of decompensation in these patients [1]. In a cohort of 377 compensated cirrhotic patients followed for 20 years, the cumulative incidence of developing ascites was 31% at 10 years and 45% at 20 years [1]. If the underlying etiology of cirrhosis is treated, the ascites may regress, and the patient re-compensates. However, in most instances, the ascites progresses through the stages of being initially diuretic responsive, then gradually becoming diuretic refractory, and eventually further complicated by other complications such as the development of spontaneous bacterial peritonitis (SBP), renal dysfunction, and hyponatremia. Therefore, the onset of ascites marks a turning point in the natural history of cirrhosis and is associated with 2- and 5-year cumulative mortality rates of 38% and 78%, respectively [1].

The Pathophysiology of Ascites Formation (Fig. 2.1)

The Peripheral Arterial Vasodilatation Hypothesis

The peripheral arterial vasodilatation hypothesis [2], as proposed three decades ago, describes the development of ascites in cirrhosis as being related to the hemodynamic changes that occur in these patients. Because of structural changes that occur as a result of liver cirrhosis, there is obstruction to portal flow. This increased resistance to portal flow leads to an increase in shear stress on the splanchnic vessels, stimulating the production of various vasodilators, the most abundant of which is

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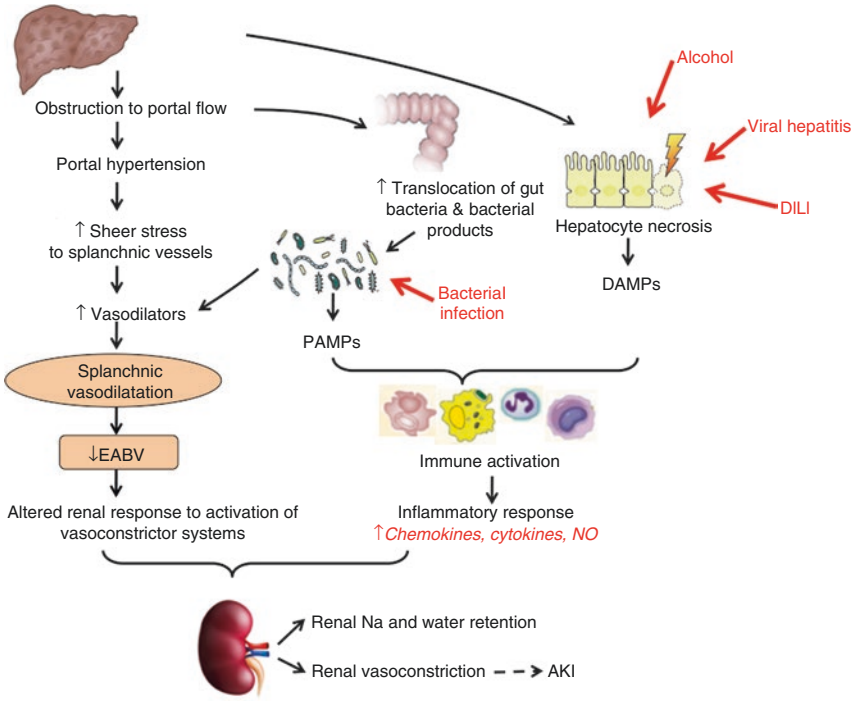

Fig. 2.1 The pathophysiology of ascites formation incorporating the traditional peripheral arterial vasodilatation hypothesis and the systemic inflammation hypothesis. AKI acute kidney injury, DAMPs damage-associated molecular patterns, DILI drug-induced liver injury, EABV effective arterial blood volume, NO nitric oxide, PAMPs pathogen-associated molecular patterns

nitric oxide, and splanchnic vasodilatation ensues. This promotes an increase in splanchnic flow [3]. Paradoxically, a relative lack of nitric oxide in the intrahepatic circulation contributes to the increased resistance to portal flow, and this together with augmented splanchnic inflow results in the development of portal hypertension [4]. Some of the splanchnic vasodilators are transferred from the splanchnic to the systemic circulation via portosystemic shunts, leading to systemic arterial vasodilatation. The splanchnic vasodilatation also causes pooling of blood volume, akin to a splanchnic steal syndrome. Therefore, the systemic circulation has an expanded capacitance but holding a relatively smaller volume of blood, a condition known as a "reduction in the effective arterial blood volume," when there has not been an actual loss of total blood volume. The physiological response is the activation of various vasoconstrictor systems in an attempt to decrease the vascular capacitance and to stimulate renal sodium retention to increase the vascular volume. While the systemic circulation is relative insensitive to the vasoconstrictor effects of these vasoconstrictor systems, which include the sympathetic nervous system, the renin angiotensin system, and the non-osmotically stimulated secretion of vasopressin, the renal circulation is particularly sensitive to the vasoconstrictor effects of these systems. This leads to renal vasoconstriction and enhanced renal sodium and water retention.

Clinically, the systemic arterial vasodilatation manifests as warm peripheries. The circulation compensates for the reduction in peripheral vascular resistance by increasing the cardiac output, in order to maintain hemodynamic stability. Therefore, patients with cirrhosis frequently have tachycardia, a bounding pulse and a wide pulse pressure, the so-called hyperdynamic circulation. As cirrhosis advances, the peripheral arterial vasodilatation becomes more pronounced, followed by further activation of the various vasoconstrictor systems. Eventually, the cardiac output will not be able to keep pace with the extent of arterial vasodilatation, and a low systemic blood pressure ensues. Frequently, cirrhotic patients with a history of systemic hypertension will gradually become normotensive as the cirrhosis advances. In the renal circulation, there is gradual increased renal vasoconstriction, leading to steady decrease in glomerular filtration, which predisposed the patient with advanced cirrhosis to the development of renal failure. The renal vasoconstriction also encourages renal sodium reabsorption, which worsens as the cirrhosis progresses. This continued worsening of renal sodium retention leads to an even expanding total body sodium and water contents. The presence of portal hypertension then preferentially localizes the excess volume into the peritoneal cavity as ascites. Gravity will also encourage some of the excess fluid to localize to the lower limbs as ankle edema.

The Systemic Inflammatory Hypothesis

Cirrhosis is an inflammatory state, related to the constant transfer of gut bacteria and bacterial products via the intestinal mucosa into the lymphatics and thence into the systemic circulation, a process known as bacterial translocation, facilitated by bacterial overgrowth, intestinal dysbiosis, and increased intestinal permeability commonly observed in cirrhosis [5, 6]. These bacteria and bacterial products express pathogen-associated molecular patterns (PAMPs), which are recognized by pattern recognition receptors (PRRs) on innate immune cells and epithelia. The binding of PAMPs to PRRs stimulates a series of reactions that ultimately lead to the production of inflammatory mediators [7]. Other forms of "sterile" inflammation can be derived from hepatic inflammatory processes such as alcoholic or viral hepatitis, which lead to the release of various damage-associated molecular patterns (DAMPs), which are also recognized by PRRs. Indeed, there have been numerous reports of increased levels of pro-inflammatory cytokines in patients with cirrhosis compared to healthy controls even in the absence of an infection [8, 9]. The extent of the inflammatory response appears to parallel the height of portal pressure [10] and the severity of liver, circulatory, and renal dysfunction [9, 11]. Of course, when a bacterial infection occurs, the inflammatory response becomes much more exaggerated.

Bernardi et al. proposed that the various pro-inflammatory cytokines contribute to the nitric oxide-mediated splanchnic and systemic vasodilatation [5], which is central to the pathogenesis of hemodynamic abnormalities that have been implicated in ascites formation and renal dysfunction in cirrhosis. In an animal model of

cirrhosis, upregulation of toll-like receptor 4 (TLR4), a PRR, was observed in the proximal renal tubules [12]. The fact that norfloxacin, an intestinal decontaminant, was able to reduce the incidence of acute kidney injury (AKI) in the same animals supports the concept that an interaction had occurred between the various PAMPs and DAMPs and their receptors, but the potential for hemodynamic mediated renal dysfunction had been attenuated by the reduction in inflammation using norfloxacin [12]. The use of norfloxacin has also been shown to decrease vascular nitric oxide production and partially reverse the hyperdynamic circulation in patients with cirrhosis [13]. In portal hypertensive animals, the use of anti-TNF-α therapies, such as anti-TNF-α antibodies [14] or thalidomide [15], attenuated the hyperdynamic circulation in these animals, further adding weights to the role of inflammation in the pathophysiology of advanced cirrhosis. An intense inflammatory response as observed in sepsis can lead to microvascular damage, organ hypoperfusion, apoptosis, and cell necrosis, eventually leading to organ failure, an example of which would be renal failure complicating an episode of infection in a patient with ascites.

The Management of Ascites

Diuretic Responsive Ascites

The majority of patients with ascites have cirrhosis as the underlying etiology, although other less common causes such as nephrotic syndrome, congestive cardiac failure, pancreatitis, malignancy, and infective sources such as tuberculosis may also be responsible. The cirrhotic etiology can be confirmed by calculating the serum ascites albumin gradient (SAAG), which should be >1.1 g/dL.

Dietary Sodium Restriction

Cirrhotic patients with ascites have excess total body sodium and water; therefore, dietary sodium restriction is the mainstay in the management of ascites in these patients. Dietary sodium restriction is not to be confused with calorie restriction, as these patients are usually very malnourished with significant protein depletion and muscle loss, and therefore should be encouraged to increase their intake of low-sodium food items. A typical North American no-added salt diet contains approximately 130–150 mmol of sodium per day. Therefore, patients will have to make the effort to source low-sodium food items in order to comply with dietary sodium restriction. Education about availability of low-sodium food items is mandatory for good adherence. An increasing supply of low-sodium recipes is also making a low-sodium diet much more palatable and acceptable to patients. The International Ascites Club recommends that patients should follow an 88 mmol sodium per day diet [16]. Morando et al. showed that severe sodium restriction to <88 mmol/day

can reduce mean daily calorie intake by 20% [17] and therefore should be discouraged. Patients who normally consume a high-sodium diet will notice a significant reduction in their ascites volume once they reduce their sodium intake. Their palate will also become accustomed to a low-sodium diet after several weeks, eventually developing a dislike for high-sodium food items.

Calculating the Sodium Balance (Fig. 2.2)

It is important to calculate the sodium balance in every patient in order to assess adherence to dietary sodium restriction. This requires the measurement of daily sodium output by doing a 24-hour urine collection. If it is not practical to do a 24-hour urine collection, a random urinary sodium/potassium (Na/K) ratio can be used as an alternative. A urinary Na/K ratio of >1 is equivalent to 24-hour urinary sodium excretion of >78 mmol/day [18]. Assuming a dietary sodium intake of 88 mmol/day, a patient who excretes 78 mmol sodium per day should be in sodium balance and therefore will not lose or gain any water weight, since there is also an insensible sodium loss of 10 mmol/day. Any patient who excretes >78 mmol/day should be in negative sodium balance and therefore should lose water weight. A patient with severe sodium retention usually excretes minimum sodium and therefore is in positive sodium balance of 78 mmol/day. This equals to 546 mmol/week. Since the ascites sodium concentration is the same as the serum sodium

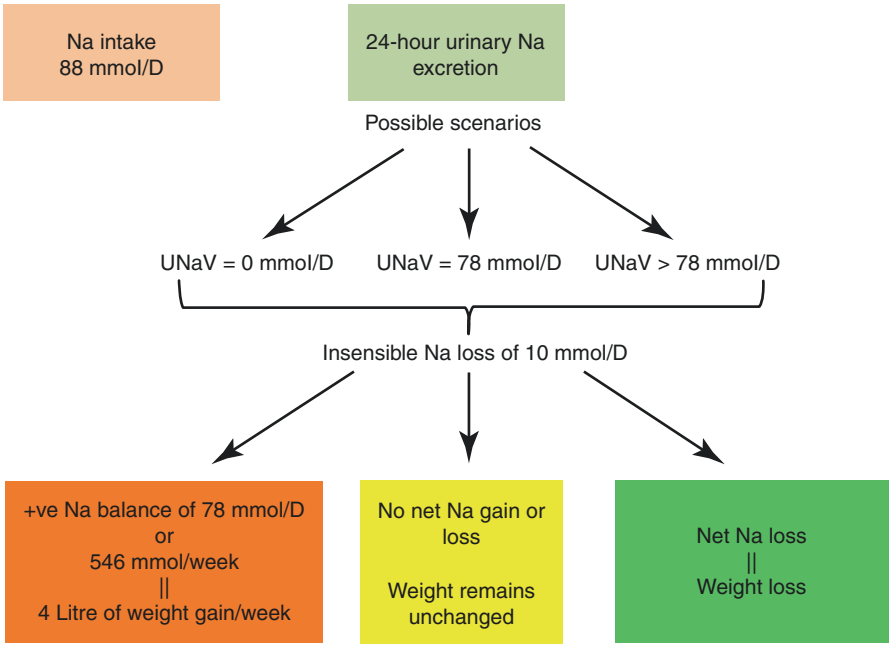

Fig. 2.2 Calculating the sodium balance. D day, Na sodium, UNaV urinary sodium excretion

concentration, the amount of fluid retained per week should be 4 liters (546 mmol/week ÷ 135 mmol/L), and therefore the maximal weight gain per week should be 4 kg. Any patient who puts on more than 4 kg per week is not adhering to the prescribed sodium restriction. A 3-day food record will usually reveal what the high-sodium food items are, and reeducation is necessary in order to improve compliance.

Diuretic Therapy

Diuretics are usually needed to increase urinary sodium excretion in addition to dietary sodium restriction in order to reduce ascites in cirrhosis, as sodium restriction alone will only eliminate ascites in approximately 10% of all these patients. In other patient populations, the main diuretic used is furosemide, a potent loop diuretic. However, in patients with cirrhosis, using a loop diuretic alone is less effective. This is because a loop diuretic will block sodium reabsorption at the loop of Henle; sodium is then delivered to the distal tubule, only to be reabsorbed at that site because of hyperaldosteronism. Therefore, it is preferable in cirrhosis to start treatment of ascites with a distal diuretic because of its aldosterone antagonism action and add a loop diuretic if necessary to improve efficacy. However, Angeli and colleagues showed that using a combination of a loop and a distal diuretic is more efficacious and associated with less side effects than using a distal diuretic and a loop diuretic sequentially [19]. The standard of care is to initiate diuretic therapy combining spironolactone starting at 100 mg/day and furosemide starting at 40 mg/day. Patients need to be monitored closely for renal dysfunction and electrolyte abnormalities. The diuretic doses can be increased by increments of spironolactone 100 mg and furosemide 40 mg per week if the fluid weight loss has been less than 1.5 kg/week, and the patient has been compliant with sodium restriction, and there has been no electrolyte abnormalities or renal impairment. The maximum spironolactone dose is 400 mg/day, and that for furosemide is 160 mg/day. It is important to recognize that the onset of action of spironolactone is slow and can take several days before an increased diuretic response is noted. Therefore, it is inappropriate to increase the spironolactone dose more frequently than once a week. It should also be noted that the dose-response curve of furosemide is sigmoidal; that is, once a maximal response is reached, increasing the dose of furosemide will not increase the diuretic response; rather, it will increase the likelihood of side effects [20].

Albumin Infusions

Albumin is the most abundant plasma protein. Apart from its oncotic effects, it also has anti-inflammatory, antioxidant, immune modulatory, endothelial stabilizing, and excellent molecule-binding properties [21]. However, in cirrhosis,

albumin is reduced in quantity due to decreased synthesis and altered in quality related to structural changes [22]. These structurally altered isoforms of albumin have impaired functional capabilities, most importantly; its binding potential is modified [22]. Furthermore, the extent of functional impairment of albumin has been correlated to severity of liver dysfunction and hence survival [23]. Therefore, albumin infusions have been proposed as a means to improve the overall prognosis of these patients, especially for patients wait-listed for liver transplantation [24]. In the very first randomized controlled trial assessing the effects of albumin in addition to standard diuretic therapy in cirrhotic patients with ascites, weekly infusions of 25 gm of albumin for a mean period of 20.0 ± 1.9 months was shown to produce significantly better diuretic response, shorter hospital stays, lower probability of re-accumulation of ascites, and lower likelihood of readmission to hospital [25], but survival was not affected. The improved ascites control is likely to be related to the oncotic properties of albumin, resulting in a better filled circulation, with consequent improved urinary sodium excretion [26]. A subsequent randomized controlled trial using virtually the same protocol, but followed patients for a much longer median period of 84 (range 2–120) months, was able to show a significantly improved mean survival of 16 months [27]. Ascites re-accumulation was also significantly reduced (51% vs. 94%, $p < 0.0001$). The corollary from this observation is that the benefits of albumin infusions can only be attained after long-term use. A more recent Italian multicenter randomized controlled trial involving 33 academic liver centers, enrolling 440 patients with cirrhosis and uncomplicated ascites, was able to demonstrate that patients who received weekly albumin infusions of 40 gm per week after the initial dose of 40 gm 2 times per week for 2 weeks had a significantly improved survival over an 18-month period ($p = 0.0285$) [28]. Furthermore, those patients who received chronic albumin infusions and standard medical care had less incidences of bacterial infections, grade III and IV hepatic encephalopathy, renal dysfunction including hepatorenal syndrome, and electrolyte abnormalities when compared to patients who received standard medical care alone ($p \leq 0.005$ for all). Ascites control was also significantly improved with patients receiving albumin having a delayed first paracentesis after enrollment and less likely to develop refractory ascites ($p < 0.001$ for both). However, one must point out that the patients enrolled into the study were at a relatively early stage of the natural history of cirrhosis, with the patients having a mean Child-Pugh score of 8 and a mean Model for End-Stage Liver Disease (MELD) score of 12–13. Whether chronic albumin infusions will have the same beneficial effects in patients at a more advanced stage of cirrhosis is unclear [29]. In another cohort of cirrhotic patients mostly with diuretic responsive ascites, but slightly more advanced liver dysfunction as indicated by a mean MELD score of 16–17, the use of albumin plus midodrine did not reduce the likelihood of developing complications of cirrhosis during follow-up ($p = 0.402$) or one-year mortality [30]. Furthermore, the costs of weekly infusions of albumin have not been balanced against the potentially decreased financial expenditures of reduced complications of cirrhosis. The currently planned chronic albumin infusion study

(PRECIOSA study: ClinicalTrials.gov Identifier: NCT03451292) in North America will help to clarify the role of albumin in the management of patients with cirrhosis and ascites.

Refractory Ascites

The International Ascites Club defines refractory ascites as either diuretic resistant or diuretic intractable and it occurs in approximately 10% of all cirrhotic patients with ascites. Diuretic-resistant ascites is ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment [16]. Patients who develop complications related to diuretic therapy, thereby precluding the use of effective diuretic doses, are said to have diuretic intractable ascites [16] (Table 2.1). Both groups of patients have the same unfavorable prognosis of 50% survival at 6 months and 25% survival at 1 year [31]. The first line of treatment is repeat large-volume paracentesis (LVP). In the appropriate patients, the insertion of a transjugular intrahepatic portosystemic stent shunt (TIPS) can eliminate the ascites. Because of their poor prognosis, patients with refractory ascites should be referred for liver transplant assessment, especially in those patients with significant liver dysfunction, and meet the minimal criteria for liver transplantation. Figure 2.3 provides an algorithm for the management of patients with cirrhosis and refractory ascites.

Table 2.1 Diagnostic criteria of refractory ascites according to International Ascites Club

Diuretic-resistant ascites
Ascites that cannot be mobilized
Early recurrence of which cannot be prevented
Because of lack of response after ≥1 week of maximal doses of diuretics:
1. Spironolactone 400 mg/day or amiloride 30 mg/day
2. Furosemide 160 mg/day
Despite adherence to dietary sodium restriction of ≤88 mmol/day
Diuretic-intractable ascites
Ascites that cannot be mobilized
Early recurrence that cannot be prevented
Because of the development of diuretic-induced complications including
1. Renal impairment
2. Hyponatremia
3. Hypo- or hyperkalemia
4. Hepatic encephalopathy
That precludes the use of effective doses of diuretics
Lack of treatment response
Mean weight loss of <0.8Kg over 4 days
Urinary sodium < sodium intake
Early recurrence of ascites
Reappearance of grade 2 or grade 3 ascites within 4 weeks of initial mobilization

Adapted from Ref. [16]

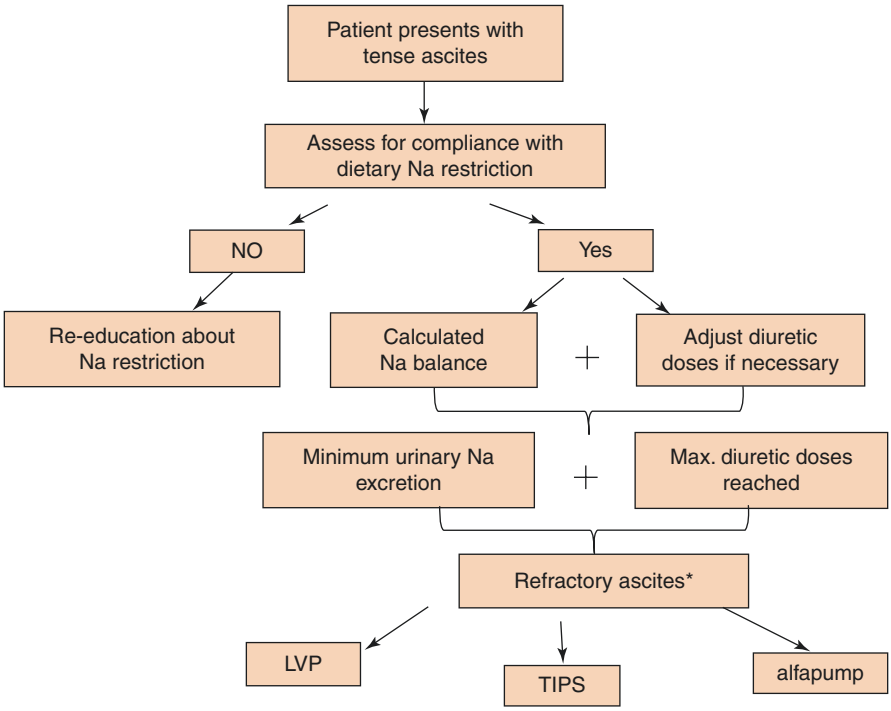

Fig. 2.3 Suggested algorithm for the management of patients with cirrhosis and tense ascites. alfapump automatic low-flow ascites pump, LVP large-volume paracentesis, Max maximum, Na sodium, TIPS transjugular intrahepatic portosystemic stent shunt. ∗ All patients with refractory ascites should be referred for liver transplant assessment unless there are contraindications

Large-Volume Paracentesis

Repeat LVP, defined as a paracentesis of more than 5 liters, is the mainstay of treatment for refractory ascites in patients with cirrhosis. LVP has been shown to be more effective and safer than diuretics in the control of refractory ascites with lower incidence of renal dysfunction, electrolyte abnormalities, and hemodynamic disturbance [32]. Survival rate, however, was not improved [32]. Usually 6–8 liters of ascites are removed every 2 weeks, together with albumin infusion to prevent the development of paracentesis-induced circulatory dysfunction (PICD) (see below). Total paracentesis with complete emptying of the peritoneal cavity has also been shown to be safe in cirrhosis [33]. However, for patients who are compliant with dietary sodium restriction, the amount of ascites collected should be no more than 4 liters per week, even in the absence of urinary sodium excretion (see subsection on "Calculating the sodium balance"). Therefore, any patient who is requesting more than 8 liters of ascites removed every 2 weeks should have a discussion about their sodium intake and dietary sodium restriction reinforced.

PICD is a condition that has been described in patients with ascites following LVP, a scenario whereby the hemodynamic disturbance following LVP can potentially lead to a more rapid re-accumulation of ascites, an increased risk of developing renal dysfunction, associated with decreased survival [34]. This is related to the fact that approximately 6 days after an LVP, there is significant further arterial vasodilatation, with subsequent further activation of various vasoconstrictor systems, predisposing the patient to the development of circulatory dysfunction [35]. This sequence of events seems to occur particularly in patients who undergo an LVP, as paracenteses of a smaller volume are not associated with significant hemodynamic changes [36]. Therefore, it is recommended that albumin infusion should be given to prevent the development of PICD following LVP. However, in the 20 years since this recommendation was proposed, there has never been any update on this recommendation despite significant improvement in the understanding of the pathophysiology of ascites formation in cirrhosis [5]. Furthermore, there has never been any dose-response study as to the appropriate dose of albumin to be given to prevent this complication. Based on expert opinions, the International Ascites Club has recommended that 6–8 gm of albumin should be given per liter of ascites removed, although half of this recommended dosage has also been shown to be equally effective in the prevention of PICD [37]. More recently, there have been questions as to the validity of the diagnostic criteria of PICD, especially since the PICD-related mortality did not take into account of the severity of liver or renal dysfunction of these patients as indicated by MELD [38]. We have recently shown that by limiting the paracentesis volume to less than 8 liters and with adequate albumin replacement at a mean dose of 9.0 ± 2.5 gm/L of ascites removed, despite the fact that 40% of the patients developed PICD, no significant deterioration in renal function or decreased survival was observed over a mean period of 2 years [39]. From the studies so far, it is likely that albumin is needed in patients who undergo LVP, the dose of which has not yet been firmly established, but most would agree that the dose of at least 6 gm of albumin per liter of ascites removed would prevent the deleterious effects of PICD. It is also likely that patients with more advanced liver disease have less physiological reserve to deal with the fluid shifts associated with LVP, and a higher albumin dose would be preferred.

Transjugular Intrahepatic Portosystemic Stent Shunt

A TIPS is a radiologically created shunt with a stent in situ that connects a branch of the hepatic vein and a branch of the portal vein. It is very effective in reducing the portal pressure. Since portal hypertension is one of the major pathophysiological factors in the initiation of sodium retention, it stands to reason that a TIPS insertion should be able to reverse the pathophysiological changes that lead to the development of ascites in cirrhosis. In a review which summarizes the results of the physiological studies related to TIPS insertion for ascites, Rössle was able to show that the activated neurohormonal systems observed in advanced cirrhosis with ascites took an average of 4–6 months to return to normal levels post-TIPS [40], thereby effecting a natriuresis with elimination of ascites. This is related to return of a

significant splanchnic volume, through the TIPS into the systemic circulation, thereby improving the filling of the effective arterial circulation, leading to improved renal hemodynamics which continues for at least 6 months after TIPS insertion [41]. Therefore, it is important to manage the expectations of patients who are undergoing a TIPS for the management of ascites that the elimination of ascites is not immediate. Serial urinary sodium measurements show that there is an increase in urinary sodium excretion 1 month after TIPS insertion, reaching approximately 100 mmol/day at 12 months post-TIPS in the absence of diuretics [41]. Ascites slowly decreases as the urinary sodium increases. Therefore, patients should be maintained on a low-sodium diet until complete clearance of ascites. Diuretic use post-TIPS insertion for ascites is controversial. The pharmacological action of diuretics is to decrease the arterial blood volume, which will slow down the refilling of the effective arterial blood volume. This counteracts the volume refilling effects of TIPS insertion, thereby delaying ascites elimination. Eventually approximately 80% of patients will completely clear their ascites. There is a portion of patients, even with a widely patent shunt will not completely eliminate their ascites. This is because portal hypertension is only one of the many pathophysiological factors that is responsible for ascites formation. Patients who cannot clear their ascites at 12 months post-TIPS should be referred for liver transplant assessment.

Complications related to the TIPS insertion procedure should be minimal in experienced hands. These include arrhythmia, liver capsule puncture leading to bleeding and hemoperitoneum, and TIPS-biliary fistulae. Complications related to the TIPS prosthesis itself include TIPS migration or kinking, TIPS stenosis due to overgrowth of endothelium over the TIPS prosthesis, foreign body-related hemolytic anemia, and stent infection. TIPS stenosis is now less of an issue since the advent of covered stents that are coated with polytetrafluoroethylene. One of the major complications related to the presence of any shunt including the TIPS is the development of de novo hepatic encephalopathy (HE) or worsening of existing HE, occurring in up to 50% of patients, especially in the early post-TIPS period [42]. In a recent study which only dilated the TIPS to maximum of 7 mm diameter instead of the usual 9–10 mm diameter in a group of cirrhotic patients who mostly received the TIPS for the management of refractory ascites, the authors were able to show that the under-dilated TIPS was able to provide the same efficacy but with less HE complications [43]. These under-dilated TIPS did not auto-expand with follow-up and therefore the beneficial effects on HE occurrence were maintained [43]. Other risk factors for the development of HE post-TIPS include older age, a past history of spontaneous HE, and more severe liver dysfunction as indicated by a high MELD. Other complications related to the presence of the shunt include precipitation of left-sided cardiac failure in patients with pre-TIPS systolic dysfunction or right-sided cardiac failure in patients with diastolic dysfunction or pulmonary hypertension. Therefore, patients should undergo careful cardiac evaluation before TIPS insertion. Since there is significant arterial vasodilatation in the initial post-TIPS period, which could potentially compromise liver and renal function post-TIPS, patients with significant baseline liver dysfunction (MELD > 18) or renal dysfunction (serum creatinine >2 mg/dL) should not receive a TIPS. Table 2.2 lists the absolute and relative contraindications to TIPS insertion.

Table 2.2 Contraindications to TIPS insertion

Absolute	Relative
Uncontrolled encephalopathy	Any infection including dental infection
Congestive cardiac failure	Noncompliance with sodium restriction
Severe pulmonary hypertension	Hepatoma, especially if centrally located
Child-Pugh score ≥12 or MELD ≥18	Portal vein thrombosis
Multiple hepatic cysts	
Uncontrolled biliary sepsis	
Primary prophylaxis for variceal bleeding	

A successful outcome following TIPS insertion with elimination of ascites is associated with an improved nutritional status; this is especially obvious in patients who are undernourished pre-TIPS [44, 45]. There is also increasing evidence to support TIPS insertion which is associated with improved transplant-free survival [46, 47]. This is especially true for young (≤50 years of age) cirrhotic patients who do not have significant liver dysfunction and whose only problem is one of portal hypertension. Such a patient would include an abstinent alcoholic patient or someone whose viral hepatitis has been eradicated, whose MELD is ≤10. In this scenario, the TIPS could be used as a definitive treatment for refractory ascites, as almost 80% of these patients will survive more than 5 years [48]. In contrast, in patients who have some degree of liver dysfunction, such as those with a MELD score of 11–15, a liver transplant may still be required [47], and therefore, the TIPS is considered as a bridge to liver transplantation. A TIPS should not be given in a patient with a MELD score of ≥18.

Because not all patients with refractory ascites respond to TIPS insertion with elimination of ascites and improved survival, a multicenter clinical study was conducted to investigate whether a TIPS inserted at an earlier stage of ascites' natural history could result in less side effects and improved survival when compared to LVP. Twenty-nine middle-aged mostly alcoholic cirrhotic patients with recurrent ascites, but still diuretic responsive, received a covered TIPS stent. Their clinical course over the following year was compared to 33 patients with similar demographics who continued to receive diuretics, LVP, and albumin infusions on an as-needed basis [49]. The patients who received a TIPS had a significantly increased transplant-free survival of 93% at 1 year, and this is significantly better than the 53% in the group who received LVP and diuretics. Interestingly, there was no difference in the incidence of HE between the groups. If the resulted can be replicated in another randomized controlled trial, then TIPS insertion could be offered at an earlier stage of ascites development in order to improve patient outcomes.

Automatic Low-Flow Ascites Pump (alfapump) (Fig. 2.4)

For patients who are not TIPS or liver transplant candidates, the only option for managing their ascites is LVP. However, the automatic low-flow ascites (alfa) pump system that is currently available in some European countries could

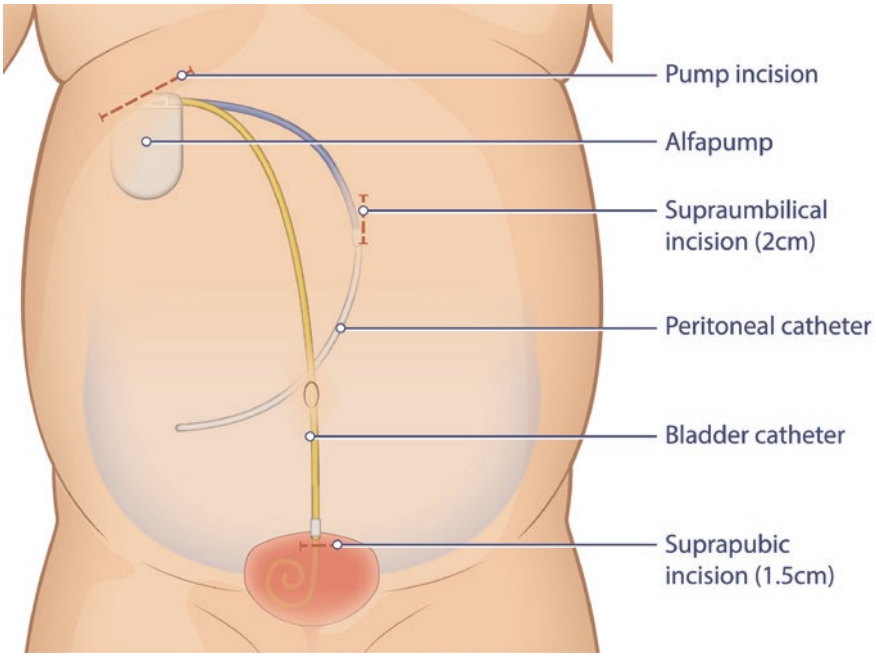

Fig. 2.4 An alfapump in situ

potentially be a treatment option. It is a device implanted subcutaneously in either one of the upper abdominal quadrants and connected to both a peritoneal catheter and a bladder catheter. Ascites is being pumped from the peritoneal cavity via the peritoneal catheter and then transported to the bladder via the bladder catheter, and the patient eliminates the ascites through normal micturition. This slow continuous paracentesis is being done for about 16 hours per day during awake hours and the pump is inactivated every night, so not to interrupt the patient's sleep. To date, all the publications on the alfapump system have confirmed its efficacy in reducing the need for LVP [50–53], associated with significant improvement in quality of life in these patients as early as 3 months after alfapump implantation. However, all studies have also reported on serious adverse events related to infections, especially before the introduction of mandatory antibiotic use with the alfapump system [51]. Adverse events relating to pump dysfunction, catheter obstruction, and/or dislodgement seem to have decreased with improved pump and catheter designs. Because the slow continuous paracentesis provided by the alfapump is being done without albumin infusions, some patients have experienced renal dysfunction, related to activation of various vasoconstrictor systems observed in some patients who have received the alfapump [54]. Future studies will have to determine if and when albumin infusions will be required with alfapump use.

Liver Transplantation

Liver transplantation remains the definitive treatment for patients with refractory ascites and liver dysfunction, especially since patients with refractory ascites have a very poor prognosis of 50% mortality at 6 months [55], and the risk of mortality parallels the severity of the ascites. The advent of the MELD-based organ allocation system means that ascites has dropped off as one of the priority factors for liver transplantation, and therefore patients with ascites as a major but without other complications of cirrhosis will be underserved by the current allocation system. Patients with ascites have been shown to have an additional mortality risk equivalent to 4.5 MELD [56] or 3.5 MELD-Na [57] score points, and this is especially true for patients whose MELD score is <21 [57]. For patients with refractory ascites and hyponatremia, their priority for liver transplantation is improved with the presence of the hyponatremia, as low serum sodium has been identified as a predictor of mortality for patients with moderate ascites [58, 59], with a 5–7% increase in waitlist mortality for every 1 mmol/L of decrease in serum sodium concentration [60]. It is anticipated that the use of the MELD sodium score in the allocation of organs will capture this group of patients, allowing them to receive a liver transplant earlier for better patient outcomes. It is important to realize that in the posttransplant period, the abnormal systemic hemodynamics will take time to reverse. Therefore, ascites may persist for several months posttransplant, and patients will need to remain on a low-sodium diet until complete elimination of ascites.

Prevention of Complications

It is important that while patients with refractory ascites are waiting for liver transplant, every effort should be made to prevent the development of other complications.

Prevention of Infections

The universal administration of primary prophylaxis against spontaneous bacterial peritonitis (SBP) in cirrhosis with ascites has not been proven beneficial [61]. However, there are subgroups of patients who are at high risk for the development of their first episode of SBP and therefore should receive primary antibiotic prophylaxis. These include patients with an acute gastrointestinal bleed, and those with a low ascites protein count of <15gm/L [62]. Of course patients who have had an episode of SBP should receive secondary antibiotic prophylaxis [62].

The Use of Nonselective Beta-Blockers

Nonselective beta-blockers (NSBBs) have been the mainstay of treatment for the prophylaxis against variceal bleeding in patients with cirrhosis. Data from a retrospective study almost 10 years ago suggested that patients with refractory ascites

should not be given NSBBs, as these increased the likelihood for the development of renal dysfunction and SBP [63, 64]. Furthermore, their use was associated with higher mortality [65]. The rationale for their deleterious effects in patients with refractory ascites was that NSBBs could potentially worsen the precarious hemodynamics that is already present in these patients [66]. However, more recent studies, both prospective and retrospective, including larger patient cohorts, failed to show deleterious effects of NSBB use. In the reanalysis of data from 3 satavaptan clinical trials that included more than 1000 patients, the use of NSBB was not associated with an increase in mortality [67]. Furthermore, for those patients who had to stop NSBB for whatever reason, there was a marked rise in mortality and coincided with hospitalization, variceal bleeding, bacterial infection, and/or development of hepatorenal syndrome. Further studies reported that the use of NSBB was associated with a reduction in bacterial translocation [68] and protects patients against the development of bacterial infections [69] and SBP [70]. In patients who were wait-listed for liver transplantation, the use of NSBB was associated with improved survival [71]. In the very ill patients with acute-on-chronic liver failure (ACLF), significantly more patients on NSBB had a reduction in their ACLF grade; the reverse was observed in patients not on NSBB [72]. So the accumulating evidence is that NSBB may not be harmful in patients with decompensated cirrhosis and ascites. In the future, we will need adequately powered prospective studies using hard end points such as survival to define whether the use of NSBB can be recommended as definitive treatment for patients with decompensated cirrhosis including those with refractory ascites.

Use of Sedatives and Analgesics

Patients with ascites frequently also have HE as one of the complications of cirrhosis and therefore disturbed sleep-wake cycles. In addition, many patients with tense ascites also report nonspecific abdominal pain. Therefore, it is not uncommon for patients with ascites to be prescribed hypnotics and analgesics. However, patients with cirrhosis have lower therapeutic/toxic thresholds for sedatives and analgesics due to reduced drug metabolism in the presence of liver dysfunction [73]. Therefore, there is an increased risk for precipitating HE from the sedating effects of hypnotics and the constipating effects of opioid analgesics [74], particularly in patients in ascites because they often have significant liver dysfunction. Therefore, it is imperative that clinicians thoroughly investigate the causes of insomnia or pain before prescribing hypnotics or analgesics. There is also recent data to suggest that the use of opioids in patients in cirrhosis was associated with altered gut microbiota and increased hospital readmissions [75].

Surgery in Patients with Ascites

Patients with cirrhosis and ascites frequently develop various hernias, which increase in size as the ascites becomes more severe. They are cosmetically unacceptable to the patients, and constant pressure from clothing can cause ulceration of

the overlying skin. Inguinal hernias can become so large that they interfere with walking. Occasionally, the hernias can also become incarcerated. Therefore, it is not uncommon for cirrhotic patients with ascites to request surgical repair of these hernias. However, even elective surgery in patients with cirrhosis and ascites is associated with significant morbidity and mortality, which tend to worsen with increasing MELD scores [76, 77]. Therefore, patients with ascites and hernias should be instructed on how to use abdominal binders and various hernia trusses in order to avoid complications and surgery. Emergency surgery is associated with significantly higher mortality than elective surgery: 22% versus 10% for patients in Child-Pugh class A, 38% versus 30% for those in class B, and 100% versus 82% for those in class C [77]. Optimization of patient's overall condition in emergency surgery may improve patient outcomes [78]. In patients who require elective surgery, the preemptive insertion of a TIPS in suitable patients prior to surgery may reduce the portal hypertension-related complications [79]. However, in one large series, which included patients who underwent TIPS insertion before major surgery such as colorectal surgery, although there was less postoperative ascites, there was no difference in 90-day mortality [80] when compared to the control group. Anecdotally, patients who received an alfapump as a means to control their ascites have also undergo successful hernia repairs.

Conclusions

The development of ascites is an important milestone in the natural history of cirrhosis. Understanding its pathophysiology has helped to improve the management of these patients. Treatment of ascites consists of dietary sodium restriction, diuretics in patients who are still responsive to their diuretic effects without complications. The use of albumin as an adjunct therapy of ascites is increasingly accepted, both in the diuretic-responsive and diuretic-resistant phases of ascites management. Patients with refractory ascites require regular large-volume paracentesis with albumin infusions. In the suitable patients, the insertion of a TIPS can eliminate ascites with improved nutritional status and quality of life. All patients with ascites and liver dysfunction should be referred for liver transplant assessment if there are no contraindications. The future management of ascites could include the use of an alfapump. All efforts should be made to prevent further complications in these patients.

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Chapter 3
Portosystemic Shunt Embolization in Overt Hepatic Encephalopathy

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Abbreviations

CT	Computed topography
HE	Hepatic encephalopathy
MELD	Model for end-stage liver disease
SPSSs	Spontaneous portosystemic shunts

Hepatic Encephalopathy and Spontaneous Portosystemic Shunts

Spontaneous portosystemic shunts (SPSSs) can cause hepatic encephalopathy (HE) by diverting blood to the shunt instead of through the liver [1]. SPSSs can be seen in a setting of cirrhosis with portal hypertension or in the absence of cirrhosis [2, 3]. The SPSSs arising from cirrhosis and portal hypertension setting will be the focus of this chapter.

The prevalence of SPSSs in cirrhotic patients with HE was reported to be between 23% and 71% [4–7]. Sharma et al. reported the SPSS prevalence of 23% in cirrhotic patients who recovered from episodic overt HE ($n = 140$) [6]. Riggio et al. reported the SPSS prevalence of 71% in cirrhotic patients with recurrent or persistent HE ($n = 14$) [5]. However, SPSSs do not always cause HE symptoms. In the same study

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by Riggio et al., SPSSs were found in 15% of cirrhotic patients without HE (control group, $n = 14$) [5]. In cirrhotic patients with portosystemic shunts ($n = 28$), Ohnishi et al. reported that only 46% had refractory HE symptom [8]. Both studies found that patients with SPSSs who had HE symptoms were less likely to have ascites and large esophageal varies suggesting that the portal blood flow was going through the SPSSs [5, 8]. The most recent study on SPSS was a retrospective multicenter study that identified 1729 cirrhotic patients. In total, 60% of patients had SPSS, 28% were large (>8 mm), and 32% were small. Splenorenal and paraumbilical shunts were the most common types. Those with large SPSS developed HE more often (48%) than their counterparts with small SPSS (34%) or without SPSS (20%) ($p < 0.001$). Patients with MELD scores ≥14 and large SPSS tended to have a more recurrent or persistent HE. Contrary to earlier reports, patients with large and small SPSS compared to those without SPSS also developed other complications of portal hypertension more frequently including bleeding, ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome. Additionally, patients with low MELD scores [6–9] and SPSS had an increased risk of death/liver transplantation (HR1.57, 95%CI, 1.08–2.30) [7].

Collectively, these data suggest that physicians should search for SPSSs in cirrhotic patients with refractory HE especially when HE is developed in relatively well-compensated patients with cirrhosis. However, incidental finding of SPSSs without HE symptom does not require treatment. The most common type of SPSSs is splenorenal shunt (Fig. 3.1). Other types of SPSSs, in the order from high to low frequency, include recanalized (para)umbilical veins, gastrorenal, mesocaval, inferior mesenteric vein caval, and mesorenal shunts [7].

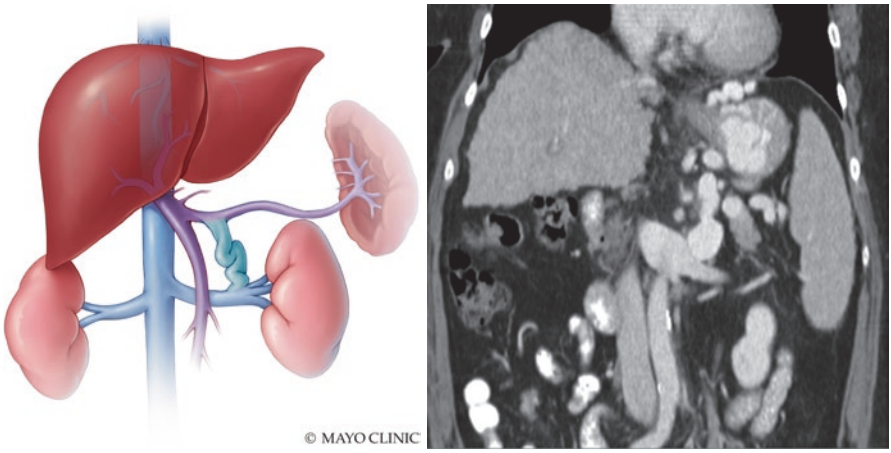

Fig. 3.1 (**a**) Splenorenal shunt, the most common type of portosystemic shunt. (**b**) Splenorenal shunt in coronal image of contrast-enhanced CT of the abdomen

Percutaneous Embolization of Spontaneous Portosystemic Shunts

Traditionally, surgical ligations were used as treatment for SPSSs [9]. However, due to its high rate of morbidity and mortality, percutaneous transcatheter embolization has been widely accepted as the first choice therapy because it is less invasive [10].

Regarding the technical aspects of the percutaneous transcatheter embolization, the embolization can be performed with either antegrade or retrograde techniques depending on the position of the SPSS (Fig. 3.2) [10]. An antegrade technique is a technique to access SPSSs directly through the portal system. The most common antegrade technique is the percutaneous transhepatic obliteration. A retrograde technique is a technique to access SPSSs through the caval system (thus, then name "retrograde"). The access site of the retrograde technique is either through the femoral vein or the internal jugular vein. Retrograde technique is less invasive but antegrade technique can provide better global images of the portal venous systems and its collateral vessels. Thus, antegrade technique is normally used in more complex shunts or in cases where the exact anatomy of the shunt is unclear from computed topography (CT) or magnetic resonance imaging.

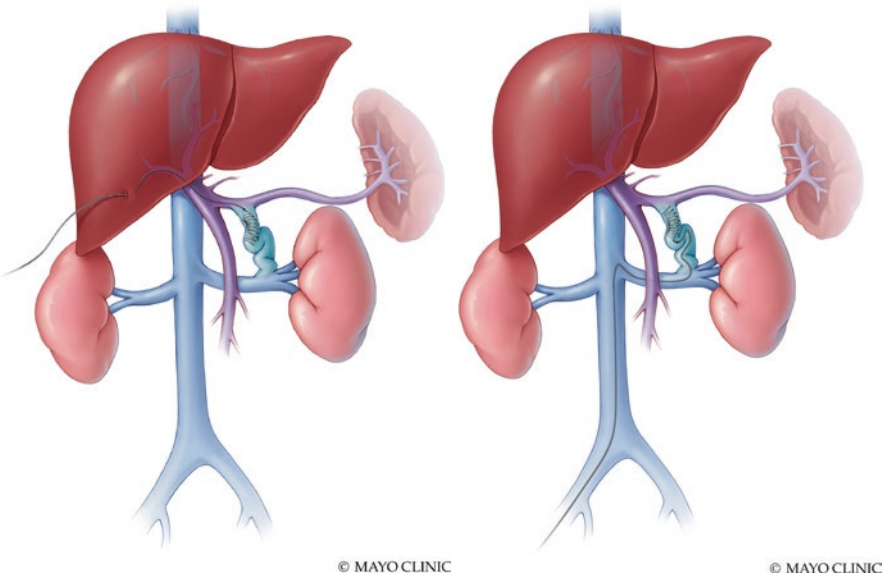

Fig. 3.2 Figures showing the coiling of portosystemic shunt using (**a**) antegrade technique (percutaneous transhepatic obliteration) and (**b**) retrograde technique with femoral veins as access sites

The goal of the embolization is to provide a permanent focal occlusion of the vein. The two main widely available options are coils and the Amplatzer plugs. Coils are easily deployed and pass easily through catheters traversing tortuous anatomy. However, many coils may be necessary to achieve the desired occlusion. A similar occlusion can be achieved with 1 or 2.

Amplatzer plugs, but they require a larger delivery system that will not track through tortuous anatomy. An additional advantage of the Amplatzer plug is that it can be deployed, a venogram can be obtained to document satisfactory position and stability, and only then is it released. If the position is unsatisfactory, they can be reconstrained by the delivery sheath and repositioned.

Efficacy and Safety of Percutaneous Embolization of Spontaneous Portosystemic Shunts

Data on the efficacy and safety of percutaneous embolization of large SPSSs are sparse and have relied mainly on retrospective studies. Several case series and case reports were published [4, 11–18]. Table 3.1 summarized previous case series of transcatheter embolization for large portosystemic shunts with refractory hepatic encephalopathy. In this table, case series were included if they included at least ten patients.

Efficacy

Multiple case series reported good short-term efficacy and acceptable long-term efficacy. However, long-term results were limited because of loss to follow-up. In the only prospective study (n = 37), Laleman et al. reported that 59% and 49% were free of HE at 3.3 months and 2 years, respectively. Importantly, the HE recurrence was less in those with Model for End-Stage Liver Disease (MELD) score of ≤11 [13]. In a US series (n = 20), Lynn et al. reported that 100% of patients achieved immediate improvement and durable benefit was achieved in 92% at 6–12 months after the procedure [14]. In an Indian case series (n = 21), Philips et al. reported that 75% and 71% were free of HE at 3 months and 9 months, respectively [4]. In a Korean case-control series (n = 17), the 2-year HE recurrence rate was lower in the embolization group (40% vs. 80%, p = 0.02) but there was no difference in the 2-year overall survival rates (65% vs. 53%, p = 0.98). In addition, they observed an improvement in overall survival in a subgroup of embolization patients (100% vs. 60%, p = 0.03) without hepatocellular carcinoma and with a MELD score <15 [11].

Table 3.1 Case series of transcatheter embolization for large portosystemic shunts with refractory hepatic encephalopathy

Reference	N	Center	Age	MELD score	Embolization technique	Short-term HE improvement	Long-term HE improvement	Major procedural complication	Portal hypertension compilation
Philips et al. 2017 [4]	21	One Indian center	56.6 ± 10.6	15.7 ± 4.18	Coil, Amplatzer plug, and surgical shunt	75% (15/20) free of HE at 3 months	71% (5/7) free of HE at 9 months	One died from hemoperitoneum and multiple organ failures	One had nonfatal variceal bleeding, two had ascites
Lynn et al. 2016 [14, 19]	20	One US center	60.9 ± 8.1	13.1 + ±3.4 (range 8–23)	Coil and Amplatzer plug	100% (18/18) at 1–4 months	92% (11/12) at 6–12 months	None	Six had ascites, one had small varices
An et al. 2014 [11]	17	One Korean center	62 (IQR 56–65.5)	13 (IQR 11–15)	Coil, Amplatzer plug, and gelatin sponges	N/A	60% at 24 months	None	Three had ascites, three had esophageal varices
Naeshiro et al. 2014 [16]	14	One Japanese center	71 (IQR 55–74)	N/A	Coil, EO, and NBCA	93% (13/14) at 2 weeks	93% (13/14) at 27 months	None	Four had esophageal varices
Laleman et al. 2013 [13]	37	Six European centers	61 ± −2	13.2 ± 0.9 (range 5–28)	Coil, Amplatzer plug, and matrix	59% (23/37) free of HE At 3.3 months	49% (18/37) at 24 months	One had capsular bleeding	Six had ascites, two had esophageal varices

Abbreviations: *EO* ethanolamine oleate, *NBCA* n-butyl-2-cyanoacrylate

Safety

Early procedural complications were mostly minor and major complications were very rare. For major complications, two cases were reported to have intra-abdominal bleeding and one died during the procedure as a result [4, 13]. Mild early complications are more frequent and include puncture site infection, puncture site hematoma, contrast-induced nephropathy, and fever [13, 14].

Long-term complications include worsening portal hypertension (i.e., ascites, portal hypertensive gastropathy, esophageal varices, esophageal variceal bleeding, or spontaneous bacterial peritonitis) and portal vein thrombosis. Previous studies reported that 22–35% of patients had either new ascites or esophageal varices at 1–2 years after embolization [11, 13, 14]. However, bleeding from esophageal varices was rare and only one nonfatal esophageal variceal bleeding was reported by Laleman et al. However, it occurred 55 months after embolization and was unlikely to be from the procedure [13]. Thrombosis of the portal vein or its branches were reported in four patients in the same study. However, the patients were asymptomatic and the thromboses were treatable with low molecular weight heparin [13].

Selection of Candidates for Embolization of Spontaneous Portosystemic Shunts

Because the spontaneous portosystemic shunts can be seen in cirrhotic patients without hepatic encephalopathy, the embolization of SPSSs should be considered only when the HE is recurrent or persistent despite medical therapy. Moreover, the embolization may not be effective in patients with advanced liver disease and the risk may outweigh the benefit in those patients. Previous studies showed that patients with high MELD score (>11) are more likely to have HE recurrence [13] or developed ascites or varices after embolization [14]. With data from previous studies, we propose that the indications for portosystemic shunt embolization in cirrhotic patients are as follows:

1. Recurrent or persistent hepatic encephalopathy despite optimal medical therapy.
2. A large portosystemic shunt $\geq$10 mm is identified.
3. Cirrhotic patients with MELD score $\leq$11 [13].

Follow-Up After Embolization of Spontaneous Portosystemic Shunts

In addition to ensuring that no early complications occur immediately after embolization, long-term follow-up is necessary to detect complications from portal hypertension. With previous studies reporting 22–35% of patients having new

ascites or esophageal varices within 1–2 years of follow-up after embolization, upper endoscopy should be obtained in the first 6–12 months to detect esophageal varices. A repeat CT or MRI at 6 and 12 months is reasonable for detection of new large shunts and for the assessment of portal vein patency, ascites, and hepatocellular carcinoma. On occasion, portosystemic shunt embolization needs to be repeated in patients who otherwise tolerate the first embolization but remain symptomatic from HE.

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Chapter 4
Gastroesophageal Variceal Bleeding Management

Alberto Zanetto and Guadalupe Garcia-Tsao

Introduction

The natural history of cirrhosis is characterized by two main stages: compensated and decompensated cirrhosis. The transition into the latter stage is determined by the development of clinically significant portal hypertension (CSPH), defined by a hepatic venous pressure gradient (HVPG) ≥10 mmHg [1, 2]. Decompensation is defined by the occurrence of ascites, portal hypertensive gastrointestinal (GI) bleeding, hepatic encephalopathy, or jaundice [3], although jaundice may belong to a more advanced stage ("further" decompensation) and is the hallmark of the so-called acute-on-chronic liver failure (refer to Chap. 11).

Compensated and decompensated cirrhosis are two distinct entities with different clinical course and prognosis. Indeed, the median survival of patients with compensated cirrhosis has been described as long as 10–12 years, with death occurring mostly after decompensation [1]. On the contrary, the median survival of decompensated patients is about 2 years [2].

Specifically regarding varices and variceal hemorrhage, CSPH plays a key role in the development, growth, and rupture of gastroesophageal varices [4–6]. In patients with compensated cirrhosis without varices, varices develop at the rate of 5–8% per year but depends mainly on the presence (or absence) of CSPH [5, 7]. In patients with varices, rupture develops at a rate of 5–15% per year but depends on the characteristics of the varices and of the patient [8, 9]. Highest bleeding rates occur in patients with large varices and red wale signs and in those with

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Child C cirrhosis. The "North Italian Endoscopic Club" index combines these risk indicators in a score that enables to identify with 1-year predicted bleeding risk from 6% to 76% [10].

The development of variceal hemorrhage (VH) constitutes the second most frequent decompensating event after ascites [11, 12] and is a medical emergency associated with a 6-week mortality rate that remains in the order of 10–20% [13] and a 1-year mortality in the range of 30–60% [11, 12]. Bleeding risk and control of bleeding are strongly influenced by the severity of portal hypertension. Indeed, bleeding does not occur when HVPG is below 12 mmHg [14]. In patients with variceal hemorrhage, an HVPG >20 mmHg is a negative prognostic predictor for the control of bleeding and is associated with a high 6-week mortality. Similar predictive accuracy can be achieved using only simple clinical variables such as Child class, which have universal applicability and strongly correlate with HVPG with more than 80% of Child C patients having an HVPG >20 mmHg [15]. In patients who have recovered from variceal hemorrhage, the rebleeding risk is influenced by the treatment of underlying portal hypertension, with 60% of untreated patients that experience rebleeding within 1–2 years, in contrast with only 30% of those given treatments that lower portal pressure [12]. Reduction of HVPG to below 12 mmHg virtually prevents recurrent bleeding episodes [16].

In a prospective, inception cohort study, mortality from variceal hemorrhage as the sole decompensating event was 20% while in patients with variceal hemorrhage and a second decompensating event (ascites or encephalopathy), this death rate increased to 88% [17]. Therefore, goals of therapy differ in these patients. In those who present with acute variceal hemorrhage as the only decompensating event, besides the control of active bleeding, prevention of early and late recurrent bleeding is crucial to avoid further decompensation and death [13]. In patients who present with variceal hemorrhage and another decompensating event, the objective of therapy is to improve survival [13].

Management of Acute Esophageal Variceal Hemorrhage

Acute VH is a medical emergency requiring intensive care. As in any patient with any major hemorrhage, it is essential to first evaluate and protect the respiratory and circulatory status of the patient according to "airway-breathing-circulation" scheme. Initial resuscitation should be initiated as soon as possible. In this scheme, specific therapy (including prophylactic antibiotics and intravenous vasoconstrictors) aimed at controlling the bleeding must be provided, as continued bleeding increases the risk of deterioration of liver function and leads to multiorgan failure where patients' survival no longer depends on controlling the bleeding itself. When hemodynamic stability is achieved, upper endoscopy must be done to diagnose the cause of bleeding and plan the following treatments (Fig. 4.1).

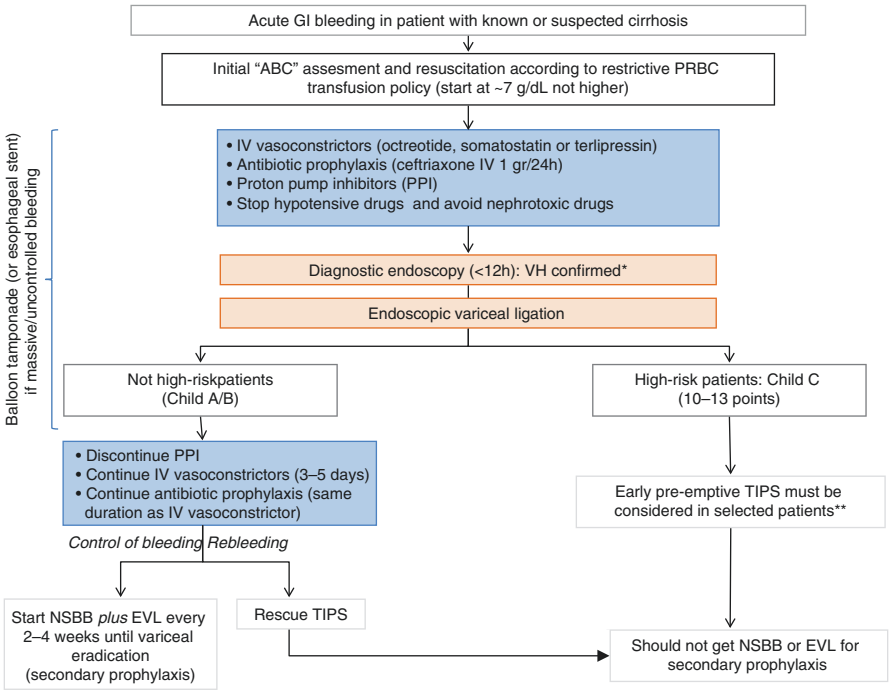

Fig. 4.1 GI gastrointestinal, ABC Airway, Breathing, Circulation, PRBC packed red blood cell, IV intravenous, PPI proton pump inhibitors, VH variceal hemorrhage, NSBB nonselective beta-blockers, TIPS transjugular intrahepatic portosystemic shunt, EVL endoscopic variceal ligation. ∗ Any of the following: varix spurting blood, varices with overlying clot or with white nipple sign, varices and no other lesion that would explain hemorrhage. ∗∗ Excluding patients age >75 years, HCC outside Milan criteria, creatinine level ≥3 mg/dL, previous combination pharmacological plus endoscopic treatment to prevent rebleeding, bleeding from isolated gastric or ectopic varices, complete portal vein thrombosis, recurrent hepatic encephalopathy, heart failure plus perhaps those with MELD <19

General Measures

Volume Restitution

Hypovolemic shock can be a consequence of acute GI bleeding and results from the acute loss of plasma and red blood cell volume. It is associated with an inadequate tissue perfusion of oxygen and substrates and ultimately leads to irreversible tissue and organ injury. Rapid restoration of oxygen delivery can reverse the progression of the shock state, and this often requires transfusions [18].

Concerns about volume restitution in patients with cirrhosis and portal hypertension have been raised [19]. Indeed, patients with hyperdynamic circulation present significant alterations of the homeostatic mechanisms that regulate blood volume [20, 21]. Following VH, blood volume depletion decreases portal venous inflow

(and therefore the portal pressure), by reducing the venous return and by causing reflex splanchnic vasoconstriction. Sudden restitution of intravascular volume can induce a rebound increase in portal pressure, which may further precipitate portal hypertensive bleeding [22, 23].

In a rat model of prehepatic portal hypertension, hemorrhage was associated with a 30% fall in portal venous pressure. However, after blood volume restitution portal pressure rose to values 20–25% higher than the baseline. This "overreaction" occurred despite unchanged splanchnic blood inflow and was caused by an increased resistance in the porto-collateral vessels induced by the release of vasoactive mediators. This rebound increase in portal pressure was not observed in normal animals, in which the portal pressure just returned to baseline [23].

Clinical studies have confirmed that blood transfusion during the course of an acute VH can significantly increase portal pressure [24, 25].

Villanueva et al. [26] performed a randomized control trial (RCT) on transfusion strategies for upper GI bleeding, comparing a restrictive vs. a liberal transfusion strategy. In a subset of 921 patients with cirrhosis, 461 were randomized to the "restrictive-strategy group" (hemoglobin threshold for transfusion of 7 g/dL with target range after transfusion of 7–9 g/dL) and 460 to the "liberal-strategy group" (hemoglobin threshold for transfusion of 9 g/dL with target range after transfusion of 9–11 g/dL). Survival probability was significantly higher with restrictive transfusion strategy in the subgroup of patients with cirrhosis and Child class A or B (HR = 0.30, 95% CI = 0.11–0.85) but not in those with Child class C (HR = 1.04, 95% CI = 0.45–2.37). In patients with VH, a baseline hemodynamic study was performed within the first 48 h and then repeated 2–4 days later. As compared with the baseline study, patients in the liberal-strategy group had a significant increase of HVPG in the second hemodynamic study (from 20.5 ± 3 to 21.4 ± 4 mmHg, $p = 0.003$) despite the administration of somatostatin. On the contrary, there were no significant differences between the two hemodynamic studies in the restrictive-strategy group.

An increase of patients with decompensated NASH cirrhosis is expected in the future [27, 28]. The majority will present cardiovascular comorbidities that may hinder the physiological response to acute anemia. Based on the findings of Villanueva et al. [26], current guidelines suggest initiating transfusions for patients with acute GI bleeding when hemoglobin levels decrease to less than 7 g/dL with a target level of 7–9 g/dL. However, this threshold may be different (e.g., 8 g/dL) in patients with NASH cirrhosis and cardiovascular comorbidities.

Replacement of fluids and electrolytes is important to prevent the development of prerenal acute kidney injury, which has been associated with increased mortality in patients with cirrhosis [29]. Nephrotoxic drugs (i.e., nonsteroidal anti-inflammatory drugs), beta-blockers, and calcium-antagonist (and other hypotensive drugs) may be interrupted during the acute phase of VH [30].

Correction of Coagulopathy

Fluid resuscitation may interfere with primary and secondary hemostasis [31–33]. In addition, it has been suggested that the "fresh" clot formed around a bleeding vessel could be dislodged when the hypotension induced by hemorrhage is counteracted by repletion of blood volume [34]. There is a significant lack of data regarding the safety and the utility of platelets and plasma transfusions in patients with cirrhosis and portal hypertensive bleeding [35–37]. Therefore, no recommendations regarding management of coagulopathy and thrombocytopenia can be given at the present time [13].

Prothrombin time (PT) is not a reliable indicator of the coagulation status in patients with cirrhosis [38], and it does not reflect bleeding risk. In fact, the administration of recombinant activated factor VII (rFVIIa), which can revert PT prolongation in patients with cirrhosis, did not show an additional beneficial effect to standard therapy in two multicenter placebo-controlled trials including patients with cirrhosis and variceal hemorrhage [39, 40]. Therefore, its use is not recommended by the current guidelines [13, 41]. Nonetheless, a recent individual patient-based meta-analysis showed a beneficial effect of rFVIIa on a primary composite 5-day endpoint of control bleeding, 5-day rebleeding and death in patients with Child B and C cirrhosis, and active bleeding [42].

Previous studies have shown that fibrinolysis deregulation might contribute to the coagulopathy of decompensated patients [43]. High level of D-dimer has been correlated with an increased risk of variceal bleeding in one prospective study including 43 patients (50% of them Child C) [44], suggesting that antifibrinolytic drugs might be useful in acute VH. In another study that included decompensated patients who bled from esophageal varices, high D-dimer was also associated with significant risk of death [45]. However, the clinic relevance of deregulated fibrinolysis in the setting of VH has not been properly evaluated yet, and the administration of antifibrinolytic drugs cannot be recommended.

Oxygenation

Diagnostic upper endoscopy in non-bleeding patients is a safe procedure. However, in cases of emergency, such as acute variceal hemorrhage, the incidence of complications increases up to 8%, being the cardiopulmonary complications the most frequent [46]. Aspiration, which is the major contributor to cardiopulmonary complications, occurs at a rate of approximately 2.4% (18 of 741) of patients with index bleeding, increasing to 3.3% of patients in cases of rebleeding, due to the presence of blood inside the stomach [47]. Therefore, elective or emergent tracheal intubation may be required for airway protection prior to endoscopy, particularly in

patients with concomitant altered consciousness due to hepatic encephalopathy [13, 48, 49]. In patients with massive uncontrolled VH when balloon tamponade is used, airway protection is strongly recommended [13, 48].

Specific Pharmacological Therapy

Antibiotic Prophylaxis

Prevention of complications should occur simultaneously to resuscitation therapies. Bacterial infections are one of the most common and severe complications and are reported in more than 50% of patients with cirrhosis who experience GI bleeding. Infections may already be present at the time of bleeding (20%), acting as a precipitating event by increasing portal pressure, by impairing hemostasis, and by worsening liver function [50–53].

Indeed, infections have been independently associated with failure to control bleeding, high risk of rebleeding, and increased mortality [50, 51, 54, 55]. Timely short-term antibiotic prophylaxis is therefore an essential step in the management of patients with cirrhosis and variceal bleeding and is recommended by both American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) guidelines independently of liver function or of the presence of ascites [30, 41]. The importance of antibiotic prophylaxis is incontrovertible in patients with advanced liver disease whereas in patients with less severe liver disease conflicting data have been recently published. In a recent retrospective study, Child A patients had lower rates of bacterial infection (2%) in the absence of antibiotic prophylaxis than Child B (14%) and C (39%) patients. The adjusted risk of mortality was also extremely low and not different from patients on antibiotics ($p = 0.4$). In contrast, antibiotic therapy was associated with a marked mortality reduction in Child C patients, from 62% to 35% [56]. However, more prospective studies are needed to assess whether antibiotic prophylaxis can be avoided in this subgroup of patients [13].

Antibiotic prophylaxis must be instituted as early as variceal bleeding is suspected, and timely administration (before or within 8 hours after endoscopy) has been associated with reduced rebleeding rate (17% vs. 29%) and lower mortality (13% vs. 35%) [57].

Ceftriaxone (intravenous [IV], 1 g/24 h) is the first choice in patients with advanced cirrhosis (defined by the presence of 2 or more severe malnutrition, ascites, encephalopathy, serum bilirubin >3 mg/dL), in those on quinolone prophylaxis, and in hospital settings with high prevalence of quinolone-resistant bacteria [13, 30, 41]. Fernandez et al. [58] demonstrated that IV ceftriaxone is associated with a significantly lower probability of any bacterial infection ($p = 0.003$), spontaneous bacterial peritonitis, or spontaneous bacteremia (0.027) when compared with oral norfloxacin. Oral quinolones (norfloxacin 400 mg b.i.d) may be used in the remaining patients. However, norfloxacin is no longer available in the United States and is

not available in most inpatient formularies. Therefore, the antibiotic of choice in most centers is IV ceftriaxone. Duration of antibiotic prophylaxis is short term, for a maximum of 7 days. Once the bleeding is controlled, antibiotics can be discontinued together with intravenous vasoconstrictors [13, 41].

Intravenous Vasoconstrictors

Specific therapy to stop variceal hemorrhage consists in the intravenous administration of vasoconstrictors [30, 41]. These drugs exert their action by reducing splanchnic blood flow, therefore lowering portal pressure. As a proof of concept, treatment with intravenous vasoconstrictors alone has been previously reported to control bleeding in more than 80% of cases [59]. In the last decades, the widespread implementation of intravenous vasoconstrictors together with the optimization of general medical care has been important for lowering mortality [60].

Three drugs are available: terlipressin (currently not available in the USA, but ongoing trials for potential implementation are underway), somatostatin, and octreotide. The recommended dose of terlipressin is 2 mg/4 h during the first 48 h, followed by 1 mg/4 h thereafter. The recommended dose of somatostatin is a continuous infusion of 250 microg/h (that can be increased up to 500 microg/h) with an initial bolus of 250 microg. The recommended dose of octreotide is a continuous infusion of 50 microg/h with an initial bolus of 50 microg. A bolus of somatostatin or octreotide can be also administered if bleeding persists. Vasoactive drugs must be started before endoscopy in order to facilitate the procedure by reducing the rate of active bleeding. This enhances the probability of control the bleeding, improving survival [61, 62]. Timing is important, as shown in a placebo-controlled trial in which terlipressin was even administered during the ambulance transfer, with an increased rate of control of bleeding and of survival in the treatment arm [62]. Therefore, current guidelines recommend starting intravenous vasoconstrictors as soon as possible, before endoscopy [13, 30, 41].

The importance of vasoactive drugs in lowering mortality has been confirmed in a recent meta-analysis that included more than 3000 patients [63]. In the study by Wells et al., the use of vasoactive agents was associated with a significant improvement in control of the bleeding (RR 1.21, 95%CI 1.13–1.30, $p < 0.001$, $I^2 = 28\%$) and with a significantly lower risk of 7-day mortality (RR 0.74, 95%CI 0.57–0.95, $p = 0.02$, $I^2 = 0\%$). Preliminary studies suggested that terlipressin might be the drug of choice [64, 65]. However, in a recent randomized non-inferiority trial there was no difference regarding hemostatic effects and safety among the three drugs, although terlipressin was used at doses lower than recommended. Seven hundred and eighty patients with VH were recruited and randomized: 261 in the terlipressin group, 259 in the somatostatin group, and 260 in the octreotide group. At the time of initial endoscopy, active bleeding was found in 43.7%, 44.4%, and 43.5% of these patients, respectively ($p = 0.748$). Treatment success was achieved by day 5 in 86.2%, 83.4%, and 83.8% of patients ($p = 0.636$), with similar rates of rebleeding (3.4%, 4.8%, and 4.4%, $p = 0.739$) and mortality (8.0%, 8.9%, and 8.8%, $p = 0.929$) [66].

In clinical practice, the choice is dictated by local availability and cost. Terlipressin is not available in all countries and is expensive and octreotide is the only vasoactive drug available in the United States. In 11 studies included in the abovementioned meta-analysis, octreotide was shown to significantly improve control of acute hemorrhage [63].

Once hemorrhage is confirmed at endoscopy, vasoactive therapy should be given for 5 days to avoid early rebleeding [30, 41]. Shorter administration (i.e., 24–48 h) has been proposed [67–70], with conflicting results. Yan et al. [71] summarized those studies in an updated meta-analysis, suggesting that there is no significant difference in the risk of 42-day mortality (RR 0.95, 95%CI 0.43–2.13, $p = 0.81$, $I^2 = 0\%$) between "3- to 5-day" regimen and "short" regimen. With regard to very early rebleeding rate, the short regimen was even better (RR 1.77, 95% CI0.64–4.89, $p = 0.70$, $I^2 = 0\%$), although the difference was not statistically significant. However, patient characteristics were not available in many of the studies included in the meta-analysis and there was no risk stratification. It may be that patients that can receive a shorter duration of therapy (3 days) are patients with the lowest risk of death, i.e., Child A patients, while all others require 5 days, but this requires further investigation.

Side effects of vasoactive drugs are usually mild, but still can lead to treatment discontinuation and are more common with terlipressin [72], with diarrhea, abdominal pain, and increased blood pressure being the most common but reversible after drug withdrawal. Serious side effects such as peripheral, intestinal, or myocardial ischemia occur in <3% of the patients [73]. Because of the possibility of producing ischemic complications and severe arrhythmias, terlipressin should be used with caution in patients with a history of ischemic heart or cerebral disease, limb or gut vascular disease, as well as in the elderly and in hypertensive subjects [74]. An acute reduction in serum sodium concentration is relatively common during treatment with terlipressin [75, 76], especially in patients with a preserved liver function and with better response to treatment. If severe (<125 mmol/L), it can be associated with the onset of neurological symptoms that usually revert after drug interruption [74]. However, few cases of osmotic demyelination syndrome have been reported [76]. Therefore, sodium level must be monitored with the use of terlipressin [13]. Octreotide is generally well tolerated by patients, being hyperglycemia the most common side effect [77, 78]. Other minor complications include diarrhea, abdominal pain, and nausea [77, 78]. The risk of major complications is lower with octreotide than with vasopressin/terlipressin, although arrhythmias, pneumonia/pulmonary edema, and severe paralytic ileus have been reported [77], with the latter that required discontinuation of therapy [79].

Other Measures

Intravenous proton pump inhibitors (PPIs) should be initiated when the patient presents with GI hemorrhage because peptic ulcers have been reported to be the cause of bleeding in up to 33% of the patients with cirrhosis admitted for upper GI hemorrhage [80]. However, they have not shown efficacy for the management of acute variceal hemorrhage and, when portal hypertensive bleeding is confirmed by

endoscopy, they should be discontinued. Indeed, PPIs have been associated with an increased risk of hepatic encephalopathy in patients with cirrhosis [81], especially in those with recent bacterial infections [82] and a recent multicenter study showed that PPI use was associated with a significant risk of early (30 days) readmission due to hepatic encephalopathy (50% vs. 32%, $p = 0.002$), independently of comorbidities, age, severity of liver diseases, and medications [83].

Recent studies suggest that either lactulose or rifaximin may prevent hepatic encephalopathy in patients with cirrhosis and upper GI bleeding. However, further studies are needed to evaluate the risk/benefit ratio and to identify high-risk patients before a formal recommendation can be made [13].

Endoscopic Therapy

Once hemodynamic stability has been achieved, patients must undergo upper endoscopy to ascertain the cause of hemorrhage (up to 30% of cirrhotic patients bleed from non-variceal causes) and to provide endoscopic therapy if indicated [13, 41]. Timing is important, and delayed endoscopy (i.e., >15 h) has been associated with increased short-term mortality (HR = 3.67; 95%CI, 1.27–10.39) [84]. Current guidelines recommend that endoscopy must be done as soon as possible after resuscitation and not more than 12 hours after presentation [13, 30, 41].

If available, erythromycin may be considered before endoscopy (250 mg IV, 30–120 min before) to facilitate the procedure by stimulating gastric peristalsis in patients who do not have QT prolongation [13, 85].

When variceal hemorrhage is confirmed, endoscopic variceal ligation (EVL) should be performed within the same procedure [13, 41]. The diagnosis of VH is considered certain when active bleeding from a varix is observed during the endoscopy or when the so-called “white nipple” sign (sign of recent variceal rupture) is present. VH should be inferred when varices are the only lesion found, and either blood is present in the stomach or endoscopy is performed within 24 hours of hemorrhage (Fig. 4.1) [41].

The combination of EVL (local hemostatic effect) and vasoactive agents (portal hypotensive effect) is more effective than the isolated use of either of these treatments alone [86, 87], and this combined approach is currently considered the standard of care [13, 30, 41]. EVL is more effective than sclerotherapy to control bleeding, with fewer adverse effects [87, 88]. Sclerotherapy can be used when ligation is not feasible due to characteristics of varices and/or position of bleeding point.

Rescue TIPS in Patients Who Fail Standard Therapy

Despite combined therapy with vasoactive drugs and EVL and prophylactic antibiotics, up to 10–15% of patients have persistent bleeding or early rebleeding with very high mortality [89]. Different factors have been independently associated with

high risk of failure of standard therapy, reflecting either the severity of hemorrhage or of underlying cirrhosis (or both): markedly elevated HVPG (>20 mmHg), Child C class, white blood cell count over 10×10^9/L, presence of portal vein thrombosis (PVT), and systolic blood pressure at admission <100 mmHg [15, 90].

If TIPS is not feasible or in case of modest rebleeding, a second session of endoscopic therapy can be attempted [30]. In addition, intravenous vasoconstrictors should also be optimized, by doubling the dose of somatostatin and/or switching to more potent vasoconstrictor such as terlipressin if not used previously [30].

If rebleeding is persistent or severe, rescue TIPS (polytetrafluoroethylene covered) is the therapy of choice [13, 41]. Selection of candidates for rescue TIPS is important. In a retrospective cohort of 144 consecutive patients who underwent rescue TIPS, Maimone et al. [91] recently showed that pre-TIPS portal pressure gradient, MELD, and Child classification were independently associated with 6-week mortality and rescue TIPS was futile in patients with too advanced liver disease (Child C with a score 14–15).

Balloon Tamponade/Stents as a Bridge to Rescue TIPS

Balloon tamponade is associated with a high incidence of severe adverse events, and it must be used only as a temporary "bridge" (maximum 24 h) to definitive treatment (e.g., TIPS) in patients with uncontrolled esophageal bleeding or rebleeding [13].

A recent small RCT compared balloon tamponade (n = 15) to endoscopically placed self-expandable metal stents (n = 13) in patients with cirrhosis and variceal hemorrhage refractory to medical and endoscopic treatment. Even though no differences in 6-week survival were found (54% vs. 40%, p = 0.46), control of bleeding was significantly higher (85% vs. 47%, p = 0.04) and severe side effects were significantly lower (15% vs. 47%, p = 0.08) with metal stents, respectively [92]. Furthermore, stents may remain in place for up to 7 days, allowing more time for deciding the definitive treatments. These preliminary results were then confirmed in a meta-analysis that included five small studies (80 patients in total) [93]. These stents are not FDA approved in the United States.

TIPS in Patients at a High-Risk of Failing Standard Therapy (Preemptive TIPS)

As mentioned above two factors are predictive of failure of standard therapy: HVPG >20 and Child C. Failure of standard therapy in this subgroup of patients is as high as 50% during the first year and mortality reaches 40% [94]. It was therefore postulated that placement of TIPS in high-risk patients *before* failure of standard therapy occurs (preemptive TIPS) would improve survival (Table 4.1). In a first trial by

Table 4.1 Early (preemptive) TIPS in patients at high risk of failure

Study, year (ref)	Patients (n)	High-risk criteria	Failure (%)	Rebleeding (%)	Hepatic encephalopathy (%)	Mortality (%)	Follow-up (months)
Randomized control trials							
Monescillo, 2004 [95]	26[a]	HVPG >20 mmHg	12	4	31	17 (6 weeks) 31 (1 year)	12
Garcia-Pagan, 2010 [94][d]	32	Child C 10–13 Child B with active bleeding	3	0	28	12.5	14.6 ± 8.4
Cohort studies							
Garcia-Pagan, 2013 [96][b]	45	Child C 10–13 Child B with active bleeding	2	4.4	51	14 (1 year) 14 (2 year)	13.1 ± 12
Rudler, 2014 [98][c]	31	Child C 10–13 Child B with active bleeding	0	3	45.1	10 (6 weeks) 29 (1 year)	7.8
Thabut, 2017 [99][c]	22	Child C 10–13 Child B with active bleeding	NA	4.2%	NA	9.1% (42 days) 22.7% (1 year)	12
Hernandez-Gea, 2018 [97][b]	66	Child C 10–13 Child B with active bleeding	0	4.5	42.4	8 (6 weeks) 22 (1 year)	12
Lv, 2018 [101][b]	206	Child C 10–13 Child B with active bleeding	0	12 (6 weeks) 22 (1 year)	25.7 (6 weeks) 37.4 (1 year)	3.6 (6 weeks) 14.1 (1 year)	22.9 ± 16.3

HVPG hepatic venous pressure gradient, *NA* not available

[a]Uncovered TIPS

[b]Retrospective study

[c]Any of the following: varix spurting blood, varices with overlying clot or with white nipple sign, varices and no other lesion that would explain hemorrhage

[d]Excluding patients age >75 years, HCC outside Milan criteria, creatinine level ≥3 mg/dL, previous combination pharmacological plus endoscopic treatment to prevent rebleeding, bleeding from isolated gastric or ectopic varices, complete portal vein thrombosis, recurrent hepatic encephalopathy, heart failure plus perhaps those with MELD <19

Monescillo et al. in 2004 [95], 26 patients per arm were enrolled. Definition of high risk was based on HVPG >20 mmHg. Treatment failure rates (12% vs. 50%) and short-term mortality (17% vs. 38%, $p < 0.05$) were significantly lower in patients who underwent preemptive TIPS (uncovered). In a second trial by Garcia-Pagan in 2010 [94], 32 patients underwent preemptive TIPS (covered) vs. 31 who were treated according to standard of care. Definition of high risk was based on the following criteria: Child C class with a score of 10–13 or Child B class with active bleeding at endoscopy. Exclusion criteria were very strict, including Child A class, Child B class without active bleeding at endoscopy, Child C class with a score of 14 and 15 points, age >75 years, HCC outside Milan criteria, creatinine level greater than 3 mg/dL, previous combination pharmacological plus endoscopic treatment to prevent rebleeding, bleeding from isolated gastric or ectopic varices, occlusive PVT, and heart failure. Overall, patients eligible for the enrollment were only 20% of those initially screened. During 1-year follow-up, none of the patients who underwent TIPS experienced rebleeding episodes, and survival was significantly higher in TIPS group than in patients treated according to standard of care (4/32 deaths vs. 12/31 deaths, respectively, $p = 0.01$).

Observational studies have not confirmed the beneficial effect on survival of early TIPS and the criterion of Child class B plus active bleeding at endoscopy has been challenged for possibly overestimating the risk of death [96–99] (Table 4.1). Hernandez-Gea et al. [97] failed to demonstrate a survival benefit of preemptive TIPS in Child B patients and active bleeding. Nonetheless, Child C patients (10–13 points) who underwent TIPS experienced a significant reduction of treatment failure/rebleeding and development of de novo ascites/worsening of previous ascites, without an increased risk of hepatic encephalopathy. Similarly, no benefit for survival was shown in patients displaying Child B cirrhosis with active bleeding at endoscopy in a French multicenter observational study [99].

In a recent large multicenter study [100], Child B patients had a significantly lower 6-week mortality than Child C patients (11.7% [25/214] vs. 35.6% [62/174]; $p < 0.001$), regardless of the presence of active bleeding. Furthermore, there was not difference between Child B patients with and without active bleeding (11.7% [16/137] vs. 11.7% [9/77]; p = not significant).

Therefore, candidates for preemptive TIPS appear to be those with Child C (score 10–13) (Fig. 4.1). Within this patient population, the subgroup of patients that are most likely to benefit need further clarification. The feasibility of using the MELD score to select patients for early TIPS has been recently confirmed in a large retrospective Chinese study including 1425 patients [101]. Among the 206 patients who underwent early TIPS, those with MELD score ≥19 had a significant survival benefit after adjusting for potential confounders. On the contrary, no difference in survival was found in patients with MELD <11 and in those with a MELD between 12 and 18, the survival benefit was observed at 6 weeks but not at 1 year.

Gastric Fundal Varices

The available data on the management of bleeding from gastric varices (GV) is much more limited than that of esophageal VH, and only few RCTs are available. The majority include a relatively small sample size and, in most cases, there is no an adequate stratification regarding the type of varices (fundal vs. non-fundal) and the severity of underlying cirrhosis (compensated vs. decompensated). Therefore, quality of evidence and strength of recommendations are relatively low.

Incidence and Classification

GV are described in up to 20% of patients with cirrhosis and portal hypertension, and the incidence of bleeding is about 25% at 2 years [102]. Hemodynamic of GV significantly differs from esophageal varices. Indeed, there is no clear correlation between GV hemorrhage and HVPG, probably due to the concomitant presence of gastro-systemic shunts and the more distal origin of the collaterals. Furthermore, bleeding episodes are frequently more severe with high risk of rebleeding (between 34% and 89%), depending upon the treatment modality and subsequent follow-up protocol [103] and mortality (up to 40–45%) [104, 105].

The most widely used classification is the one initially proposed by Sarin in 1992 [102], and it is still recommended by guidelines because it has a good correlation with risk of bleeding and treatment strategy (Table 4.2).

Table 4.2 Classification of gastric varices

Type	Definition	Relative frequency	Overall bleeding risk without treatment
GOV1	Esophageal varices extending below cardia into lesser curvature	70%	28%
GOV2	Esophageal varices extending below cardia into fundus	21%	55%
IGV1	Isolated varices in the fundus	7%	78%
IGV2	Isolated varices else in the stomach	2%	9%

GOV gastroesophageal varices, *IGV* isolated gastric varices, *GI* gastrointestinal, *ABC* airway, breathing, circulation, *PRBC* packed red blood cell, *IV* intravenous, *PPI* proton pump inhibitors, *VH* variceal hemorrhage, *NSBB* nonselective beta-blockers, *TIPS* transjugular intrahepatic porto-systemic shunt, *EVL* endoscopic variceal ligation

Type 1 gastroesophageal varices (GOV1), which represent 75% of GV, are esophageal varices extending below the cardia into the lesser curvature. Because the outcomes of bleeding are the same as for bleeding esophageal varices, they are managed according to guidelines for esophageal varices [13, 41].

GOV type 2 (GOV2) are esophageal varices extending into the fundus (21% of GV). Isolated GV type 1 (IGV1) are located in the fundus (IGV1, 7% of GV). GOV2 and IGV1 are commonly referred to as "cardiofundal varices". Because bleeding from these varices is more severe and difficult to control, they require specific therapy other than that recommended for esophageal VH [13, 41].

Cardiofundal varices are more frequent in patients with PVT and/or splenic vein thrombosis, and the finding of these varices should prompt imaging to exclude the presence of such thromboses [30, 41].

Several risk factors for GV bleeding have been identified including location and size, presence of red color sign over varices, severity of underlying cirrhosis, concomitant presence of HCC, concomitant presence of portal hypertensive gastropathy, and high MELD score (i.e., >17) [106–109].

Management of Acute Bleeding from Gastric Fundal Varices

The initial management of GV hemorrhage is the same as described above and includes volume resuscitation, vasoactive drugs, and antibiotics before endoscopy.

Endoscopic Therapy

Injection therapy with cyanoacrylate ("glue") is recommended over EVL as the endoscopic hemostatic treatment when GOV2 or IGV varices are considered the source of hemorrhage [13, 30]. In a recent Cochrane review of the literature and meta-analysis [110], three RCTs showed that glue injection and EVL were equally effective for initial hemostasis, but cyanoacrylate was superior in preventing rebleeding. However, estimates regarding all-cause and bleeding-related mortality, failure of intervention, adverse events, and control of bleeding were uncertain due to the very low quality of the evidence. Furthermore, the meta-analysis was at high risk of bias (few trials with very few patients included in each one, internal heterogeneity across trials, publication bias) and significantly influenced by the larger study including only GOV1 varices.

Size of GV is important, and EVL should be limited to those smaller fundal varices (rare) in which both the mucosal and contralateral wall of the vessel can be suctioned into the ligator; otherwise, major hemorrhage may occur in several days, when the band falls off from the incompletely banded varix [41].

Cyanoacrylate glue injection is not approved for treatment of GV in the United States and should be performed only in centers where expertise is available [41].

Transjugular Intrahepatic Portosystemic Shunt

TIPS has shown to be very effective in the treatment of bleeding GV and is currently recommended by AASLD guidelines as the treatment of choice for the control of bleeding from cardiofundal varices (GOV2 or IGV1) [41].

In a study by Chau et al. [111], 84 patients with uncontrolled esophageal VH and 28 patients with uncontrolled fundal VH underwent TIPS, with more than 90% success rate for initial hemostasis in both groups. During a median follow-up period of 7 months, 20 patients in the EV group (24%) and 8 patients in the GV group (29%) developed rebleeding, with similar mortality rates.

To date, TIPS has not been compared to endoscopic cyanoacrylate injection or to EVL for the initial control of bleeding in a randomized setting. In a retrospective study comparing the outcome of 61 patients with GV (type of GV not defined) treated by cyanoacrylate injection with 44 patients who underwent TIPS as first-line treatments for bleeding GV, there were no significant differences in 72-h, 3-month, and 1-year rebleeding rates, as well as in overall survival [112]. However, patients who underwent TIPS had a higher risk of rehospitalization (41%) compared to cyanoacrylate (1.6%) (p <0.0001). In another retrospective study [113], 140 patients in the TIPS arm and 29 patients in the cyanoacrylate were enrolled, respectively. All GV treated with cyanoacrylate were GOV2. On the contrary, no description of GV treated with TIPS was reported. Furthermore, 29 of the 140 patients who underwent TIPS also received various endoscopic treatments (7 patients received sclerotherapy, 4 received epinephrine, 2 received glue, 8 received banding, 4 received clips). No differences were found regarding rebleeding within 30 days (17.4% vs. 17.2%), median length of stay in the hospital (4.5 days vs. 6.0 days), or inhospital mortality (9.0% vs. 11.1%).

The choice of first-line treatment (glue vs. TIPS) should take into consideration different factors: availability of TIPS and/or cyanoacrylate, local expertise, individual patient's presentation and comorbidities and severity of liver disease [114], and cost. However, in the case of fundal varices, which have a higher risk of early rebleeding, the option of TIPS should be considered earlier than for other types of varices, provided that patient is an appropriate candidate for such a procedure [30, 41].

Prevention of Rebleeding in Patients Who Have Recovered from an Episode of Acute Variceal Bleeding

Patients who had a TIPS performed during the acute episode do not require specific therapy for secondary prophylaxis of VH (nonselective beta-blockers [NSBB] *plus* EVL), but should be considered for transplant evaluation if patient has complications other than VH [41]. Thus, the following paragraph refers to patients who did not have TIPS placed during hospitalization for acute VH.

The management of patients who recovered from an episode of esophageal VH depends on two distinct scenarios. The first includes patients with esophageal hemorrhage as the only decompensating event, at relatively low risk of death. The goal of therapy in this condition is to prevent the development of other complications (e.g., ascites), including rebleeding. The second includes patients with multiple decompensating events, at high risk of death. The goal of therapy in this condition is to improve survival. However, previous RCTs were not designed according to these outcome measures and therefore strong data are lacking. Thus, the present paragraph is mainly focused on the prevention of recurrent VH (so-called secondary prophylaxis).

NSBB Plus EVL

Following the first episode of VH, 60–70% of the patients will experience rebleeding within 1 year, and 20–30% of them will die. Thus, patients should receive therapy to prevent recurrence before they are discharged from the hospital [89].

In the last 50 years, different treatments have evolved to reduce such risk, including portocaval surgical shunts, endoscopic injection sclerotherapy, EVL, nonselective beta-blockers (NSBB), and nitrates.

Combined therapy with NSBBs (propranolol or nadolol) plus EVL is the first-line therapy in prevention of rebleeding [30, 41], and NSBBs are the cornerstone of combined therapy. Puente et al. [115] first showed that the addition of NSBBs (± nitrates) to EVL was associated with a significant reduction of GI bleeding risk (RR = 0.44, 95%CI = 0.28–0.69) and with a trend toward lower mortality (RR = 0.58, 95%CI = 0.33–1.03). On the contrary, the addition of EVL to NSBBs (± nitrates) had no significant effect on GI bleeding (RR = 0.76, 95%CI = 0.58–1.00). Moreover, there was a nonsignificant tendency for increased survival with drugs alone (RR = 1.24, 95%CI = 0.90–1.70).

These findings were confirmed in a meta-analysis by Albillos et al. [116] that included individual data from three trials comparing EVL plus NSBBs vs. NSBBs (389 patients) and from four trials comparing EVL plus NSBBs vs. EVL (416 patients). Compared with NSBBs alone, EVL + NSBBs reduced overall rebleeding in Child A (incidence rate ratio 0.40; 95%CI, 0.18–0.89; $p = 0.025$) but not in Child B/C, without differences in mortality. Conversely, compared with EVL, EVL + NSBBs reduced rebleeding in both Child A and B/C, with a significant reduction in mortality in Child B/C (incidence rate ratio 0.46; 95%CI, 0.25–0.85; $p = 0.013$).

Thus, in patients who do not tolerate NSBBs, TIPS should be considered, particularly if there is another indication (e.g., ascites) [41, 117].

The addition of isosorbide mononitrate (ISMN) has a greater effect in reducing portal pressure than NSBBs alone. However, in a recent meta-analysis no difference regarding rebleeding and mortality between the combination of NSBBs and ISMN vs. NSBBs alone was found. Furthermore, patients on dual therapy experienced high rate of side effects (headache and lightheadedness) [118].

NSBBs act on portal hypertension by reducing portal flow (splanchnic vasoconstriction) and by reducing cardiac output. Among NSBBs, carvedilol has been associ-

ated with a greater reduction in portal pressure through its action on α-1 receptors that reduces intrahepatic resistance [119]. In the last years, concerns have been raised regarding the safety of NSBBs in patients with advanced liver disease, particularly in those with refractory ascites and/or spontaneous bacterial peritonitis [120]. In patients with refractory ascites, NSBBs were hypothesized to have a detrimental effect leading to a further decrease in cardiac output and may thereby trigger renal hypoperfusion, acute kidney injury, and death [120–122]. The so-called window hypothesis [123] was then challenged by other reports suggesting increased survival with NSBBs even in decompensated patients [124–127]. Non-hemodynamic effects of NSBBs, like reduction of intestinal permeability, inflammation, and bacterial translocation, might be the reason for this beneficial effect [128–130], even in very advanced patients. But more importantly, in a recent meta-analysis, patients with decompensated cirrhosis (ascites) who had bled from varices and who responded to NSBBs (defined as a decrease in hepatic venous pressure gradient to <12 mmHg or decrease >20% from baseline) had a significantly lower risk of death/transplant (29/102) than patients who did not show this response (80/178) (HR, 0.36; 95%CI 0.20–0.63), indicating that the beneficial effect of NSBB lies in the reduction of portal pressure [122].

Some considerations based on the current literature can be proposed. Studies that have shown a deleterious effect of NSBB have used higher doses associated with a decrease in mean arterial pressure [131]. In fact, in a propensity-matched study by Bang et al. [124] that included 644 patients with cirrhosis and refractory ascites, propranolol was associated with a longer survival for those on NSBB (compared to those not on NSBB), except for the subgroup of patients that received 160 mg/day or higher in whom a reduced survival was noted. Therefore, current guidelines recommend that, in patients with ascites, propranolol should be capped to 160 mg/day and nadolol be capped to 80 mg/day [41]. Furthermore, the dose of NSBB should be reduced or discontinued in patients with refractory ascites and severe circulatory dysfunction (systolic blood pressure <90 mm Hg, serum sodium <130 meq/L, or acute kidney injury) [41]. Carvedilol should not be used in patients with decompensated cirrhosis given its vasodilating effect [13, 41].

Transjugular Intrahepatic Portosystemic Shunt

Regarding prevention of recurrent hemorrhage using TIPS, three RCTs comparing uncovered TIPS to first-line therapy (NSBBs + EVL) agreed that TIPS is very effective in preventing rebleeding, but it carries a high risk of encephalopathy [132–134]. Furthermore, no survival benefit was described in TIPS groups. Recently, these data were confirmed in two RCTs in which covered TIPS was used [135, 136]. Based on that, TIPS is considered the recommended rescue treatment in patients who experience recurrent hemorrhage despite combination therapy NSBBs + EVL [30, 41].

The lowest rebleeding rates are observed in patients on secondary prophylaxis who are HVPG responders (defined as a reduction in HVPG below 12 mm Hg or >20% from baseline) [11]. A recent RCT of covered TIPS versus HVPG-guided therapy (propranolol and isosorbide mononitrate) showed lower rebleeding rates in

patients randomized to TIPS (7% versus 26%) without differences in survival and with a higher incidence of encephalopathy in the TIPS group [137]. Accordingly, HVPG-guided therapy performed in centers where HVPG measurements are readily available would be a reasonable strategy [41]. However, this approach has relevant drawbacks such as invasiveness and limited availability and, therefore, cannot be widely recommended.

A recent multicenter, placebo-controlled RCT showed that the addition of simvastatin (40 mg per oral every day) was not associated with a reduction in rebleeding ($p = 0.58$), but was associated with a significant improvement in survival in Child A and B patients (HR, 0.39; 95%CI, 0.15–0.98; $p = 0.03$), mainly related to a decrease in deaths from bleeding or infections [138]. However, there was a higher-than-expected incidence of rhabdomyolysis, limited to patients with severe liver dysfunction (bilirubin >5 mg/dL). Results of confirmatory studies are required before this additionally therapy can be recommended.

In a recent small randomized trial [139], patients with cirrhosis (Child A and B) and PVT (occluding >50% of portal lumen) who experienced VH in the previous 6 weeks were randomly assigned to TIPS ($n = 24$) or EVL plus propranolol ($n = 25$). After a median follow-up of 30 months, TIPS was more effective than EVL + propranolol for the prevention of rebleeding (15% vs. 45% at 1 year and 25% vs. 50% at 2 years, respectively; HR = 0.28; 95%CI 0.10 to 0.76; $p = 0.008$), although survival rate was similar between the two groups (67% vs. 84%; $p = 0.152$). Furthermore, TIPS group patients had higher probability of PVT resolution (95% vs. 70%; $p = 0.03$) and lower rate of re-thrombosis (5% vs. 33%; $p = 0.06$). Current guidelines recommend TIPS only in patients who experience recurrent bleeding despite secondary prophylaxis with EVL and NSBB [13, 30, 41]. However, PVT has been associated with a longer time to variceal eradication, with a higher risk of variceal relapse, and with a higher risk of rebleeding in patients with cirrhosis who underwent EVL [90, 140, 141]. Therefore, once the acute VH has been controlled, the option of TIPS might be considered earlier rather than later in patients with PVT. This might be particularly relevant in patients awaiting liver transplantation, in whom the presence of PVT has been associated with an increased risk of short- and medium-term mortality after the transplant [142].

Prevention of Rebleeding in Patients Who Have Recovered from an Episode of Acute Fundal Variceal Bleeding

Endoscopic Therapy and NSBB

In the RCT by Mishra et al. [143], patients with GOV2 with eradicated esophageal varices or with IGV1 who had bled were randomized to cyanoacrylate injection ($n = 33$) or NSBBs ($n = 34$). During a median follow-up of 26 months, repeated cyanoacrylate injection was superior to NSBBs in preventing rebleeding from

cardiofundal varices (risk of bleeding, 15% vs. 55%; $p = 0.004$), with a significantly lower mortality rate (3% vs. 25%, $p = 0.026$).

In a second RCT [144], the addition of NSBBs to cyanoacrylate was not associated with a significant reduction of rebleeding episodes ($p = 0.336$) neither with an improvement of survival ($p = 0.936$) during a follow-up of 18 months.

Transjugular Intrahepatic Portosystemic Shunt

A RCT comparing TIPS to glue injection showed that TIPS was more effective in preventing rebleeding from gastric varices (4/35 [11%] vs. 14/37 [38%]; $p = 0.014$; HR, 3.6; 95%CI, 1.2–11.1) [145]. However, no benefit in terms of survival was found (cumulative 2- and 3-year survival rates were 70% and 55% in the TIPS group and 83% and 68% in the cyanoacrylate group; $p = 0.17$), and the rate of hepatic encephalopathy was significantly higher in the TIPS group (9 patients vs. 1 patient; $p < 0.01$).

Current guidelines recommend TIPS or balloon-occluded retrograde transvenous obliteration (BRTO) as first-line treatments in the prevention of rebleeding in patients who have recovered from GOV2 or IGV1 hemorrhage. Cyanoacrylate glue injection is an option for cases in which TIPS or BRTO are not technically feasible, but it is not approved for the treatment of GV in the United States and should be performed only in centers where the expertise is available [41].

Balloon-Occluded Retrograde Transvenous Obliteration

Balloon-occluded retrograde transvenous obliteration (BRTO) has been developed in Japan as a therapeutic method for the prevention of rebleeding of GV in patients with large gastro- or splenorenal collateral [146]. After retrograde cannulation of the left renal vein, gastro- and/or splenorenal collateral and fundal varices are obliterated through the injection of sclerosant.

BRTO has pro and cons over TIPS. The main theoretical advantage is that portal blood flow is not diverted, preventing liver ischemia and leading to improved liver perfusion and consequent improvement in liver function. On the other hand, the procedure can be associated with an increase of portal pressure and might lead to development/worsening of ascites and/or esophageal variceal bleeding [147–152].

The 5-year rebleeding rate after BRTO following GV bleeding was reported to be between 0% and 5.5% in retrospective cohorts [147, 153, 154]. However, no RCTs have compared BRTO with other therapies. Until further studies become available, the decision to perform glue injection, TIPS or BRTO should be made on a multidisciplinary basis (hepatologist, interventional radiologist and endoscopist), and should take into consideration pro and cons of each possible procedure as well as patients' preference.

Concluding Remarks

The management of varices and acute variceal hemorrhage must be taken in the context of the severity of portal hypertension and the presence (or absence) of other complications. Over the last decades, the advances in the therapy of portal hypertension have resulted in lower rates of decompensation and death, particularly for therapies associated with a decrease of portal pressure. In the future, risk stratification and improvements in therapies of patients with cirrhosis and acute variceal hemorrhage are expected.

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Chapter 5
Renal Dysfunction in Patients with Cirrhosis

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Introduction

Acute kidney injury (AKI) is a common complication of end-stage cirrhosis. It may occur in up to 50% of hospitalized patients but with important variations according to different populations and different diagnostic criteria [1–3]. Circulatory changes observed in end-stage cirrhosis, namely, hyperkinetic state with renal vasoconstriction leading to decreased kidney blood flow, are central in the development of AKI, whatever the phenotype and the precipitating factors [4–7]. The development of AKI impacts short- and long-term mortality [8] and reduces kidney function following liver transplantation [9–11]. Early identification of the etiology of AKI is crucial since hepatorenal syndrome (HRS) type justifies vasopressors in combination with albumin [9, 12, 13]. Kidney biopsy is a gold

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standard. However, biopsy is rarely performed to clearly determine the cause of AKI, as it is invasive and often contraindicated due to coagulation changes in cirrhosis patients. Therefore, there is a need for noninvasive tools to accurately determine the cause of kidney dysfunction, to better assess the prognosis, to target therapy, and to determine the potential for reversibility after liver transplantation (LT). There is currently no specific blood or urine biomarker that can reliably identify the cause of AKI in cirrhotic patients. In addition to AKI, chronic kidney disease (CKD) is a growing concern in patients with cirrhosis. While hepatitis C virus infection can now be easily cured with direct antiviral agents, the proportion of patients with cirrhosis related to nonalcoholic steatohepatitis (NASH) is steadily increasing. Patients with NASH have more comorbidities such as diabetes or a history of arterial hypertension. Patients with alcoholic cirrhosis also have frequent comorbidities. These patients may have underlying chronic kidney changes that preclude recovery. A clear distinction between acute and chronic kidney changes may be difficult to discern in the critically ill cirrhotic patient. This chapter focuses on new definitions of AKI, pathophysiology, prevention, and management in the context of critically ill cirrhotic patients, taking into account the possible impact of underlying CKD.

Assessment of Kidney Function in Cirrhosis

Assessment of kidney function in patients with cirrhosis remains a challenging issue. Although serum creatinine (sCr) is the most commonly used clinical index of kidney function, it overestimates glomerular filtration rate (GFR) in patients with advanced cirrhosis due to the combination of decreased creatine production by the liver, muscle wasting, and large volume of distribution in the setting of fluid overload [14]. In patients with AKI, sCr can lag by days despite a significant decrease in GFR especially in patients with fluid overload [15, 16]. In addition, in patients with high serum bilirubin, sCr can be inaccurate if colorimetric-based Jaffe assays are used, as bilirubin interferes with the color reaction. Enzymatic assays should be preferred when available. There is no evidence that other serum markers of kidney function such as cystatin C are superior to sCr in patients with cirrhosis even though cystatin C is less influenced by confounding factors such as age and muscle mass [14, 17].

GFR is considered the best estimate of kidney function although there is no universally accepted gold standard for measurement. Several exogenous markers can be used including isotopes. However, even exogenous agents can be confounded by changes in volume of distribution, due to ascites and extracellular volume expansion. Direct measurement of GFR with exogenous agents is not routinely used in clinical practice due to reasons of cost, convenience, and availability. Measuring true GFR is impractical in critically ill patients when measurements have to be repeated at close intervals. GFR can be measured by creatinine clearance with timed urinary collection. However, in addition to inherent limitations related to incom-

plete urine collection, tubular secretion of creatinine increases as GFR declines in cirrhosis which is a source of error [18, 19].

The Modification of Diet in Renal Disease 6 (MDRD-6) equation has been shown to be the most accurate creatinine-based equation in cirrhosis, although a recent study (Glomerular Filtration Rate Assessment in Liver Disease [GRAIL], www.bswh.md/grail) was more precise and had less bias than MDRD-6 in the setting of low (<30 mL/min/1.73 m^2) GFR during pre- and post-LT [19–22]. Before LT, GRAIL correctly classified 75% as having mGFR <30 mL/min/1.73 m^2 versus 52.8% in MDRD-6, P <0.01

Furthermore, an eGFR <30 mL/min/1.73 m^2 by GRAIL predicted development of CKD (26.9% versus 10.5% MDRD-6) in center data and needing kidney transplant after LT (48.3% in both GRAIL and MDRD-6, compared to other formulas in this study, P <0.01) in national data within 5 years after LT. Equations based on cystatin C, with or without sCr (i.e., CKD-EPI creatinine-cystatin C equation), may be superior to creatinine-based equation [23, 24]. However almost all equations tend to overestimate true GFR. In addition, all the equations were based on study populations with CKD and stable sCr. In a recent study in critically ill patients with AKI, estimating equations performed poorly when compared to true GFR [25]. Therefore, unstable conditions, using sCr-based equations to estimate GFR can be inaccurate. Despite the many limitations sCr remains the basis of existing clinical definitions of AKI and is a key component in the Model for End-Stage Liver Disease (MELD) score, which is a robust tool to predict early mortality in cirrhosis.

Definition of AKI

Due to decreased muscle mass, patients with cirrhosis tend to have lower sCr values than the general population for a given value of GFR. In 2010, the Acute Dialysis Quality Initiative (ADQI) recommended not to use the Acute Kidney Injury Network (AKIN) criteria [26] fixed cutoff value of 1.5 mg/dL to define AKI in patients with cirrhosis [27]. Since then, AKIN criteria in predicting mortality have been validated in several studies of hospitalized patients with cirrhosis including ICU patients [1, 8, 28, 29]. The term hepatorenal disorders has also been proposed to encompass the full range of conditions where liver and kidney disease coexist [27]. Recently, the definition of HRS and AKI in patients with cirrhosis has been revisited by the International Club of Ascites (ICA) [30]. Definitions are shown in Table 5.1. AKI in cirrhosis is defined by an increase in sCr ≥0.3 mg/dL within 48 hours or a percentage increase in sCr ≥50% from baseline [30]. Type-1 HRS is one of the phenotypes of AKI in cirrhosis now termed HRS-AKI (Table 5.1) characterized by the absence of response to a challenge of volume expansion with albumin. The ICA suggested that a baseline sCr result within the previous 3 months should be used as the reference. If no baseline exists, then the admission sCr can be used as the reference [30]. Urine output has not been included in the definition of AKI since oliguria is a common feature in advanced cirrhosis. However, recent data showed that urine output is

Table 5.1 Diagnostic criteria for hepatorenal syndrome which is one of the phenotypes of AKI in cirrhosis [30]

Diagnostic criteria of hepatorenal syndrome
Diagnosis of cirrhosis and ascites
Diagnosis of AKI according to the ICA-AKI criteria
No response after two consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg)
Absence of shock
No current or recent use of nephrotoxic agents (NSAIDs, aminoglycosides, iodinated contrast media, etc.)
No signs of structural kidney injury defined by: Absence of proteinuria (>500 mg/d) Absence of microhematuria (>50 RBCs per high-power field) Normal finding on renal ultrasonography

a sensitive and early marker for AKI in ICU patients and is associated with adverse outcomes, including in patients with cirrhosis [31–33]. Ideally, definitions should be based on GFR rather than sCr levels or changes in sCr. However, existing sCr-based equations are too inaccurate to be used in definitions of AKI in cirrhosis.

Pathophysiology of Hepatorenal Syndrome in Cirrhosis

AKI in cirrhosis is driven by several mechanisms which are different in nature and which may coexist (Fig. 5.1). These mechanisms include systemic and splanchnic circulatory changes, intrinsic kidney circulatory changes, and systemic inflammation [4, 6]. Cirrhosis is characterized by portal hypertension with splanchnic vasodilatation and increased splanchnic blood volume. In parallel, there are systemic circulatory changes with hyperkinetic state. Hyperkinetic state includes decreased systemic vascular resistance and increased cardiac output. In early cirrhosis, decreased vascular resistance may result in a mild decrease in mean arterial pressure, which is balanced by increased cardiac output that maintains kidney perfusion. At this stage, GFR is normal. At a more advanced stage, systemic vasodilation is more pronounced and results in a state of central hypovolemia that activates systemic vasoconstrictor systems: renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and arginine vasopressin. Systems leading to water and sodium retention are also activated. Although cardiac output is increased, this stage is characterized by a decrease in kidney blood flow. At the most advanced stages of cirrhosis, intense renal vasoconstriction can no longer be balanced by increased cardiac output. There is a marked decrease in kidney blood flow resulting in oliguria and decreased GFR [34]. The relative decrease in cardiac output may be related, at least in part, to the so-called cirrhotic cardiomyopathy, a syndrome characterized by diastolic dysfunction and blunted myocardial contractility [35].

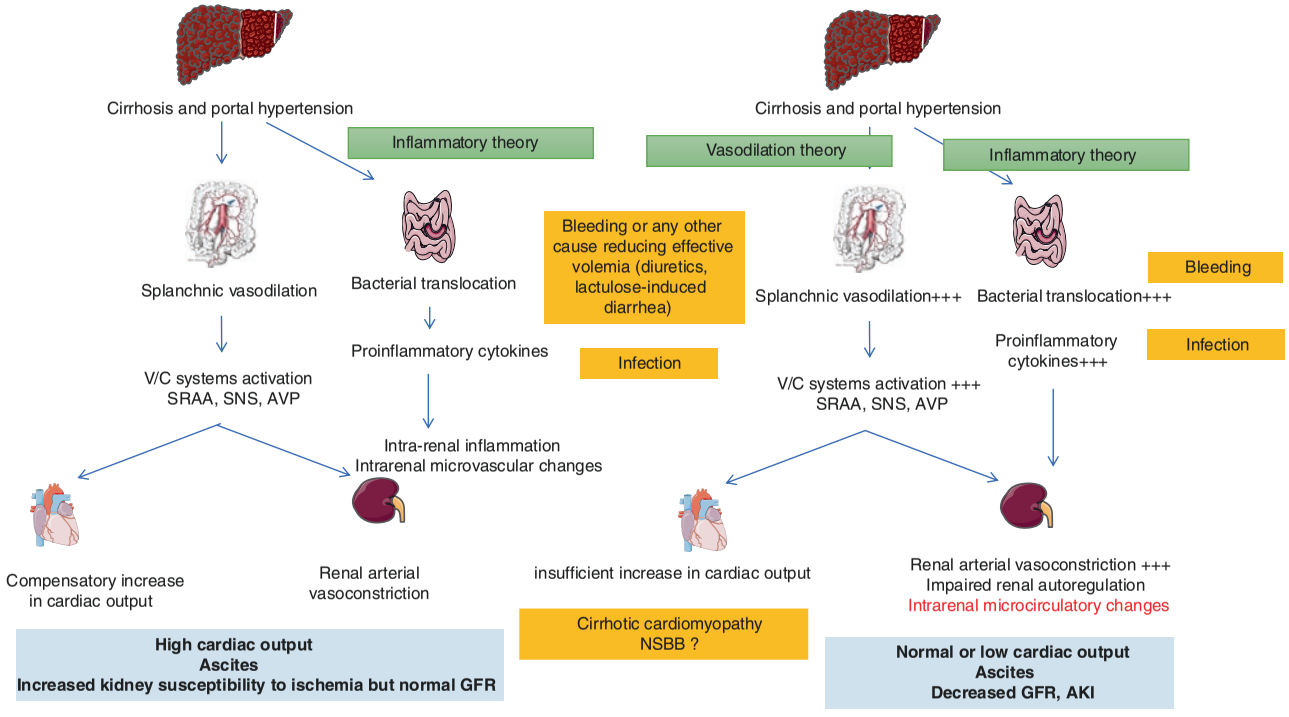

Fig. 5.1 Left panel: In decompensated cirrhosis, both vasodilation secondary to portal hypertension and systemic inflammation induced by gut bacterial translocation tend to induce renal arterial vasoconstriction, due to the activation of vasoconstrictive systems (renin-angiotensin-aldosterone system (RAAS), sympathetic nervous sytem (SNS), and arginine vasopressin (AVP)) in response to decreased effective blood volume and to intrarenal inflammation inducing microvascular changes. These changes result in a hyperdynamic state characterized by increased cardiac output, ascites, and normal glomerular filtration rate but increase susceptibility of the kidney to AKI. Right panel: The onset of HRS-AKI corresponds to the most advanced stages of these changes, with an intense renal vasoconstriction and impaired renal autoregulation leading to a decrease in GFR. Any event further decreasing hypovolemia (bleeding, diuretics overdose, lactulose-induced diarrhea, etc.), decreased cardiac output (cirrhotic cardiomyopathy, Non-selective beta blocker (NSBB)), or systemic inflammation (with or without overt sepsis) can precipitate HRS-AKI

Changes in intrarenal hemodynamics with impaired autoregulation may contribute to decreased GFR [7]. These intrarenal changes are mediated by inflammatory changes. Systemic and splanchnic circulatory changes interact with systemic inflammatory changes, both of these factors contributing to AKI [30]. In non-cirrhotic patients, hemodynamic changes and systemic inflammation are involved the development of sepsis-associated AKI [36]. In severe sepsis, AKI may develop in the absence of decreased renal blood flow due to intrarenal microvascular changes with an imbalance between preglomerular and postglomerular vascular tone [37–39]. In addition, it has been hypothesized that sepsis could lead to intrarenal redistribution of blood flow out of the cortex, thus inducing corticomedullary junction ischemia with subsequent tubular injury [39].

Similar changes can be observed in cirrhosis, even in the absence of overt bacterial infection. Cirrhosis, indeed, is characterized by a state of systemic inflammation. The level of inflammatory response correlates with the severity of liver disease and portal hypertension [30]. Alterations of gut permeability, a characteristic feature of cirrhosis, facilitate translocation of bacteria and bacterial products (pathogen-associated molecular patterns or PAMPs) from the lumen of the digestive tract to lymph nodes and the bloodstream. Translocation induces a wide spectrum of genes encoding molecules involved in inflammatory response via specific receptors called pattern recognition receptors (PPR) [30]. Patients with bacterial translocation have increased levels of circulating pro-inflammatory cytokines (tumor necrosis factor-α [TNF- α] and interleukin-6 [IL-6]) as well as increased levels of vasoactive factors (such as NO) as compared to patients without bacterial translocation [40, 41]. Systemic pro-inflammatory mediators may then trigger extrahepatic organ dysfunction, including the kidney.

A substantial proportion of patients with HRS have bacterial infection and/or systemic inflammatory response syndrome (SIRS) as a precipitating factor [42]. Interestingly, about 30% of patients with HRS have SIRS without documented bacterial infection [42].In an experimental model of cirrhosis, inflammatory insult induced by lipopolysaccharide resulted in increased expression of the PPR toll-like receptor 4 (TLR4) in proximal renal tubules resulting in tubular cell injury [43]. In experimental models, digestive decontamination reduced expression of TLR4 as well as tubular damage [43]. Overexpression of tubular TLR4 has been observed in patients with cirrhosis and renal dysfunction [44]. In some patients with HRS both overexpression of TLR4 in tubular cells and evidence of tubular cell damage can be observed. These findings indicate that HRS does not exclude some degree of structural changes.

Etiology of Renal Dysfunction Other than HRS in Cirrhosis

Besides HRS, other forms of renal dysfunction can occur in patients with cirrhosis, such as prerenal AKI, acute tubular necrosis (ATN), or glomerulonephritis. About two-thirds of cirrhotic patients with persistent AKI have HRS or ATN. Postrenal

AKI is rare, only accounting for 0.2% of cases [45]. Prompt workup of other possible causes of renal dysfunction is crucial. The most common cause of AKI in hospitalized patients with cirrhosis is prerenal AKI, accounting for approximately 68% of the cases [46, 47]. It is caused by hypoperfusion without damage to the glomeruli or tubules and is classified according to volume responsiveness. In patients who are volume responsive, AKI can occur in the setting of volume depletion due to diuretics, gastrointestinal bleeding, infection/sepsis, diarrhea, nausea/vomiting, or large-volume paracentesis without albumin. ATN is the most common cause of intrarenal AKI in patients with advanced cirrhosis which may be precipitated by sepsis or direct injury from nephrotoxins such as nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, IV contrast, or amphotericin [47]. Similar to HRS, patients with ATN carry a grim prognosis, with 40% requiring renal replacement therapy (RRT) and 60% dying by 90 days [48].

Bile cast nephropathy, also known as cholemic nephrosis, can cause ATN in patients with liver failure [49]. It is characterized by epithelial injury in distal nephron segments and intraluminal biliary cast formation. Bilirubin can cause decreased aquaporin-2 expression in collecting ducts. Reduced renal aquaporin-2 reflects decreased collecting duct sensitivity to antidiuretic hormone, which prevents reabsorption of water. This not only leads to loss of renal water handling but also increases interstitial fibrosis [50]. Bile cast nephropathy tends to be underdiagnosed due to the small number of patients undergoing kidney biopsies in this population.

Glomerulonephritis accounts for ~9% of the cases of AKI in liver failure [51]. The glomerulonephritis that is most commonly associated in liver cirrhosis, especially in alcoholic cirrhosis, is secondary IgA nephropathy [52, 53]. The pathophysiology is thought to be due to impaired removal of IgA-containing complexes by the Kupffer cells in the liver [54]. Some patients may have proteinuria, hematuria, and renal insufficiency, while others may have minimal to no urinary abnormalities. Some patients with cirrhosis and IgA nephropathy can have progression of disease in the form of CKD [55]. Infection-associated glomerulonephritis is common in patients with hepatitis B (HBV) and C (HCV). Membranous nephropathy is the most common glomerulonephritis associated with HBV, while membranoproliferative glomerulonephritis (MPGN) is more commonly associated with hepatitis C. The primary pathological feature of HBV-membranous nephropathy is due to inflammatory changes in HBV infection, which also causes slight decrease in complements. These patients present with nephrotic syndrome and renal and hepatic dysfunction [56]. Hepatitis C may be caused by cryoglobulin deposition (cryoglobulinemia) or deposition of HCV-containing immune complexes (MPGN). Clinical disease may be relatively silent with mild proteinuria and hematuria or readily apparent with nephrotic syndrome (more than 3.5 grams of proteinuria over 24 hours) in MPGN. Focal segmental glomerulosclerosis and minimal change disease are also associated with hepatitis C, presenting with nephrotic syndrome, but these patients often present with CKD.

The prevalence of underlying CKD in patients with cirrhosis who develop AKI ("acute-on-chronic kidney disease") is unknown. However, it can be reasonably assumed that patients with advanced cirrhosis frequently have chronic kidney

changes due to comorbidities (e.g., diabetes and hypertension) and/or specific causes of CKD (e.g., IgA nephropathy, viral-induced glomerulopathy) [57]. The combination of acute and chronic kidney changes makes it even more difficult to predict reversibility in the absence of biopsy. Finally, evidence for close interconnections between AKI and CKD emerged recently in the general population [58]. These interconnections are likely to exist in patients with cirrhosis. Patients with underlying CKD are at 10 times higher risk of developing AKI as compared to patients without CKD [59]. In parallel, the risk of developing CKD is higher in patients with severe or repeated episodes of AKI [58]. The rate of CKD after one episode of AKI is as high as 8 per 100 patient-years [60]. Maladaptive repair after tubule cell necrosis is one of the main mechanisms leading to progression from AKI to CKD [61, 62]. Since patients with end-stage cirrhosis are prone to develop repeated episodes of AKI as a consequence of events such as sepsis, hypovolemia, paracentesis-induced circulatory changes, and HRS, it can be suspected that these patients with repeated episodes of AKI eventually develop irreversible chronic kidney changes.

Prevention of AKI

AKI should be prevented at any stage of cirrhosis as it is associated with a worse prognosis [47, 63]. However, special attention should be paid to patients with advanced cirrhosis as they are at higher risk to develop AKI. Prevention of infections and hypovolemia is crucial as they are major sources of AKI. Prevention of spontaneous bacterial peritonitis (SBP) with antibiotics [64–66], IV albumin use in combination with antibiotics in patients with SBP [67] and in patients undergoing large-volume paracentesis (>5 L) [4], early transfusion, and fluid resuscitation along with antibiotic prophylaxis [68–70] have all been shown to decrease the incidence of AKI, specifically HRS. In patients with bacterial infections other than SBP, albumin also prevents or delays AKI even though no clear survival benefit has been documented [71, 72]. It has been shown recently that long-term administration of albumin (40 g weekly IV) in patients with decompensated cirrhosis was associated with a reduced incidence of AKI and significantly improved survival [73].

Drugs that impair intrarenal blood flow (e.g., NSAIDs, renin-angiotensin-aldosterone system blockers) and drugs with direct tubule toxicity (e.g., aminoglycosides, vancomycin, amphotericin B) should be avoided. It has been suggested that cirrhosis may not be a predisposing factor for contrast media-induced nephropathy [74]. Diuretics should be used with caution with measurements of sCr at close intervals. Increase in sCr should lead to discontinue diuretics. N-Acetyl-cysteine may prevent HRS in patients with alcoholic hepatitis [75]. Nonselective beta-blockers are widely used to prevent gastrointestinal bleeding in patients with grade II-IV esophageal varices. However, nonselective beta-blockers were shown to be associated with reduced survival in patients with refractory ascites [76, 77]. In these

patients, beta-blockers may be associated with more pronounced paracentesis-induced circulatory dysfunction and, possibly, AKI. In addition, reduction in cardiac output due to beta-blockers may precipitate AKI and decrease survival in patients with end-stage cirrhosis [34].

Abdominal compartment syndrome defined as increased intra-abdominal pressure to >20 mmHg can be a consequence of tense ascites and may lead to AKI by increasing venous pressure [78]. Improvement in renal function has been shown in these patients following paracentesis in combination with albumin [79, 80].

Biomarkers of AKI

Since usual markers such as urine output, fractional excretion of sodium or urea, and proteinuria are potentially biased in advanced cirrhosis, original biomarkers are needed to identify AKI at an earlier stage and to determine the phenotype. In candidates for LT, for instance, there is a poor correlation between conventional markers and biopsy findings [57, 81]. In recent years, several innovative biomarkers of AKI have been developed and tested in patients with cirrhosis [82]. Research mainly focused on biomarkers of acute tubular injury. Proximal tubule is particularly exposed to ischemia-related events leading to hypoxic injury following reperfusion with an increase in excreted low molecular weight proteins into urine. The most promising biomarkers of tubular injury in AKI are (i) neutrophil gelatinase-associated lipocalin (NGAL), (ii) interleukin 18 (IL-18), and (iii) kidney injury molecule 1 (KIM-1).

NGAL is a protein (25 KDa) produced by several organs including kidney [83]. In experimental models, NGAL kidney expression and urine release is markedly increased following ischemic insults. Urinary concentration increases as early as 2 hours following ischemic insult [83, 84]. Recent studies have shown that NGAL measurement in either urine or serum helps detect AKI at an early stage in numerous clinical situations (sepsis, septic shock, contrast-induced nephropathy, cardiac surgery, polytrauma, and hypothermia) [85–91]. In addition, NGAL may be useful in monitoring delayed kidney graft function [92, 93], kidney allograft rejection [94], and IgA nephropathy [95]. Recently, it has been suggested that NGAL may help differentiate ATN from HRS in patients with cirrhosis [60, 96–98]. On average, urinary NGAL is higher in patients with ATN compared to patients with HRS-AKI, other phenotypes of AKI, or CKD [60, 97]. Urinary NGAL is also significantly higher in patients with persistent AKI as compared to patients with transient AKI [96]. Among patients with type-1 HRS, urinary NGAL was significantly higher in those with concomitant infections. In addition, elevated urinary NGAL is predictive of early mortality in cirrhotic patients with AKI [96, 98]. Initial enthusiasm for NGAL, however, has been tempered by some limitations [99]. Urinary NGAL level increases during AKI but also during other conditions such as chronic and acute inflammation (including sepsis) as well as CKD [100–102]. A cut of value of 220 μg/g creatinine has been proposed to differentiate ATN from other causes of

AKI [103]. However, there is a significant overlap between groups which is more pronounced with plasma NGAL levels [97, 98]. Finally, in studies exploring NGAL, a diagnosis of ATN was based on clinical criteria without a definitive gold standard since biopsy cannot be obtained in the majority of patients with cirrhosis.

IL-18 is a pro-inflammatory cytokine overexpressed in proximal tubule and released in urine following AKI [104, 105]. Studies have shown that urinary IL-18 levels are increased in AKI and/or ischemic kidney changes [106] whereas levels remain low in nephrotoxic AKI and CKD. In ICU patients with AKI, urinary IL-18 may predict a poor outcome [107]. In patients with cirrhosis, significantly higher urinary IL-18 levels have been observed in patients with a clinical diagnosis of ATN as compared to other phenotypes [108]. However, similar to urine NGAL, there was overlap between groups.

KIM-1 is a transmembrane protein which is a marker of proximal tubule injury [109]. Urinary KIM-1 is increased in patients with ATN whereas no increase is observed in those with prerenal azotemia, urinary tract infections, or CKD [110, 111]. Few studies have explored KIM-1 in patients with cirrhosis and AKI [60, 112]. Urinary KIM-1 levels are increased in ATN compared to other causes of AKI. However, substantial overlap in urinary KIM-1, similar to that observed with NGAL and IL-18, has been observed between patients with a diagnosis of ATN as compared to patients with other causes of AKI [60].

Serum osteopontin has been shown to be predictive of early mortality in ICU patients with AKI [113, 114]. Osteopontin is a broadly expressed cytokine that is upregulated during inflammation. Osteopontin expression and mRNA levels are increased in proximal and distal tubular cells [115]. Urinary osteopontin level seems markedly higher in patients with cirrhosis and AKI [104]. Urinary osteopontin level is higher in patients with a clinical diagnosis of ATN as compared to other causes of AKI but with overlap between groups [104]. A recent study suggests that the combination of elevated plasma osteopontin and TIMP-1 levels, age <57, and absence of diabetes pretransplantation are relatively accurate at differentiating patients with reversible AKI from patients with irreversible AKI after liver transplantation [116]. Activation of toll-like receptors (TLR) may play a role in interstitial fibrosis in AKI [117]. Irrespective of the initial trigger of AKI, necrotic tubular cells release potential TLR ligands which could activate other tubular cells or resident immune cells in the kidney [117]. High levels of urinary TLR-4 have been found in patients with cirrhosis and AKI [44].

Overall, several urinary or plasma biomarkers may help (i) to recognize impaired renal function at an earlier stage as compared with sCr, (ii) to identify the mechanisms involved in AKI, and (iii) to improve prognostication. However, none of these markers are specific of any part of the nephron. In addition, overlap between groups still represents a limitation. Sequential assessment and/or combinations of biomarkers should be tested since it could help determine the phenotype of AKI and also predict the outcome.

Treatment

Medical Management

Volume expansion is the first step in patients with cirrhosis and AKI. By definition, HRS-AKI is unresponsive to volume expansion with albumin. In the absence of response after a 48-hour trial of albumin, treatment of HRS-AKI is based on vasopressors [30]. Terlipressin with albumin is the preferred combination with an initial recommended dose of 1 mg/4–6 h intravenously [65, 118–125]. If decrease in sCr is less than 25% compared to the initial value after 3 days, the dose of terlipressin can be increased up to 2 mg/4 h [65]. Terlipressin can be administered as continuous infusion or boluses with similar efficacy. However, the rate of adverse events seems lower with continuous infusion [118]. In the absence of response, terlipressin should be discontinued by day 14 (Table 5.2). Lower rates of response were observed in studies where the dose of terlipressin did not exceed 4 mg/d. However, it must be noted that even in responders, 3-month transplant-free survival may not exceed 50%. Recurrence of HRS-AKI after discontinuation of vasopressors is common [119, 120]. Therefore, terlipressin should be considered a bridge to transplantation rather than a cure for HRS, although terlipressin is currently not readily available worldwide.

Noradrenaline is an alternative vasopressor with similar response rate compared to terlipressin [121, 124]. A combination of midodrine octreotide and albumin is associated with lower response rates compared to terlipressin [126]. Terlipressin and albumin is also the reference for type-2 HRS [127, 128]. However relapse after discontinuation of therapy is common and even in responders, mortality is high.

Renal Replacement Therapy

The ideal timing for initiation of renal replacement therapy (RRT) has not been explored in patients with cirrhosis. Initiation of RRT should be made on clinical grounds, including electrolyte disturbances, oliguria, and increasing volume overload. RRT may be required to prevent fluid accumulation and should be considered when patients cannot maintain an even or negative daily fluid balance. Continuous RRT is generally preferred to intermittent dialysis as it provides greater cardiovascular stability. Recent studies in critically ill patients without liver disease suggest that early RRT initiation may have a beneficial impact on survival [129, 130]. However, no such evidence exists in cirrhosis.

Table 5.2 Controlled trials of terlipressin in the treatment of hepatorenal syndrome

Author	Year	Design	Treatment	Patients	HRS reversal	Mortality without transplantation	Transplantation
Alessandria et al. [119]	2007	Randomized trial	Terlipressin + albumin	12	83%	90%	66%
			Norepinephrine + albumin	10	70%	100%	70%
Sharma et al. [121]	2008	Randomized trial	Terlipressin + albumin	20	50%	45%	–
			Norepinephrine + albumin	20	50%	45%	–
Sanyal et al. [122]	2008	Randomized trial	Terlipressin + albumin	56	34%	87%	–
			Placebo + albumin	56	13%	91%	–
Martin-Llahi et al. [123]	2008	Randomized trial	Terlipressin + albumin	23	43.5%	73%	0
			Albumin	23	8.7%	81%	4%
Singh et al. [124]	2012	Randomized trial	Terlipressin + albumin	23	39%	61%	0
			Norepinephrine + albumin	23	43%	52%	0
Cavallin et al. [126]	2015	Randomized trial	Terlipressin + albumin	27	70%	41%	0
			Midodrine + albumin	22	29%	57%	4%
Boyer et al. [125]	2016	Randomized trial	Terlipressin + albumin	97	24%	42%	–
			Albumin	99	15%	46%	–
Cavallin et al. [118]	2016	Randomized trial	Terlipressin I + albumin[a]	37	76%	47%	–
			Terlipressin B + albumin[b]	34	65%	31%	–
Arora et al. [162]	2018	Randomized trial	Terlipressin + albumin	60	40%	51.7%	–
			Noradrenaline + albumin	60	16.7%	80%	–

[a]Terlipressin I denotes continuous infusion of terlipressin
[b]Terlipressin B denotes bolus infusion of terlipressin

Acute Kidney Injury Post-Liver Transplantation

The incidence of AKI post-liver transplantation (LT) may exceed 50%. Ten to fifteen percent of patients after LT may temporarily require renal replacement therapy [131]. Pretransplant AKI is a predisposing factor for posttransplant CKD and patients with kidney dysfunction pretransplant have a worse outcome especially in patients with ATN prior to LT as compared to patients with HRS [9, 132]. Studies suggest that the cumulative incidence of stage ≥4 CKD 5 years after LT varies from 15% to 25% according to different populations and different methods of GFR assessment [132]. In addition, 50–60% of liver transplant recipients develop stage 2–3 CKD in the long term. Furthermore, GRAIL is a new formula that can predict pre- and post-LT kidney dysfunction, specifically at low GFR levels (as discussed above) [22].

Risk Factors for AKI

Recipients and Donor Factors

Patients with end-stage liver disease and a high MELD score are at higher risk of AKI posttransplantation. The kidney of patient with decompensated cirrhosis is more prone to ischemia in the perioperative period, due to renal vasoconstriction induced by the activation of endogenous vasoactive systems [6, 47]. Chronic kidney disease is a risk factor for developing posttransplant AKI [58]. Donor factors include severe ischemia reperfusion with risk factors being advanced age, steatosis, and prolonged cold and warm ischemia times [133]. Donation after circulatory death was also found to be associated with a higher incidence of posttransplant AKI compared to deceased after brain death donors [133].

Surgical Factors

Any hemodynamic changes resulting in kidney hypoperfusion may result in posttransplant AKI. During the pre-anhepatic phase, several etiologies have been implicated which can lead to hypoperfusion from blood loss including portal hypertension, portal vein thrombosis, and retransplantation. Reperfusion syndrome after unclamping of the portal vein is characterized by decreased systemic vascular resistance, increased pulmonary resistance, and impaired cardiac output leading to ischemia [134]. This ischemia reperfusion leads to a pro-inflammatory state via cytokines such as IL-6 or TNF-α which increases risk of AKI [135].

Postoperative Factors

Postoperative risks include use of calcineurin inhibitors (CNIs) which is the mainstay of immunosuppression regiments after LT. While CNIs have led to improvements in both graft and patient survival, they have been associated with renal

toxicity and renal failure in patients undergoing solid organ transplants. CNIs can cause an acute drop in the GFR due to renovascular effects. In addition to the aforementioned functional toxicity, CNIs can lead to early and chronic histopathological changes in the kidney. In the early phase, changes include patchy, mild, and potentially reversible arteriolar hyalinosis, tubular microcalcification, peritubular and glomerular capillary congestion, toxic tubulopathy, juxtaglomerular hyperplasia, and isometric tubular vacuolization of proximal tubular epithelial cells. These mechanisms are relatively dose dependent and potentially reversible with CNI reduction or withdrawal with a 30% improvement in the GFR. Other postoperative factors related to AKI post-liver transplantation include sepsis, bleeding, and heart failure [136].

Immunosuppressive Sparing Strategies

Meta-analysis showed that CNI minimization can preserve and improve kidney function [137]. Short-term strategies include combining a CNI with early use of a mammalian target of rapamycin (mTOR) inhibitor. Use of sirolimus within the first month of the postoperative phase has had conflicting data regarding preservation of renal function [138–140]. Several studies have demonstrated that sirolimus beyond the first month can have renal protective effects although the rates of acute cellular rejection and adverse events such as new onset diabetes and cardiovascular events have been high [139, 140]. Administration of short-term induction therapy with monoclonal or polyclonal antibodies with delayed introduction of CNIs has also been employed in the immediate post-LT period as a renal protective strategy [141–144]. Introduction of mTOR inhibitors, both sirolimus and everolimus, to replace CNIs beyond the first year of transplant has not been proven to be beneficial in the prevention of AKI [145, 146]. There are some suggestions that reducing CNI doses with continued use of MMF may be beneficial in terms of improving renal function with no increase in rejection rates [147]. However, use of MMF alone with complete withdrawal of CNI is associated with increased rates of ACR and possible graft loss [147]. Furthermore, liver transplant recipients are at an increased risk of developing hypertension and diabetes in addition to nephrotoxicity from CNI. Therefore, the appropriate management of these comorbid conditions plays an essential role in minimizing development of CKD.

Liver Transplant Versus Simultaneous Liver and Kidney Transplant

Kidney dysfunction is a common complication of liver cirrhosis and an important predictor of morbidity and mortality risk both before and after LT. End-stage liver disease patients with kidney dysfunction may not recover kidney function after LT and may require simultaneous liver kidney (SLK) transplant. With the introduction

of the MELD donor allocation system in 2002, there has been approximately a 300% increase in SLK performed in the USA [148]. Furthermore, approximately 5% of transplanted deceased donor kidneys are taken away from kidney transplant alone (KTA) candidates, which has risen the concern in the kidney transplant community, especially due to the uncertain benefit compared with the well-defined benefit of KTA. Many analyses have found outcomes between SLK and liver transplant alone (LTA) in candidates with severe renal dysfunction to be comparable or to favor SLK, although few have found superior outcomes for SLK for those candidates not on dialysis [149–153]. However, the fundamental differences between the recipients of a LTA and SLK such as cause and duration of renal dysfunction and time on dialysis are either not well characterized or absent in the database [154]. Therefore, the implication regarding the benefit or lack of kidney transplantation in these patients is difficult to assess. Even once listed, SLK candidates and recipients present additional challenges. The additional kidney transplant procedure carries extra operative risk. SLK candidates who are sensitized have additional restrictions on access; while the impact of sensitization on kidney outcomes in SLK recipients is known to be less than KTA, it is not negligible, and quantitative donor-specific antibody (DSA) thresholds have not been well established. The novel approach of machine perfusion for recovered kidneys has potential to improve management and outcomes of SLK recipients; it has been recently demonstrated that excellent patient and kidney outcomes can be achieved with delayed kidney transplant up to 81 hours utilizing pumping. This allows for potential stabilization of the recipient following liver transplant and even for returning the kidney back to the donor pool in cases of perioperative mortality or rapid renal recovery.

Throughout the years, many authors have proposed criteria for SLK transplantation based on dialysis duration or GFR cutoff [154–156]. Due to significant regional variation in SLK allocation [157], in 2017, OPTN introduced a new policy. These allocation modifications by the OPTN have the potential to have an impact on practice and SLK volumes nationally. Listing criteria for SLK now exist based on prior and current consensus recommendations and include elements such as duration, need for dialysis, and evidence of CKD (Table 5.3). However, those criteria are moderately liberal in recognition of the weak evidence base and the difficulty of predicting renal recovery after LTA, and therefore the predicted impact on SLK activity is debatable [158]. A unique proposal in this new OPTN policy is the safety net approach. Under this approach, patients who develop renal failure (either hemodialysis dependence or GFR $\leq$20 ml/min) between 60 and 365 days after LT are granted priority for kidney listing. Kidney transplant recipients with a prior liver transplant (KALT) have better outcomes compared to liver transplant recipients remaining on dialysis and SLK recipients [159]. However, overall KALT outcomes are inferior to KTA and they are similar for those KALT recipients transplanted within 3 years of LTA, which provides additional justification for enhanced priority on the kidney wait list [160, 161]. While selection biases clearly exist when comparing KALT recipients to SLK recipients, from the kidney utilization perspective KALT represents a better use of organ compared to SLK

Table 5.3 United States OPTN liver-kidney candidate eligibility for candidates 18 years or older

Diagnosis	Eligibility for simultaneous liver-kidney transplantation
Chronic kidney disease (CKD) with a measured or calculated glomerular filtration rate (GFR) less than or equal to 60 mL/min for greater than 90 consecutive days	At least one of the following: That the candidate has begun regularly administered dialysis as an end-stage renal disease (ESRD) patient in a hospital based, independent nonhospital based, or home setting At the time of registration on the kidney waiting list, that the candidate's most recent measured or calculated creatinine clearance (CrCl) or GFR is less than or equal to 30 mL/min On a date after registration on the kidney waiting list, that the candidate's measured or calculated CrCl or GFR is less than or equal to 30 mL/min
Sustained acute kidney injury	At least one of the following, or a combination of both of the following, for the last 6 weeks: That the candidate has been on dialysis at least once every 7 days That the candidate has a measured or calculated CrCl or GFR less than or equal to 25 mL/min at least once every 7 days. If the candidate's eligibility is not confirmed at least once every 7 days for the last 6 weeks, the candidate is not eligible to receive a liver and a kidney from the same donor
Metabolic disease	A diagnosis of at least one of the following: Hyperoxaluria Atypical hemolytic uremic syndrome (HUS) from mutations in factor H or factor I Familial non-neuropathic systemic amyloidosis Methylmalonic aciduria

and is therefore more acceptable to the kidney transplant community. Eventually these measures are intended to reduce SLK both by restricting access and providing incentive for transplant physicians to select LTA for candidates with borderline indications.

Conclusion

Cirrhosis is a condition that predisposes to several phenotypes of AKI and HRS-AKI is a specific complication of end-stage cirrhosis. AKI is especially common in critically ill cirrhotic patients and it is associated with a worse outcome. Different phenotypes of AKI are associated with different outcomes. However, both ATN and HRS-AKI are both associated with a high short-term mortality. Early diagnosis of AKI is an important step in critically ill cirrhotic patients and mild changes in sCr may have a major decrease in GFR. NGAL helps differentiate ATN from other phenotypes and a cutoff value has been proposed in cirrhosis. However, using this cutoff value exposes to a substantial rate of misclassification. In addition, a cutoff

value for the diagnosis of ATN has been determined based on clinical variables but without a gold standard. Patients with cirrhosis frequently have risk factors for CKD and the role of CKD is probably underestimated. Prediction of reversibility after liver transplantation is an unresolved issue and innovative biomarkers are needed. Even in critically ill cirrhotic patients who are not candidates for transplantation, cirrhosis is not a contraindication for RRT. A trial of RRT can be started for 48–72 hours with limitation in patients with multiple organ failures who do not improve rapidly.

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Chapter 6
Intensive Care Management of Patients with Cirrhosis

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Introduction

Cirrhosis is the final common pathway of any condition which results in chronic liver inflammation. Cirrhosis must be regarded as a spectrum of illness which ranges from mild asymptomatic disease to the most severe forms resulting in multiorgan system failure and death. Patients with cirrhosis may be categorized into those with compensated disease (no visible manifestations of decompensation) and those with decompensated disease (hepatic encephalopathy, variceal bleeding, ascites, etc.). Patients with stable compensated disease or ambulatory patients with decompensated disease may suffer an acute deterioration resulting in a need for intensive care unit (ICU) support, a condition known as acute-on chronic liver failure (ACLF). Patients suffering from ACLF frequently develop multisystem organ dysfunction and have a high risk of short-term mortality. This chapter will focus on the common complications of cirrhosis (not covered elsewhere in this text) which result in or complicate intensive care unit (ICU) admission and approaches to their management in the ICU setting.

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Intensive Care Management of Common Complications of Cirrhosis

Neurological Complications

Neurological dysfunction in cirrhotic patients presenting to the ICU is commonly due to complications of hepatic encephalopathy (HE). The pathophysiology of HE has been reviewed elsewhere in this text. HE remains largely a clinical diagnosis and can be made on the basis of a thorough neurological examination coupled with a review of patient history, and a prior diagnosis of HE is the single most important risk factor for a recurrent episode [1]. Measurement of serum ammonia has a limited role in the diagnosis and management of HE in the cirrhotic patient given the correlation between ammonia levels and the clinical course of HE is highly variable. In cases where the diagnosis of HE is uncertain, measurement of arterial ammonia may be useful as the finding of a normal serum ammonia should prompt a search for an alternative etiology of altered mental status in the critically ill cirrhotic patient [2]. Focal neurological deficits are described in HE [3] but are not common; thus, focal neurological findings should also prompt a search for an alternative diagnosis. Brain imaging for the evaluation of HE should be reserved for patients who fail to respond to standard therapies for HE or in those who present with focal neurological exam findings [4].

For critically ill cirrhotic patients with HE, the first priority in treatment is the assessment of the patient's ability to protect the airway, and in patients with advanced grade HE and/or a Glasgow Coma Score of ≤ 8, orotracheal intubation should be considered. This should be followed by a thorough assessment for the potential precipitants of HE. Classically, infections, gastrointestinal bleeding, diuretic overuse, and electrolyte abnormalities (principally hyponatremia) have been heralded as the most common precipitants of HE [5, 6]. However, a study by Cordoba et al. in patients presenting with HE in the setting of ACLF, found on multivariate analysis, only prior episodes of HE were predictive of HE (OR 3.75; 95% confidence interval (CI) 2.16–6.51; $p < 0.001$), and the presence of neither GI bleeding nor bacterial infection was independently associated with HE [1]. Lastly, failure of patients to adequately manage outpatient HE therapy may result in exacerbation of HE and subsequent hospitalization.

Specific therapies for the treatment of HE include agents such as the nonabsorbable disaccharide lactulose, polyethylene glycol solution, and the antibiotic rifaximin. Though there is an absence of randomized controlled trials comparing lactulose to placebo, lactulose remains the cornerstone of therapy for HE. In the outpatient setting, lactulose is typically titrated to two to three soft stools per day; however, in the intensive care unit, such titration may prove difficult, particularly when fecal management systems are in place. When such systems are in use, the optimal amount of stool output is unknown as patients may be obtunded; however, in our center, we typically recommend not to exceed 500 mL of stool output daily that could be measured by a rectal tube insertion in an appropriate clinical setting. For

patients with persistent alteration in mental status, more aggressive administration of lactulose resulting in higher volume stool output results in neither more rapid nor more complete resolution of HE, but in fact the opposite may occur. Over-aggressive use of lactulose may in fact worsen HE, particularly when patients develop hypernatremia [7]. In the intensive care unit, lactulose may be administered orally, via nasogastric tube, or by retention enema. Typical oral doses are 20–30 g three to four times daily to achieve goals as described above. For retention enema, a dose of 200 g every 4–6 hours is appropriate. A recent retrospective study comparing patients with HE receiving oral ($n = 963$) versus rectal lactulose ($n = 400$) found that patients who received rectal lactulose had longer length of stay (12 vs 8.5 days; $p < 0.001$), higher incidence of hypernatremia (8% vs. 5%; $p = 0.0348$), longer time to clearance of HE (4.7 vs. 3 days; $p = 0.462$), and had higher in-hospital mortality (24% vs 11%; $p < 0.001$), while having a lower MELD score (14.5 vs 23.2; $p = 0.047$) [8]. These findings suggest that alternatives to rectal lactulose administration should be utilized when possible.

Rifaximin is a minimally absorbed antibiotic which has been shown in randomized trials to decrease HE-associated events and hospitalization in the outpatient setting when used in combination with lactulose [9]. In a more recent study, evaluating the impact of rifaximin in patients admitted to the hospital with overt HE demonstrated that compared to lactulose alone, rifaximin plus lactulose resulted in a significant decrease in mortality (the primary endpoint) (23.8 vs 49.1%; $P < 0.05$) accompanied by a decrease in the hospital length of stay (5.8 vs. 8.2 days; $P < 0.001$) [10]. It is our practice to add rifaximin to the treatment of overt HE in our critically ill cirrhotic patients (Box 6.1).

Lactulose is fermentable and thus results in increased intestinal gas. This feature of lactulose is potentially undesirable in critically ill cirrhotic patients as it may exacerbate ileus and is more likely to result in intestinal pseudo-obstruction [11]. Three recent studies have evaluated the use of polyethylene glycol (PEG) solution for the treatment of overt hepatic encephalopathy in hospitalized patients. In the first study by Rahimi et al., 25 patients were randomized to standard therapy with lactulose or to treatment with 4 L of PEG-3350 electrolyte solution. The primary endpoint was the improvement of one point or more in the hepatic encephalopathy scoring algorithm (HESA) score; this was achieved by 52% of patients in the lactulose arm compared to 91% of patients in the PEG arm ($p < 0.01$); in furthermore patients, the PEG arm had a more rapid complete resolution of HE with a median of 1 day compared to 2 days in the standard-of-care arm ($p = 0.01$) [12]. In the second study, 100 patients were randomized to the standard of care with lactulose or to treatment with the PEG solution. The primary endpoint was the number of patients achieving at least one-point improvement in the HESA score at 24 hours; this was met by 72% of patients in the standard-of-care arm compared to 94% of patients in the PEG arm ($p < 0.01$). The time to complete resolution of HE was shorter in the PEG group, 1.46 versus 2.81 days ($p < 0.001$), as was the hospital length of stay, 3.73 vs. 5.43 days ($p < 0.001$) [13]. A smaller study evaluated 40 overt HE patients [14] following the original study by Rahimi et al. [12]. It validated an improvement in one HESA grade at 24 hours, with a 74% response rate in the standard lactulose

Box 6.1 Management of Common ICU Complications of Cirrhosis

	General considerations	Specific situations
Hepatic encephalopathy	Avoid/minimize sedatives and central nervous system acting agents with particular attention to avoidance of benzodiazepines Consider rifaximin 550 mg BID Consider PEG 3350	Patients with ileus or bowel obstruction: Avoid PO lactulose Consider lactulose retention enema (use with caution) Hypernatremia: Decrease or hold lactulose Correct free water deficits
Coagulation abnormalities	Avoid correction of abnormal coagulation tests in the absence of bleeding Do not correct INR for routine procedures (paracentesis, thoracentesis, central line placement)	Active bleeding or planned major surgical procedure: Use viscoelastic testing for guidance of product replacement if available Correct platelet count to >50 K/μL Correct fibrinogen to >1.5 g/L Consider use of massive transfusion protocols for severe bleeding
Cardiovascular abnormalities	Use dynamic measures of volume status Goal MAP of >65 mmHg	Refractory hypotension: Consider adrenal insufficiency Consider use of pulmonary artery catheter to guide resuscitation
Goals of care	Do not use transplant eligibility in isolation to determine futility of care Involve transplant teams early to determine potential transplant eligibility Assessment of response to therapy should occur over 3–7 days before decisions regarding futility are made	

group compared to a 95% response rate in patients receiving PEG ($p = 0.05$). Time to complete resolution of HE was not evaluated; however, the hospital length of stay was shorter in the PEG (7 days) versus lactulose (9 days) group ($p = 0.03$). While these studies were not specific to patients in the ICU, the study findings coupled with the ease of use, patient tolerability, and lack of intestinal fermentation make PEG an attractive agent for the treatment of HE in ICU.

For patients with cirrhosis in the intensive care unit, sedation, if required, should be used with caution. Appropriate selection and dosage of agents is required to prevent excessive undesired effects of sedation. Benzodiazepines should typically be avoided in patients with cirrhosis due to the marked impact these agents have on neurological function, an effect which is not dependent on the rate of drug clearance [15]. In cirrhotic patients, when sedation is required, appropriate levels of sedation

can often be achieved with intermittent doses of opioid agents such as fentanyl (25–100 mcg every 30 minutes to 1 hour) or by the use of short acting agents such as propofol (dose range 5–50 mcg/kg/hour). The non-GABA agent dexmedetomidine may be considered; however, because of the extensive metabolism by the liver, dosage reduction should be considered. In our practice, the dosing strategy is modified to omit the loading infusion and start the initial infusion at 0.5–0.7 mcg/kg/hour titrated to maintain the desired level of sedation. For patients presenting with HE who require mechanical ventilation simply as a tool for airway protection, sedatives should be strictly avoided.

Pulmonary, Cardiovascular, and Hemodynamic Considerations

Pulmonary complications in patients with advanced liver disease may be categorized broadly into two groups: acute complications such as acute lung injury/acute respiratory distress syndrome, infectious, and hepatic hydrothorax, and those complications which are a direct consequence of portal hypertension in cirrhosis, for example, portopulmonary hypertension and hepatopulmonary hypertension.

Patients with decompensated cirrhosis have been excluded from major trials in acute respiratory distress syndrome; therefore, current recommendations for the management of acute respiratory failure in patients with cirrhosis are extrapolated from the general critical care literature. The use of low tidal volume (≤8 mL/kg ideal body weight) has been shown in large randomized trials to decrease mortality [16] and is thus recommended in the cirrhotic patient with acute respiratory failure. Fluid retention such as pleural effusion (hepatic hydrothorax) and abdominal ascites are commonly encountered in patients with decompensated cirrhosis. Because the abdominal compartment is a factor in thoracic compliance, the effect of tense abdominal ascites must be considered in patients with respiratory compromise. For patients with tense abdominal ascites and respiratory complications, treatment with large volume paracentesis + albumin is indicated, as this results in improvements in hemodynamics, respiratory compliance, and renal function [17–19].

Hepatopulmonary syndrome (HPS) is a disorder of impaired arterial oxygenation arising in the setting of portal hypertension and is the most common cause of respiratory insufficiency in advanced liver disease with an estimated prevalence of 12–32% (dependent on diagnostic criteria) [20]. The etiology of HPS is centered in the development of pulmonary vascular dilation which impairs gas exchange. Molecular mediators implicated in the development of HPS include nitric oxide (NO), carbon monoxide, endothelin-1, heme oxygenase-1, tumor necrosis factor-α, and vascular endothelial growth factor-A [21–26]. The diagnosis of HPS requires the demonstration of arterial hypoxia and the presence of intrapulmonary shunting in the setting of portal hypertension. Contrast enhanced echocardiography demonstrating delayed entry of agitated saline microbubbles into the left atrium after 3–6 cardiac cycles remains the gold standard for the identification of intrapulmonary shunts. Alternatively, 99m-Technicium-labeled microaggregated albumin scan may

be utilized. During physical exam, finger clubbing may be seen; however, the severity of HPS is classified based on the severity of hypoxia when the arterial partial pressure of oxygen is measured in patients sitting at rest without supplemental oxygen. Pulmonary vascular dilations are more prominent in the lower lung fields; as a result, patients may experience orthodeoxia (decrease in PaO_2 of more than 4 mmHg moving from supine to upright) or platypnea (subjective worsening of dyspnea when moving from the supine to upright position). The implications of HPS on patients admitted to the intensive care unit are primarily related to contributions to respiratory failure and hypoxemia. For example, a patient with severe HPS who suffers a secondary lung insult such as infection or aspiration event will require more aggressive ventilatory support and may be more difficult to be liberated from mechanical ventilation. In addition, in patients who do not have a pre-existing diagnosis of HPS, but who have persistent or unexplained hypoxia, the diagnosis of HPS should be considered. Long-term oxygen use is required for more advanced forms of the syndrome, and if PaO_2 can be corrected with high-flow oxygen, the only definitive treatment for HPS remains liver transplantation, and liver transplant evaluation should ensue.

Portopulmonary hypertension (POPH) is a pulmonary vascular disorder which may present in patients with portal hypertension (with or without cirrhosis). The prevalence in patients undergoing liver transplant evaluation is approximately 5% [27]. As with HPS, the molecular mediators of vascular tone are implicated in the pathogenesis of the disorder, resulting in both vasoconstriction and vascular remodeling Key mediators include; endothelin-1A, thromboxane A2, interleukin-1, interleukin-6, and angiotensin-1 [28–30]. The hemodynamic criteria required for diagnosis include: the presence of portal hypertension, mean pulmonary artery pressure of >25 mmHg, pulmonary vascular resistance >240 dyne/s/cm^{-5}, and a pulmonary capillary wedge pressure <15 mmHg when measured during right heart catheterization. Treatment options for POPH do exist and include vasodilators, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin. In appropriately selected patients, liver transplantation may serve as a definitive therapy. For patients in the intensive care unit in whom pulmonary hypertension may be a contributor to hemodynamic compromise, use of pulmonary artery catheterization may aid in both the diagnosis of POPH and in the guidance of treatment, particularly as it relates to the management of volume resuscitation.

In advancing stages of cirrhosis, both circulatory and cardiac abnormalities develop, resulting in a fragile hemodynamic balance. The typical hemodynamic profile of advanced liver disease is that of a hyperdynamic circulatory state, which includes high cardiac output and low systemic vascular resistance (SVR) and lower mean arterial pressures (MAP). Nitric oxide is a key mediator in the development of the vasodilated circulatory profile of cirrhotic patients [31]. Patients with decompensated liver disease experience increases in both total blood and plasma volume; however, due to vascular dilation and associated pooling of the splanchnic vasculature, “effective” circulating blood volume falls [31, 32]. In the presence of ineffective circulating volume, compensatory mechanisms are activated; these include activation of the neurohormonal axis with increases in sodium and water retention

and increases in heart rate. These compensatory mechanisms maintain acceptable end-organ perfusion in the stable patient; however, patients who suffer slight perturbations in this system rapidly lose their ability to maintain appropriate organ perfusion and suffer organ dysfunction. In addition to circulatory abnormalities, cirrhosis may also induce functional and structural cardiac abnormalities which further complicate hemodynamic stability. Cirrhotic cardiomyopathy is a condition which develops in 40–50% of patients. Key features of cirrhotic cardiomyopathy include systolic and/or diastolic dysfunction and electrophysiological abnormalities such as QT prolongation occurring in the absence of the known structural cardiac disease. Clinically, patients who develop cirrhotic cardiomyopathy may have a blunted ability to compensate for the circulatory abnormalities exacerbating hemodynamic compromise and thus have poorer survival rates [33]. New techniques utilizing tissue Doppler and speckle-tracking-derived strain coupled with alternative diagnostic criteria have been proposed and may be more sensitive and specific for the identification of cirrhotic cardiomyopathy [34, 35].

For cirrhotic patients admitted to the intensive care unit who present with hypotension and end-organ dysfunction, a systematic approach to the assessment of volume status and hypotension should be utilized to restore adequate organ perfusion. Invasive monitoring techniques including arterial catheters and central venous catheters may be utilized to guide resuscitation; these become increasingly important in the critically ill cirrhotics, as the assessment of effective volume status may be extremely difficult in the presence of ascites and edema. Dynamic measures of volume status and circulatory function including echocardiography, passive leg raise, and assessment of CVP in response to volume challenge are recommended over static measures. Similarly, noninvasive hemodynamic monitors have failed to demonstrate acceptable accuracy in cirrhotic patients undergoing liver transplant [36].

Endpoints of resuscitation in patients with cirrhosis have not been systematically studied. Current recommendations are made by consensus opinion. A goal MAP of 60–65 mmHg is an appropriate target in the patient with impaired end-organ function. Given lactate clearance is impaired in the presence of liver disease [37], use of a fixed lactate value as a resuscitation endpoint may not be appropriate and instead trends may be more instructive. The choice of resuscitation fluid should be guided by the patient's overall clinical status with 0.9% NaCl, balanced salt solutions, or colloid (albumin) being appropriate choices. Albumin (20–25% solution) has proven benefit in the management of spontaneous bacterial peritonitis, in hepatorenal syndrome [38–41], and may be a preferred volume expander in patients with ascites and excess body water or in patients in whom an additional sodium or chloride load is undesirable (e.g., patients with hyperchloremic acidosis). When volume resuscitation does not result in the achievement of a desired MAP, use of vasoactive medications is required. First-line agents include norepinephrine (typical dose range 0.01–0.3 mcg/kg/min) and vasopressin (typical dose 1.8–2.4 units/hour). The presence of adrenal insufficiency has been demonstrated in critically ill cirrhotic patients and should be considered in cases of shock which does not respond to standard resuscitation techniques [42, 43]. When adrenal insufficiency is suspected, hydrocortisone, 200 mg daily in four divided doses, is appropriate [44, 45].

Hemostatic Abnormalities

The critically ill cirrhotic patient frequently present with abnormalities in conventional tests of coagulation and hemostasis (prothrombin time [PT], international normalized ratio [INR], partial thromboplastin time [PTT], platelet count, and fibrinogen). It is of key importance to recognize that abnormalities in these tests do not automatically translate into bleeding or thrombosis risk in patients even when undergoing invasive procedures. Extensive clinical evidence demonstrates patients with advanced liver disease experience a rebalanced yet fragile state of hemostatic equilibrium [46, 47]. Infection, endothelial dysfunction, renal failure, and production of endogenous heparinoids may disrupt this equilibrium [48]. The INR, which is extensively used as a prognostic marker in patients with liver disease, lends itself to misinterpretation in the setting of assessment of bleeding risk. The INR is a derivative of PT and thus is dependent on the levels of procoagulant factors. In the setting of the liver disease, the production of anticoagulant factors is also disturbed and not accounted for in the INR; thus, despite a prolonged INR, patients may in fact be hypercoagulable. Routine correction of the INR with fresh frozen plasma in the absence of bleeding or prior to procedures in patients with cirrhosis has no basis in evidence and is difficult to achieve even with standard doses of FFP (30 mL/kg) [49], and may result in harm [50–53].

Thrombocytopenia is also a common feature of advanced liver disease. Thrombocytopenia is a liver disease caused due to a combination of portal hypertension with splenomegaly (sequestration) and decreased hepatic production of thrombopoietin. Platelet interaction with the vessel wall represents the primary response to a bleeding event, and low platelet count is counterbalanced by the elevated levels of von Willebrand factor and low levels of ADAMTS 13 [54, 55], resulting in preserved platelet adhesion. In vitro assays demonstrate that a platelet count of >50 K/μL results in adequate thrombin formation, thus making this an appropriate clinical target in the presence of active bleeding or before major invasive procedures. Optimal levels of fibrinogen are not known, and previous studies have recommended a fibrinogen level of greater than 1 g/L [56, 57], though more recent guidelines from the trauma literature suggest a higher level (1.5–2 g/L) may be beneficial in bleeding patients [58]. In a study comparing a restrictive hemoglobin (7 g/dL) vs. liberal (9 g/dL) transfusion strategies in patient with upper gastrointestinal bleeding, patients assigned to the restrictive group had a higher probability of survival and fewer adverse events as compared to the liberal transfusion group [59]; thus, a restrictive transfusion strategy based on hemoglobin levels is recommended.

Viscoelastic tests (e.g., thromboelastometry or thromboelastography) are in vitro whole-blood assays which offer a rapid and more comprehensive assessment of hemostasis. When used in liver transplantation and cardiothoracic surgery, viscoelastic testing results in decreased requirements for blood product administration, lower cost, and improved outcomes [60, 61]. In addition, viscoelastic testing offers insight into the contribution of fibrinolysis to the assessment of bleeding complications

which cannot be readily assessed by standard tests available in most laboratories. A recent randomized controlled trial of thromboelastography vs. standard tests (platelet count and INR) guided the management of coagulopathy in cirrhotic patients and demonstrated that a decreased use of blood products without an increase in bleeding events in the thromboelastography group was more favorable [62]. Where available, viscoelastic testing is recommended for the assessment and management of blood product administration in patients with cirrhosis.

Patients with cirrhosis are at risk for the development of deep vein (DVT) and portal venous thrombosis (PVT) in spite of prolonged INR and thrombocytopenia [63, 64]. Patients with cirrhosis and PVT have demonstrated improved outcomes (improved survival and fewer manifestations of decompensation) when treated with low-molecular-weight heparin [65, 66]. In the absence of obvious contraindications such as active bleeding or severe thrombocytopenia, consideration for DVT prophylaxis should be considered.

Prognostic Considerations

In critically ill cirrhotic patients, determining which patients will benefit from the ongoing aggressive ICU support and those in whom such care is futile is a particularly challenging issue. The use of liver transplant eligibility as the sole determinant of futility is inappropriate. However, liver transplant eligibility cannot be eliminated from the equation entirely, for a patient with persistent organ failures and no viable transplant option is not likely to survive (see discussion below). Numerous attempts at determining the best prognostic scoring system have been made. Perhaps the most widely accepted prognostic scoring system is the Model for End-Stage Liver Disease (MELD) score and its more recent iteration, the MELD-Sodium (MELD-Na), which is a robust predictor of short-term (90-day) mortality. MELD-Na is currently used (since January 2016) in the United States to determine the priority for organ allocation.

More recently, in one of the largest prospective trials in ACLF, to date, the European Association for the Study of the Liver-Chronic Liver Failure Consortium (EASL-CLIF) has developed findings which may offer guidance in the prognostication of cirrhotic patients with multisystem organ failure. Key findings in this study of 1349 patients hospitalized with the complications of cirrhosis were that ACLF is a dynamic disorder and the validation of a scoring system which may serve as an important tool for prognosis [67]. ACLF grade is derived from a modification of the sequential organ failure assessment (SOFA) score ranging from ACLF grade 1 to grade 3 (See Table 6.1 and Box 6.2) [68]. When assessed over a time period of 3–7 days, changes in ACLF grade demonstrated important prognostic information; not surprisingly, those who had resolution of organ failures had better outcomes than those who either had no improvement or who developed additional organ failures [67]. Furthermore, the addition of the EASL-CLIF Consortium ACLF score (CLIF-C ACLFs) has proven effective in predicting short-term (28-day) and mid-

Table 6.1 Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA score)

Organ System	0	1	2	3	4
Liver (bilirubin in mg/dL)	<1.2	≥1.2 to <2	≥2 to <6	≥6 to <12	≥12
Kidney (Creatinine mg/dL)	<1.2	≥1.2 to <2	≥2 to <3.5	≥3.5 to < 5	≥ 5
			Or on renal replacement therapy		
Cerebral (HE Grade)	No HE	I	II	III	IV
Coagulation (INR)	<1.1	≥1.1 to <1.25	≥1.25 to <1.5	≥1.5 to <2.5	≥2.5 or platelet count below 20K/μL
Circulation (MAP, mmHg)	≥70	<70	Dopamine ≤5 mcg/kg/min or Dobutamine or Terlipressin	Dopamine > 5 or Epinephrine ≤ 0.01 or Norepinephrine ≤0.1 mcg/kg/min	Dopamine >15 or Epinephrine > 0.01 or Norepinephrine > 0.1 mcg/kg/min
Lungs					
PaO_2/FiO_2	>400	>300 to ≤400	>200 to ≤300	>100 to ≤200	≤100
SpO_2/FiO_2	>512	>357 to ≤357	>214 to ≤ 357	>89 to ≤214	≤89

The shaded areas indicate the diagnostic criteria for declaring an organ failure.

Box 6.2 ACLF Grades

ACLF Grade 1	Patients with single kidney failure OR Patients with single failure of the liver, coagulation, circulatory, or respiratory system with creatinine ranging from 1.5 to 1.9 mg/dL and or mild-to-moderate hepatic encephalopathy OR Patients with single cerebral failure who had a serum creatinine ranging from 1.5 to 1.9 mg/dL
ACLF grade 2	Two organ failures
ACLF grade 3	Three or more organ failures

See Table 6.1 for diagnostic criteria for defining organ failure

term (90-day) mortality, and patients who had ACLF grade 3 and ≥4 organ failures with a CLIF-C ACLFs >64, 3–7 days after diagnosis of ACLF had 100% 28- and 90-day mortality [67]. A multinational study demonstrated the CLIF-C ACLFs had superior discrimination of mortality at 90 days as compared to the Acute Physiology and Chronic Health Evaluation II (APACHE II), and Child-Turcotte-Pugh scores but not the MELD score, a CLIF-C ACLFs of >70 in patients assessed at admission or day 3 was associated with a 90-day mortality of 90%, similar to the previous

study, patients with ACLF grade 3 who demonstrated improvement in ACLF grade between day 1 and 3 had decreased 90-day mortality compared to those who had no improvement (40% vs 79%) [69]. These findings indicate that decisions regarding prognosis should only be made after the assessment of the response to ICU support occurring over 3–7 days. In patients with ACLF grade 3 and high CLIF-C ACLFs scores (>70) in whom organ transplant is not an immediate option, consideration of the withdrawal of support and transitioning to comfort may be more appropriate. An online calculator for CLIF-C ACLFs can be found at www.clifconsortium.com. Given the complexity of care for this patient population, multidisciplinary teams, which include intensivists and transplant specialists (hepatologists and transplant surgeons), and palliative care should be utilized when possible to determine what options are available and to ensure the best possible outcomes.

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Chapter 7
Infections in Critically Ill Cirrhosis Patients

Jawaid Shaw and Jasmohan S. Bajaj

Introduction

Cirrhosis, along with its complications of decompensation like hepatic encephalopathy (HE), ascites, and variceal bleeding, is the end-stage manifestation of chronic liver disease. In the United States, for the year 2010, liver cirrhosis led to nearly 49,500 deaths and was among the top 10 leading causes of death [1]. Among the cirrhosis patients in the United States, around 10% of the nearly 200,000 patients who get admitted to the hospital in a year would need intensive care unit (ICU) level of care [2]. The burden is no different in Europe, wherein nearly 14–26/100,000 of the population, of new cases of cirrhosis, get diagnosed, resulting in 170,000 deaths per year [3]. Bacterial infections are common in cirrhosis patients and much more common in those with decompensated liver cirrhosis [4, 5]. An increase in the short-term mortality, with bacterial infections as high as four times, has been reported in decompensated cirrhotics [6]. Some of these decompensated cirrhosis patients are prone to get severely sick during their clinical course, requiring management in the ICU setting, with severe sepsis being the most common cause of such admissions [7]. The mortality rate of such ICU-managed patients is very high, ranging from 40% to 60% [8]. However, what is more worrisome is that almost no improvement in the mortality rates has been noted over the last decade or so, despite optimal management [9]. The development of resistance to various antibiotics used in the

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treatment of these patients has added another layer of complexity to their care [10]. All of these perhaps reflect the overall seriousness of the situation we are faced with, and much is at stake.

Changing Epidemiology and Emergence of Multidrug Resistance Organisms (MDROs) in Cirrhosis Patients

First of all, patients with cirrhosis are perfectly poised not only to develop infections, but they are at enhanced risk in developing drug resistance also because of the following reasons. These patients exhibit altered immune responses, get frequently admitted to the hospital for various illnesses and invasive procedures (e.g., paracentesis), are exposed to antibiotics either as prophylaxis (primary vs. secondary) and/or for treatment purposes, are at a higher risk of being colonized with methicillin-resistant *Staphylococcus aureus* (MRSA), and owing to the translocation of bacteria from the gut are predisposed to bacteremia and spontaneous bacterial peritonitis (SBP) [11, 12].

Figure 7.1 shows the possible reasons for the development of infections including MDRO infections in cirrhosis patients.

The definitions of multidrug-resistant (MDR), extensive drug-resistant (XDR), and pan-resistant (PDR) organisms are as per the acquired nonsusceptibility to the

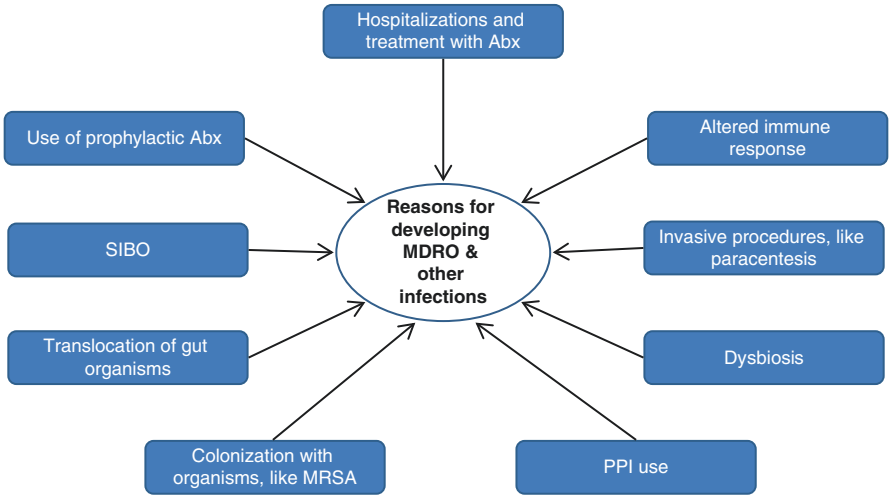

Fig. 7.1 Possible reasons for the development of infections including MDRO infections in cirrhosis patients. *Abbreviations*: Abx antibiotics, SIBO small intestinal bacterial overgrowth, MRSA methicillin-resistant *Staphylococcus aureus*, MDRO multidrug-resistant organisms, PPI proton pump inhibitors

number of some or all antimicrobial groups, respectively [13]. For cirrhosis patients, the most important multidrug-resistant organisms (MDROs) which show geographical variations in resistance patterns are MRSA, Vancomycin-resistant enterococci (VRE), *E. faecium*, extended-spectrum β-lactamase (ESBL)- producing enterobacteriaceae, and carbapenemase-producing enterobacteriaceae (*E. coli*, *K. pneumonia*) [10]. In North America, the prevalence of MDROs ranges between 16% and 37% [10]. VRE is the leading cause of infections in the US liver centers [14]. The earlier data from Europe are no different and have shown a disturbing increase in the rates of MDROs in XDR/PDR organisms over a period of a decade or so, ranging from <10% to 36% [15, 16].

The results from the International Club of Ascites Global Study, which is a prospective multicenter/cross-continental study on the hospitalized cirrhotic patients at 46 centers ($n = 1302$), showed that the overall prevalence of MDR bacterial infections is around 34%, varying by geography [17]. The independent risk factors for the development of MDR infections include prior antibiotic use in the last 3 months and healthcare system exposure(s), anatomical location of infections, and infections in Asian countries like India. MDR infections were associated with poorer outcomes along with higher in-hospital mortality stemming from organ failures and shock [17]. In the same vein, the results of the study from the European Foundation for the Study of Chronic Liver Failure (EF-CLIF) group using the prospective data from two geographically diverse areas, the Canonic series ($n = 1146$) and the other series ($n = 883$), on the hospitalized decompensated liver cirrhosis patients have emerged [18]. Further, the prevalence of MDROs was found to be 29.2% in the larger (Canonic) series and 23% in the other series, with the overall prevalence of infections being around 40% in the earlier series; the factors found to independently predict MDR infections included hospital-acquired infections (OR, 2.74), ICU admission (OR, 2.09), and being hospitalized recently (OR, 1.93) [18]. Overall, in the European liver centers, the prevalence of the MDR infections is as high as 70%–80%, which really paints a gloomy picture of marching of these infections in this fragile population [18]. The top three MDR bacteria responsible for infections in the Canonic series were ESBL, VSE, and MRSA organisms, respectively [18]. Overall, the fecal carriage of ESBL organisms seems to be on the rise all over the globe, and this trend seems to be true for the cirrhosis patients as well [10]. One of the problems is that, while MRSA and VRE organisms are mainly confined to hospitals, ESBL organisms do not respect these boundaries and spread both in the community and in the hospital settings secondary to their intestinal residence, and it is hence hard to control its dissipation [10]. While on one hand, the newer bacteriological profile of infections in cirrhosis is emerging with the increases in gram-positive and MDROs, on the other hand, the culture-negative and fungal infections are on the rise as well due to the incessant usage of antibiotics for cirrhotic patients [14, 19, 20]. Furthermore, the spectrum and causative organisms are evolving, with many being culture- negative [21].

Nosocomial (Hospital-Acquired) Infections Lead to Worse Outcomes in Cirrhosis Patients and Are Potential Targets for Prevention

Of late, multiple studies enriching our knowledge on the various aspects of infections in hospitalized infected cirrhosis patients and their subsequent outcomes post discharge have emerged from the North American Consortium for the Study of End-stage Liver Disease (NACSELD) database. NACSELD is a multicenter prospective database of liver cirrhosis patients (n = ≈3000) admitted with infections, from 16 tertiary care liver centers who were enrolled during nonelective in-patient hospitalization and followed for 1 year. The nosocomial infections in the liver cirrhosis patients serve as a second hit vis-a-vis mortality and independently predict early death in these patients. This knowledge comes from Bajaj et al., who looked at the factors influencing infection-related mortality in cirrhosis patients using a subset of NACSELD cohort (n = 207) and found that the first infections were mainly healthcare-associated (HCA) in 71%, and the second infections, while hospitalized (nosocomial), were seen in 24% patients and could potentially be preventable [20]. The main causes of these second infections include: respiratory, UTIs including foley-induced, fungal infections, and *Clostridium difficile*-induced diarrhea (CDAD) in 28%, 26%, 14%, and 12% of patients, respectively, and the body sites affected by

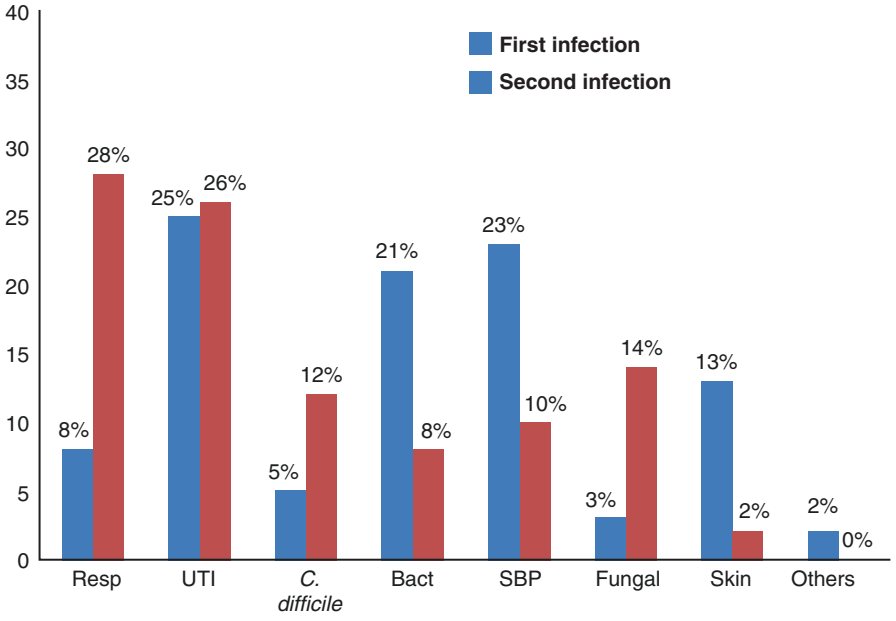

Fig. 7.2 First and second infections and difference in the two by body sites [20]. (Used with permission)

the first and second infections are different as well (Fig. 7.2); the 30-day mortality rate was 23.6%, and among these 49 deaths, the second infections were significantly responsible (49% versus 16%, $P < 0.0001$) for these deaths with the model for mortality among other variables being significant as well (OR, 4.42), and the researchers concluded that the second infections in the cirrhosis inpatients, irrespective of the underlying severity, are independent predictors of mortality, and these infections may possibly be preventable [20]. Furthermore, these nosocomial infections are responsible for higher readmissions, and hence if we are able to prevent these infections, it will go a long way in improving the outcomes. These details came from Bajaj et al., using the NACSELD data, who evaluated readmissions at 3 months in the hospitalized cirrhotics ($n = 1177$) with 1013, having 3-month outcomes [22]. There were 53% ($n = 535$) readmissions during this period, with the leading causes being liver-related ($n = 333$), and these patients had index-stay nosocomial infections as a predictor for HE, renal/metabolic, and infections (OR, 1.9–3.0). The researchers concluded that the readmission rate at 3 months was high and was associated with nosocomial infections among other factors, that this was a potential target for preventive measures to diminish this undesirable event [22]. Bajaj et al. described the risk factors and outcomes for *Clostridium difficile*-associated disease (CDAD) using the Nationwide Inpatient Sample (NIS) from 2005 on cirrhosis patients (1165 with vs. 82,065 without CDAD) along with the data from the transplant center-hospitalized patients (54 with vs. 108 without CDAD) and found that patients who develop CDAD carry significantly higher mortality, have increased length of stay, and hence incur higher healthcare costs as compared to those without CDAD according to the NIS data. From the inpatient transplant center data set, antibiotic and proton pump inhibitors (PPIs) usage were the risk factors for CDAD development [23]. Hence, unnecessary exposure to antibiotics and PPIs, which in themselves have become an epidemic of sorts, is the key to prevent CDAD, which can otherwise spell disaster in these patients.

The Role of Dysbiosis and Alcohol in Propagating Infections

The human microbiome is very diverse, consisting of as high as 100 trillion organisms including bacteria, viruses, and fungi with even a suggestion to consider it as a new "human organ" [24]. Although the human microbiome consists of thousands of different species, the majority (nearly 99.9%) belong to few but more diverse species only, the so-called rare biosphere. These later species have greater importance in both health and disease processes [25]. The microbiome is responsible to maintain health and hemostasis at the local (intestines) and at the systemic levels, and the maintenance of this balance is important for optimal health [26]. The resident phyla that are important in the cirrhosis patients include the Firmicutes, Bacteroidetes, and Proteobacteria. Out of these, the most prominent phylum is the Firmicutes which is essential for the maintenance of homeostasis in cirrhosis by the synthesis of short-chain fatty acids which have nutritional and barrier-stabilizing properties

for the colonic epithelial cells along with their assistance in the bile acid metabolism [27–29]. The nonresident phyla include *Escherichia coli* and *Klebsiella*, which are responsible for infections [11]. To put it simply, in cirrhosis, there occurs an imbalance between the resident (good) and the nonresident (bad) phyla, hence leading to resultant changes in the microbiome with an increase in the pathogenic species called as "dysbiosis." Small intestinal bacterial overgrowth (SIBO) set up by diminished bile acid synthesis, which exerts a direct toxic effect on bacteria and influences antibacterial properties at the mucosal level in cirrhosis, has been proposed to contribute to dysbiosis and an increase in the intestinal permeability leading to disease processes [30–32]. Both in humans and animal models, it has been demonstrated that alcohol alters the intestinal microbiota qualitatively, quantitatively, and diversity-wise [33]. Bajaj et al., have shown that there is an imbalance between the resident-beneficial and the potentially harmful genera with the preponderance of the latter in patients with cirrhosis, especially HE, and this is associated with inflammation leading to these cognitive issues in HE [34].

There is evidence in existence that using alcohol alters the bacterial intestinal microbiota in an adverse manner. Excessive alcohol ingestion leads to impairment of intestinal mucosal barrier, the so-called "Leaky Gut", secondary to portal vein delivery of pathogen-derived molecular patterns (PAMPs). This, combined with the direct toxicity of alcohol and its metabolites, makes the hepatocytes prone to inflammation and injury through the release of damage- associated molecules (DAMPs). The end result is the activation of the Kuppfer cell and innate immunities in the liver cells in alcohol-induced liver disease [33]. New evidence now points toward alcohol-induced changes in fungal microbiome, "fungal dysbiosis", leading to inflammatory damage in the liver cells by decreased diversity and increase in the fungal genera in part mediated by increased fungal β-glucan translocation [25, 35].

Fungal Infections in Cirrhosis Patients and the Role of Mycobiome

Probably some of the same factors, which predispose the cirrhosis patients to increased bacterial infections, make them susceptible to fungal infections as well. These include exposure to steroids, malnutrition, having invasive lines, and undergoing invasive procedures in the background of being immunosuppressed among others [36, 37]. In certain situations, candida infections need to be treated with systemic antifungal therapies like in those with positive blood cultures for fungal species and empirically in those septic cirrhotic patients who do not show any clinical improvement after 48 hours of being on antibacterial medications. This may be more relevant for the sick ICU patients with multiple risk factors for fungal infections [38, 39]. Appropriate de-escalation is in order after final identification, and sensitivities of fugal species become available. However, cirrhotic patients with colonization with fungal species without any clinical evidence of infection should just be watched carefully. Similarly, candiduria in a cirrhotic patient with a foley

catheter without clinical evidence of infection initially might resolve infection with foley removal/exchange. The finding of candida in the bronchoalveolar lavage (BAL) may as well reflect colonization in the appropriate setting [40]. Upfront involvement of the infectious disease consultants whenever possible may be helpful for proper guidance and management of these complex ill patients. Of late, attention has been drawn toward fungal organisms in the stools (rare biosphere), the most common genera being *Saccharomyces*, *Candida*, and *Cladosporium* in the stools of healthy individuals, called as fungal microbiome or "mycobiome", and this tempers the larger bacterial microbiome and may play some role in inflammation and metabolic disturbance in the host [25, 41]. The nature of the exact relationship between bacterial and fungal microbiota and their effects on the intestines in itself is not clear at this time and is an area of active research [42]. The recent results from the NASCELD data set (n = 2743; 918 pts. with bacterial infections vs. 134 pts. with fungal infections) found that all the fungal infections (12.7%) developed while the patients were hospitalized. Using multivariable analysis, the risk factors for the development of these fungal infections included ICU stay (OR, 3.17), presence of bacterial infections at admission (OR, 2.15), having diabetes mellitus (OR, 1.79), and acute kidney failure (OR, 1.74) [43]. The top three fungal infections were urinary (n = 57), blood/fungemia (n = 16), skin/soft tissue-related (n = 16), with a majority of these caused by the *Candida albicans* species [43]. The 30-day survival was adversely affected for fungus-infected patients versus bacteria-infected ones (66% vs. 86%) [43]. An earlier study by Bajaj et al., conducted on outpatients/inpatients (n = 143) with 26 patients in the control arm revealed that the fungal diversity, was adversely affected if subjects were exposed to antibiotics either as outpatients or in the hospitalized setting with more abundance of Candidal species in the hospitalized setting [12]. Hence, fungal dysbiosis can be considered to stem from antibiotic use in cirrhosis patients and is a risk factor for it [12].

Infections and Acute-on-Chronic Liver Failure (ACLF)

Acute-on-chronic liver failure (ACLF) is a relatively recent entity, the definition of which is still evolving but manifests mainly as an acute worsening of liver function or organ failure(s) in the setting of acute decompensation in cirrhosis or chronic liver disease patients, leading to increased short-term mortality [44, 45]. ACLF is graded into stages 1 through 3 depending on the number of organ failures and is estimated to be present in between 10% and 30% of the cirrhosis patients, who get hospitalized [44, 45]. None of the current prognostic scoring systems like the model for end-stage liver disease (MELD) score, the chronic liver failure sequential organ failure assessment (SOFA) score, NACSELD score, and so on are specific for prognosis in ACLF, and this represents an unmet need [45]. It seems that bacterial infections are one of the important triggers for systemic inflammation, which somehow get amplified in ACLF, resulting in systemic circulatory dysfunction, which ultimately leads to organ failure mediated through inflammatory cytokines [45–47].

The leading causes of admissions and readmissions to the hospitals in the cirrhosis patients are HE and infections, which reflect a certain shift as well [22].

The Bajaj et al. study results from the NACSELD database determined that infections in ACLF (I-ACLF)-decompensated cirrhosis patients, as defined by ≥2 organ failures, predict poor survival [48]. In this study (n = 507), the top two infections were urinary tract infections (28.5%) and SBP (22.5%), with 15.8% of these infections developing in the hospital itself; the extrahepatic organ failure including HE, shock, respiratory failure requiring artificial ventilation, and renal failure requiring hemodialysis developed in 55.7%, 17.6%, 15.8%, and 15.1%, respectively, with the 30-day survival increasingly worsening in those with a higher number of organ failures as defined above [48].

Aggressive management of all infections—community-acquired and nosocomial—and the implementation of strategies to prevent second infections along with early recognition and treatment of fungal infections may help in the avoidance of ACLF [20, 49]. Multidisciplinary approach including the early involvement of palliative care side has been advocated for the optimal management of ACLF patients, and in particular, the selection for liver transplantation candidacy should be carefully weighed [45, 50]. This is because ACLF patients admitted in the ICU with higher MELD scores have increased mortality in the post-LT period [51]. However, this notion has been dispelled by a recently published data from the NACSELD database, where in it was shown that post-LT survival and recovery in those with ACLF versus non-ACLF were similar at 6 months [52]. Of note, recent results suggest that ACLF patients who score a high (≥70) on the European Foundation for the study of chronic liver failure (CLIF-C ACLF) score after 48 hours of ICU management may need early palliative care support as the mortality in these cases is 100% at 28 days [53]. More recent literature from the ICU patients with cirrhosis and ACLF suggests that arterial lactate levels at admission followed by repeat levels to document lactate clearance predicts organ failure and short-term mortality at 28 days independently [8]. This multicenter study (n = 678) showed that lactate, which is a readily available marker, may have some utility for predicting outcomes in these critically sick patients and some scoring systems have already incorporated lactate for this purpose [8, 54]. Previous literature supports this notion, as for cirrhosis patients with fulminant hepatic failure in the ICU, higher lactate levels meant poorer outcomes [55].

Difficulties in Identifying and Prognostication of Sepsis in Cirrhosis

To further complicate the issue of identifying and predicting the outcomes in the infected septic cirrhotic patients as compared to noncirrhotic patients, the clinical prognostic scoring tools such as systemic inflammatory response syndrome (SIRS), sequential organ failure assessment (SOFA), and even the quick sequential organ failure assessment (qSOFA) score are not that helpful [56, 57]. Patidar et al.

evaluated hospitalized cirrhotic patients (n = 547; 124 infected vs. 423 uninfected patients), with 33 infected patients managed in the ICU, and found that the qSOFA score was not helpful in differentiating between infected and uninfected cirrhotic patients, and neither the in-hospital nor 30-day mortality between the two groups [57]. However, another externally validated study (n = 259) on prospectively infected cirrhosis patients assessing sepsis-3 criteria and qSOFA found that the earlier criteria have better accuracy than SIRS criteria alone in these patients for predicting severity, ICU transfer, and shock, while the later score has some use in predicting worse outcomes in such patients [58]. Weil et al. performed meta-analyses on 13 studies (n = 2523) trying to prognosticate cirrhosis patients admitted to the ICU and trying to discern predictors of mortality in such patients and report that the mortality in the ICU was 42.7%, in hospital 54.1%, and at 6 months, mortality was 75.1%. In patients with baseline SOFA >19 (O.R., 8.54), the ICU mortality was found to be higher, but higher SOFA scores did not predicate mortality at 6 months [59]. Of the infection-related variables, the prominent ones predicting mortality in the ICU were sepsis-related oliguria (O.R., 10.61), fungal infections (O.R., 4.38), SIRS (O.R., 2.44), and pneumonia (O.R., 2.18). In the end, the authors concluded that while infection had a short-term impact on mortality, the renal and liver failure had a sustained effect on mortality [59]. Majumdar et al. seem to agree with the above study with regard to organ involvement and mortality in which 16 years of data from nonelectively admitted cirrhosis patients in the ICU (n = 17,044), which constitute 2.2% of the total ICU admits for the cohort, described a decreased in-hospital mortality at 32.4% with cirrhosis being independently associated (O.R. = 1.10) with mortality mostly shown to be driven by a number of organ failures [60].

The NACSELD-ACLF score, using the definition of ≥2 extrahepatic organ failures, has been independently validated as a simple tool to predict survival at 30 days in all hospitalized cirrhosis patients (infected or not) [61]. A simple "app" which is freely downloadable from the Apple app store is available for predicting 30-day survival and fungal infection development for cirrhotic patients. The app walks you through a set of simple questions and displays the risk in percentage. Figure 7.3 shows the screenshots of the NACSELD app.

Accurate Assessment of Volume Status in the Critically Ill Cirrhotic Patients: A Challenge

At baseline, in the cirrhotic patients, there is altered pathophysiology, wherein essentially, we have a hyperdynamic circulatory state sustained by splanchnic and peripheral vasodilation mediated by vasodilator substrates like nitric oxide, etc. This manifests as a decreased vascular resistance and low blood pressures despite a high cardiac output state [62]. These physiological changes lead to a well-known state of "effective hypovolemia" despite having high total plasma and blood volumes with peripheral edema and ascites [63]. Because of the above changes, the

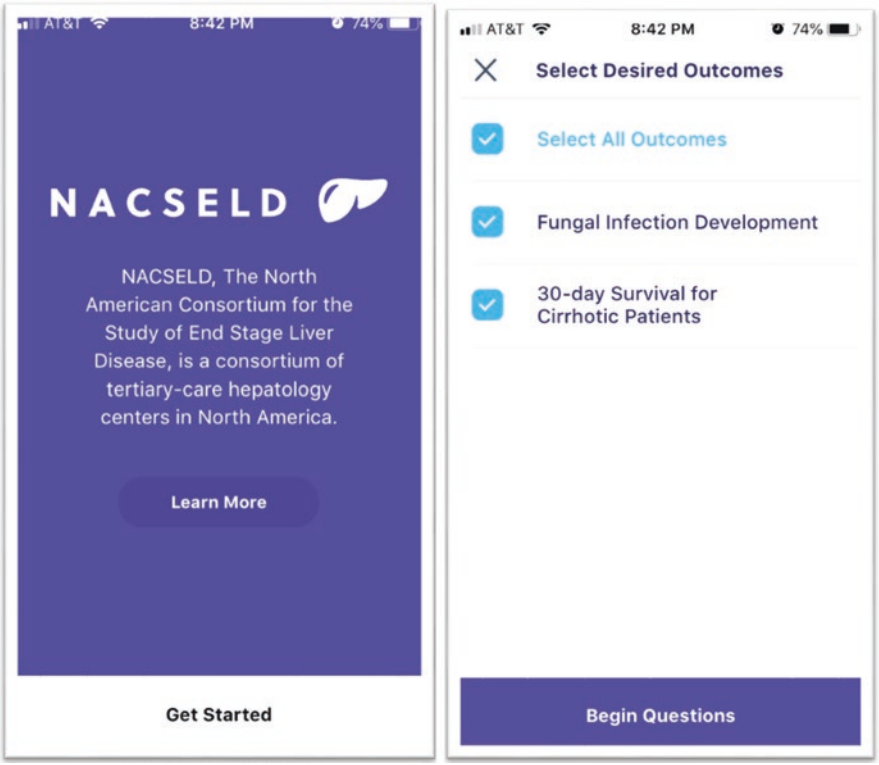

Fig. 7.3 Screenshots of the NACSELD app

proper assessment of the volume status in hypotensive septic cirrhotic patients with multiple organ failures may become challenging at times. However, the overarching goal is the optimal resuscitation of these patients in the ICU. Various methods, clinical, hemodynamic, or laboratory, may be used to gauge the volume status, but none is/are perfect, and hence, possibly a combination of methods with individualization of the approach may work [64]. The key is to carefully titrate volume resuscitation, keeping in mind not to go overboard and risk third spacing, in case of septic shock patients, with the goal of achieving a mean arterial pressure (MAP) of ≥60 mmHg [65]. The type of fluids depends on the metabolic profile of the patients, but the initial fluid resuscitation should be carried with normal saline (0.9%), which may need to be switched to balanced salt solutions in case patient develops hyperchloremic acidosis [66, 67]. However, in some situations, albumin use is recommended: in the setting of SBP (1 mg/kg and 1.5 mg/kg on days 1 and 3), after large volume paracentesis (6–8 g/L of ascites removed), and for prevention/treatment of type 1 hepatorenal syndrome (HRS) [68]. If despite appropriate fluid resuscitation, a patient has refractory shock, epinephrine should be used as the preferred vasopressor given its friendly side effect profile [69]. Steroid medications intravenously (200–300 mg/day) may be used in cases where higher dosage of vasopressors are

required in those patients who are still in refractory hypotension, but the data on survival benefit with steroid usage are mixed [62, 64]. Invasive arterial and central venous catheters for measuring central venous pressures (CVP) are often used for optimization and monitoring of volume status in the ICU setting [64]. Circulatory assessment using dynamic measures like echocardiography may have more value, but this is usually a single observation, and hence, other methods like CVP monitoring and passive leg raising in patients without ascites may be helpful in gauging the responsiveness to resuscitative efforts [70, 71].

Management of Infections and Sepsis in Cirrhosis Patients

The initial evaluation of infected cirrhotic patients should include a thorough history and physical examination including the assessment of vital signs to determine hemodynamic stability which may determine the level of care. Appropriate basic blood work, diagnostic imaging as per case-to-case basis, and culture samples should preferably be collected prior to starting antibiotics. Diagnostic tap of the ascitic fluid to rule out SBP should be performed in a timely manner (usually within 6 hours of presentation). Additional inflammatory marker like C-reactive protein (CRP) [64] may be requested along with the serum lactate levels [8]. As severe sepsis can commonly complicate the acutely decompensated cirrhosis patients[72], the initial clinical and lab data may guide healthcare providers regarding the appropriate disposition of the patient from the emergency room to either the ICU or floor level. It is of utmost importance not to delay the administration of appropriate antibiotic therapy as this will cost dearly in terms of outcome [73]. However, as to what initial empiric antibiotic(s) to use will depend upon the severity of infection and/or the organ systems involved, keeping in view the local microorganism's resistance patterns. Inappropriate and a delay in antibiotic administration increases mortality in cirrhosis patients [73]. Recent data suggest that for healthcare-associated infections in cirrhosis patients, those who were randomized to broad-spectrum antibiotics versus standard treatment had better outcomes in regard to lower treatment failure (18% vs. 51%, $p = 0.001$) and lower length of stay (12 days vs. 18 days, $p = 0.03$) [74]. Another study as well showed that the combination of Meropenam plus Daptomycin was significantly more effective than Ceftazidime in the treatment of nosocomial SBP [75]. However, as soon as the culture data become available (usually in 48–72 hours) along with the clinical improvement of the patients, appropriate de-escalation of the antibiotic regimen should ensue [10]. Earlier de-escalation can be possible if quicker methods of identification of MDROs as noted below become available. Consideration about changing/broadening of empiric antibiotic regimens and/or adding antifungal regimens should be made if there is no clinical improvement of the patients. The role of advanced imaging like computed tomography (CT) scanning should be re-evaluated in such a scenario [64]. It is prudent to manage these complex, ill patients using a team approach early on, with the involvement of hepatology, the infectious disease, and the critical care consultants along

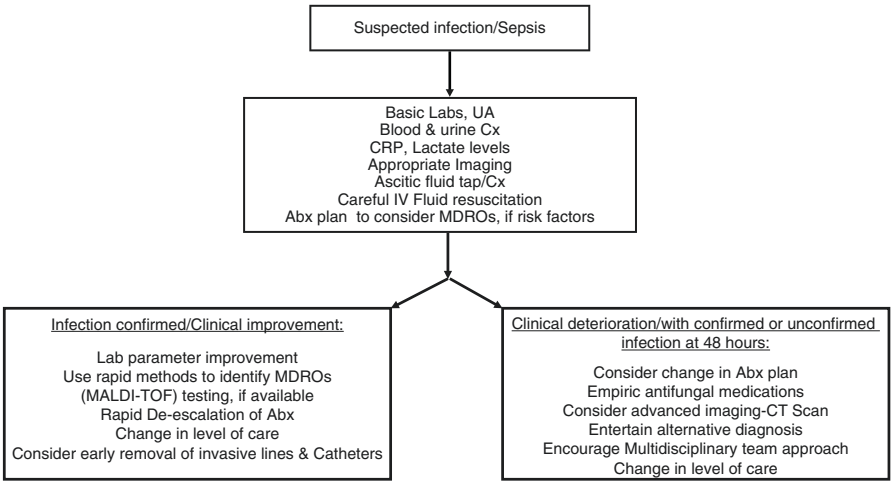

Fig. 7.4 Approach to the management of suspected infections and sepsis in cirrhotic patients. *Abbreviations*: UA urine analysis, Cx culture, CRP C-reactive protein, Abx antibiotics, MDROs multidrug-resistant organisms, IV intravenous, MALDI-TOF matrix-assisted laser desorption ionization time-of-flight, CT computerized tomography

with the primary teams for devising optimal management plans and improving outcomes. Appropriate fluid, vasopressor, and ancillary management should be embarked upon as already discussed above. To recap, a high index of clinical suspicion, flexible, rapid, and appropriate antibiotics along with the prevention of acute kidney injury are required to improve survival in these patients. Figure 7.4 shows the algorithmic approach to the management of suspected infections and sepsis in cirrhotic patients.

Preventive Strategies for All Infections (Including Fungal) and MDRO Infections

Prevention of further infections remains a challenge. However, multiple studies have concluded that better preventive strategies aimed at both the prevention of the first and the subsequent infections in the hospitalized patients should be utilized, as the treatment of the infections in the decompensated cirrhotic patients especially with MDROs is difficult, costly, and still leads to high early mortality [17, 18, 20, 48]. However, no one single preventive strategy yields results in prevention/spread of MDROs, and a combination of strategies may need to be employed which may include, but are not limited to, the following: (1) Prophylaxis for SBP, as primary prophylaxis for the low-protein ascites patients in high-risk patients (i.e., CTP-C); and (2) secondary prophylaxis in all patients after experiencing a first episode of

SBP; and (3) prophylaxis with ceftriaxone after variceal GI bleeding as the standard of care [64]. However, the recent results emerging from the Bajaj et al. (NACSELD) study have shaken the concept that all SBP prophylaxes are good by performing comparison outcomes in cirrhotic inpatients on primary versus secondary SBP prophylaxis after the two groups were propensity-matched for MELD and admission of serum albumin: Patients on primary prophylaxis were more likely to have admission SIRS ($P = 0.02$), higher ICU admissions (31% vs. 21%; $P = 0.05$), and inpatient mortality (19% vs. 9%; $P = 0.01$) as compared to the secondary prophylaxis group, and despite antibiotic prophylaxis, a high proportion of patients developed SBP, which was associated with mortality [76]. Figure 7.5 shows the summary of the NACSELD study. Hence, caution should be exercised in selecting the patients to be put on primary SBP prophylaxis particularly.

Furthermore, in view of the development of antibiotic resistance, some studies have suggested using rifaximin as a fluoroquinolone-sparing strategy, but the final verdict on this is not out yet and may be of interest [10]. The enhanced standard infection control policies need to be employed if MDROs are recognized, and these patients should be promptly isolated with barrier and contact precautions [77]. Establishment of robust antibiotic stewardship programs, focused to the needs of these patients, would include early and correct empirical antibiotic selections as per the risk factors and local resistance patterns if known, followed by early de-escalation policies for antibiotics [10]. By using culture-independent, rapid methods of identification for MDROs for gene targets for ESBLs, MRSA, and carbapenemases, using methods like polymerase chain reaction (PCR) or matrix- assisted laser desorption/ionization time-of-flight mass spectroscopy (MALDI-TOF MS), efficient de-escalation can occur [10, 78]. Reduction of all unnecessary interventional procedures, including invasive central lines, catheters, monitoring devices, etc., and if these are necessary, reassessment for early removal or exchanging of lines becomes important. Identification and treatment of MDRO carriers, in the ICU and on the regular hospital floors, by using nasal and rectal swabs will help in preventing the spread of MDROs [79]. Withdrawal of unnecessary proton pump inhibitor (PPI) use is also essential, as PPIs have been shown to "oralize" the gut microbiota in healthy individuals, and both the compensated and the decompensated cirrhotic patients and reverses after withdrawal of PPIs have an effect on readmissions [80]. As there are reports of associations with PPI and infections,most reports have questioned the inappropriate use of PPIs as quality assurance issues in cirrhotic patients [81]. Similarly, using antibiotics in general only when genuinely indicated in these patients, and for the shortest duration as possible, can prevent breeding of resistance and development of CDAD. Prevention of first infections with age-appropriate vaccinations, and immunizations against hepatitis A and B as indicated, will go a long way in preventing these infections in the already high infectious risk population. Strategies that reduce the burden of antibiotic resistance and fungal infections can potentially improve outcomes. Last but not the least, there should always be concerted efforts toward alcohol cessation in liver disease patients to prevent further decompensation of liver disease.

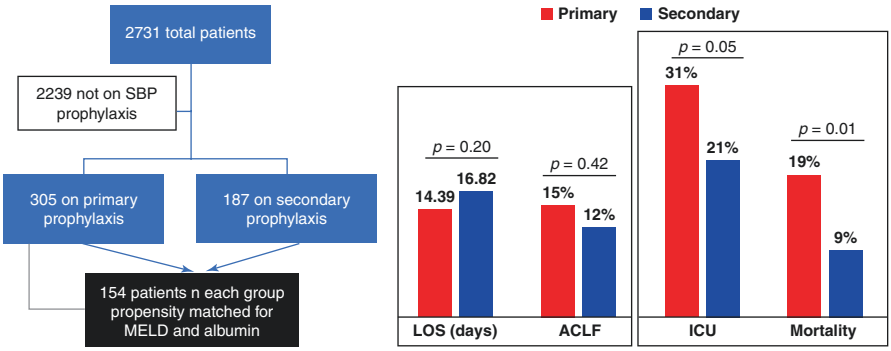

Fig. 7.5 Summary of comparison outcomes for patients on primary and secondary SBP prophylaxis [76]

Ensuring appropriate follow-up and monitoring of these patients with the primary care providers and outpatient hepatologists cannot be overstressed to make the transition of care safer for the cirrhotic patients.

Conclusion

Infections profoundly affect the natural history of cirrhosis. There is a lack of well-designed studies addressing the ICU management of critically ill cirrhotic patients, and this is an open area for research [82]. Currently, the principles used to manage other critical care illnesses along with expert consensus opinions are used for the management of cirrhosis patients in the ICU which may or may not be optimal [64, 82]. Hence, there is need for more robust studies to address these gaps. The future seems promising toward targeting and modulation of gut microbiota for various therapies to reverse the dysbiosis including fecal microbiota transplantation, which may improve already poor long-term outcomes in patients with liver cirrhosis. Newer antibiotics against the emerging infections along with institutional-level policy and planning for infection prevention strategies, both bacterial and fungal, for this frail subgroup of patients, may show future promise.

Conflict of Interest Statement The authors have no conflicts of interest to disclose.

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Chapter 8
Obesity and the Critically Ill Cirrhotic Patient

Tiffany Wu and Vinay Sundaram

Introduction

Obesity is becoming an increasingly prevalent condition, associated with the development of chronic medical comorbidities including diabetes, cerebrovascular accidents, and cardiovascular disease. The World Health Organization defines obesity as a body mass index (BMI) greater than or equal to 30.0 kg/m^2, with further classification into class I (BMI 30 to <35), class II (BMI 35 to <40), and class III or "morbid obesity" (BMI ≥40) [1]. The prevalence of obesity has increased dramatically over the past few decades, among all age groups, genders, and race/ethnicities. According to the National Health and Nutrition Examination Survey in 2009–2010, the overall age-adjusted prevalence of obesity was 35.7% (95% CI 33.8–37.7%) of adults in the United States and was similar between men (35.5%) and women (35.8%) [2]. Furthermore, among higher classes of obesity (class II or III), non-Hispanic black women demonstrated greatest prevalence compared to other groups.

Given the rising prevalence of obesity in the United States, strategies should be developed to care for this population. One important aspect of caring for these patients is the management of critical illness in the intensive care unit (ICU), as over 30% of ICU patients are obese [3]. Within the intensive care setting, a meta-analysis showed similar mortality between obese and nonobese patients in the ICU (RR 1.00, 95% CI 0.86–1.16, $p = 0.97$), though the obese group had a higher survival

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rate compared to the nonobese group at the time of discharge (RR 0.83, 95% CI 0.74–0.92, $p < 0.001$) [3]. On the contrary, nonobese patients had slightly improved outcomes in other parameters including duration of mechanical ventilation and length of ICU stay [4, 5].

Additional concerns have been raised regarding the ICU management of obese individuals. For instance, obese patients are thought to have excess burden on cardiovascular and pulmonary functions, altering the physiological response to illness and injury. Metabolism and biochemical clearance are also variable, resulting in potential underdosing of therapeutic medications. However, excess adipose tissue may prevent long-term complications of illness due to the presence of adipocyte-secreting hormones, leptin and interleukin-10 (IL-10), which may reduce inflammatory cytokine release to improve patient survival. The effects of obesity are widespread, and its impact on critical illness remains a topic of controversy.

Obesity in End-Stage Liver Disease

There are several challenges regarding the assessment of obesity in the patient with end-stage liver disease. One is determining obesity in the setting of ascites, as there is no standardized method to adjust for ascites in the calculation of BMI. One method to potentially correct this problem is to subtract ascites volume from the patient's body weight when calculating BMI, equating 1 L of ascites with 1 kg. A study which utilized this correction resulted in the movement of 11–20% of patients with BMI >25 kg/m^2 to lower BMI categories, demonstrating the significance of ascites volume on weight consideration for transplant [6]. However, this technique has not been validated. Another flaw with using BMI to determine obesity is that it does not always reflect the distribution of fat deposition, which may have greater effect on outcomes in patients with cirrhosis [7]. Focus has therefore shifted from sites of excess to sites of depletion, and a new term has arisen called "sarcopenic obesity," defined as severe muscle depletion in the setting of obesity [7]. Sarcopenic obesity has been reported in 30–42% of obese patients with cirrhosis [8–11].

Inflammatory Response in Obesity

Accumulation of excess adipose tissue leads to physiological alterations that affect nearly every organ system. Fundamental to these changes is systemic inflammation associated with obesity as a result of chronic upregulation of the innate immune system [12], as evidenced by elevated cytokines, chemokines, and acute-phase reactants in the peripheral blood of obese individuals [13]. When adipocytes expand, various immune cells, such as macrophages, lymphocytes, natural killer T cells, and mast cells infiltrate to create an environment of local inflammation [12, 14].

Adipose tissue drives this inflammatory response by producing and secreting proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF-α). IL-6 has a broad range of action on clinical and immunological manifestations of inflammation, as well as regulatory action on endocrine and metabolic functions. For instance, IL-6 induces the production of acute-phase proteins that serve as protective mechanisms to limit tissue injury. It also serves as a principal mediator of clinical manifestations of tissue injury and stress response. The production of TNF-α induces the production of IL-6, further augmenting this response [15]. Both IL-6 and TNF-α have been implicated in insulin resistance through altered local regulatory action and impaired insulin receptor signaling. However, it has also been proposed that TNF-α inhibits lipoprotein lipase within adipocytes, stimulating lipolysis and releasing fatty acids into circulation. With increased fatty acids and dysregulated lipid storage, the inflammatory process has been linked to the ectopic deposition of lipids in other organs, further contributing to end-organ dysfunction [16]. The increase in cytokine production correlates with the degree of adipocyte accumulation. As such, the higher the BMI, the greater is the cytokine production and the resulting inflammatory state [14, 17]. This constant, lipotoxic state of inflammation is considered the initial step in immune and metabolic derangements of obesity.

Effect of Obesity on Nonhepatic Organs

In addition to the increase in systemic inflammation, obesity can also directly affect organ system function. In the respiratory system, excess adipose tissue surrounding the pharynx may lead to airway collapse and increased upper airway resistance [18], while increased abdominal fat pushes the diaphragm upward, decreasing lung volumes and increasing total lung resistance [19]. Functionally, obese patients have decreased expiratory reserve volume and functional residual capacity, resulting in poor dependent ventilation and a baseline ventilation–perfusion mismatch. This makes patients at risk for hypoxemia, especially at times of increased respiratory rate [20]. Obese patients also have a greater work of breathing, with subsequent higher resting oxygen consumption due to this metabolic cost, which leads to a neural mechanism that takes effect to compensate for increased ventilation and muscle fatigue [21]. Though individuals may experience different severities of change, obesity effectively restricts pulmonary reserve capacity and makes patients with critical illness susceptible to respiratory failure.

Regarding the cardiovascular system, obese patients have greater end-organ perfusion requirements in addition to increased baseline oxygen consumption, leading to a subsequent increase in stroke volume and cardiac output [22]. Individuals are also more susceptible to left ventricular hypertrophy from increased preload and hypertension, as well as left ventricular dysfunction, left atrial enlargement, and atrial fibrillation [23]. The right ventricle may also enlarge, causing reduced right-sided systolic function as well as increased pulmonary vascular resistance [24].

Although limited studies have looked at the correlation of obesity with cardiovascular dysfunction, it is likely that baseline anatomical and physiological changes may similarly increase the risk for cardiovascular compromise during severe illness.

Finally, in the renal system, obesity is also a risk factor for acute and chronic kidney disease. Although the pathophysiology of obesity and kidney injury has not been well defined, the relationship is likely multifactorial in nature. One aspect of injury is related to glomerular transformation from the increased likelihood of diabetic and hypertensive nephropathy and renal hypoperfusion. Another component is the presence of circulating inflammatory mediators, including those produced by adipose tissue as well as cytokines induced during acute illness. For example, plasma TNF-α level, which is increased in the presence of obesity, has been shown to be significantly elevated in both acute and chronic renal failure and has also been correlated with mortality outcome [25]. There may also be a role of leptin, a polypeptide hormone that is produced by adipocytes and primarily metabolized by the kidneys. Although leptin concentration does not differ significantly between healthy, lean patients and patients with acute renal failure, leptin levels are increased in the setting of chronic renal failure [26]. There is potentially a shared mechanism between elevated leptin levels seen in both chronic renal failure and obesity, which requires further investigation. Urinary interleukin-18 (IL-18), which similarly increases with BMI, is also associated with increased development of acute kidney injury in critical illness and has also been identified as an independent predictor of mortality due to acute respiratory distress syndrome (ARDS) [27]. Additionally, patients with greater visceral adiposity are at risk for increased intra-abdominal pressure and occurrence of kidney failure from congestion and poor forward flow [28].

The "Obesity Paradox"

There is increasing evidence that obesity is associated with an increased occurrence of organ failure in critically ill patients [29]. This association has been most pronounced among trauma patients and patients with ARDS. However, fundamental components of care may be applied to any setting of critical illness. One framework for assessing the impact of obesity on critical care is through the "two-hit model" of proliferative immune response. Obesity sets in place a baseline upregulation of immune activity, or a low-grade systemic inflammatory response, as the first hit, which is then compounded by a second hit of critical illness, such as sepsis [30]. Although this impact has been well elucidated [29, 31], the association between obesity and mortality outcomes is less clear. Some studies have suggested the relationship between BMI and ICU mortality to display a "U"- or "J"-shaped curve, with lower mortality in patients with class I or II obesity and higher mortality among patients with class III obesity or lean and underweight patients (BMI <20) [32, 33]. This phenomenon is termed the "obesity paradox" in critical illness, suggesting that obesity grants a survival advantage to patients in the ICU (Fig. 8.1)

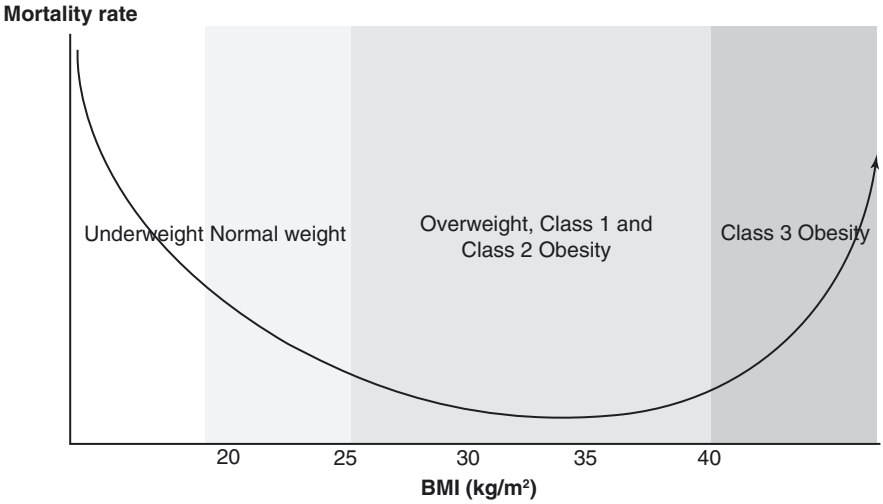

Fig. 8.1 The obesity paradox. (Reproduced with permission from Wichansawakun et al. [99])

Different hypotheses have been raised regarding the "obesity paradox." Some studies cite the benefits of increased adiposity as providing increased nutritional reserve [34], hormonal response, and release of immunomodulatory regulators such as leptin and IL-10. Leptin has been well studied and found to induce proliferation and activation of hematopoietic cells and regulate T-helper cell balance, propagating greater immune activity and response to insults [35, 36, 37]. However, the rationale for an inflection point between survival benefit in class I or II obesity and class III has not been fully explained. Studies have suggested that BMI may not be the best parameter to assess risk for mortality, and other factors such as central adiposity, comorbidities, or frailty index may be more accurate [38].

Obesity and Hepatic Decompensation

The impact of obesity on liver decompensation was initially demonstrated in the landmark study by Berzigotti et al., which found that increased BMI was an independent predictor of liver decompensation (HR 1.06, 95% CI 1.01–1.12, $p = 0.02$). In a sample size of 161 patients, 48 patients had clinical decompensation after 59 months of follow-up, with increasing rate when stratified by BMI (15% with normal BMI, 31% with overweight BMI, and 43% with obese BMI, $p = 0.011$) [39]. Obese patients developed clinical decompensation at a significantly higher rate than patients with normal BMI ($P = 0.002$), and the cumulative probability of decompensation among obese patients was 21% (95% CI 10–32%) and 37% (95% CI 23–50%) at 2 and 5 years, respectively [39].

In terms of decompensation related to hospitalization or death related to complications of cirrhosis, studies have demonstrated results in accordance with the "obesity paradox." In a cohort study by Ioannou et al., BMI ≥30.0 kg/m^2 was found to be a risk factor for death or hospitalization related to cirrhotic decompensation (HR 1.69, 95% CI 1.0–3.0) with a follow-up time of 13 years [40]. In another large cohort study, obesity was demonstrated to be associated with infection in hospitalized patients with end-stage liver disease, with particularly higher prevalence of skin and soft tissue infections [41]. A recent analysis of the UNOS registry data further found that patients with acute-on-chronic liver failure (ACLF) at the time of listing had a greater proportion of patients with class III obesity (23.1%, $p < 0.001$) compared to class I or II (16.5%) or normal BMI (15.9%), indicating that class III obesity is a risk factor for ACLF development. Survival analysis showed that the likelihood of developing ACLF among those with obesity was 22.3% at 5 years [42].

The mechanism as to why obesity can lead to liver decompensation has not been fully established. This may be partially related to greater portal pressure gradients among obese patients, along with a reduced response to beta-blockers [39]. Additionally, the proinflammatory cascade associated with obesity is implicated, due to the production of adipokines and cytokines contributing to the progression of hepatic inflammation, fibrogenesis, and angiogenesis [43]. The systemic inflammatory response related to obesity is similar to that found in ACLF [44].

Pathophysiology of Obesity and Sepsis

Adipose tissue has been increasingly recognized as an endocrine organ, producing "adipokines," or bioactive molecules such as leptin, adiponectin, resistin, and other proinflammatory cytokines [45]. Obesity predisposes individuals to altered expression of adipokines and cytokines, which affect infection risk and hemodynamic response. One commonly implicated protein is leptin, which is elevated in both obesity and liver dysfunction [46]. Leptin itself exerts a protective effect by activating neutrophils, inducing lymphocyte proliferation and activation, regulating monocyte and macrophage activity, and promoting wound healing [47]. This impact has been demonstrated in studies of genetically modified mice, where deficiency of leptin was associated with increased sensitivity to macrophage-activating stimuli, defective phagocytosis, and suppressed T-cell function. As a result of such impaired response, the mice were susceptible to bacterial infections, particularly by gram-negative organisms such as Listeria and Klebsiella species [48].

The role of leptin in sepsis is more controversial. Animal models have suggested that obese animals demonstrate more exaggerated response in sepsis compared to lean counterparts [49]. The outcome of that response, however, has been mixed, with earlier studies suggesting improvement in survival with increased leptin [35] and others without clear association [50, 51]. In scenarios of sepsis, the lower levels of adiponectin and resistin among obese patients may be more influential. Adiponectin

and resistin are both anti-inflammatory regulators of insulin sensitivity and glucose metabolism, and lower levels of adiponectin have been associated with insulin resistance [52]. Obesity and sepsis have been linked by this tendency toward insulin resistance, with studies proposing that the overlapping effect of increased blood glucose levels may impair morbidity and mortality in critically ill patients [53].

The correlation between obesity and critical illness is best demonstrated by the finding of comparable adipocytokine profiles between both morbidly obese and septic patients. Hillebrand et al. showed reduced adiponectin levels, along with elevated MCP-1, active PAI-1, IL-1α, IL-6, and IL-10, among both patients with morbid obesity and sepsis [54]. While leptin was elevated in obesity alone and resistin elevated in sepsis alone, this similarity among increased proinflammatory cytokines and altered adipokines exhibits an association between the mechanism of immune dysregulation in obesity and sepsis.

While infection risk varies among different organ systems, overall sepsis-related morbidity and mortality may be increased among obese individuals. This response is likely attributed to the systemic effects of inflammatory cytokines that disrupt hemodynamic stability. However, obesity has also been correlated with increased oxidative stress through mediation of reactive oxygen species (ROS) that cause cellular injury. Furukawa et al. showed that the adipose tissue of obese mice comprised an increase in NADPH oxidase and decrease in antioxidative enzymes, leading to imbalance among adipocytokines such as IL-6, monocyte chemotactic protein-1, and plasminogen activator inhibitor-1 [55]. Further, oxidative stress and the presence of ROS have been linked to diaphragmatic dysfunction. Barreiro et al. demonstrated the impact of heme oxygenase inhibition among obese septic individuals, where an increase in heme oxygenases has been associated with contractile dysfunction and subsequent respiratory failure [56].

The reason why obese patients with end-stage liver disease may be predisposed to infection is uncertain; however, it is likely multifactorial involving baseline chronic low-grade inflammation as well as malnutrition in obesity, commonly referred to as sarcopenic obesity [57]. Alterations in the gut microbiome may further contribute to infection risk. A metagenomic study found that obese patients may have a high or low variability of microbial gene richness, with high variability correlating with greater prevalence of anti-inflammatory bacterial species [58]. Obesity is also associated with increased gut permeability and potential for bacterial translocation into portal circulation [59]. Synergistically, the presence of proinflammatory microbiota and increased intestinal permeability may create an additive risk of infection in obese patients with cirrhosis.

Management of Organ Failure in the Obese Patient

There are several challenges regarding the management of sepsis in obese patients with end-stage liver disease. First, antibiotic dosing must be considered given the impact of body composition on the therapeutic effect. Obesity may present a risk for

treatment failure due to physiological changes that impact pharmacology, including the distribution, metabolism, and clearance of antibiotics [60]. For instance, lipophilic medications may bind to excess adipose tissue to create a higher volume of distribution [61], and increased GFR in obese patients may enhance antibiotic clearance [62]. Studies have shown that obese patients are more likely than lean patients to receive subtherapeutic doses for treatment [63] or prophylaxis [64].

Second, fluid resuscitation may not be adequate in obese patients. Studies have shown that obese patients receive significantly less fluid volume in burn injuries compared to lean patients when using actual body weight [65]. Additionally, when fluid requirements were indexed to BMI in obese patients with sepsis, the volume of fluid administered was often underestimated, since blood volume increases in a nonlinear fashion with BMI [66]. In a retrospective cohort study of 2882 patients with septic shock, obese patients received significantly lower volumes of crystalloid and colloids per kilogram during the initial resuscitation phase [67]. Therefore, methods to assess volume requirements should be improved to account for elevated BMI. Early studies have suggested using adjusted body weight, instead of actual or ideal body weights, to calculate initial fluid resuscitation in suspected septic shock [68]. Adjusted body weight was associated with improved mortality; however, further studies are needed to develop an optimal strategy for resuscitation.

Additionally, management of mechanical ventilation must be considered among critically ill obese patients. Due to the physiological impairments to respiratory function as previously described, obese patients are at increased risk for developing ARDS with subsequent higher lengths of stay [69]. The recommended strategies to improve pulmonary function include patient positioning and ventilatory adjustments. For instance, use of prone or reverse Trendelenburg position, along with low tidal volume ventilation according to ideal body weight and intermittent high airway pressures, may provide benefit to obese patients [70].

Considerations for Liver Transplantation

Over the past two decades, there has been an increase in the number of obese patients listed for liver transplantation, now comprising up to one-third of transplant candidates [71]. In this context, studies have been performed to assess waiting list mortality in obese individuals. One study revealed transplant candidates listed from 2002 to 2006 with a BMI >35 kg/m^2 had significantly lower rates of transplantation, due to receiving fewer MELD exception points and longer waitlist times [72]. A separate analysis of the UNOS database found class III obesity to be an independent predictor of delisting (HR 1.27), likely attributed to higher rates of infection and decompensation that may make candidates too sick to be transplanted [73]. A larger study of the same registry demonstrated that waitlist mortality was significantly higher among patients with BMI >40 kg/m^2 when compared to candidates with BMI <30 kg/m^2 (HR 1.16, 95% CI 1.08–1.26), with obese patients subsequently having mortality benefit from transplantation [74].

Most centers consider a BMI above 40 kg/m^2 as a contraindication to liver transplantation. Therefore, strategies for weight loss among transplant candidates are imperative. One prospective study of 44 morbidly obese patients demonstrated 84% success rate in reaching target BMI of less than 35 kg/m^2 with lifestyle interventions alone [75]. However, if bariatric surgery is required, this can be done successfully either prior or during transplantation, with favorable graft and patient survival [75–77]. Currently, no studies have directly compared the types of bariatric surgery to suggest a recommended protocol, though it has been established that patients with decompensated cirrhosis do show higher postprocedural mortality rate (16.3%) when compared to patients with compensated cirrhosis (0.3%, $p < 0.001$) [78].

Nutrition in Obesity and Critical Illness

There is often misunderstanding surrounding nutritional deficiencies among critically ill obese patients. Many are nutritionally deficient with a high incidence of sarcopenia, most readily depicted by increased visceral adiposity and associated muscle atrophy. As such, BMI alone is a poor surrogate for the level of nutrition, especially in critical illness where excess catabolism may accelerate protein loss and muscle breakdown [79]. Comorbid liver disease portends another cause of malnourishment. Malnutrition is present in 40–90% of patients with cirrhosis and increases with the severity of disease [80]. When present, malnutrition is associated with an increased risk for immune dysfunction, delayed recovery time, and mortality [81]. The etiology of malnutrition in cirrhosis includes diminished nutrient intake from early satiety, ascites, loss of appetite or hospitalizations, and hypermetabolism from cytokines and compromised gut barrier function. Additionally, patients with cirrhosis have altered metabolism of both micro and macronutrients due to loss of body protein and decreased hepatic glycogen reserves [82].

Nutrition Assessment

A general assessment of nutrition includes first an understanding of the patient's energy intake, with methods such as diet recall or calorie counting. Biochemical assessments with prealbumin and serum albumin are regarded as poor markers of nutrition status, especially in advanced liver disease, though they do have use as markers of disease severity, underlying illness, and inflammation [83]. Specifically, there may be a correlation between serum prealbumin and albumin to baseline nutrition status, but this link is confounded in the presence of comorbidities and critical illness. Although serum prealbumin may be preferred to albumin due to a shorter half-life of 2–3 days compared to the 21-day half-life of albumin (produced in the

liver), prealbumin has limited sensitivity in evaluating the nutritional status or adequacy of calorie or protein support during critical illness and does not correlate with the other biomarkers of inflammation [84, 85]. Levels of micronutrients such as serum vitamins and trace elements may also be contributory, though they are not found to be directly correlated with the nutrition status.

Screening tools are used to evaluate the nutrition status; however, only two scoring systems incorporate disease severity to provide a nutrition risk in critically ill patients. These include the NRS 2002 and NUTRIC scores [86, 87]. Patients deemed high risk from these scoring systems are likely to benefit from early enteral nutrition, with improved outcomes including fewer complications and improved mortality [86]; however, these tools need further refinement to help guide interventions in the ICU. Table 8.1 displays these screening tools for critical illness, as well as cirrhosis-specific nutrition risk tools that have been developed.

Currently, there are no tailored assessment tools for critically ill obese patients, and predictive calculations of energy expenditure among this specific population are generally imprecise [88]. Global nutritional assessment tools have been proposed, such as the subjective global assessment (SGA) which includes components of loss of subcutaneous fat, peripheral or sacral edema, muscle wasting, weight loss over 6 months, dietary changes, and gastrointestinal symptoms. However, this method requires further validation [89]. Among patients with end-stage liver disease who may have concurrent multiorgan failures, use of body composition assessments, such as total-body electrical conductivity, bioelectrical impedance, or dual-energy X-ray absorptiometry, have also been reviewed [90]. Yet, total body volume must be considered. In a study using bioelectrical impedance analysis among cirrhotic patients with and without ascites, the estimated body cell mass demonstrated a deviation of <0.2 kg/L of ascitic fluid. While useful as a bedside tool for analysis, variations in fluid retention must be taken into account [91].

Instead, significant research has recently identified that low muscle mass or function in patients with cirrhosis independently predicts reduced quality of life, hepatic decompensation events, and mortality [89, 92]. Data among liver transplant recipients also suggest that greater visceral adiposity with lean psoas muscle mass is associated with increased post-transplant mortality [93]. As a result, quantitative measures of sarcopenia have become more readily available, evaluating the skeletal muscle mass with cross-sectional imaging studies such as computed tomography (CT) scan or magnetic resonance imaging (MRI). Although early findings suggest strong correlation with clinical outcomes, further investigation is required to validate these conclusions. Functional assessments such as hand-grip strength and tests of physical frailty, such as chair stands and balance, are also being used to complete the evaluation of sarcopenia, and new indices are emerging to improve the predicted risk of waitlist mortality over current scoring systems [94].

Table 8.1 Nutrition screening tools for critical illness and liver disease

Screening tool	Components	Advantages	Disadvantages
RFH-NPT	Alcoholic hepatitis or tube feeding Presence of fluid overload Dietary intake reduction Unplanned weight loss	Simple, quick Reproducible Good external validity against RFH-SGA Predicts clinical deterioration, transplant-free survival	Not used for monitoring nutrition therapy
Liver Disease Undernutrition Screening Tool	Nutrient intake Weight loss Subcutaneous fat loss Muscle mass loss Presence of fluid overload Decline in the functional status	High positive predictive value	Subjective to patient judgment of each measured parameter Needs further validation
SGA	Historical parameters: Weight loss Change in dietary intake Presence of gastrointestinal symptoms Functional capacity Metabolic stress of underlying diagnosis Physical parameters: Loss of subcutaneous fat Loss of muscle mass Presence of edema/ascites	Global assessment tool Uses multiple subjective and objective parameters Correlates with postoperative outcomes in patients without cirrhosis	Underestimates prevalence of sarcopenia Limited predictive capacity in patients with cirrhosis
RFH-SGA	BMI Mid-arm muscle circumference Dietary intake	Global assessment tool Simple, few parameters	Unclear generalizability between both men and women Not well validated
NRS-2002	BMI Weight loss Dietary intake Disease severity	Practical Predictive, validated Considers disease severity	Not specific to liver disease Does not account for volume status
NUTRIC	Age APACHE II and SOFA scores Comorbidities Hospital days Interleukin-6	Externally validated in critical illness	Not specific to liver disease Complex, requires training Interleukin-6 testing is not readily available

Information adapted from: Tandon et al. [90]
Abbreviations: *BMI* body mass index, *NRS-2002* Nutritional Risk Screening 2002, *NUTRIC* Nutrition Risk in Critically Ill, *RFH-NPT* Royal Free Hospital-Nutritional Prioritizing Tool, *RFH-SGA* Royal Free Hospital-Subjective Global Assessment, *SGA* Subjective Global Assessment

Therapies

While the optimal nutrition regimen for obese patients has not been established, low-calorie high-protein feeding has been suggested to reduce fat while retaining lean mass, reduce protein catabolism, and prevent hyperglycemia, and beneficial results have been demonstrated in observational studies and randomized trials [95]. The overall strategy must address the inflammatory process and exaggerated immune response that accompanies both obesity and critical illness.

Among patients with end-stage liver disease, the European Society for Parenteral and Enteral Nutrition (ESPEN) recommends a daily target intake of 35–40 kcal/kg/d and 1.0–1.5 g/kg/d of protein [96]. Enteral nutrition is the preferred route, and standard whole-protein formulae are suggested. Although previously speculated that supplementation with branched-chain amino acids (BCAAs) would help manage hepatic encephalopathy while permitting protein intake, there is insufficient evidence to suggest added benefit of BCAAs if patients are already on first-line therapy of lactulose and rifaximin [97]. Waller et al. suggest that for critically ill patients in the ICU, requirements may slightly vary. If at risk for refeeding, the recommended daily target intake is 15–20 kcal/kg/d with 1.2 g/kg/d of protein. If requiring maintenance caloric support, the target intake is 25–30 kcal/kg/d with 1.5 g/kg/d of protein. If in a catabolic state such as sepsis or septic shock, the requirements increase to 35–50 kcal/kg/d [98].

For critically ill obese patients, repletion therapy has thus far been recommended based on indirect calorimetry or use of prediction models estimating caloric requirements. However, no standard nutrition regimens exist at this time. Additional prospective studies are needed to assess for clinical outcomes of targeted therapies for patients with multiple comorbidities including obesity, critical illness, and liver disease. As discussed, the use of new surrogates for obesity, such as sarcopenia and frailty, may provide a reliable method to quantify and systematize guidelines for therapy.

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Chapter 9
Frailty and Sarcopenia in the Critically Ill Patient with Cirrhosis

Ammar Hassan and Elliot B. Tapper

Introduction

Commonly recognized complications of cirrhosis include ascites, hepatic encephalopathy, variceal bleeding, and hepatocellular carcinoma. However, chronic protein calorie malnutrition, severe muscle loss (sarcopenia), and frailty are common, though mostly covert complications in patients with advanced liver disease. Each of the complications is documented to negatively impact quality of life, increase the risk of complications (and critical illness), lead to a maladaptive stress response to critical illness, and diminish overall survival [1, 2].

Definition of Key Terms

Malnutrition

Malnutrition can be defined as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease." [3] Malnutrition is classified as nondisease-related malnutrition (Non-DRM) (secondary to hunger in the setting of food deprivation and/or socioeconomic or physiology-related mechanisms) or disease-related malnutrition (DRM). DRM can be further classified into DRM associated with inflammation (which may be either acute or chronic) or without inflammation. Malnutrition related

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to cirrhosis is multifactorial; however, acute changes are often classified as DRM with inflammation. In practice, the definition of malnutrition can be operationalized as a dichotomy; however, there are discrepancies among professional societies [4]. Classical definitions such as reduced body mass index (BMI) < 18.5 kg/m may or may not be applicable to patients with sarcopenia or ascites. Other parameters indirectly reflect malnutrition such as low energy intake, loss of muscle mass, loss of subcutaneous fat, fluid accumulation, and poor handgrip strength.

Sarcopenia

Sarcopenia is a syndrome characterized by the progressive and generalized loss of skeletal muscle mass, strength, and function (performance) with a consequent risk of adverse outcomes [5]. As compared to primary sarcopenia which can occur due to the phenomenon of aging, sarcopenia in the setting of cirrhosis is secondary to the underlying disease process, low physical activity (e.g., disuse), and/or due to poor nutrition (e.g., malnutrition) [6]. To date, diagnostic criteria for sarcopenia have not been firmly established. Investigations assessing sarcopenia include a myriad of validating techniques serving to assess both muscle mass (including loss of) and muscle strength and function (including reduction in). Quantification of muscle mass can be obtained using dual x-ray absorptiometry (DXA), bioelectric impedance analysis (BIA), or computed tomography (CT) scanning [7]. Muscle strength and function can be ascertained utilizing investigations such as handgrip strength, gait speed, and 30-second chair stands [8, 9].

Sarcopenic Obesity

Sarcopenic obesity is defined as sarcopenia in combination with obesity which is commonly encountered in obese patients with chronic liver disease, especially nonalcoholic fatty liver disease (NAFLD). In these patients, inflammation and/or inactivity-induced muscle catabolism induce muscle loss [10]. Currently, there are no commonly accepted criteria for sarcopenic obesity beyond those for sarcopenia and obesity separately [11].

Frailty

Frailty is a state of vulnerability and nonresilience with limited functional reserve capacity in major organ systems leading to reduced capability to withstand stress such as trauma or disease predisposing to dependence and disability. Frailty encompasses nutrition-related components (e.g., weight loss), dysregulated energy expenditure (e.g., catabolism associated with ascites), and cognitive deficits (e.g., hepatic

encephalopathy), all of which are linked to sarcopenia [9, 12, 13]. In clinical practice, frailty can be thought of as disability (poor performance of activities of daily living) or physical weakness with respect to a validated cutoff on a test such as handgrip [13, 14].

Clinical Implications

Pathogenesis of Hepatic Encephalopathy

Malnutrition and sarcopenia have been shown in several studies to be independent predictors of self-reported poor quality of life, rates of hepatic decompensation, and overall mortality [1, 2, 15]. As both liver and muscle function are essential pathways for ammonia metabolism, HE can be seen as an epiphenomenon of malnutrition and sarcopenia. Studies have shown that the prevalence of overt HE was higher in patients with muscle depletion and decreased muscle strength, and venous blood ammonia levels also were higher with those who had sarcopenia [16, 17]. Protein malnutrition is also tightly associated with overt hepatic encephalopathy (HE) [18, 19].

Wait-List Mortality

In cirrhotic patients listed for liver transplantation, frailty and sarcopenia have been shown to be predictors of higher wait-list mortality [16, 20]. Adjusting for ascites, HE, creatinine, bilirubin, and albumin study, sarcopenia was an independent risk factor for mortality (hazard ratio 2.18) [21]. Furthermore, in a recent multicenter study, frailty was shown in adjusted models to be independently associated with wait-list mortality compared to ascites and HE [22]. Although the impact of sarcopenia and frailty is mediated in part by HE [13], a risk score incorporating psoas thickness outperformed MELD-Na in discriminating mortality [23].

Risk of Infection

In elderly patients, sarcopenia has been associated with a twofold increased risk of infection [24]. Cirrhosis is an independent risk factor for sepsis-associated mortality [25], and those with sarcopenia are at the highest risk of death [21, 26]. Muscle-derived cytokines (myokines) are essential to the compensatory anti-inflammatory response in the setting of infection; given their depletion in the setting sarcopenia, the result can be unchecked/progressive inflammation [27]. This disorder persists through the post-transplant period, where pretransplant sarcopenia is associated with an increased infection risk [28].

Post-Liver Transplant Outcomes

Sarcopenia in the setting of cirrhosis has been associated with negative post-transplant outcomes, including increased length of in-hospital stay, need for blood transfusion, increased infection risk, as well as higher rates of graft rejection and increased overall mortality [17, 29, 30]. Recent studies have shown that each unit decrease in the skeletal muscle index at L3 (L3-SMI) was met with a 5% increase in overall mortality in male post-liver transplant recipients [31]. Although traditional complications of cirrhosis and portal hypertension tend to improve in the post-transplant period, the degree of sarcopenia present may remain and could in fact worsen post-transplant, especially in male recipients [32–34]. Conversely, patients who show an increase in muscle mass and functionality in the post-transplant period were found to have shorter in-hospital stays and decreased mortality [31, 35].

Pathogenesis

Multiple factors contribute to the development and propagation of malnutrition, sarcopenia, and frailty in patients with cirrhosis and critical illness (Fig. 9.1).

Malnutrition

Reduced overall caloric intake has been observed in cirrhotic patients with sarcopenia [36]. Various factors contribute to this including anorexia secondary to chronic alcohol intake or chronically elevated inflammatory cytokines (e.g., TNF-alpha), nausea, abdominal pain and bloating secondary to increased intraabdominal pressure due to ascites, abdominal pain, and altered gut motility [37–39]. Dysgeusia is common in patients with cirrhosis; additionally, salt restriction may contribute to diet unpalatability [40]. Now relatively uncommon, but patients may still be under the outdated recommendation of protein restriction to prevent HE.

Physical Inactivity

Physical activity is a positive determinant of muscle anabolism. Unfortunately, most patients with cirrhosis, especially transplant-listed patients, are sedentary, engaging in minimal structured physical activity [41]. This is likely due to a combination of multiple clinical factors, some of which are not significantly modifiable [42].

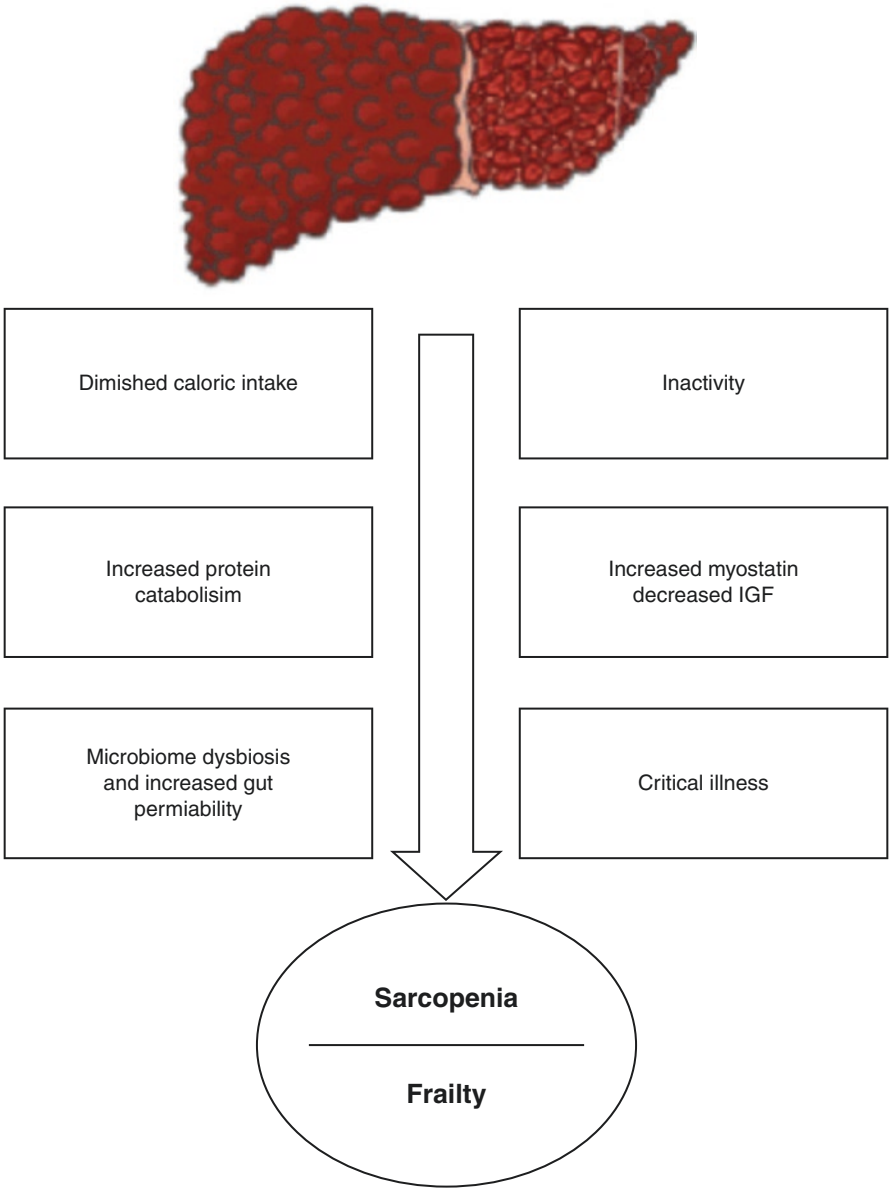

Fig. 9.1 Multiple factors contribute to the pathogenesis of sarcopenia and frailty in critically ill, inactive patients with cirrhosis. These include the underlying illness, often infections/sepsis, that compound increased inflammatory burden due to gut-barrier disruption, metabolic dysfunction owing to decreased insulin growth factor (IGF), and defective myostatin signaling in the presence of hyperammonemia. In the context of pre-existing and exacerbated malnutrition, patients experience increased catabolic drive

Malabsorption

Malabsorption may also contribute to the net negative energy balance in cirrhosis despite adequate or near-adequate caloric intake. Chronic alcohol use can concomitantly lead to cirrhosis and chronic pancreatitis with pancreatic insufficiency with impaired nutrition absorption. Cholestatic liver disease with biliary malabsorption can lead to fat-soluble vitamin deficiency and fat malabsorption [43]. In addition, there is increasing evidence that altered gut motility, small bowel bacterial overgrowth, and changes to the gut microbiota in cirrhosis can negatively affect nutrient absorption and utilization [44]. In the critical illness setting, prolonged hospitalization, frequent blood draws, and frequent/prolonged periods of fasting for imaging/endoscopy or other tests also add to protein and calorie malnutrition.

Hyperammonemia

Recent studies have elaborated a significant correlation between the presence of hepatic encephalopathy and sarcopenia in cirrhotic patients, with the prevalence of sarcopenia increasing in correlation the grade of hepatic encephalopathy (30% in patients without encephalopathy, 49% in patients with minimal hepatic encephalopathy, and 56% with overt hepatic encephalopathy) [18]. In vitro studies have shown that hyperammonemia is associated with an increased expression of myostatin, inhibiting protein synthesis and activating the ubiquitin proteasome and autophagy-mediated proteolysis [45, 46]. Hyperammonemia also causes mitochondrial dysfunction with the resultant generation of reactive oxygen leading to oxidative stress and tissue damage in skeletal muscle tissue, as studied in neural tissue [47, 48]. To compensate for the impaired ammonia scavenging and clearance in the diseased liver, skeletal muscle serves as a metabolic partner to the liver, increasing ammonia uptake leading to altered Kerb's cycle metabolism, decreasing adenosine triphosphate (ATP) synthesis, further impairing muscle function [46, 49]. Thus, in cirrhotic patients with sarcopenia, reduced circulating BCAA levels, increased muscle uptake of BCAA, and reduced muscle mass contribute to impaired ammonia clearance in a viscous cycle, promoting both muscle wasting and HE [50].

Myostatin

Skeletal muscle growth and repair requires the recruitment and proliferation of satellite cells, which are precursors to new muscle fibers. BCAAs, exercise, and testosterone upregulate the activation of satellite cells via protein kinase B (PCK/AKT) activation mediated via IGF-1 [51, 52]. Myostatin belongs to the transforming growth factor beta (TGF-B) superfamily and is a prime negative regulator of

satellite cell differentiation and proliferation [53]. Patients with cirrhosis have significantly higher serum and intramuscular levels of myostatin than controls [54, 55]. Elevated levels of myostatin in cirrhosis are thought to be mediated due to multiple factors including hyperammonemia [46], lower levels of serum testosterone [56], and IGF-1 levels [57].

Metabolic Alternations

Resting energy expenditure (REE) is increased by as much as 120% of the expected value in the studied majority of patients with cirrhosis [58]. This is mainly driven by a combination of chronically elevated proinflammatory cytokine-driven hypermetabolism and hyperdynamic circulation, leading to systemic vasodilation, activation of the sympathetic nervous system, and ultimately greater utilization of macronutrients and micronutrients [59–61].

Due to the loss of hepatic glycogen stores in advanced liver disease and the chronic inflammatory state, cirrhosis mimics a state of starvation with the inappropriate use of body fat and protein for gluconeogenesis. This proteolysis and lipolysis can occur even during short periods of lack of adequate oral intake such as an overnight fast [62]. A number of iatrogenic factors such as multiple large-volume paracentesis, use of diuretics, occult or overt blood loss from esophageal and gastric varices, and ulcerations/portal enteropathy add to the protein loss [63].

These forces combine to shape profound consequences. Given insufficient liver stores, during and overnight fast, energy use derived from carbohydrate metabolism was only 13% compared to 39% in normal subjects; the incremental difference in the resultant protein and fat catabolism is equivalent to what is seen when a healthy subject fasts for 72 hours [64]. Other studies have documented increased ketogenesis [65], amino acid consumption [66], and a reduced respiratory quotient (carbon dioxide production as compared to oxygen consumption) in cirrhosis, reflecting a lower proportion of energy derived from carbohydrate [67]. Whole body protein turnover is therefore substantially increased in patients with cirrhosis, degrading lean body mass [65]. Driven by the inflammatory burden of cirrhosis [68], there is an overall increase in resting energy expenditure, further increasing the use of branched chain amino acids (BCAAs) as a baseline energy source, exacerbating proteolysis [69, 70].

Chronic Inflammatory State

Gut barrier function is compromised in cirrhosis due to portal hypertension and dysbiosis, leading to translocation of bacterial products called pathogen-associated molecular patterns (PAMPs) by immune cells [38, 71, 72]. This leads to a proinflammatory state, with elevated levels of cytokines such as TNF-alpha,

interleukin- 1, and interleukin-6, which is further exacerbated in the setting of acute critical illness secondary to complications such as spontaneous bacterial peritonitis, pneumonia, or sepsis [73]. Experimental cirrhosis models utilizing muscle biopsy data demonstrate a strong correlation between muscle TNF-alpha levels and muscle degradation utilizing both ubiquitin-proteasome pathway (UPP) and autophagy [74, 75]. Thus, in critical illness, cirrhotic patients may experience deterioration in their general health and nutritional status.

Assessment of Protein Energy Malnutrition, Sarcopenia, and Frailty in Cirrhosis

Indirect Calorimetry

Indirect calorimetry involves measuring of tissue metabolism metrics (such as oxygen consumption per minute (VO_2) and carbon dioxide production per minute (VCO_2)), used in calculating total energy expenditure and the nonprotein respiratory quotient (npRQ). In cirrhotic patients, npRQ is lower than in noncirrhotic controls due to a shift of preferred energy metabolism from carbohydrate to lipidoxidation. A study in cirrhotic patients showed that the survival rate was significantly lower in patients with a low npRQ (<0.85) than in patients with scores above 0.85 [76]. Indirect calorimetry is a valid test, but its clinical utility is unclear given its cost and complexity.

Anthropometric Measurement

Nutritional status can be assessed by the determination of total body bulk skeletal muscle volume using anthropometric indices such as triceps skinfold thickness (TSF), arm muscle circumference (AMC), and arm circumference (AC). These parameters have been used to assess protein energy malnutrition and sarcopenia in cirrhotic patients with decreased AMC and TSF correlating with malnutrition and decreased liver functional reserve [77, 78]. In addition, there is accumulating evidence of a significant association between nutritional status estimated by anthropometric measurement and outcomes in cirrhotic patients. A recent study suggested that the utilization of AMC and TSF may improve the prognostic capacity of Child-Pugh scores in cirrhotic patients with the prognostic power of AMC higher than that of TSF [79, 80]. Though the anthropometric measurements are simple and inexpensive to obtain, the assessment and interpretation of such values are limited to confounding factors (e.g., edema/anasarca), mechanistic issues resulting in inaccuracy and bias, and limitations to longitudinal assessment [81, 82].

Bioimpedance Analysis

Bioimpedance analysis (BIA) assesses the skeletal muscle volume utilizing tissue conductivity [83, 84]. Specifically, the phase angle (PA) (arctangent reactance/resistance ×180°/π) has been shown to be a promising parameter for the assessment of the overall nutritional status and survival in patients with cirrhosis [85, 86], as previously validated in preoperative patients and those on hemodialysis [87, 88]. Several studies have shown that the estimated values of skeletal muscle mass obtained through BIA correlate well with the assessment by magnetic resonance imaging (MRI) or dual-energy X-ray absorptiometry (DXA) [83, 89].

Cross-Sectional Imaging

Computed tomography (CT) allows for the precise measurement of skeletal muscle volume. Conventionally, this is performed at a specific lumbar level. Muscles at the third lumbar (L3) vertebra consist of the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. A recent analysis revealed that the calculated L3 muscle area accurately represents the whole-body skeletal muscle volume [90], especially utilizing the L3 skeletal muscle index (L3 SMI), which is the L3 muscle area normalized for stature (cm^2/m^2), with the established cutoff values of 38.5 cm^2/m^2 for women and 52.4 cm^2/m^2 for men [91]. A major drawback of this technique is that many patients lack CT scans to the L3 level. Recent data suggest that scans that quantify muscles at higher levels such as those obtained in the CT scans of the chest or abdomen perform as well as the pelvic/lumbar scans, while expanding the pool of evaluated subjects [92, 93]. Skeletal muscle can also be assessed utilizing MRI [83, 94, 95] and DXA, which also allows for the measurement of bone, fat, and lean-tissue content with less radiation exposure, lower costs, and comparable quantification [96].

Frailty

A basic index of frailty with high specificity because it captures disability is patient (or caregiver)-reported ADL performance. ADLs can be obtained by clinical nurses. Dependence with ADL (e.g., feeding, toileting, dressing) is associated with adverse outcomes including death, delisting, and discharge to a nursing facility [14, 20, 97]. The Karnofsky Performance Scale (KPS) has been extensively validated in patients with cirrhosis. KPS is both a continuous value from 0 (death) to 100 (perfect health) and a trichotomized scale: A (able to work), B (unable to work but can complete ADLs), and C (disabled). Poor KPS is clearly associated with pretransplant mortality [98, 99]. A decline in KPS from waitlisting to transplant as well as poor KPS

after transplant was strongly, independently associated with lower graft and patient survival [100].

Loss of skeletal muscle volume is usually reflected in decreased muscle strength. Previously shown to be a practical measure of muscle strength and sarcopenia in geriatric patients [7], handgrip strength has been shown to be a useful *quantitative* marker for the assessment of nutritional status in cirrhotic patients [101]. Handgrip strength can also provide prognostic information regarding transplant-free survival and the risk of cirrhotic decompensation [13, 102].

Two frailty indices combine subjective assessments with quantitative measurements. First, the Braden Scale is an index of pressure ulcer risk that is widely utilized by inpatient nurses, which includes sensory perception, skin moisture, activity, mobility, and nutritional intake. Braden was found to be associated with mortality in pretransplant patients and suboptimal functional status after transplant [14, 103]. Second, the Fried physical frailty phenotype (PFP) is the most widely validated tool for frailty assessment. PFP includes patient-reported weight loss, activity, and exhaustion as well as measured weakness (handgrip) and walk speed. Each category is dichotomized, and frail performance for ≥ 3 categories is characterized as indicating frailty. In a cohort of patients evaluated for liver transplant in Michigan, Derck [104] and Cron [105] demonstrated that, more so than the severity of liver disease, frailty was a better indicator of depression [105] and diminished health-related quality of life [104]. However, PFP can be confounded by disease factors. Our group recently showed that PFP was not predictive of transplant-free survival in patients with treated HE [13].

Therapeutic Interventions

Critical illness in patients with advanced liver disease is a significant event, often requiring prolonged and extensive ICU management, with limitations in regards to degree of possible therapeutic interventions given the usual presence of multisystem organ failure, physical immobility given mental status abnormalities and/or mechanical ventilation, and other external factors. With this in mind, established treatment strategies can be modified in the critical care setting for a positive effect.

High-Energy/High-Protein Diet

Due to the underlying hypercatabolic state in cirrhosis, a high-energy diet is required to prevent significant muscle breakdown and exacerbation of frailty. Studies have shown that a general increase in caloric intake alone does not suffice [106], rather evidence exists for a high energy (35–40 kcal/kg total energy intake per day) along with appropriate protein supplementation (1–1.5 gm/kg per day) [65]. Sufficient nutritional intake will shift metabolic processes from catabolic lipid oxidation to the

preferred carbohydrate metabolism [106]. Diets rich in BCAA may be better utilized by skeletal muscle and could facilitate ammonia clearance [107, 108]. Most important, however, is ensuring nocturnal feeding. Randomized trial data support the role of nighttime snacks on preserving and improving total body protein [109]. These data should be extrapolated to ensure that patients receive nutritious snacks or nocturnal tube feeds while hospitalized. Additionally, efforts to avoid unnecessary prolonged fasting prior to procedures should be pursued at the level of unit or hospital policy.

As above, nutrition should ideally be delivered via the enteral route. This may require flexibility and adaptation. In patients with ileus, aggressive enteral feeding may worsen the risk of bacterial translocation and worsen sepsis; so, consideration should be given to mixed enteral and parenteral nutrition [110]. In critically ill patients with cirrhosis, the protein requirement may be adjusted on the basis of the degree of catabolism and the presence of renal failure. In patients on hemodialysis (HD) or continuous renal replacement therapy (CRRT), the goal of protein supplementation is preventing the development of net nitrogen loss. Caloric requirements are increased in the presence of critical illness. Critical illness is accompanied by a hypermetabolic state related to the activation of various catabolic hormones. This situation results in elevated energy expenditure (EE), increasing the risk of malnutrition among patients [111]. Underfeeding is associated with an increased hospital length of stay, incidence of complications such as infections and organ failure, and overall mortality [112]. Hence, nutritional support must be modified to maintain normoglycemia. A moderate blood glucose range of 140–180 mg/dL is generally recommended, as a recent, large, randomized, controlled trial in patients without cirrhosis suggests that "tight" glucose control is undesirable [113].

Micronutrients

Thiamine deficiency is common in the majority of patients with chronic liver disease, often with absent classic findings associated [114]. Thus, empiric parenteral replacement with a dose of 100 mg thiamine given intravenously daily for 3–5 days is recommended. Trace mineral deficiencies such as zinc and selenium are well documented in cirrhosis [115]. Zinc replacement at a dose of 25–50 mg elemental zinc three times daily is recommended [116, 117], while there is insufficient evidence at present to recommend routine replacement of selenium. In patients with alcoholic cirrhosis, continued alcohol consumption contributes to anabolic resistance and muscle degradation by suppressing mTOR activity; therefore, a complete alcohol cessation is recommended [55, 118]. Finally, as above, low serum BCAAs in cirrhotic patients have been shown to accelerate muscular protein catabolism, decreased albumin synthesis, hyperammonemia, and associated HE [119]. Though the data are mixed, supplementation is safe and possibly beneficial where BCAA are available [120–122].

Exercise

Although moderate exercise is safe and possibly effective in reversing or forestalling sarcopenia and clinical frailty, [123] data are lacking regarding safety and efficacy in patients with cirrhosis and critical illness. However, established recommendations from critical care guidelines parallel exercise recommendations for cirrhotic patients in the outpatient setting and can be instituted in lieu [124, 125]. Specific measures include minimization of sedation, "sedation holidays," and early mobilization and physical therapy even for patients undergoing mechanical ventilation.

Ammonia-Lowering Measures

The principle benefit of HE-directed therapy is to treat the cognitive dysfunction that could interfere with nutritional or physical activity goals. At the same time, chronically elevated serum ammonia levels in cirrhosis are considered a major contributor of muscle catabolism by impairing protein synthesis and increasing proteolysis by autophagy [46, 126, 127]. Ammonia-lowering therapies are therefore exciting options in studies that aim to reverse sarcopenia [128]. However, so far, there are no published studies to show the impact of these therapies on prevention or reversal of sarcopenia.

Amelioration of Portal Hypertension

Improvement in the degree of portal hypertension has the theoretical advantage of altering nutritional balance by improving nutrient absorption (by reducing portal hypertensive gastropathy), nutritional intake (decrease in ascitic volume, increased appetite), and nutritional balance (reduced metabolic rate by decreasing hyperdynamic circulation). TIPS has also been shown to increase adiponectin production, suggesting an anabolic state [129]. Though one uncontrolled study demonstrated an increase in muscle mass and overall prognosis in patients with successful TIPSS placement, further validation studies are needed [130].

Hormonal Supplementation

In studies, as many as 90% of male patients with cirrhosis have low total testosterone levels, likely due to an amalgamation of defects across the hypothalamic–pituitary–testis axis and diminished sex hormone-binding globulin [131–133]. Low serum testosterone is associated with both sarcopenia and mortality [134].

Testosterone supplementation is associated with improved muscle function, albeit in one small trial [135]. Cirrhosis is also associated with low growth hormone secretion compounded with impaired end-organ responses to the hormone [136, 137]. Growth hormone promotes mTORC1 signaling in the muscles via insulin-like growth factor-1, but studies so far have not shown adequate benefit of growth hormone supplementation in clinical studies [138]. In summary, there is insufficient evidence to recommend hormone treatment in cirrhosis to improve muscle mass.

Experimental Treatments

As above, chronic liver disease is associated with metabolic alterations of diminished activity of mTOR (diminishing protein synthesis) and increased activity of myostatin (increased protein catabolism). Therefore, theoretically, myostatin antagonists and mTORC1 activators have great potential to reverse sarcopenia in cirrhosis. A recent phase 2 proof-of-concept study in elderly, sarcopenic patients [139] found that humanized monoclonal antimyostatin antibody increased lean muscle mass as well as gait speed. Follistatin, a myostatin antagonist, has been proven in animal studies [140]. These serve as exciting potential future additive therapies.

Liver Transplantation

Liver transplantation is the definitive treatment for end-stage liver disease and removes several contributing factors to pathogenesis of sarcopenia. Liver transplantation restores normal hepatocyte function, reduces portal pressure, and augments metabolic alterations promoting muscle catabolism. Conversely, standard immunosuppressive medications such as corticosteroids, calcineurin inhibitors, and mTOR inhibitors are known to adversely affect muscle mass by activating myokines and also increase fat mass (sarcopenic obesity). Studies have shown that after liver transplantation, muscle mass can either stabilize, increase, or decrease [141, 142]. Thus, the role of liver transplantation is to primarily correct underlying hepatic dysfunction and portal hypertension, while it is imperative to timely recognize and intervene on underlying sarcopenia and frailty prior to liver transplantation to improve post-transplant outcomes and to prevent further muscle breakdown in the post-transplant, immunosuppressive period.

Conclusion

Frailty and sarcopenia are common and often under-recognized and overlooked complications of cirrhosis and can occur even in the earliest stages of disease. Sarcopenia is clinically significant as it increases the risk of complications,

decompensation, and overall mortality in patients with cirrhosis. This complication does persist and can even worsen after liver transplantation. Early recognition using the tools outlined above is imperative in assessing and ameliorating sarcopenia and frailty to improve the overall survival in patients with advanced liver disease.

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Chapter 10
Acute Alcoholic Hepatitis

John P. Rice

Epidemiology

According to the World Health Organizations (WHO) 2018 "Global Status Report on Alcohol and Health", in 2016 over half (57% or 3.1 billion) people aged 15 years or older had consumed alcohol in the previous year [1]. The total amount of alcohol consumed per capita for those 15 years of age and older in 2016 was 6.4 liters of pure alcohol, stable from 2010, but increased from 5.5 liters in 2005. Worldwide, there is wide variation in alcohol consumption [1]. The highest rates of alcohol consumption, with current drinking rates in excess of 50%, are found in the WHO Americas, Europe, and Western Pacific regions [1]. The lowest rates of alcohol consumption are found in the WHO Eastern Mediterranean and South-East Asian regions. Economic wealth of countries is associated with higher alcohol consumption and a higher prevalence of active drinkers worldwide. In terms of heavy drinking, the WHO defines heavy episodic drinking as the consumption of more than 60 grams of pure alcohol on at least one occasion at least once a month [1]. For a reference, in the United States, one standard drink contains 14 grams of alcohol, or the amount of alcohol found in one standard beer (5% alcohol weight/volume), 5 ounces of wine (~12% weight/volume), or 1.5 ounces of liquor (~40% weight/volume). Heavy episodic drinking has decreased globally from 22.6% in 2000 to 18.2% in 2016 of the total population, but remains common in active drinkers with the highest rates of heavy drinking in Eastern Europe and some sub-Saharan African countries [1]. In the United States, data from the third National Epidemiologic Survey on

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Table 10.1 DSM-V diagnosis of alcohol use disorder [3]

1. Had times when you ended up drinking more or longer than you intended	The presence of at least 2 of these symptoms indicates an Alcohol Use Disorder (AUD). The severity of the AUD is defined as: Mild: The presence of 2 to 3 symptoms Moderate: The presence of 4 to 5 symptoms Severe: The presence of 6 or more symptoms
2. More than once wanted to cut down or stop drinking, but couldn't	
3. Spent a lot of time drinking or being sick and getting over the after-effects	
4. Wanted a drink so badly you couldn't think of anything else	
5. Found that drinking, or being sick from drinking, interfered with taking care of your home or family? Or caused job problems? Or school problems?	
6. Continued to drink even though it was causing problems with your family or friends?	
7. Given up or cut back on activities that were interesting to you, or gave you pleasure, in order to drink?	
8. More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?	
9. Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?	
10. Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?	
11. Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?	

Alcohol and Related Condition showed that 14% of adults currently met DSM-V criteria (Table 10.1) for alcohol use disorder while 29% met criteria for alcohol use disorder at some point in their lives [2, 3].

Worldwide, harmful alcohol consumption accounted for approximately 3 million deaths, or 5.3% of all deaths, in 2016 [1]. The highest rates of alcohol-related deaths were found in the WHO Americas and European regions. In the United States, alcohol consumption is the third leading cause of preventable death [4]. The most common causes of death attributable to alcohol are diseases of the digestive tract (including liver disease), unintentional injuries, cardiovascular disease, and malignant neoplasms [1]. The association between alcohol consumption and the development of alcoholic liver disease (ALD) is well described [5]. Rates of ALD are higher in areas of the world with greater alcohol consumption [6]. Worldwide, alcohol was attributed in 48% of the deaths from cirrhosis and 10% of the deaths from liver cancer [1]. However, despite the clear association between harmful drinking and ALD, only a small proportion of heavy drinkers develop alcoholic cirrhosis or end-

stage liver disease (ESLD), defined as cirrhosis plus a complication of decompensation such as variceal hemorrhage, the formation of ascites, or hepatic encephalopathy. The risk of development of cirrhosis and ESLD is dose related to the amount of alcohol consumed. The point prevalence of alcoholic cirrhosis is 1% in those consuming 30–60 grams of alcohol per day up to about 5.7% in those consuming in excess of 120 grams per day [5]. Multiple additional variables including chronic viral hepatitis, body mass index and the metabolic syndrome, sex, age, and genetics likely play a role in the risk of development of cirrhosis in the individual with harmful alcohol consumption [7, 8].

Pathophysiology of ALD

Upon ingestion, ethanol is rapidly metabolized to acetaldehyde by the enzyme alcohol dehydrogenase (ADH) located within the gastric mucosa [9]. The gastric mucosa contains a high concentration of ADH isozymes and the conversion of ethanol to acetaldehyde results in a high first pass metabolism of alcohol and a protective effect against hepatotoxicity by preventing absorption of ethanol in the small and large intestines with subsequent delivery to the portal circulation [10, 11]. This effect is confined to the stomach as ADH is not found in intestinal mucosa. The conversion of ethanol to acetaldehyde in the stomach is variable and dependent on a number of factors. Men have a higher amount and activity of ADH in the gastric mucosa compared to women which leads to higher systemic ethanol concentrations in women with a similar alcohol ingestion [11]. In addition, consuming alcohol with a meal increases gastric emptying time and can lead to a greater amount of ethanol converted to acetaldehyde in the stomach [12]. Chronic, excess ethanol ingestion can lead to decreased ADH activity in the stomach and thus increased serum ethanol concentrations [10]. Finally, disorders of gastric motility or a history of gastric surgery, such as gastric bypass, may have a significant impact on the delivery of ethanol to the small intestine [13].

Upon transit to the small intestine, ethanol is rapidly absorbed by the mucosa of the small bowel and delivered to the portal circulation. Only a small amount of alcohol is typically delivered to the distal small intestine or large intestine. Ninety percent of absorbed ethanol is eliminated by oxidation in the liver [14]. The duration of drinking and amount of ethanol consumed leads to increasing demands for the metabolism of ethanol and potentiates hepatotoxicity [9].

The exact mechanism of the development of ALD from alcohol is not completely understood. However, major advances have been made in the understanding of how ethanol leads to progressive liver injury. The first mechanism of liver injury is the metabolism of ethanol to acetaldehyde in the hepatocytes [14]. The predominant pathway of ethanol metabolism is conversion to acetaldehyde via ADH present in the hepatocyte cytosol. Catalysis of this reaction requires conversion of NAD+ to NADH. Additional metabolism of ethanol occurs through the enzyme catalase and

cytochrome P450-2E1, the latter being utilized in heavy ethanol consumption and generating reactive oxygen species (ROS) [9, 15].

Acetaldehyde can bind to microtubules impairing the normal excretion of proteins from the hepatocyte leading to hepatocyte swelling [16]. Metabolism of acetaldehyde to acetate occurs via acetaldehyde dehydrogenase (ALDH) generating further NADH. Excess NADH is a source of ROS via mitochondrial oxidation [17].

The second mechanism of hepatotoxicity occurs via actions of the Kupffer cells. Alcoholic steatohepatitis is associated with the formation of the proinflammatory Kupffer cell, or M1 phenotype [18, 19]. Under direct exposure to ethanol or indirectly via gut-derived lipopolysaccharide (LPS), a major membrane component of gram-negative bacteria (GNB), Kupffer cells can mediate a local inflammatory state by creating free radicals and releasing proinflammatory cytokines [9, 20]. Concentrations of LPS are markedly increased following ethanol ingestion, and thus LPS may play a pivotal role in the development of alcohol-induced hepatotoxicity [20]. Finally, and perhaps the strongest argument for the pivotal role of the Kupffer cell in the development of ethanol-mediated hepatotoxicity is that alcohol-mediated liver injury is largely prevented in rats treated with gadolinium chloride to inactivate Kupffer cells [21].

A third implicated mechanism of ethanol-induced hepatotoxicity is the dysregulation of the intestinal microbiome. Ethanol ingestion can lead to intestinal dysbiosis, or alterations in the bacterial diversity of the human gut [22, 23]. Ethanol consumption leads to a decrease in *Bacteroidetes* and an increase in *Proteobacteria* in the colonic microbiome [22]. This dysbiosis correlates with LPS production in certain patients. The mechanism of increased LPS may be related to dysbiosis leading to impairments in tight junction proteins and an increase in gut permeability and thus increased LPS access to the portal circulation [24]. Supporting the theory of dysbiosis in the pathophysiology of AH, fecal transplantation from humans with severe AH to germ-free mice conferred an increased risk of ethanol-induced hepatotoxicity compared to fecal transplantation from alcoholics without AH [25]. In addition to alterations in bacterial populations, chronic ethanol ingestion can lead to dysbiosis of the fungal population of the colon as well. Finally, both intestinal bacteria and fungi have the ability to both generate ethanol and metabolize ethanol [9, 26]. The role of ethanol generation or metabolism by the microbiome in the development of or protection from alcoholic liver disease has not been well studied.

Finally, it is clear that genetics play a critical role in the development of or protection from ethanol-induced hepatotoxicity. Genetic variation in the activity of ADH, ALDH, and enzymes that counteract oxidative stress such as glutathione-S transferases and superoxide dismutases may have significant impact on the hepatotoxicity of alcohol ingestion and the individual susceptibility to the development of ALD [9, 27]. Similarly, polymorphisms in genes coding for cytokines released by proinflammatory Kupffer cells may increase the individual risk for hepatotoxicity [28, 29]. Finally, genetic variations in patatin-like phospholipase domain-containing protein 3 (PNPLA-3), a lipase mediating hydrolysis of triacylglycerol molecules, have conferred risk for the development of both alcoholic and non-alcoholic fatty liver diseases [30].

Histopathology

ALD encompasses a spectrum of histopathologic injury ranging from asymptomatic simple hepatic steatosis to severe inflammatory steatohepatitis. Fibrosis related to alcohol injury is likewise variable from minimal fibrosis to cirrhosis.

Hepatic Steatosis and Cirrhosis

Hepatic steatosis or the accumulation of lipid droplets in the cytoplasm of the hepatocytes can occur after only a few days of heavy drinking. The steatosis typically begins to accumulate in the centrilobular hepatocytes and progress toward the periportal zones [31]. Alcoholic steatosis frequently starts as microvesicular steatosis which can coalesce into large fat droplets that displace the nucleus to the periphery termed macrovesicular steatosis. By definition, if greater than 5% of hepatocytes contain fat droplets, it is considered pathologic. It is also important to note that other disease processes, particularly the metabolic syndrome, can also lead to hepatic steatosis. In simple steatosis, there is no evidence of inflammation or fibrosis associated with the hepatic steatosis and the disease is almost never symptomatic. With alcohol abstinence, simple steatosis will resolve. However, continued heavy alcohol use can lead to progressive fibrosis of the liver and eventually cirrhosis. Ongoing heavy alcohol use leads to activation of hepatic stellate cells leading to collagen deposition [31]. Similar to the accumulation of steatosis, fibrosis tends to begin centrilobular and progress perivenular. The accumulation of fibrosis has a distinct pericellular or "chicken-wire" pattern of collagen deposition surrounding the individual hepatocytes. If ongoing alcohol-related damage continues, then fibrous septa form between the portal tracts and central veins eventually leading to bridging fibrosis and frank regenerative nodule formation, the hallmark of cirrhosis.

Alcoholic Steatohepatitis (ASH)

In addition to simple steatosis and cirrhosis, long-standing heavy alcohol use can lead to alcoholic steatohepatitis (ASH). It is important to distinguish the clinical syndrome of AH and the histopathologic finding of ASH [31, 32]. First, while the majority of patients who present with clinical AH will have ASH on biopsy, other histological variants can be seen. These variants include alcoholic foamy degeneration (AFD) and alcoholic fatty liver with cholestasis (AFLC) [31]. Additionally, some patients with a clinical syndrome compatible with AH have only findings of cirrhosis on biopsy without significant steatosis or inflammation suggesting ACLF, or the sudden development of hepatic decompensation and often multiple organ

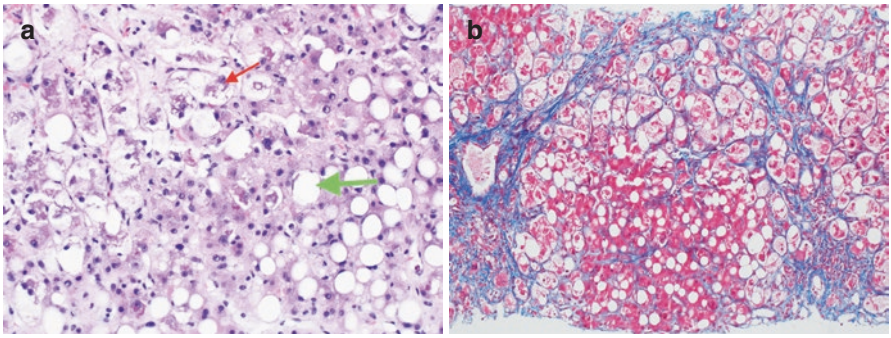

Fig. 10.1 (**a**) Histopathology of alcoholic steatohepatitis (Hematoxylin and eosin (H & E) stained, 200× magnification). Macrovesicular steatosis (green arrow) droplets in the hepatocytes displacing the nucleus to the periphery. Abundant ballooned hepatocytes containing pink cytoplasmic inclusions called Mallory-Denk bodies (red arrow). (**b**) Trichrome stain reveals advanced fibrosis deposition (blue) in a pericellular or "chicken-wire" pattern typical for alcoholic steatohepatitis

failure in a patient with previously stable cirrhosis. Conversely, many patients with histologic ASH may be asymptomatic with only deranged aminotransferases evident clinically termed "walking AH."

ASH is defined by the presence of hepatic steatosis in addition to hepatocyte injury and inflammation (Fig. 10.1). Hepatocyte injury is most frequently seen as hepatocyte ballooning caused by cytoskeletal damage and oncotic swelling which can eventually lead to hepatocyte necrosis. Ballooned hepatocytes appear rounded as opposed to the polygonal appearance of a normal hepatocyte. The cytoplasm of a ballooned hepatocyte appears cleared and reticulated, frequently with the presence of ropey, eosinophilic inclusions classically known as Mallory-Denk bodies. The inflammatory infiltrate of ASH is most notable for lobular neutrophilic infiltrate, often surrounding ballooned hepatocytes, a phenomenon termed satellitosis. Portal inflammation is typically milder than seen in other forms of chronic hepatitis and is typically of mixed cell lineage. Hepatocyte steatosis, typically macrovesicular, is almost always present to some degree, but is not requisite to make a diagnosis of ASH. Fibrosis is near universal and deposited in the "chicken-wire" pericellular pattern typical for ALD. Fibrosis is usually quite advanced and up to 90% of patients with histologic ASH will also have concomitant cirrhosis. Other features of ASH include sclerosing hyaline necrosis or the obliteration of central veins by thick bands of collagen, a finding considered pathognomonic for alcohol-related injury, enlarged mitochondria termed megamitochondria, and ductular reaction.

AFD is defined pathologically by the development of abundant microvescicular steatosis with a relative paucity of the macrovesicular fat, hepatocyte ballooning, Mallory-Denk bodies, and inflammatory infiltrate seen in ASH. Fibrosis can be variable. AFD can present clinically as AH. The pathogenesis of AFD is hypothesized to be driven by hepatocyte degeneration related to mitochondrial dysfunction rather than inflammatory injury.

AFLC is defined pathologically by the development of abundant macrovesicular steatosis and cholestasis again with paucity of ballooning, Mallory-Denk bodies, and inflammation. Fibrosis is also variable. AFLC can present with typical clinical AH, but also as biliary obstruction.

Differentiation from Other Diseases

The histologic features of ALD overlap considerably with other diseases, and no pathologic feature can reliably be used to distinguish ALD from other diseases. The most common cause of macrovesicular hepatic steatosis and steatohepatitis is non-alcoholic fatty liver disease (NAFLD) related to the metabolic syndrome, with co-morbidities such as type 2 diabetes mellitus, hypertension, dyslipidemia, and obesity. While there are typically some subtle differences in the histologic appearance of ASH and NASH, only the presence of microvesicular steatosis or sclerosing hyaline necrosis is seen in ASH alone. In addition, many patients with alcohol use disorders also have features of the metabolic syndrome and NAFLD, thus making a singular diagnosis difficult. In addition to the metabolic syndrome, Wilson's disease can present with macrovesicular steatosis, steatohepatitis, and Mallory-Denk bodies. Multiple medications are also known to cause macrovesicular hepatic steatosis and steatohepatitis, most commonly amiodarone, methotrexate, and tamoxifen, as well as total parenteral nutrition [31].

Liver injury marked by microvesicular steatosis is less common than macrovesicular steatosis. Prominent microvesicular steatosis is seen in acute fatty liver of pregnancy and in drug-induced liver injury. Drugs known to cause microvesicular steatosis include aspirin (Reye's syndrome), non-steroidal anti-inflammatory medications, valproic acid, and nucleoside reverse transcriptase inhibitors to treat human immunodeficiency virus (HIV) [31].

Clinical Presentation

AH is a clinical illness characterized by the sudden development of jaundice in the setting of heavy antecedent alcohol use. Heavy alcohol use is invariable in the history of AH. The exact amount of alcohol consumption necessary for the development of AH is largely unknown; however, in healthy volunteers, drinking 10 drinks per day over 2–3 weeks will consistently lead to hepatic steatosis [33]. Most patients with clinical AH report similar levels of drinking or more, often for decades, prior to the development of AH. However, it is important to note that only a minority of individuals at that level of drinking will develop AH. The National Institute of Health (NIH) has created consensus criteria (Table 10.2) that set a minimum threshold of 3 standard drinks per day (40 grams/day) for women and 4 standard drinks (~50–60 grams/day) for men for the development of AH [32]. For a diagnosis of AH, this

Table 10.2 NIAAA consensus definitions in the diagnosis of alcoholic hepatitis (AH) [32]

Minimum criteria for a diagnosis of alcoholic hepatitis:	**Definite alcoholic hepatitis**: Clinical AH and biopsy-proven AH
Serum bilirubin >3.0 mg/dL Consumption of more than 3 standard drinks (40 grams) per day for women and 4 drinks (50–60 grams) per day for men for greater than 6 months Less than 60 days from last drink to the development of jaundice AST > 50 IU/L but AST/ALT less than 400 IU/L AST:ALT ratio of >1.5	**Probable alcoholic hepatitis**: Meets minimum criteria for AH without confounding factors Negative immune markers (ANA <1:160, ASMA <1:80 dilution) Absence of sepsis, shock, cocaine use, or drug use at risk of DILI within 30 days *Biopsy not required for diagnosis*
	Possible alcoholic hepatitis: Does not meet minimum criteria OR potential confounders Inconsistent alcohol history Atypical laboratory studies (AST < 50, ALT/AST > 400, or AST:ALT ratio < 1.5) Recent shock (hemorrhagic or septic) Positive immune markers (ANA >1:160 or ASMA >1:80) Suspicion of DILI *Biopsy recommended to confirm diagnosis*

Abbreviations: *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ANA* antinuclear antibody, *ASMA* anti-smooth muscle antibody, *DILI* drug-induced liver injury

threshold of daily alcohol consumption should have occurred for more than 6 months although short periods of abstinence may have occurred. In practice, most patients with AH greatly exceed this minimum threshold of alcohol consumption prior to developing jaundice. Jaundice should occur within 60 days of the last drink [32].

Because AH is a disease of heavy drinking, taking an accurate alcohol use history is the most important step in making a diagnosis. It is essential that the provider takes an alcohol history in a non-judgmental way and reassures the patient that the information is needed for an accurate diagnosis and to provide appropriate medical care rather than for punitive purposes. However, obtaining an accurate alcohol history can be challenging for a number of reasons. Patients may not be forthright in providing an accurate alcohol use history [34]. Patients may experience a great deal of shame related to their alcohol use and its consequences. In addition, the nature of alcohol addiction can lead to misrepresentation of alcohol use to protect the substance relationship. Some patients may worry that acknowledgement of alcohol abuse may lead to inferior care or judgment by the medical staff. Finally, some patients may hide their drinking from family and colleagues and thus fear consequences in their relationships or employment.

Amounts and patterns of drinking may change over time often in a pattern of recovery and relapse. Additionally, in the weeks leading up to clinical presentation with AH, many patients may drastically reduce the amount of alcohol consumed or abstain altogether due to a decline in health. Therefore, it is important to take a thorough alcohol history throughout the patient's life. Questions about past legal, health, or social consequences of alcohol use may help identify problem drinkers suspected of under reporting their drinking. With permission, interviewing relatives

or friends may provide accurate information when there is a high suspicion for AH, but an alcohol history inconsistent for AH.

The clinical syndrome of AH varies from largely asymptomatic with mild derangements in liver function to florid liver failure with the development of complications of end-stage liver disease [35, 36]. Variceal hemorrhage, ascites and hepatorenal syndrome, and hepatic encephalopathy are common in severe AH and may be the event that leads the patient or their family to seek medical attention. Additional features of AH include fever and/or leukocytosis without a clear infectious source identification, anorexia, and sarcopenia. Many patients will report difficultly eating in the days to weeks leading up to clinical presentation and commonly are receiving a majority of their daily caloric intake in the form of alcoholic beverages. Abdominal pain may be present, typically as a dull, constant ache in the right upper quadrant and is thought to be secondary to hepatomegaly induced by severe hepatic steatosis and inflammation.

On physical examination, relative hypotension and tachycardia may be seen as a consequence of portal hypertension leading to splanchnic vasodilation and a compensatory increase in cardiac output termed "cirrhotic cardiomyopathy." In fact, many patients with AH will meet criteria for the systemic inflammatory response syndrome (SIRS), defined as two or more of the following: a temperature above 38 °C (100.4 °F) or below 36 °C (96.8 °F), heart rate greater than 90 beats per minute, respiratory rate greater than 20 respirations per minute or a $PaCO_2$ less than 32 mmHg, and a white blood cell count greater than 12,000/mm^3 or less than 4000/mm^3 or greater than 10% bands. Patients with AH often meet SIRS criteria even in the absence of a clinically evident infection. Jaundice is universal and typically quite overt in AH, particularly when severe, but in milder cases, only sublingual jaundice or faintly icteric sclera may be noted. Spider angiomata, telangiectatic lesions notable for radiating red tendrils around a central red spot, are very common in AH and often readily identifiable on the face, neck, and upper chest. Cardiac examination may reveal tachycardia and a systolic flow murmur related to elevated cardiac output. Abdominal examination may be notable for tender hepatomegaly which can be massive related to marked hepatic steatosis and hepatocyte swelling [37]. A hepatic bruit may be heard. Splenomegaly is also common, but typically not massive. Abdominal distention related to ascites and generalized anasarca related to portal hypertension and hypoalbuminemia may be present. Muscle wasting and cachexia, often marked, are frequently observed secondary to malnutrition [38]. Alterations in mental status are common and may be related to multiple coexisting factors including gastrointestinal bleeding, hepatic encephalopathy, uremia secondary to AKI, infection/sepsis, and/or alcohol withdrawal.

On laboratory testing, AH is minimally defined with a serum total bilirubin in excess of 3 mg/dL by the NIH consensus criteria (Table 10.2) [32]. Elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are typically moderate with values exceeding 50 IU/mL, but not greater than 400 IU/mL [32]. AST is higher than ALT in a ratio greater than 1.5 [32]. Coagulopathy is usually evident as prolongation of the prothrombin time (PT) and international normalized ratio (INR). The etiology of the disturbances in PT and INR is typically impaired

hepatic synthesis of serum clotting factors secondary to hepatic dysfunction. However, vitamin K deficiency secondary to malnutrition may also lead to prolongation of the PT/INR. Serum albumin is typically low secondary to hepatic synthetic dysfunction and malnutrition. Abnormalities in peripheral blood count are very common. A neutrophil predominant leukocytosis is common in the absence of concurrent infection [39]. Occasionally, profound leukocytosis is seen and is associated with a poor prognosis [40]. Anemia, frequently macrocytic, is common and is often secondary to multiple factors including anemia of chronic disease, bone marrow alcohol toxicity, a deficiency in iron, folic acid, and/or vitamin B12, gastrointestinal hemorrhage, renal failure, and hemolysis secondary to spur cell anemia or disseminated intravascular coagulation. Many patients have multiple competing risk factors for anemia. Thrombocytopenia is commonly seen and most commonly secondary to splenic sequestration secondary to portal hypertension. Alcohol bone marrow toxicity can also result in reversible thrombocytopenia. Finally, due to the inflammatory nature of AH, acute phase reactants are elevated. Serum levels of ferritin, ceruloplasmin, and alpha-1-antitrypsin are frequently elevated in patients with AH thus limiting the diagnostic utility of those tests for concomitant liver disease.

On ultrasound imaging, the liver may appear enlarged and echogenic consistent with hepatic steatosis. Given the frequency of underlying cirrhosis, the liver may appear nodular. On cross-sectional imaging, recanalization of the umbilical vein may be noted as well as other features of portal hypertension such as splenomegaly, the presence of varices, and ascites. Hepatocellular carcinoma should be considered as a possible etiology in the development of decompensated alcoholic liver disease even in cases of clinically probable AH. Likewise, the development of portal vein thrombosis can be an event precipitating variceal hemorrhage or the worsening of pre-existing encephalopathy.

Diagnosis

Despite the unique presentation of AH, making a clinical diagnosis of AH can be challenging. Previous studies have shown clinical diagnostic inaccuracy up to 46% of patients presenting with possible AH [41–43]. Some patients with a possible diagnosis of AH may have another concomitant liver disease or, in some cases, an alternative diagnosis altogether. Risk factors for chronic viral hepatitis B (HBV) and C (HCV) may be present in patients with alcohol use disorders and testing for HBV and HCV should be performed. As mentioned previously, since ferritin is an acute phase reactant, laboratory evidence of iron overload is common and while concomitant hereditary hemochromatosis should be considered, the vast majority of patients with AH and an elevated ferritin will not have hemochromatosis. Many patients with AH may present in septic or hemorrhagic shock leading to the development of hepatic ischemia or “shock liver.” Drug-induced liver injury (DILI) should also be considered in patients recently starting on a medication with hepatotoxicity risk. In cases in which there is some diagnostic uncertainty or the potential

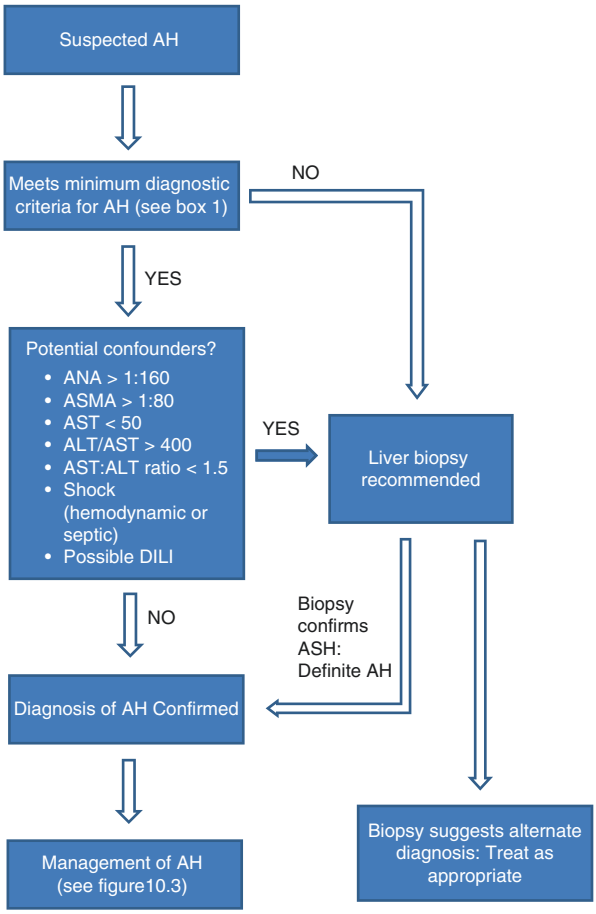

Fig. 10.2 Diagnostic algorithm in suspected alcoholic hepatitis

for a confounding diagnosis exists, a liver biopsy is appropriate (Fig. 10.2). Liver biopsy may provide an alternate diagnosis in approximately 10–20% of cases of possible AH [44]. In addition, liver biopsy findings may be predictive of outcome in AH [45]. While liver biopsy may provide some utility in making a diagnosis of AH and predicting outcomes, in practice, liver biopsy is rarely performed in this population, particularly in the United States. Patients with AH are often coagulopathic and thrombocytopenic, and thus there is a risk of bleeding. In addition, many patients with severe AH may have ascites. As a result, transjugular liver biopsy is considered the preferred method of biopsy in most AH patients. However, many centers lack the capability and expertise in performing transjugular biopsy and thus rely on clinical features to make a diagnosis of AH.

Given the lack of practicality and real-world applicability of liver biopsy for the confirmation of histopathologic AH, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Alcoholic Hepatitis Consortia created consensus criteria for

the diagnosis of AH (Table 10.2) [32]. These recommendations provide guidance for practitioners in determining who would benefit from liver biopsy in making a diagnosis of AH. Biopsy-proven AH are considered to have definite AH. Patients meeting clinical criteria for AH without potential confounding factors are given a diagnosis of probable AH, and a biopsy is not necessary for diagnosis. For patients with either an atypical history for AH or potential confounding factors, a diagnosis of possible AH is given and biopsy is recommended to confirm the presence of ASH and absence of an alternative diagnosis [32].

An algorithm for the diagnosis of AH is found in Fig. 10.2.

Acute on Chronic Liver Failure (ACLF) and AH

ACLF, discussed further in Chap. 11, is a recently defined entity manifested as the acute deterioration in liver function and organ failure with associated high short-term mortality [46]. While there are several different definitions for ACLF endorsed by different scientific societies, the underlying concept of ACLF as a consequence of the systemic inflammatory response is shared.

Clinically, it is clear that there exists a considerable overlap between the diagnoses of severe AH and ACLF. First, the vast majority of patients with severe AH have underlying alcoholic cirrhosis. In addition, alcohol consumption is a common precipitant of ACLF. In a European observational study, excess alcohol consumption in the previous 3 months was the second most common precipitant of ALCF behind bacterial infection [47]. In South Asia, alcohol consumption is the most common precipitant of ACLF [48]. Additionally, many patients with severe AH will also meet criteria for ACLF and the primary cause of death in severe AH is the development of multi-organ failure as defined in ACLF.

What is not clear is what proportion of patients with ACLF and recent alcohol use have AH. Given that most patients with ACLF are in the ICU setting, coagulopathic, and may be hemodynamically unstable, liver biopsy may be hazardous and, in practice, rarely performed. The distinction between pathologic AH and "bland" cirrhosis may have some importance in terms of therapeutics and prognosis for recovery. Traditionally, in the absence of a liver biopsy confirming ASH, it is likely that ACLF related to severe AH and ACLF in alcoholic cirrhosis without concomitant ASH have been managed similarly. Whether or not therapeutic agents specific for AH provide benefit in patients with ACLF without AH is unclear.

Determining Short-Term Prognosis in AH

When a diagnosis of AH is confirmed, it is essential to determine the severity of illness. Mild-to-moderate AH has a generally good prognosis with alcohol abstinence, nutritional optimization, and best supportive care. However, severe AH is a critical illness with high short-term mortality. In addition, patients with severe AH may

Table 10.3 Scoring systems for determining severity/prognosis in alcoholic hepatitis (AH)

	Discriminant Function	Model for End-stage Liver Disease (MELD)	Glasgow Alcoholic Hepatitis Score (GAHS)	Age, Bilirubin, INR, Creatinine (ABIC)	Lille Model[a]
Variables collected	Serum total bilirubin Prothrombin time Control prothrombin time	Serum total bilirubin INR Serum creatinine	Age WBC Blood urea nitrogen Prothrombin time Control prothrombin time	Age Serum total bilirubin INR Serum Creatinine	Age Serum albumin at day 0 Serum creatinine at day 0 Prothrombin time at day 0 Serum total bilirubin at day 0 Serum total bilirubin at day 4 or 7
Interpretation at diagnosis	*Severe AH*: DF ≥ 32	*Severe AH*: Undefined Values > 20–25 considered high mortality risk	*Poor prognosis*: ≥ 9	*High mortality risk*: > 9 *Intermediate risk*: 6.71–9.00 *Low risk*: < 6.71	*NA*
Interpretation after 7 days of corticosteroid treatment	*NA*	*Favorable prognosis*: MELD decline by ≥2.6 points	*Favorable prognosis*: GAHS decline by ≥1	*Favorable prognosis*: ABIC decline by ≥0.29	*Favorable prognosis*: Lille model <0.45 *Poor prognosis*: Lille >0.45

[a]The Lille model is calculated from serum data on the date of corticosteroid initiation (Day 0) and at day 4 or 7 of corticosteroid therapy

benefit from additional pharmacologic therapy. There are several validated models for determining severity in AH that utilize laboratory variables that are generally widely available (Table 10.3). Each system generally performs well, and calculators are widely available both online and in smartphone applications. These scoring systems are the discriminant function (DF), model for end-stage liver disease (MELD), Glasgow alcoholic hepatitis score (GAHS), the age, bilirubin, INR, and creatinine (ABIC) score, and the Lille model. In addition to the aforementioned scoring systems, histology may provide prognostic information in AH.

Discriminant Function (DF)

The DF was the first validated scoring system to define the severity of AH. It was derived from a prospective, double-blinded, placebo-controlled trial of prednisolone for the treatment of AH utilizing the serum total bilirubin and prothrombin time

(PT) [49]. A value of greater than 32 had a 1-month mortality of 30–50%. Furthermore, in patients with a DF greater than 32, treatment with prednisolone resulted in a 30-day survival benefit [49]. DF has been widely adopted and has traditionally been the predominant scoring system used for determining severity in AH for both clinical care and for enrollment in clinical trials of severe AH.

The DF does have some limitations. First, while the sensitivity of DF is very good for determining patients at risk for short-term mortality, it lacks specificity and many patients with a DF greater than 32 will recover, even without steroids. In addition, the use of PT is problematic in centers in which the PT and control are not readily reported. Finally, the DF is used as a singular determination at the time presentation with AH, but not as a dynamic scoring system to assess response to treatment and changes in mortal risk. Recent studies using other static assessments of disease severity both in isolation and as part of "joint-effect" models with dynamic assessments (Lille model, see below) have demonstrated that DF performed inferiorly to other the other static assessments of disease severity and compared to joint-effect models [50].

Model for End-Stage Liver Disease (MELD)

The MELD score has been tested and validated as a prognostic marker in AH. Similar to the DF, MELD uses serum total bilirubin and the PT, reported as the INR. In addition, MELD incorporates serum creatinine which has been shown independently to be predictive of outcome in AH [51]. MELD has the advantage of being widely used in the practice of hepatology and utilizing variables available in a hospital laboratory. However, the MELD score that defines severe AH as a threshold for determining short-term mortality and a potential benefit from corticosteroid treatment has not been defined. In one study, a MELD score of greater than 11 had a sensitivity and specificity of 86% and 81%, respectively, in predicting 30-day mortality [52]. In another study, MELD performed similarly to DF in predicting 30-day mortality and a score of 21 or greater had a sensitivity and specificity of 75% in predicting 90-day mortality [53]. A third study identified a MELD score greater than or equal to 20 as having a 91% sensitivity and 89% specificity in predicting in-hospital mortality [54]. In addition, a MELD score increase of 2 or greater during the first week of hospitalization predicted mortality [54].

Finally, a recent evaluation of the STOPAH database, the largest prospective, randomized controlled trial of prednisone and pentoxifylline in AH, suggested that a MELD threshold of 25 best identified patients at high risk of mortality and a benefit from corticosteroids [50]. MELD was assessed both at diagnosis and then again at day 7. For patients with a MELD <25 at both diagnosis and at day 7, mortality was low at 28 days (8.6%) and not impacted by use of corticosteroids. For patients with an initial MELD <25, a subsequent rise above 25 at day 7 indicated a poor prognosis with 28 and 90-day mortality of 52.2% and 60.9%, respectively. Interestingly, no mortality benefit was seen with corticosteroid use in patients with

an index MELD >25. For patients with an initial MELD >25 and without gastrointestinal bleeding or sepsis, a decline in MELD of at least 2.6 points on day 7 predicted a favorable prognosis [50].

Interestingly, a novel scoring system combining MELD score and hepatic gene expression accurately predicted 90- and 180-day survival with an area under the curve of 0.86 and 0.83, respectively [55]. The scoring system requires a liver biopsy which might limit its generalizability in the community.

Glasgow Alcoholic Hepatitis Score (GAHS)

The GAHS is based on a multivariable-derived model utilizing age, serum total bilirubin, peripheral white blood cell count (WBC), blood urea nitrogen (BUN), and PT. The original validation study was performed in 195 patients with severe alcoholic hepatitis [56]. A GAHS greater than or equal to 9 had a lower sensitivity, but higher specificity than a DF > 32 in predicting 28-day mortality (81% vs. 96% and 61% vs. 27%, respectively) [56]. A second validation study of 225 patients with AH and a DF > 32 determined that patients with a GAHS ≥9 had a mortality benefit when treated with corticosteroids at 28 days and 84 days [57]. However, patients with a GAHS <9 had no mortality benefit from corticosteroids [57]. In an analysis of the STOPAH database, GAHS at diagnosis predicted mortality similar to MELD and ABIC, but superior to DF [50]. Persistently favorable GAHS at diagnosis and day 7 (score < 9) predicted a favorable prognosis with or without corticosteroids (5.9% mortality at 28 days). In patients without gastrointestinal bleeding or sepsis that presented with an index GAHS ≥9, treatment with prednisolone improved 28-day survival (21% vs. 29.3%, P = 0.04). Finally, a decline in the GAHS by greater than or equal to 1 predicted a favorable prognosis in patients treated with prednisolone [50].

Age, Bilirubin, INR, Creatinine (ABIC)

The ABIC model was derived and validated from a biopsy-proven cohort of AH. In the 103 patients with AH in the study cohort, the ABIC independently predicted mortality at 90 days and at 1 year [58]. The ABIC stratifies patients into low, intermediate, and high risk of death. In the analysis of the STOPAH database, ABIC performed similarly to MELD and GAHS in predicting mortality from AH and actually performed superiorly to DF [50]. An ABIC <6.71 at presentation and at 7 days had a low mortality at 28 days (6.6%), and prednisolone had no mortality benefit. For patients treated with corticosteroids, a fall in ABIC score by ≥0.29 at day 7 indicated a favorable prognosis [50]. For patients presenting with a high ABIC at presentation (≥ 6.71) and without sepsis or gastrointestinal bleeding, treatment with prednisolone improved mortality (14.6% vs. 21% 28-day mortality,

$P = 0.02$) [50]. It should be noted that a threshold ABIC of ≥9 predicted mortality in the original derivation which is higher than what was predictive in the STOPAH database.

Lille Model

The Lille model is considered a "dynamic" model of prediction because the model is based on the evolution of AH over time. The model is based on the observation that a decline in serum total bilirubin in patients with severe AH treated with corticosteroids is a favorable prognostic sign [59]. The model was derived from a cohort of 295 patients with severe AH treated with corticosteroids [60]. The model incorporates the variables of patient age, serum total bilirubin, INR, albumin, and PT at the initiation of corticosteroids and then the serum total bilirubin on day 7 of treatment. In a validation cohort, a Lille model >0.45 after 7 days of corticosteroids predicted a low 6-month survival (25% vs. 85%) [60]. A pooled meta-analysis using patient data from five randomized controlled trials of corticosteroids in severe AH of the Lille model was independently predictive of 28-day survival [61]. A subgroup analysis divided the patients as complete responders (Lille model ≤0.16, ≤35th percentile), partial responders (Lille model 0.16–0.56, 36th to 70th percentile), and non-responders (Lille model ≥0.56, greater than 70th percentile) [61]. Twenty-eight-day survival was strongly associated with the Lille model (91.1 ± 2.7% vs. 79.4 ± 3.8% vs. 53.3 ± 5.1%, $P < 0.0001$) [60]. Additionally, corticosteroids were only found to be of benefit in complete and partial responders.

A more recent publication determined that a 4-day Lille model was as accurate in predicting response to corticosteroids and mortality as the 7-day model [62].

Joint-Effect Modeling

Recently, attempts to further refine prognosis in AH have focused on utilizing both the static (DF, MELD, ABIC, GAHS) severity models and the dynamic Lille model. This "joint-effect" modeling was first derived and validated in a cohort collected from databases of patients with severe AH treated with corticosteroids in the United Kingdom and France [63]. They compared the performance of DF plus Lille, MELD plus Lille, and ABIC plus Lille in predicting survival at 2 and 6 months. All three joint-effect models better predicted outcome than the static or dynamic models alone. MELD-Lille performed best in predicting survival [63].

In addition to using serial assessments of the static models over 7 days as detailed above, the STOPAH trial database was also used to compare the performance of static models when combined with the Lille model. When combined with the static assessments, the Lille model had the highest AUC for predicting 28-day (0.732) and 90-day (0.722) mortality with hazard ratios (HR) of 11.13 and 8.15, respectively [50]. However, this was not statistically significant when compared with serial

assessments of the static scores at day 7 [50]. There was no difference in the outcome between responders and partial responders, and a Lille model of 0.45 was optimal for determining prognosis [50].

In conclusion, the assessment of severity of AH using modeling is critical in decision making in the management of AH. At the point of presentation, static modeling is essential for determining the severity of AH and the potential benefit of pharmacotherapy specific to the management of AH. The use of serial static model measurements at day 7 or the Lille model at day 4 or 7 is important for determining prognosis and the decision to continue corticosteroids or discontinue them in those not deriving benefit. Given that the existing tools do not greatly outperform one another in prediction, the choice of application of one measurement versus another is less important than understanding the critical role of these models in determining disease severity, response to therapy, and prognosis. In addition, minimizing exposure to high-dose corticosteroids is essential in those not receiving benefit to minimize infection risk in an otherwise highly vulnerable population. An analysis of the STOPAH database revealed an increased risk of serious infection in patients with severe AH treated with prednisolone [64]. The infection risk was highest after completion of corticosteroid treatment. Development of a serious infection was associated with a higher 90-day mortality in patients treated with prednisolone, independent of MELD score or Lille model.

Histology

The alcoholic hepatitis histology score (AHHS) is a prediction model based on biopsy findings in AH. The model was derived from 121 patients in Spain with AH using logistic regression to determine histologic variables predictive of death [45]. The scoring system was then tested and refined on 96 patients with AH in the United States and Europe. The AHHS was then validated in an additional 109 patients. Histologic features predictive of mortality were degree of fibrosis, degree of neutrophilic inflammation, type of bilirubinostasis, and the presence of metamitochondria. The biopsy was then characterized as low (0–3 points), medium, (4–5 points), or high risk (6–9 points) which predicted 90-day mortality (3%, 19%, and 51%, respectively; $P < 0.0001$) [45]. The use of histology may limit the widespread use of AHHS in the clinical setting.

Management of AH

General Management

The initial management of AH should include an assessment of hemodynamic and respiratory stability, and surveillance for infection (Fig. 10.3). Patients with AH may require critical care management at the point of presentation or develop

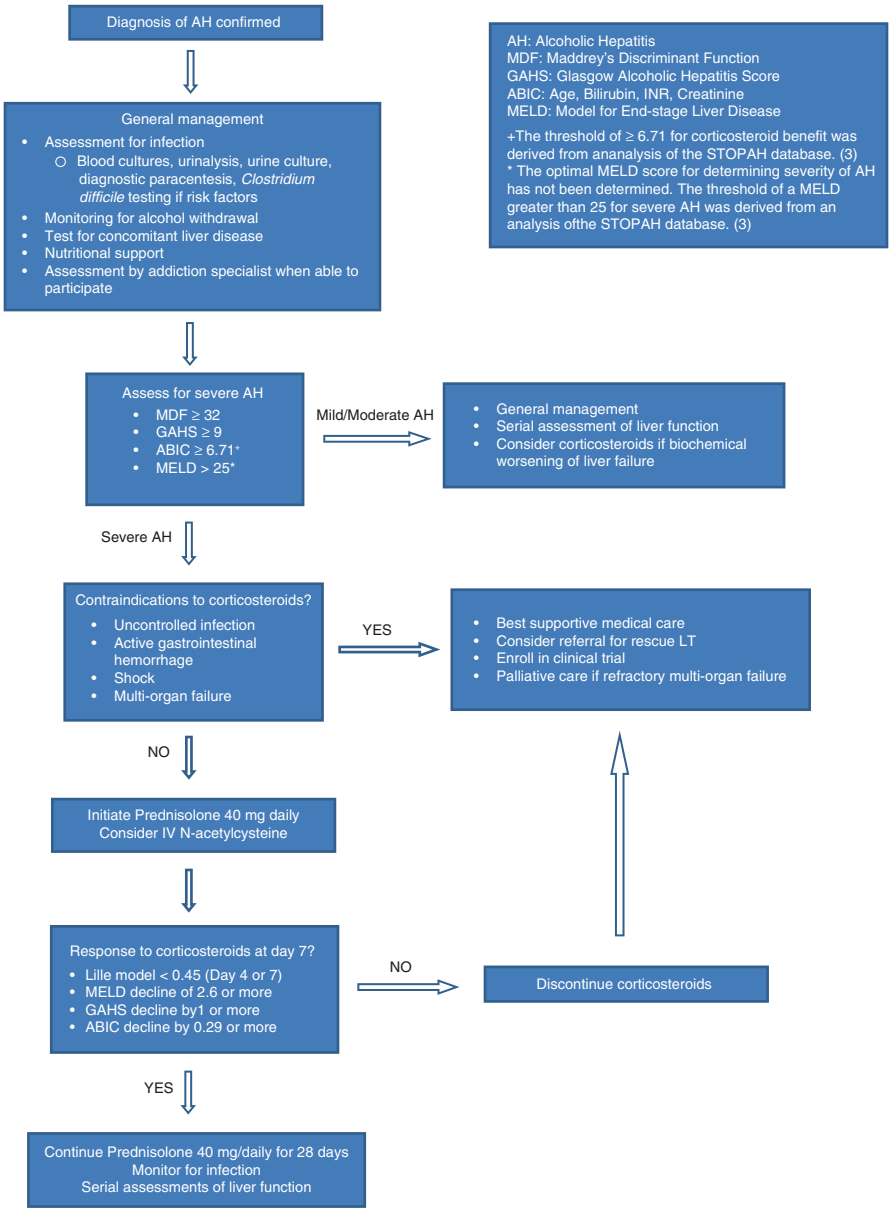

Fig. 10.3 The management of alcoholic hepatitis

life-threatening complications over the course of their care. Life-threatening gastrointestinal hemorrhage, sepsis and septic shock, renal failure, respiratory failure, and severe alterations in cognition to the point of coma may present at any point in the management of severe AH.

Infection is of particular concern in AH. Patients with AH, and ACLF in general, are at a high risk of developing infection and subsequently death from infection [46]. In a study of 246 patients with severe AH, infection at the time of presentation was present in 25.6% of the population [65]. The most common source of infection at presentation was SBP (44%), followed by pulmonary infection and urinary tract infections.

Surveillance for infection should be performed at the time of admission, especially in patients with severe AH and those with hemodynamic or respiratory instability. Blood and urine cultures should be obtained, and a chest X-ray is performed to diagnose pneumonia. In patients with significant ascites, diagnostic paracentesis should be performed to exclude SBP, regardless of symptoms. The absence of abdominal pain does not exclude SBP and a high index of suspicion is needed. Stool testing for *Clostridium difficile* is appropriate in hospitalized or recently hospitalized patients with diarrhea.

Monitoring for alcohol withdrawal should be initiated at the time of presentation, regardless of the last reported drink.

Management of the specific complications of portal hypertension is discussed in Chaps. 2, 3, and 4.

An assessment for co-morbid liver diseases is likewise important. Serum testing for HBV surface antigen (sAg), surface antibody (sAb), and core antibody (cAb) and HCV antibody is appropriate with reflex HCV RNA PCR testing in patients that screen positive for HCV antibody. Serologic testing for antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), is likewise appropriate. Imaging of the liver to evaluate concomitant hepatocellular carcinoma or portal vein thrombosis is warranted at the time of admission. Common findings in AH include hepatic steatosis, hepatomegaly, and surface nodularity consistent with cirrhosis. Any suggestion of a hepatic mass or portal vein thrombosis should reflex to a dedicated multi-phase CT or MRI of the liver. An assessment of serum alpha-fetoprotein can be considered.

As mentioned previously, the specificity of serum testing of ferritin, alpha-1 antitrypsin levels, and ceruloplasmin is markedly decreased in the setting of a severe inflammatory illness like AH. Results of testing should be interpreted with caution.

Alcohol Abstinence

The essential AH management is alcohol abstinence. With time and alcohol abstinence, there can be dramatic improvement in synthetic function and complications of portal hypertension. However, ongoing alcohol use leads to an increased risk of deterioration in liver function, complications of portal hypertension, the development of hepatocellular carcinoma and death [66]. Despite the importance of alcohol abstinence in the ultimate outcome of AH, data regarding the optimal management of alcohol use disorders in the setting of AH are largely unknown. Medications for management of alcohol cravings have not been studied in AH, and the risk of

drug-induced hepatotoxicity has limited enthusiasm for their use. Similarly, data on psychotherapy in the setting of AH are sparse. Nevertheless, given that abstinence is essential to recovery from AH, an assessment by an addiction specialist and a plan for alcohol treatment should be established as soon as the patient is able to participate.

Nutritional Support

Most patients with AH, particularly those with severe AH, suffer from protein calorie malnutrition, often severe. Anorexia is a common complaint in those suffering from AH, often manifest in the weeks to months leading up to hospitalization. Adequate nutrition is essential to the management of AH and may provide some clinical benefit. A small, randomized controlled study of enteral nutrition consisting of 2000 kcal/day was compared to prednisolone for 28 days [67]. Survival rates were similar in both arms. A follow-up trial compared intensive nutritional support plus corticosteroids with conventional nutritional support plus steroids. Intention to treat analysis revealed no survival benefit but patients with an intake of less than 21.5 kcal/kg/day had a higher 6-month mortality rate [68]. While adequate nutrition is essential in the management of AH, patients with AH are at risk for refeeding syndrome. In addition to adequate protein and calories, supplementation of thiamine and folate is recommended and daily monitoring of potassium, magnesium, and phosphate with repletion as needed.

Ensuring adequate nutrition in a patient with AH can be challenging, particularly when severe. Anorexia remains a significant challenge and small, frequent meals may be necessary. In addition, tense ascites can limit the ability of the stomach to expand to accommodate a meal and tense ascites may promote a sense of satiety. Hepatic encephalopathy and other changes in cognition are common and may limit the ability of a patient to cognitively and safely adhere to nutritional recommendations. For those that cannot meet their caloric needs, a nasogastric tube should be inserted to allow for enteral feedings. Nasogastric tubes are safe for use in end-stage liver disease and do not increase the risk of, nor precipitate, variceal hemorrhage.

Corticosteroids

The use of corticosteroids in AH goes back several decades and remains the first-line pharmacotherapy in the treatment of severe AH. Both the American Association for the Study of Liver Disease (AASLD) and European Association for the Study of Liver (EASL) practice guidelines recommend corticosteroids, prednisolone 40 mg daily, for up to 28 days in the treatment of severe AH [69, 70]. There have been several randomized, controlled trials (RCTs) of corticosteroids in the treatment of AH over the past few decades. However, many of these trials have been limited by

small sample sizes, heterogeneity in study design and study population, inconsistent formulation and dosing of corticosteroids, and changing definitions of severe AH. Outcomes of these RCTs have inconsistently showed benefit of corticosteroid therapy in AH. A 1995 Cochrane review found no benefit to corticosteroids after adjusting for confounding variables in the study populations [71]. A subsequent Cochrane review in 2008 showed a mortality benefit to corticosteroid therapy in patients with a DF ≥ 32 or hepatic encephalopathy [72].

The benefit of corticosteroids is largely derived from a gold-standard meta-analysis performed on patient data from more than 400 patients accrued in five separate RCTs of prednisolone therapy in AH [61]. All patients had severe AH, defined as a DF ≥ 32, and biopsy-proven ASH. The meta-analysis demonstrated a survival benefit at 28 days in patients with severe AH treated with corticosteroids (79.97 ± 2.8% vs. 65.7 ± 3.4%, P = 0.0005) [61].

The largest prospective RCT of pharmacotherapy in AH was multicenter STOPAH trial in the United Kingdom [73]. This double-blinded, 2 × 2 factorial trial enrolled 1103 patients with a DF ≥ 32 into four arms: placebo/placebo, prednisolone/placebo, pentoxifylline/placebo, and prednisolone/pentoxifylline. All diagnoses of AH were based on clinical criteria, and liver biopsy was not required for inclusion. Subjects were randomized based on risk stratification with high-risk patients defined as those with recent gastrointestinal hemorrhage, renal insufficiency, or sepsis.

There was no significant survival benefit at 28 days with prednisolone compared to placebo (OR 0.72; 95% confidence interval [CI], 0.52–1.01; $P = 0.06$). However, on a post hoc multivariable analysis, prednisolone was associated with a decreased 28-day mortality (OR 0.609, $P = 0.015$), but not at 90 days or 1 year [73].

While the STOPAH trial is, by far, the largest RCT of prednisolone therapy in AH, several factors may have led to marginal benefit from corticosteroid therapy. First, the lack of liver biopsy for inclusion may have unintentionally led to enrollment of patients with alternative diagnoses. That being said, in most community practice, the diagnosis of AH is determined without a liver biopsy and thus the STOPAH results reflect a "real-world" study. In addition, the mortality rates in all four arms of the study were significantly lower than previously seen in RCTs of severe AH, and thus the study may not have been adequately powered to detect a more robust benefit from corticosteroids.

Finally, a recent updated meta-analysis involving patient data (2111 patients) from 11 RCTs compared corticosteroids, pentoxifylline, or their combination in patients with severe AH. Corticosteroid treatment significantly decreased risk of death within 28 days compared with controls (hazard ratio [HR] 0.64; 95% confidence interval [CI] 0.48–0.86) [74].

Given the generally modest benefit of corticosteroids in severe AH, the potential adverse effects of corticosteroids should be considered prior to the initiation of therapy. Active gastrointestinal hemorrhage and uncontrolled infection are considered absolute contraindications to the initiation of corticosteroids. Corticosteroids, particularly when ineffective as therapy, significantly increase the risk of serious infection and should be discontinued if there is no evidence of efficacy by day 7 [64, 65].

Liver Transplantation

For many years, AH was, for the most part, considered an absolute contraindication to liver transplantation (LT). Most LT programs in the United States and Europe had adopted the "6-month" rule which mandated at least 6 months of monitored sobriety prior to consideration of LT as a therapeutic option [75]. Given that heavy alcohol use within 60 days of presentation is part of the diagnostic criteria for AH, all patients with severe AH will be well short of this 6-month interval of sobriety [32]. In addition, in patients with severe AH that fail medical therapy or have multisystem organ failure, the prognosis is quite poor and 6-month survival is unrealistic. The origins of the 6-month rule were primarily intended for the opportunity for improvement in liver function, potentially obviating the need for LT altogether. However, it became used as a minimum surrogate for future sobriety despite weak evidence for the validity of the practice [76, 77].

However, in 2011 a multicenter study from France and Belgium utilizing rescue LT in patients with severe AH refractory to medical therapy demonstrated a significant survival advantage to early LT [78]. Two-hundred thirty three patients with severe AH were evaluated during the study period and ultimately 85 patients were non-responders to medical therapy and at high risk for short-term mortality. Ultimately, 26 patients underwent liver transplantation among the medical non-responders. In this population, survival at 6 months was markedly higher in those patients that underwent early LT (77 ± 8% vs. 23 ± 8%, $P < 0.001$) [78]. The selection process used during this process was rigorous. To be considered for early LT, patients had to meet the following criteria: nonresponse to medical therapy (as defined above), severe alcoholic hepatitis as the first liver-decompensating event, presence of close supportive family members, absence of severe coexisting or psychiatric disorders, and agreement by patients (with support from family members) to adhere to lifelong total alcohol abstinence. In order to qualify for LT, unanimous agreement across four different "circles" of the care team was needed. LT for AH consisted of only 2.9% of all LT performed during the study period [78]. Of the 26 patients who underwent early LT, only 3 returned to alcohol use after transplant.

In the United States, a large multicenter, retrospective analysis examined survival and alcohol relapse in a large cohort of patients with AH who underwent early LT. This analysis included 12 centers geographically dispersed across the United States and included 147 patients in the analysis [79]. The selection process was more heterogeneous than in the French/Belgian trial; however, the same general principles of commitment to abstinence, insight to AUD, and the presence of social support were generally followed. Of the centers that could provide detailed selection results, only 35.9% of patients evaluated for LT were approved for LT. Survival at 1 and 3 years was excellent (94% and 84%, respectively). In terms of alcohol relapse, 25% used any alcohol at 1 year post-transplant and 34% used any alcohol at 3 years post-transplant. However, only 11% and 17% had sustained alcohol used at 1 and 3 years post LT, respectively. Sustained alcohol use after LT was a risk factor for death post LT [79]. Both studies provide evidence that LT can be performed successfully in selected patients with severe AH that fail to respond to medical therapy.

Despite the encouraging results from these small studies, early LT for AH remains controversial. Despite the ability of the prediction scores in identifying patients with a poor prognosis, recovery from severe AH is possible even in those with poor prognostic signs. In terms of LT, optimal selection criteria have not been clearly established and medium to long-term outcomes have not been reported. In addition, the disease burden of AH is high and conversion to rescue LT candidacy is low thus straining the resources of LT programs to evaluate patients for LT with severe AH that fail medical therapy. Legitimate concerns exist regarding the rigor of the selection process particularly in an era of increased organ sharing coupled with MELD-based organ allocation. While undoubtedly the high MELD scores seen in AH represent a real mortal risk, concerns that competing interests might erode rigorous selection in this high-risk population are not unfounded as are concerns that transplantation for AH could lead to a "race to the bottom" in terms of increasing center transplant volume at the expense of selection rigor. In addition, given the existing organ shortage, it is possible that LT for AH may worsen this shortage and put patients with a high symptom burden but comparatively low MELD score at a further allocation disadvantage.

On the other hand, while it can be said with certainty that LT does not treat the underlying AUD, there is a strong perception that AH is a self-inflicted disease and that the use of a donor organ in a patient with AH over a patient with another form of liver disease is unethical. However, competing arguments can be made that the predominant causes of end-stage liver disease have always been "self-inflicted," and thus AH should not be treated differently. In addition, if the primary purpose of the "6-month rule" is as a tool of risk stratification and the rule itself poorly predicts the risk of future alcohol relapse, then patient selection for LT in ALD based on such a rule is seemingly unethical.

At the present time, it is likely that LT as a rescue therapy for AH will remain controversial until further studies on LT outcomes are performed and quality assurance measures are put into place.

Potentially Beneficial Therapies

N-Acetylcysteine

N-Acetylcysteine (NAC), widely used in the treatment of acetaminophen overdose, reconstitutes glutathione stores and may have a potent anti-oxidative effect in the liver. A randomized, controlled trial compared prednisolone plus NAC versus prednisolone plus placebo in a multicenter study from France [39]. The dose of NAC was the standard acetaminophen dosing for 2 days and then 100 mg/kg/day from day 2 through day 5. There was improved survival in the prednisolone/NAC arm at 1 month (8% vs. 24%, $P = 0.006$), but no significant difference in survival at 6 months (27% vs. 38%, $P = 0.07$) [39]. Death due to the hepatorenal syndrome was less frequent in the prednisolone-N-acetylcysteine group than in the

prednisolone-only group at 6 months (9% vs. 22%, $P = 0.02$) [39]. Since the primary end point was 6-month survival, this was considered a negative study and further studies of the potential benefit of NAC in addition to prednisolone are warranted. However, given the low toxicity profile of NAC, improved 1-month survival, and trend toward improved 6-month survival, the addition of NAC to prednisolone should be considered in severe AH.

Granulocyte Colony Stimulating Factor (G-CSF)

In addition to its hematopoietic effects, G-CSF has been shown experimentally to increase hepatocyte growth factor and induce proliferation of hepatic progenitor cells [80]. A small, randomized, open label, trial of G-CSF in addition to standard of care showed a significant reduction in Child-Turcotte-Pugh (CTP) score, MELD score, and DF at 1, 2, and 3 months in patients treated with G-CSF [81]. In addition, there was improved survival in the GSF-treated patients (78.3% vs. 30.4%; $P = 0.001$) at 90 days. Larger trials are ongoing to follow up this promising small study.

Other Therapies

There are numerous ongoing investigational trials of novel agents for the treatment of AH.

Ineffective Therapies

Pentoxifylline

The historical use of pentoxifylline in the treatment of severe AH was based on a single RCT of pentoxifylline versus placebo in severe AH (DF > 32) [82]. Patients in the placebo arm had an improved survival owing to the decreased incident of hepatorenal syndrome. However, since that trial, multiple RCTs, including the large STOPAH trial, have failed to demonstrate any benefit to pentoxifylline in the treatment of AH [73, 83]. In addition, a meta-analysis failed to reveal a benefit to pentoxifylline in AH [84]. As a result, pentoxifylline is not recommended for use in AH.

Anti-tumor Necrosis Factor Antibodies

Tumor necrosis factor-α is believed to play a role in the pathogenesis of AH and thus potentially a target for inhibition in the management of AH. The anti-TNF antibodies etanercept and infliximab have both been studied in the treatment of AH and

both yielded disappointing results. Both agents led to an increased risk of serious infection and death in controlled trials and were abandoned as potential therapeutic agents in AH [85, 86].

Other Ineffective Therapies

A number of other therapies have been investigated in AH without a demonstration of clear benefit. These include the anabolic steroid oxandrolone and antioxidants including vitamin E and S-adenosylmethionine (SAM-E).

Extracorporeal cellular therapy (ELAD) utilizing hepatoblastoma-derived C3A cells was recently studied in a randomized trial of standard of care plus ELAD versus standard of care alone. No survival benefit was seen [87].

Prognosis

The short-term prognosis of AH is related to the severity disease at presentation and the response to medical therapy. Mild-to-moderate AH generally has a good prognosis with alcohol abstinence and nutritional support alone. Mortality rates at 1 month are less than 10% [73]. As detailed earlier, severe AH is a critical illness with short-term mortality rates from 25–50% at 1 month. Studies of ACLF in severe AH have shown that multiple organ failure at presentation or developing during the course of severe AH worsens prognosis [88]. Infection during the course of hospitalization predicted the development of ACLF and subsequent short-term mortality. Patients with three or more organ failures during hospitalization had a 28-day mortality of 72% [88].

Despite the value of predictive models, the outcome of the individual patient with severe AH can be unpredictable owing to the regenerative capacity of the liver and the dramatic improvement in liver function that can occur with time and alcohol abstinence.

Longer term survival is largely determined by the maintenance of alcohol abstinence. A Spanish study of 142 survivors of biopsy-proven AH revealed a 38% mortality at a mean of 55-month follow-up [89]. On multivariable analysis, the maintenance of alcohol abstinence was associated with survival ($P < 0.05$). A contemporary study from France of 398 corticosteroid-treated patients revealed a cumulative risk of alcohol relapse of 25.2%, 33.7%, and 35.2% at 1, 3, and 5 years, respectively [90]. In patients who survived more than 6 months, alcohol use greater than 30 g/day was associated with mortality (hazard ratio, 3.9; $P < 0.0001$). There was a dose effect to alcohol use with higher doses associated with higher mortality. Clearly, improvements in the management of alcohol use disorder are needed to improve the long-term prognosis in alcoholic liver disease.

Conclusion

In summary, AH is characterized by the onset of jaundice in the setting of heavy antecedent alcohol use, often for many years. While mild-to-moderate AH carries a generally good prognosis with alcohol abstinence, severe AH is a critical illness with a high short-term mortality. Numerous tools exist to identify patients with severe AH and a high risk of death. Multi-organ failure, or ACLF, is common in severe AH and may be present at the time of initial presentation or during the course of care. ACLF is also often the proximate cause of death in patients with severe AH. Therefore, the management of severe AH in the critical care setting is common. Despite numerous clinical trials of investigational agents in the treatment of severe AH, corticosteroids remain the only therapy with short-term efficacy in severe AH although the benefit is, at best modest and likely limited to patients without multiple organ failure, sepsis, or gastrointestinal hemorrhage at presentation. When treating a patient with corticosteroids for severe AH, it is critical to utilize existing tools to assess response to therapy and discontinue corticosteroids in non-responders to decrease risk of infection. LT can be considered as salvage therapy for AH that is non-responsive to medical treatment, but the practice remains controversial and should be limited to a highly selected group with a favorable prognosis and limited to transplant centers with adequate resources to assist in recovery from AUD. Finally, remarkable improvement in liver function can be experienced even in patients with severe AH who fail medical therapy, but such recovery is uncommon.

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Chapter 11
Acute on Chronic Liver Failure

Mark R. Pedersen and Shannan R. Tujios

Abbreviations

ACLF	Acute on chronic liver failure
APACHE-II	Acute physiology and chronic health evaluation score II
APASL	Asian Pacific Association for the Study of the Liver
CARS	Compensatory anti-inflammatory response
CLIF-SOFA	Chronic liver failure-sequential organ failure assessment
CpG	Cytosine guanine
CTP	Child-Turcotte-Pugh
DAMPs	Damage-associated molecular patterns
EASL	European Association for the Study of the Liver
Epi	Epinephrine
FiO2	Fraction of inspired oxygen
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HMGB1	Chromatin-associated protein high-mobility group box-1
IFN	Interferon
IL	Interleukin
LPS	Lipopolysaccharide
MELD	Model for End-Stage Liver Disease
MIP	Macrophage inflammatory protein
NACSELD	North American Consortium for the Study of End-Stage Liver Disease
NADH	Nicotinamide adenine dinucleotide

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NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
Nor	Norepinephrine
PAMPs	Pathogen-associated molecular patterns
PIRO	Predisposition, injury, response, organ
PMN	Polymorphonuclear
PSE	Portosystemic encephalopathy
SBP	Spontaneous bacterial peritonitis
SpO2	Peripheral capillary oxygen saturation
Th1	T helper cell type 1
Th2	T helper cell type 2
TIPS	Transjugular intrahepatic portosystemic shunt creation
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor alpha
VCAM	Vascular cell adhesion molecule

Introduction

Cirrhosis, or end-stage fibrosis of the liver, is characterized by disrupted intrahepatic blood flow, portal hypertension, and eventually liver failure. Cirrhosis is often classified as compensated or decompensated, with decompensations including jaundice, ascites, variceal hemorrhage, and portosystemic encephalopathy (PSE). The annual risk of decompensation in patients with compensated cirrhosis is approximately 10% [1]. Once decompensation occurs, the annual risk of mortality increases from 1–2% up to 20–60% depending on the degree of decompensation that has occurred [1]. At this stage, liver transplant evaluation is recommended for suitable candidate [2].

While the presence of a decompensating event portends decreased survival in the long term, the effect of a decompensation on short-term survival can vary markedly between patients. Consider two patients with cirrhosis and ascites. One may be easily managed on diuretics, while the other develops hypotension and renal failure progressing to anasarca and hyponatremia. Both patients have decompensated cirrhosis, but this term is inadequate to describe the full range of physiologic dysfunction occurring in the second patient scenario. The term "acute on chronic liver failure" (ACLF) has been adopted to describe the scenario, characterized by (1) a patient with chronic liver disease that develops a (2) new or worsening decompensation with (3) marked dysfunction of other extrahepatic organs and (4) an increased short-term mortality.

ACLF Defined

The variation in the types of liver disease seen around the world initially led to the rise of multiple competing definitions of ACLF. The Asian Pacific Association for the Study of the Liver (APASL) conceptually defined ACLF in 2009 as an "acute

hepatic insult, manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy with previously diagnosed or undiagnosed liver disease" [3]. This definition notably requires the presence of either PSE or ascites and includes patients with noncirrhotic chronic liver disease, such as patients with chronic hepatitis B who subsequently undergo decompensation. Absent from this definition is the presence of non-hepatic organ failure. In addition, patients with extrahepatic infections were traditionally excluded from the APASL model of ACLF.

Separately, the European Association for the Study of the Liver (EASL) and the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) empirically developed relatively similar definitions. Given the higher prevalence of more chronic and insidious liver diseases such as hepatitis C and alcohol in these areas, both definitions presuppose the presence of cirrhosis. NACSELD developed a functional definition of ACLF by examining patients with new or worsening decompensation and high mortality at 30 days [4]. ACLF was defined by the presence of two or more organ failures, and this model would be validated in patients with infectious and non-infectious triggers (Table 11.1) [4, 5]. While patients without ACLF were found to have 30-day survival of 94–95%, those with ACLF had

Table 11.1 NACSELD-ACLF score. The shaded boxes represent two or more organ failures, or ACLF

Organ failures, defined		
1. Cerebral failure, defined as grade III or IV PSE 2. Circulatory failure, defined as a mean arterial pressure < 60 mmHg or a reduction of 40 mmHg in systolic blood pressure despite adequate fluid resuscitation and cardiac output 3. Respiratory failure, defined as need for mechanical ventilation 4. Renal failure, defined as the need for dialysis or other forms of renal replacement therapy		
Number of organ failures	**30-day survival (infected) (%)**	**30-day survival (uninfected) (%)**
0	94	95
1	80	90
2	62	84
3	42	65
4	24	0

Based on O'Leary et al. [5]

survival ranging from 62% to 84% with two organ failures and as low as 0–24% with four organ failures. This definition specifies the presence of a new or worsening decompensation, and the presence of ACLF depends on the presence of extrahepatic organ failures.

EASL also developed a tool to define ACLF known as the chronic liver failure-sequential organ failure assessment (CLIF-SOFA) to differentiate three grades of ACLF based on 28- and 90-day mortality. The score is based on the function of six different organs, each with different definitions of failure (Table 11.2a). Patients were deemed to have an acute decompensation (not ACLF) if they had (1) no organ failure, (2) a single "non-kidney" organ failure with a creatinine <1.5 and no PSE, or (3) cerebral failure with a serum creatinine <1.5. Mortality prediction ranged from 4.7% 28-day and 14% 90-day mortality with a simple acute decompensation to 76.7% and 79.1% mortality, respectively, for grade 3 ACLF (patients with three organ failures) (Table 11.2b) [6]. This definition requires the presence of organ failure, but not necessarily a hepatic decompensation.

In 2014, the World Gastroenterology Organization created an international working group to reconcile the three definitions. Three different forms of ACLF were endorsed, officially recognizing ACLF as a syndrome and not a singular clinical entity (Fig. 11.1). Type A, or noncirrhotic, ACLF describes patients with chronic liver disease that experience a sudden flair of their disease resulting in hepatic decompensation. A prototype would be a flare or reactivation of hepatitis B, but could also be a flare of autoimmune hepatitis, or any type of liver disease with a secondary viral infection (such as hepatitis A or hepatitis E). Type B, or compensated cirrhotic, ACLF is seen in patients with compensated cirrhosis who rapidly decompensate after an insult. Type B ACLF would include patients with compensated cirrhosis who decompensated after an infection or surgery, or patients with alcoholic cirrhosis who developed superimposed alcoholic hepatitis. Type C, or decompensated cirrhotic, ACLF is seen in patients with a history of decompensated cirrhosis who develop a new or worsening decompensation. Patients with cirrhosis and ascites who develop spontaneous bacterial peritonitis with resultant renal failure and encephalopathy would be considered to have type C ACLF [7].

Pathophysiology of ACLF

The pathophysiology of an acute decompensation is related to a progressively deteriorating liver. Ascites and variceal hemorrhage are the result of intrahepatic portal hypertension. Progressive scarring of the liver with fibrosis lined capillaries leads to increased resistance to blood flow and increased pressure in the pre-hepatic venule vasculature [8]. Encephalopathy and jaundice reflect decreased metabolic functions of the liver. Though not entirely understood, encephalopathy is thought to be due to insufficient catabolism of amino acids leading to accumulation of ammonia and glutamine [9]. Jaundice results from decreased conjugation and excretion of heme products [10].

Table 11.2 EASL ACLF. (a): Criteria for organ failure are in the shaded boxes. Epi, epinephrine; Nor, norepinephrine; SpO2/FiO2, peripheral capillary oxygen saturation/fraction of inspired oxygen. (b): Criteria for ACLF with associated mortality

(a) Organ failures, defined			
Liver	Bilirubin ≥12.0 mg/dL		
Kidney	Creatinine ≥2.0 mg/dL or the need for renal replacement therapy		
Cerebral	Stage III (somnolent, obtunded) or IV (comatose) encephalopathy		
Coagulation	International normalized ratio ≥2.5 or platelet count $\leq 20 \times 10^5$/L		
Circulation	Use of any vasopressor (dopamine, dobutamine, terlipressin, epi, norepi)		
Pulmonary	$PaO_2/FiO_2 \leq 200$ or $SpO_2/FiO_2 \leq 214$		
(b) Grades of ACLF			
Grade	Defined	28-day mortality	90-day mortality
No ACLF	Patients with no organ failure Patients with a single "non-kidney" organ failure with a creatinine <1.5 mg/dL and no PSE Patients with cerebral failure and serum creatinine <1.5	4.7%	14%
Grade 1	Patients with kidney failure Patients with a single "non-kidney" organ failure (excluding cerebral failure) and a creatinine from 1.5 to 1.9 mg/dL Patients with cerebral failure and a creatinine from 1.5 to 1.9	22.1%	40.7%
Grade 2	Patients with 2 or more organ failures	32.0%	52.3%
Grade 3	Patients with 3 or more organ failures	76.7%	79.1%

Based on Moreau et al. [6]

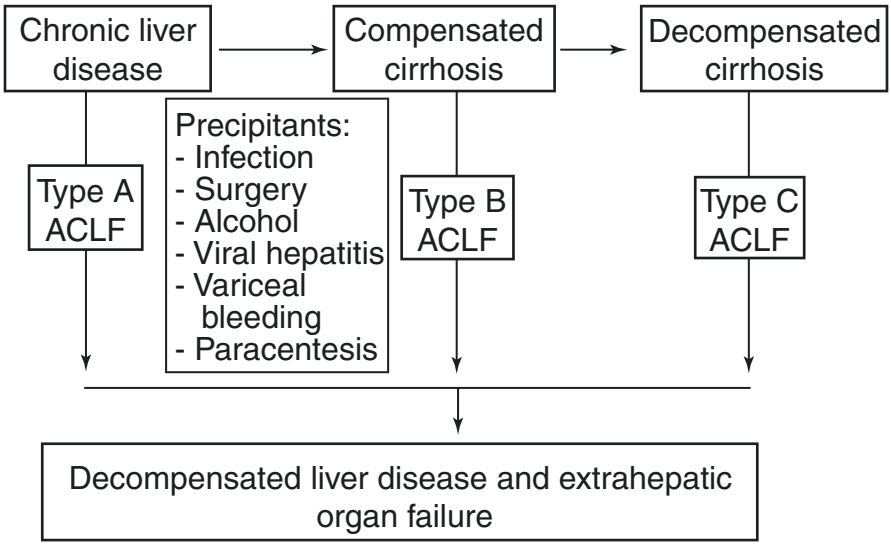

Fig. 11.1 Current unifying structure of ACLF. (Based on the definition from Jalan et al. [7])

The pathophysiology of ACLF, on the other hand, is the product of an exaggerated immune response on the liver and extrahepatic organs that is induced by a precipitant. The PIRO concept (predisposition, injury, response, organ) is often applied to the pathophysiology of ACLF [11]. Patients are predisposed to inflammation by their underlying chronic liver disease often with associated malnutrition. Key events or injuries, most commonly infections, surgery, alcohol, and viral hepatitis, precipitate inflammation leading to the hepatic and extrahepatic organ dysfunction seen in ACLF. These ACLF events and their recovery also explain the non-linear progression of liver disease (Fig. 11.2).

Patients with cirrhosis are predisposed to infection and inflammation as a consequence of malnutrition, an altered microbiome, and increased gut permeability in the setting of portal hypertension. Malnutrition is frequently observed in patients with advanced chronic liver disease and can lead to immune dysfunction. Low albumin levels, for example, are associated with increased tumor necrosis factor (TNF)-induced nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) activation and vascular cell adhesion molecule (VCAM) upregulation, as well as increased capillary permeability [12]. Zinc deficiency, particularly common in alcoholic liver disease, is also associated with lymphopenia and compromised adaptive immune response [13]. Progressive liver disease is also associated with worsening gut dysbiosis (such as increased proportions of the pathogenic bacteria *Enterococcus* and *Enterobacteriaceae*) and increased gut permeability leading to detection of endotoxin and bacterial DNA in the bloodstream [14, 15].

Though the precipitants of ACLF may be infectious or non-infectious, inflammation results through a common pathway. Infectious precipitants are recognized through direct recognition of small non-mammalian molecules, known as pathogen-

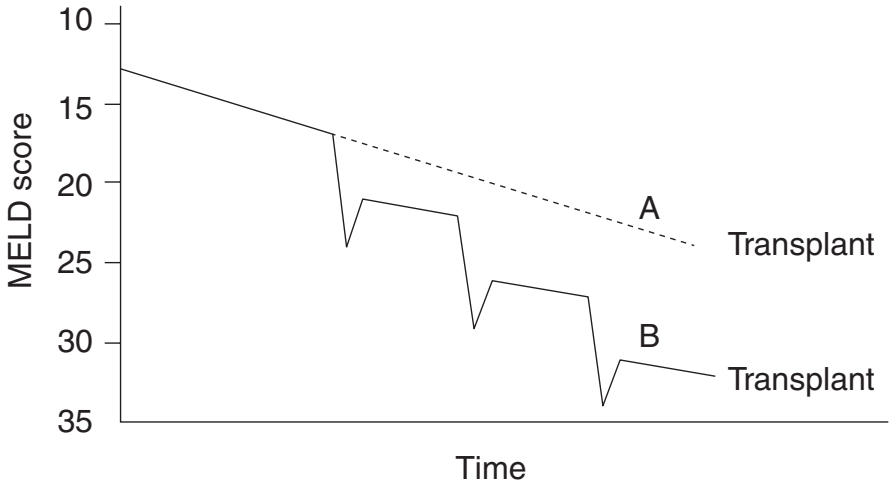

Fig. 11.2 The progression of liver disease. Progression A, a steady decline in liver function to the time of transplant, is less common than progression B, periods of stability punctuated by episodes of ACLF with some recovery

associated molecular patterns (PAMPs), or indirectly through the presence of virulence factors. Common PAMPs include lipopolysaccharide, or endotoxin, found in the cell wall of gram-negative bacteria, as well as double-stranded viral RNA and unmethylated CpG oligonucleotides [16]. These PAMPS are recognized by pattern recognition receptors, a category of receptors that includes Toll-like receptors and NOD-like receptors [17]. Alternatively, the presence of a virulence factor may be sensed by the immune system. For example, pore-forming exotoxins and viroporins, which form ion channels in the membranes of host cells, can activate functional recognition receptors [18].

Inflammation that is the result of non-infectious triggers is associated with damage-associated molecular patterns (DAMPs). These are typically naturally occurring nuclear or cytosolic proteins that, when released from the cell after tissue injury, also interact with pattern recognition receptors [17]. Common non-infectious triggers include alcohol use, drug-induced injury, and surgery. DAMPs are also released in the setting of infection and contribute to the pathogenesis of infectious inflammation. The presence of PAMPs, DAMPs, or virulence factors include expression of inflammatory cytokines.

Several studies have compared the differences in the cytokine milieu of patients with decompensated cirrhosis and patients with ACLF compared with each other and healthy controls. Patients with decompensated cirrhosis displayed increased levels of interleukin (IL)-6, IL-8, IL-10, IL-12, and TNF-α compared to healthy controls [19–22]. Most studies of patients with ACLF have shown further increases in cytokine levels, including IL-10, TNF-α, and macrophage inflammatory protein (MIP)-1β, but most notably IL-6 and IL-8 (Table 11.3) [19, 20, 22]. The exaggerated immune response is sometimes referred to as a "storm" of inflammatory cytokines [23].

Table 11.3 Cytokine levels in patients with ACLF compared with decompensated cirrhosis. The arrow represents the level of the cytokine in ACLF with respect to patients with decompensated cirrhosis

Cytokine	Predominant function	Characteristic	ACLF compared to non-ACLF decompensated cirrhotic patients			
			Dirchwolf et al. *N* = 77	Claria et al. *N* = 562	Mehta et al. *N* = 60	Sole et al. *N* = 55
IL-1β	Pro-inflammatory	Acute phase reactant, associated with fever, inflammation, etc.	↔	–	–	↓
IL-2	Pro-inflammatory	Proliferation, survival, and differentiation of T and B cells	↔	–	–	↓
IL-6	Pro-inflammatory	Regulation of acute phase response to injury and infection; chemotaxis of neutrophils and stimulation of B cells	↔	↑	↑	↔
IL-7	Pro-inflammatory	Promotes T and B cell differentiation and maturation	↓	↑	–	↔
IL-8	Pro-inflammatory	Induces chemotaxis of neutrophils and stimulates phagocytosis	↑	↑	↑	–

IL-10	Anti-inflammatory	Inhibits macrophage and neutrophil cytokine production; promotes Th2 in T lymphocytes	↓	↑	↑	↔
IFN-γ	Pro-inflammatory	Promotes Th1 differentiation; Activates macrophages to secrete IL-12	↓	↑	–	↔
G-CSF	Pro-inflammatory	Influences growth and differentiation of cells of neutrophil lineage	↔	↑	–	↔
GM-CSF	Pro-inflammatory	Influences growth and differentiation of granulocyte and macrophages	↔	↑	–	↓
TNF-α	Pro-inflammatory	Acute phase reactant, associated with fever, inflammation, etc., similar to IL-1β	↓	↑	↑	–
MIP-1β	Pro-inflammatory	Promotes chemotaxis of monocytes and lymphocytes	–	↑	–	↑

Th1 T helper cell type 1, *Th2* T helper cell type 2, *IL* interleukin, *IFN* interferon, *G-CSF* granulocyte colony-stimulating factor, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *TNF* tumor necrosis factor, MIP macrophage inflammatory protein [20–22, 24]

This disordered immune response is associated with clinical consequences. Mehta et al. observed that the elevation of white blood cell count, C-reactive protein, and IL-6 and IL-8 levels in patients with ACLF were associated with increased portal hypertension measured as increased hepatic venous pressure gradient, increased hepatic resistance, and decreased hepatic blood flow (Fig. 11.3) [22]. Furthermore, elevation of IL-6 and IL-8 has been shown to correlate positively to the patient's Model for End-Stage Liver Disease (MELD) score [21]. Similarly, IL-6 has been shown to correlate positively with the patient's CLIF-SOFA at day 7 [21].

As the precipitant of ACLF is managed, the immune system gradually switches from an inflammatory response to a compensatory anti-inflammatory response (CARS). This state is manifest by lymphocyte apoptosis, increased expression of anti-inflammatory cytokines such as IL-10, and antigen anergy, sometimes referred to as a state of "immune paralysis" (Fig. 11.4) [25]. This state can predispose patients to acquire new infections and aggravate a new episode of ACLF. It is hypothesized that patients who do not survive ACLF are those with refractory CARS who can no longer amount an appropriate immune response to new precipitants [26].

Precipitants of ACLF

One of the defining features of ACLF is that it is precipitant driven. These precipitants can be infectious or non-infectious and are believed to incite the inflammatory response that leads to ACLF (Table 11.4). Infection is the most common cause of ACLF in North America and Europe and the second most common cause of ACLF in Asia [5, 6, 27]. The most common precipitant of ACLF in Asia is reactivation of hepatitis B infection [27]. The second most common cause of ACLF in Europe is alcohol, followed by gastrointestinal hemorrhage [6]. Avoidance of the trigger, or appropriate management when it occurs, is key to mitigating the multi-organ dysfunction of ACLF.

Infection

In the western hemisphere, extrahepatic infection is the most common cause of ACLF. In the European EASL-CLIF study, 32.6% of patients had ACLF with infection as a precipitant; 44.7% of patients with grade 3 ACLF had infection as a precipitant [6]. In North America, 40.3% of patients in the NACSELD study group had infection as a precipitant [4]. In patients with ACLF, the presence of any infection has been associated with an increased risk of mortality [28].

For reasons discussed previously, patients with cirrhosis are predisposed to infection due to bacterial translocation, malnutrition, and a disordered immune

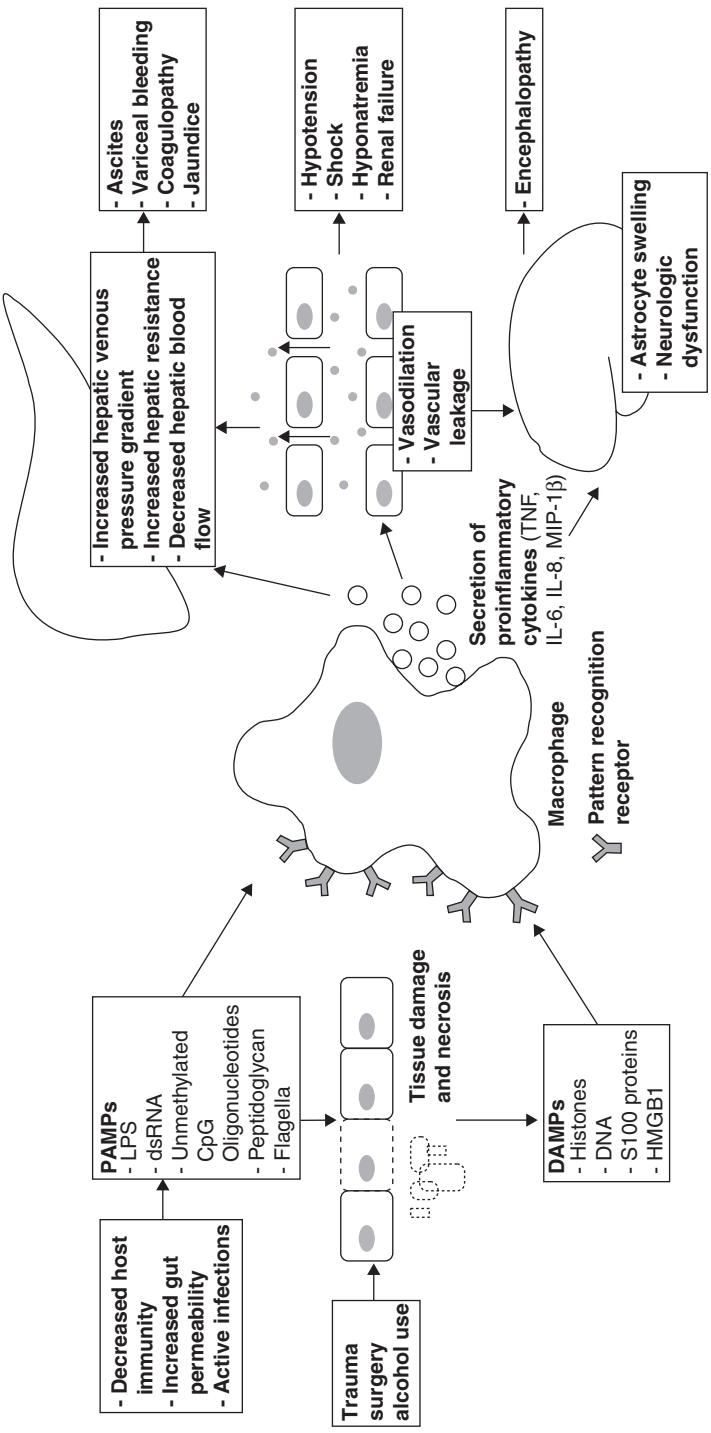

Fig. 11.3 Pathophysiology of ACLF. Exposure to infection and/or tissue damage lead to immune activation. The secretion of inflammatory cytokines (e.g., TNF, IL-6, IL-8, MIP-1β) leads not only to vasodilation and vascular leakage, but also increased portal hypertension and neurologic dysfunction. The results are the clinical manifestations of ACLF – ascites, encephalopathy, variceal bleeding, coagulopathy, jaundice, shock, and renal failure. PAMP pathogen-associated molecular pattern, DAMP damage-associated molecular pattern, LPS lipopolysaccharide, HMGB1 chromatin-associated protein high-mobility group box 1, CpG cytosine guanine, TNF tumor necrosis factor, IL interleukin, MIP macrophage inflammatory protein

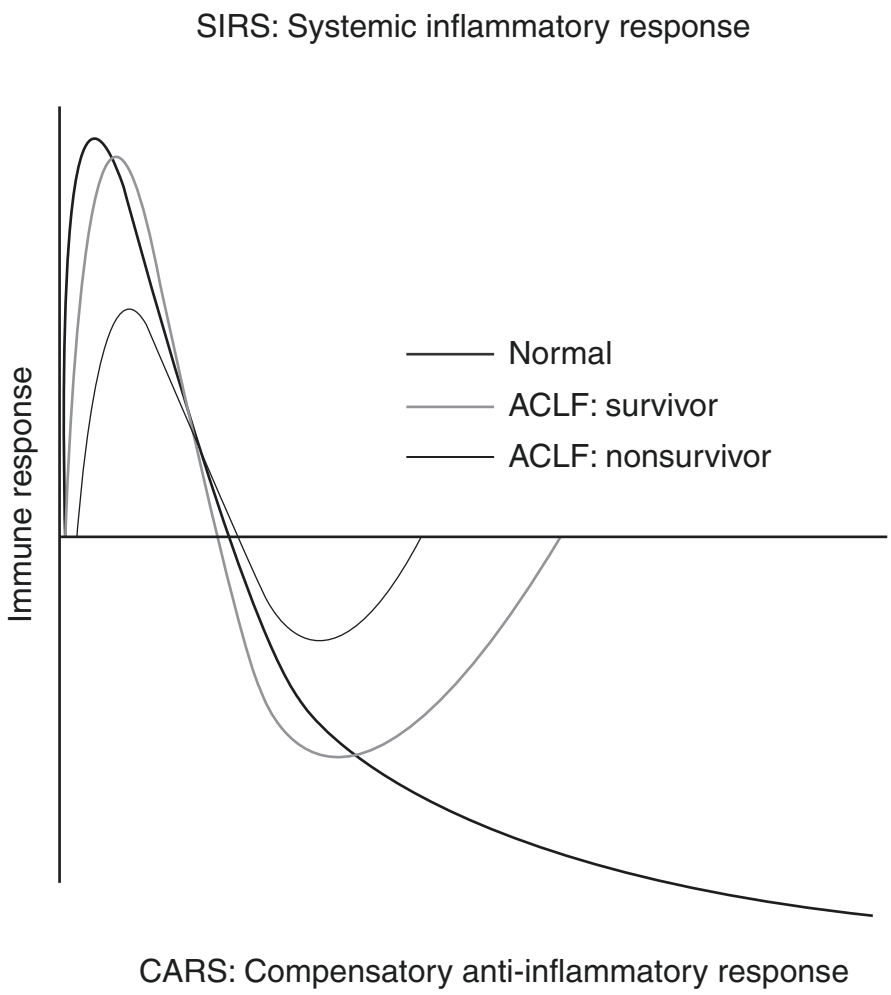

Fig. 11.4 Comparing the inflammatory and compensatory anti-inflammatory responses. Death from ACLF may be associated with an unresolving CARS state. (Based on Rahimi and Rockey [74])

system. These infections may not always be detected by traditional laboratory testing. For example, bacterial DNA has been detected in the ascites of patients without polymorphonuclear (PMN) cell counts or cultures indicative of spontaneous bacterial peritonitis (SBP) and in the bloodstream of patients with negative blood cultures [29, 30]. This bacterial DNA is associated with a cytokine profile identical to patients diagnosed with SBP and can be abrogated by antibiotics [31]. For patients with ACLF, infection should be suspected and treated even when negative cultures exist.

Table 11.4 Frequency of the precipitants of ACLF by study regions [5, 6, 27]

	EASL-CLIF (*N* = 303) [6]	**NACSELD (*N* = 2675) [5]**	**APASL (*N* = 322) [27]**
Infection	98 (32.9%)	1079 (40.3%)	113 (27.9%)
Alcohol abuse	69 (24.5%)	–	25 (6.2%)
Gastrointestinal hemorrhage	40 (13.2%)	–	4 (1.0%)
Hepatitis B	–	–	145 (35.8%)
Other	34 (3.5%)	–	
No identified event	126 (43.6%)	–	83 (20.5%)

Certain infections may be more deleterious to patients with cirrhosis than others. Fungal infections, for example, are associated with a 30% mortality rate, which increases to >50% for fungemia and fungal peritonitis [32]. *C. difficile*-associated diarrhea also carries a high fatality rate of up to 40% [33]. Second infections, or an infection separate from but following a first infection during the same hospitalization, are particularly detrimental to patients with cirrhosis. These infections are more frequently respiratory, fungal, or *C. difficile*-associated diarrhea and carry a mortality rate of nearly 50%. When controlling for MELD score, albumin, and heart rate, a second infection is associated with an increased odds of mortality (OR 4.416, $p = 0.0002$) [33].

Infections commonly affect patients with ACLF, which may or may not be detected by routine culture methods, and impart increased mortality risk beyond the ACLF prediction models. These patients also tend to be exposed to more antibiotics and have a higher risk of developing an infection from a multi-drug-resistant organism [28]. This highlights the need to have a high suspicion for infection for patients with ACLF, to start antibiotics early, and to consider broadening antibiotics if the patient is not responding.

In addition to early, aggressive treatment of infections, the use of prophylactic antibiotics is warranted in certain situations. Antibiotics (trimethoprim-sulfamethoxazole, a second-generation quinolone, or an oral third-generation cephalosporin) should be given indefinitely to patients with ascites who have had a previous episode of SBP, or for 5–7 days in patients who have had an episode of gastrointestinal bleeding [34–36]. Current guidelines also suggest prophylaxis for patients who have low protein ascites (protein <1.5 g/dL) along with either renal failure (creatinine ≥1.2 g/dL, BUN ≥25 mg/dL, or serum Na ≤130 meq/L) or liver failure (Child score ≥9 and bilirubin ≥3) [37, 38]. Finally, medications that predispose to infections, such as proton pump inhibitors which have been associated with a decreased cellular oxidative burst and an increased risk of SBP, should be avoided when possible [39, 40]. *For further discussion of infections in patients with cirrhosis, please refer to* Chap. 7.

Direct Hepatic Insults

Alcoholic hepatitis has long been recognized as a clinical entity and is now being classified as a subset of ACLF based on similar pathophysiology. Ethanol increases intestinal permeability and results in the translocation of bacteria and associated PAMPs into the portal circulation. Furthermore, the intrahepatic metabolism of alcohol leads to an accumulation of nicotinamide adenine dinucleotide (NADH) and inability to oxidize fatty acids and triglycerides. These fatty changes stress the endoplasmic reticulum and can lead to caspase activation and apoptosis, releasing DAMPs into circulation as well [41].

While alcoholic hepatitis has unique prognostic scores (e.g., the Maddrey discriminant function, the Lille score), both the NACSELD-ACLF and the EASL-CLIF can be applied to this population [42, 43]. Like all ACLF patients, those with alcoholic hepatitis have a high rate of occult infections which warrants routine infection screening [44]. Identification and treatment of infection are of particular importance in the population given the most common initial management strategy of alcoholic hepatitis is steroids [45]. *For further discussion of the treatment of alcoholic hepatitis, please refer to* Chap. 10.

In the eastern hemisphere, hepatitis B flare and reactivation are the most common cause of ACLF [27]. It is important to distinguish between a hepatitis B flare or reactivation and an infection with another virus, such as delta-virus, hepatitis A, or hepatitis E. In patients with e-antigen-negative hepatitis B, reactivation is known to occur in 20–30% with or without seroconversion to hepatitis e antibody positivity [46]. Risk factors for hepatitis B reactivation include stopping hepatitis B anti-viral therapy, hepatitis C therapy, and the initiation of immunosuppression (in particular, chemotherapy and anti-CD20 monoclonal antibodies such as rituximab).

Each of the major hepatology societies (AASLD, EASL, and APASL) has guidelines for the treatment of chronic hepatitis B, and all recommend indefinite treatment for patients with cirrhosis. Treatment with nucleos(t)ide inhibitors with a high barrier to resistance (entecavir, tenofovir alafenamide, or tenofovir disoproxil) is recommended over those with lower barriers to resistance (adefovir dipivoxil and lamivudine). In addition, prophylaxis is recommended for any patient who will receive anti-CD20 therapy or undergo a stem cell transplant and has a positive hepatitis B core antibody regardless of surface antigen status [47]. Prophylaxis should be considered for a broader range of immunosuppression when both hepatitis core antibody and surface antigen are present, including for long-term high dose steroids, chemotherapy, and certain biologics [48].

Surgical Procedures

Surgical and non-surgical procedures are increasingly recognized as precipitants of ACLF in patients with cirrhosis. Some of these risks are specific to the type of procedure. Cardiac surgery, for example, may require the use of cardiopulmonary bypass

and perioperative vasopressor support, which are associated with increased mortality in cirrhosis [49]. Abdominal surgery, on the other hand, can decrease hepatic arterial blood flow and is associated with mortality rates up to 76% in patients with Child-Turcotte-Pugh (CTP) class C cirrhosis [50]. All surgical and many non-surgical procedures carry the general risks of anesthesia-induced hypotension, post-procedural hemorrhage, infection, and renal failure which can in turn precipitate ACLF [49].

The detrimental effect of surgery on patients with liver disease has been recognized for several decades and was the basis for the first prognostic scoring system for patients with cirrhosis, the Child-Turcotte score in 1964 [51]. This score was initially derived to predict which patients would survive surgical intervention for bleeding esophageal varices. It was revised to its final form in 1972 to become known as the Child-Turcotte-Pugh score [50].

More recently, the Model for End-Stage Liver Disease, or MELD, score was described in 2002 to predict which patients would fare best after a transjugular intrahepatic portosystemic shunt (TIPS) creation and was found to be superior to the CTP score in this scenario [52]. A variant on the MELD score, the Post-operative Mortality Risk in Patients with Cirrhosis, is also available to help determine the risk of post-operative mortality after major surgery. Generally, patients with cirrhosis and a MELD score less than 12 likely have an acceptably low risk of perioperative mortality. For patients with cirrhosis and a MELD of 12 or greater, it is advisable to avoid elective surgery. In cases when surgery cannot be avoided, a transplant evaluation prior to surgery should be considered in the event of ACLF afterward [49].

Gastrointestinal Hemorrhage

Gastrointestinal hemorrhage is a relatively uncommon precipitant of ACLF. It is debated as to whether or not gastrointestinal hemorrhage is actually a precipitant of ACLF or the consequence of the increased portal hypertension that accompanies the condition. It may in fact be both. In the event of a gastrointestinal hemorrhage in a patient with cirrhosis, it is important to remember it could be due to portal hypertensive or non-portal hypertensive (e.g., peptic ulcer disease) causes. Initial medical treatment should be aimed at both etiologies and includes therapy with octreotide and a proton pump inhibitor. Antibiotic prophylaxis is recommended for all patients with gastrointestinal hemorrhage and has been shown to improve short-term mortality when used resulting in a potential decrease in rates of infection and decreased recurrent variceal hemorrhage [34, 53].

Endoscopy should be performed when the patient is stabilized to evaluate and treat the cause of bleeding. For patients with esophageal variceal bleeding, variceal banding followed by secondary prophylaxis with non-selective beta-blockers (propranolol, nadolol, carvedilol) is recommended. Beta-blockers have been associated with reduced mortality in patients with ACLF provided they are discontinued in the presence of a low mean arterial pressure [54, 55]. *For further discussion of gastrointestinal hemorrhage, please refer to* Chap. 4.

Extrahepatic Manifestations of ACLF and Their Management

The key distinction between decompensated liver disease and ACLF is the presence of multi-organ dysfunction. The primary extrahepatic organ failures include renal, brain, respiratory, and circulatory failure.

Kidney Failure

Acute kidney injury, as defined by the international ascites club, is an increase in serum creatinine ≥0.3 mg/dl within 48 hours, or a percentage increase in serum creatinine ≥50% from baseline within the 7 days. This functional definition applies to patients with normal baseline renal function and to patients with baseline chronic kidney disease. The definition of kidney failure in ACLF depends on which scoring system is used. In the CLIF-EASL definition, kidney failure is a creatinine ≥2.0 mg/dL or greater, or the need for renal replacement therapy. In the NACSELD definition, kidney failure only needs patients to qualify for renal replacement therapy.

Kidney function plays an important role in the prognosis of cirrhotic patients. Creatinine, for example, is the second most powerful driver of the MELD score. Kidney function also plays a key role in the grading of ACLF under the CLIF-EASL definition. Any organ failure with a creatinine ≥1.5 mg/dL qualifies as grade 1 ACLF with a 90-day mortality of 40.7%. The same patient with a serum creatinine <1.5 mg/dL does not qualify as ACLF and has a 90-day mortality of 14% [6].

Of the causes of acute kidney injury in patients with cirrhosis, one-third are due to intrinsic kidney disease, mostly acute tubular necrosis. The remaining two-thirds are due to renal hypoperfusion in the setting of decreased effective arterial blood flow. Of these, approximately two-thirds are volume responsive. The other third of patients receive a diagnosis of hepatorenal syndrome [56]. The management of acute kidney injury in patients with cirrhosis begins with distinguishing intrinsic renal disease and renal hypoperfusion by examining urine electrolytes, urinalysis with microscopic examination for casts, and a renal ultrasound. As with all patients presenting with ACLF, health-care providers should have a low threshold for evaluating for infections as a precipitant of renal dysfunction.

Management of acute kidney injury involves holding diuretics and, if hypotension is present, beta-blockers as well. A volume challenge is often performed, with the choice of fluid depending on the clinical scenario. In general, the use of albumin should be considered given its anti-inflammatory and oncotic properties [12, 57]. Patients who receive a diagnosis of hepatorenal syndrome may benefit from the addition of albumin with either terlipressin (currently not available in the United States; however, clinical trials are underway) or midodrine with octreotide. *For further discussion of kidney injury in cirrhosis, please refer to* Chap. 5.

Brain Failure

Brain failure, or encephalopathy, is defined similarly throughout the ACLF literature as West Haven grade III or IV (obtunded to comatose). Specifically, this type of encephalopathy refers to type C encephalopathy, resulting from cirrhosis. Patients with cirrhosis often develop portosystemic shunting, resulting in type B encephalopathy, which can also contribute to this picture. Type A encephalopathy, cerebral edema, and herniation are associated with acute liver failure and not seen in patients with ACLF.

Similar to acute kidney injury, even lower grade encephalopathy was found to have predictive power in the EASL-CLIF cohort. The presence of one organ failure with grade I encephalopathy is sufficient to qualify as grade 1 ACLF [6]. In the NACSELD cohort, grade III or IV encephalopathy was found to be associated with higher in-hospital and 30-day mortality, independent of any extrahepatic organ failures [58]. The general management of encephalopathy includes (1) ruling out alternative explanations for altered mental status, (2) evaluation for precipitants of encephalopathy, such as sedating medications, infection, or renal dysfunction, (3) initiation of empiric treatment of encephalopathy (lactulose), and (4) intubation for patients who cannot protect their airway [59]. *For further discussion of portosystemic encephalopathy, please refer to* Chap. 3.

Circulatory and Respiratory Failure

Circulatory and respiratory failures are defined similarly in the EASL-CLIF and NACSELD studies. EASL-CLIF defines circulatory failure as the need for medication to support the blood pressure. NACSELD defines circulatory failure numerically as a mean arterial pressure <60 mmHg or a decrease of systolic blood pressure by 40 mmHg below baseline despite adequate fluid resuscitation. Clinically, however, these patients are also going to need blood pressure support medications, in line with the EASL-CLIF definition. Respiratory failure, however, is defined numerically by EASL-CLIF, based on the PaO2/FiO2 and SpO2/FiO2 ratios, while it is defined clinically by NACSELD, based on the need for mechanical ventilation. Again, the degree of reduction of the patients' PaO2/FiO2 ratio is equivalent to the reductions seen in moderate to severe respiratory failure and suggests that patients are likely on mechanical ventilation or will be soon.

The management of patients with cirrhosis who have circulatory or respiratory failure is similar to patients without cirrhosis. The need for invasive lines and monitoring, the use of echocardiography to evaluate for cardiac dysfunction, the choice of vasopressors or inotropes, and the use of lung protective ventilation with low tidal volumes are the same [57]. A few key differences would include: (1) mean arterial pressure should be targeted to ≥60 mmHg, lower than patients without cirrhosis; (2) elevated lactate levels may take longer to clear, though their elevation is

still clinically important; and (3) there should be a low threshold to start empiric antifungal therapy, particularly in patients with risk factors for fungal infections such as use of total parenteral nutrition, renal replacement therapy, or cholestatic liver disease as well as patients without improvement at 24 hours [57]. *For further discussion of the care of patients with cirrhosis in the intensive care unit, please refer to* Chap. 6.

Prognosis and Outcome Management

The models developed for the assessment of ACLF are robust at predicting mortality. The primary predictive models associated with ACLF were mentioned earlier: the CLIF-SOFA and the NACSELD-ACLF scoring systems. CLIF-SOFA has since undergone validation in other global populations, while the NACSELD-ACLF score to date has only been validated with its own cohorts [60, 61]. Other scoring systems applied to cirrhotic patients, such as the MELD or MELD-Sodium score, and to all-comers, such as the Acute Physiology and Chronic Health Evaluation Score II (APACHE-II), have been applied to patients with ACLF with some success. Comparing the MELD, APACHE-II, and CLIF-SOFA, the latter appears to be the most robust with an AUROC of 0.84 in one study of 971 patients [60].

The definitive management of ACLF, outside of temporizing the underlying precipitant, is limited to liver transplantation. Other methods of liver support have been studied in the ACLF population without success. For patients with ACLF who are not liver transplant candidates, the high mortality associated with 3 or more organ failures should guide physicians as they set expectations on recovery and prompt consideration of palliative care consultation.

Liver Transplantation

The decision whether a person with chronic liver disease is a transplant candidate is ideally made when the MELD score approaches ≥15, clinical decompensations arise, or hepatocellular carcinoma develops [62]. Early evaluation of patients allows for a decision about transplantation status to be made prior to the onset of potential future episodes of ACLF, when patients may be too sick to complete all required transplant evaluation and testing. The decision to remain on the list should be re-evaluated with the onset of new medical conditions or if their functional status declines.

When to proceed with liver transplantation for patients with ACLF is not yet well defined. In the United States, where liver allocation is based on the MELD score, these patients tend to be very competitive for organ offers, but may not be able to proceed with transplant due to uncontrolled infection or severe multi-organ system failure. Unfortunately, survival at 180 days and 1 year tend to be lower than

Table 11.5 Comparison of survival after liver transplant for patients with ACLF and patients without ACLF [63–68]

Study	Criteria for ACLF	ACLF survival after transplant	Non-ACLF survival after transplant	*p*	Notes
Bahirwani et al. [64]	Increase in MELD >5 within 4 weeks	74.5% at 180 days	83.4% at 180 days	0.05	When dual organ transplants were excluded, there was no significant difference
Finkenstedt et al. [65]	APASL	87% at 1 year	–	–	
Gustot et al. [66]	EASL-CLIF	75% at 1 year	–	–	Early transplant, days 3–7
Reddy et al. [68]	NACSELD	95% at 180 days	–	–	No reported deaths, two patients were lost to follow-up
Levesque et al. [67]	EASL-CLIF	70% at 1 year	91% at 1 year	< 0.01	Simultaneous liver-kidney patients excluded
Artru et al. [63]	EASL-CLIF	83.9% at 1 year	90% at 1 year	NS	

patients transplanted without ACLF (Table 11.5) [63–68]. Nonetheless, survival is much higher with transplant than if these patients were not transplanted (83.9% vs. 7.9% for grade 3 EASL-CLIF ACLF at 1 year in Artru et al.) [63]. In addition, in one multivariate analysis of liver transplant recipients, ACLF was not associated with recurrent liver disease, eGFR less than 30 ml/minute, or need for retransplantation [64].

With the varied definitions of ACLF used across these studies, it is difficult to delineate the population of ACLF for whom transplantation would be most beneficial. For example, in the study from Levesque et al., it was observed that only 21.4% to 23.5% of patients with grade 1 or 2 ACLF (based on EASL-CLIF) died within 1 year of liver transplant, while 56.7% of patients with grade 3 ACLF died. These results suggest that earlier stages of ACLF may better tolerate liver transplant [67]. More recently, however, even patients with grade 3 ACLF have been transplanted with one-year survival approaching 84% [63]. All 73 of the patients in this study, however, had at least one post-operative complication, including infectious, biliary, cardiac, vascular, and/or pulmonary complications [63].

In current practice, the decision to proceed with transplant is made on a case-by-case basis. Even within a single grade of EASL-CLIF ACLF, there is a spectrum. For example, a patient could be on terlipressin or a combination of three different vasopressors and still qualify as circulatory failure. There would be much less hesitance to transplant the first patient than the second. The decision to transplant a patient with ACLF should be based on whether (1) the underlying precipitant is controlled and (2) the organ dysfunction is controlled and/or improving, and (3) the organ dysfunction would be expected to improve after transplant (e.g., hepatorenal syndrome).

Liver Support Devices

Despite some early success with the use of extracorporeal albumin dialysis in the improvement of encephalopathy, there was no survival benefit [69–71]. Both the HELIOS study group and the RELIEF study group, with a total of 172 patients between the two trials, failed to demonstrate improvement in survival in study follow-up [69, 71]. Without new data to refute these findings, the routine use of extracorporeal liver support cannot be recommended.

Palliative Care

The use of palliative care in patients with liver disease who are not transplant candidates is under-utilized. One study from 2014 found that only ~10% of patients removed from the transplant list were referred for palliative care consultation, though this percentage may have increased some in recent years [72, 73]. Palliative care services are often beneficial to patients with cirrhosis, who may have ongoing issues with pain and nausea. Furthermore, it is important to explain prognosis and discuss goals of care with these patients. These patients may not realize that, even with a simple infection, they can face high short-term mortality. Clarification of goals of care prior to the onset of ACLF can guide the treatment team to perform only the interventions the patient would have desired. *For further discussion of palliative care, please refer to* Chap. 16.

Future Directions

Many unmet needs still exist in the field of ACLF. The concept of ACLF can be further clarified to determine its exact frequency, precisely identify its precipitants, increase its generalizability, and investigate biomarkers that may provide diagnostic and prognostic value. The pathogenesis can be investigated to identify why some patients and not others develop ACLF, and if there are any specific cytokine signatures that correlate with grades of ACLF as well as targets for therapy. The exact role of the gut microbiome also has yet to be clarified. Advances are needed in the prevention of ACLF as well as optimal management of organ failure(s). Further work is needed to determine the role of liver transplant in ACLF and what bridging therapies (such as liver assist devices) can be developed.

ACLF is still an emerging concept with an increasingly refined definition that is being more recognized by clinicians. To this point, the majority of this textbook is a study of the precipitants and management of ACLF. Despite much improvement in the management of liver disease over the last decade, the morbidity and mortality associated with ACLF remain high. As the concept continues to evolve, health-care providers should focus on the early identification of any precipitants and early aggressive therapy in an effort to halt the progression of ACLF.

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Chapter 12
Anticoagulation in the Hospitalized Patient with Decompensated Cirrhosis: Management of a Delicate Balance

Jessica P. E. Davis and Nicolas M. Intagliata

Introduction

Historically, patients with chronic liver disease were thought to be "auto-anticoagulated" in the setting of a prolonged international normalized ratio (INR) and thrombocytopenia. However, current paradigms suggest that hemostasis in cirrhosis is "rebalanced" due to decreased synthesis of both pro- and anti-hemostatic factors (Fig. 12.1) [1–4]. This concept is supported by evidence from clinical and translational studies [5].

Patients with decompensated cirrhosis are at risk to develop both thrombotic and bleeding events [6–8]. In clinical practice, platelet level and prothrombin time or INR are often used as measures of the hemostatic system in patients to gauge bleeding risk. In patients with cirrhosis, the INR is misleading as it reflects only deficiencies of *anti*coagulant factors, failing to account for concurrent deficiencies of *pro*coagulant factors in patients with liver disease (e.g., protein C and antithrombin) [9, 10]. The lack of correlation between bleeding risk and INR in cirrhosis has been known for years [11]. More recently, global coagulation studies have expanded our understanding of the pathophysiology of coagulopathy in decompensated cirrhosis, and patients with cirrhosis display preserved thrombin generation [9, 10, 12–16]. As patients with cirrhosis often have thrombocytopenia from splenic sequestration, there is also concern surrounding the risk of bleeding in patients with low platelet counts, particularly bleeding associated with procedures performed in the hospital. However, the association of thrombocytopenia and bleeding in cirrhosis remains controversial [17]. Elevated von Willebrand factor and factor VIII may compensate for thrombocytopenia in patients with cirrhosis [14, 18].

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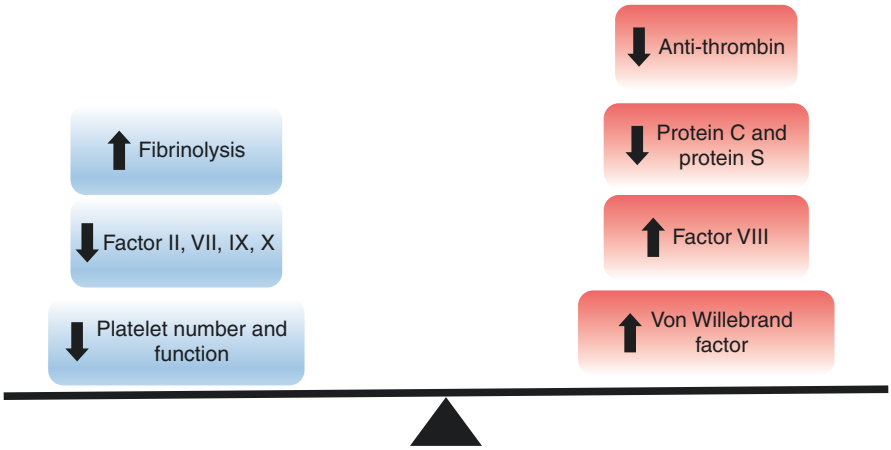

Fig. 12.1 Schematic of hemostasis in liver disease. Changes in procoagulant (red) and anticoagulant (blue) factors lead to a "rebalanced" hemostasis

An appreciation of the delicate "rebalanced" hemostasis system in patients with chronic liver disease is critical when caring for the hospitalized patient with cirrhosis. Scenarios requiring decisions to provide prophylaxis and treatment are common as hospitalized patients with cirrhosis are prone to both clotting and bleeding (Fig. 12.2) [6–8]. Patients with cirrhosis are at risk for hypercoagulability [19, 20]. Clinical studies indicate that patients with cirrhosis are at increased risk to develop venous thromboembolism [21–25]. Furthermore, the prevalence of portal vein thrombosis (PVT) is high in cirrhosis compared to the general population [6]. Patients with different etiologies of liver disease may have differences in hemostasis as well; cholestatic liver diseases, for example, have been observed to be more hypercoagulable than their counterparts [26, 27]. Non-alcoholic steatohepatitis (NASH) has been associated with increased risk of PVT [28]. Patients with cirrhosis are at higher risk of arterial thromboses as well [29]. NASH is associated with increased risk of cardiovascular disease [30].

Given the tendency toward thrombotic events in this population, there are multiple scenarios in which prophylactic or therapeutic anticoagulation may be desired. Anticoagulation, however, can be particularly challenging as the coagulation system is often affected by concurrent issues such as acute kidney injury, infection, variceal bleeding, acute liver failure, hepatic encephalopathy, and malignancy [31–35].

Anticoagulation in Patients with Cirrhosis

Patients with liver disease are excluded from large trials examining safety and efficacy of anticoagulants. Consequently, studies in patients with cirrhosis are limited to uncontrolled retrospective cohort or case series [36–56]. The vast majority of research in this field has examined the role in prevention and treatment of portal vein thrombosis. There is very limited knowledge regarding the treatment of venous thromboembolism (VTE)

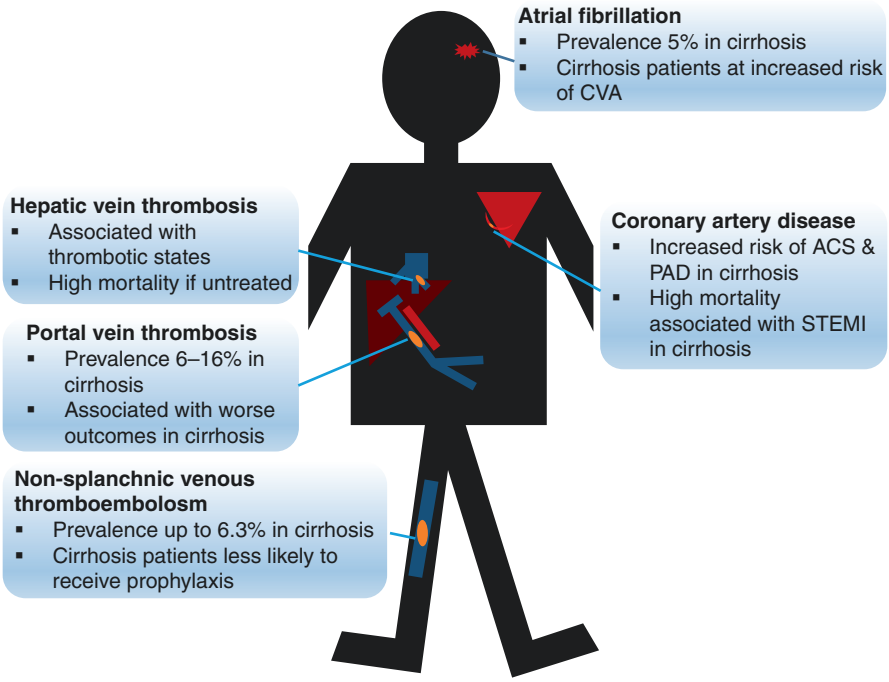

Fig. 12.2 Common thrombotic events in patients with cirrhosis (ACS acute coronary syndrome, CVA cerebrovascular accident, PAD peripheral arterial disease)

and prevention of thromboembolism in atrial fibrillation. Similarly, knowledge on the pharmacology of anticoagulants and metabolism is extremely sparse.

The largest clinical experience with anticoagulation (AC) in patients with liver disease compromises cohorts treated with low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKAs) (Table 12.1). Despite significant experience, VKAs have several drawbacks including difficulty in monitoring. Heparins have been used in patients with liver disease and are useful in the hospitalized, critically ill patient given their short half-life. However, as heparins require antithrombin, the dosing and monitoring of both unfractionated heparin and LMWH are challenging [57–59]. While the efficacy of LWMH in patients with liver disease is now established, the requirement of subcutaneous dosing renders these medications unattractive for long-term use. The newest generation of anticoagulants, direct oral anticoagulants (DOACs), is emerging as a potentially advantageous option in compensated liver disease. Several small observational studies have suggested that the bleeding risk of DOACs is similar to that of VKAs in patients with chronic liver disease [46, 47, 49]. Development of reversal agents for DOACs that can be used in the setting of bleeding or pre-procedurally has further increased their appeal. Dabigatran, for example, has been used prior to liver transplant with minimal intra-operative bleeding after administration of idarucizumab peri-operatively [60]. More recently, andexanet alfa has been FDA-approved for reversal of anticoagulation in patients treated with apixaban or rivaroxaban experiencing

Table 12.1 Advantages and disadvantages of available anticoagulant agents in patients with cirrhosis

Anticoagulant	Mechanism	Pros	Cons
Vitamin K antagonist	Depletion of vitamin K-dependent coagulation factors	Significant data in cirrhosis Oral formulation	Difficult to monitor in setting of baseline INR abnormalities which may lead to under-dosing
Unfractionated heparin	Inhibition of thrombin and factor Xa via antithrombin	Short half-life Can be used in renal disease	Difficult to monitor given elevated PTT and decreased FXa in cirrhosis Low antithrombin levels in cirrhosis could theoretically reduce efficacy at standard dosing Intravenous dosing
Low-molecular-weight heparin	Inhibition of factor Xa via antithrombin	Evaluated prospectively in cirrhosis with minimal bleeding at prophylaxis dose	Subcutaneous dosing Low antithrombin levels in cirrhosis could theoretically reduce efficacy at standard dosing
Direct oral anticoagulant	Inhibition of thrombin and factor Xa	Available direct reversal agents Oral formulation No dose adjustment	Least safety and efficacy data in cirrhosis

life-threatening or uncontrolled bleeding, although this agent is not yet widely available and is associated with high cost [61].

Despite thrombocytopenia and a prolonged PT/INR, patients with cirrhosis are at risk to develop venous and arterial thromboses. There are no prospective, randomized, controlled data evaluating the safety or efficacy of *therapeutic* anticoagulation in patients in cirrhosis. Overall bleeding risks are likely increased in patients with cirrhosis compared to patients without cirrhosis due to portal hypertension and alterations in hemostasis. Despite this increased bleeding risk, anticoagulation may be necessary and even beneficial in patients with cirrhosis. When possible, bleeding risk should be minimized prior to initiation of anticoagulation with serial endoscopic variceal ligation and/or beta blockade [5]. Clinical decision-making should always be based on individualized approaches with multidisciplinary cooperation. Below we review common clinical scenarios encountered in hospitalized decompensated patients with cirrhosis and review the role of anticoagulation.

Non-splanchnic Venous Thromboembolism

Risk

The risk of venous thromboembolism (VTE) is high in critically ill medical patients [22]. Approximately 26,000 patients with cirrhosis require intensive care each year in the United States [62]. In patients with liver disease, the prevalence of VTE is

high as well, ranging from 0.5% to 6.3% [23]. Several studies show that patients with cirrhosis are at increased risk of VTE compared to controls [7, 21, 24, 25, 63–65]. In one nationwide case-control study that compared 99,444 patients with VTE to 496,872 controls, patients with cirrhosis had a relative risk of VTE of 1.74 (CI 1.54–1.95) [24]. A systematic review aggregated several studies including a total of 695,012 cirrhotic patients compared to 1,494,660 non-cirrhotic patients and found a significantly increased risk of VTE in patients with cirrhosis (OR 1.7 (95% CI 1.3–2.2; $p < 0.0001$)) [7]. While VTE in patients with cirrhosis is associated with increased 30-day mortality [66], hospitalized patients with cirrhosis are less likely to receive VTE prophylaxis [67, 68]. Given the high prevalence and significant mortality implications of VTE in critically ill cirrhosis patients, providers should be particularly attuned to appropriate VTE prophylaxis and treatment in this population.

Prophylaxis

Patients with cirrhosis are less likely to receive thromboprophylaxis while hospitalized [67, 68]. This tendency grew from the now disproven historical perception that patients with cirrhosis are "auto-anticoagulated" with an increased risk of bleeding. Given the relative rarity of VTE events overall in this population, data for efficacy of thromboprophylaxis in patients with cirrhosis are minimal. Medical thromboprophylaxis does not appear to significantly increase bleeding risk in small observational studies [48, 56]. However, in a subgroup analysis, unfractionated heparin (UFH) was associated with an increased risk of bleeding compared to low-molecular-weight heparin (LMWH) (OR 2.38, 95% CI 1.15–4.95) [56]. Ideally, according to the American College of Chest Physicians guidelines, risk should be individually quantified with validated risk assessment models (RAMs) to determine the benefits and risks of medical thromboprophylaxis [69]. The Padua Prediction Score (PPS) [70] has been recommended for use in non-surgical patients and was found to be predictive of VTE in patients with cirrhosis in a retrospective study of 163 patients [71]. The IMPROVE RAM incorporates hepatic dysfunction into its estimates of bleeding and thrombosis risk and included patients with hepatic disease in validation studies [72–74]. In a prospective study in ambulatory patients with cirrhosis without PVT, thromboprophylaxis with LMWH was safe without bleeding events [37]. Expert guidelines support use of thromboprophylaxis in hospitalized patients with liver disease in the absence of a strong contraindication (e.g., severe thrombocytopenia) [5]. Given existing safety data, LMWH is preferred over UFH [56].

Therapy

There are minimal data available regarding the safety and efficacy of treatment of non-splanchnic VTE in patients with cirrhosis. Several studies have evaluated the safety and efficacy of treatment of PVT, which provides data to support the use of

AC for non-splanchnic VTE. Studies are limited overall by variable definitions of bleeding, heterogeneous cohorts, and no standard treatment outcome definitions. One particularly challenging aspect unique to patients with cirrhosis is establishing the relationship between bleeding provoked by anticoagulation (hemostatic failure) and bleeding inherent to portal hypertension (pressure related). This is important to consider as variceal bleeding is likely driven by portal hypertension rather than underlying anticoagulation. Furthermore, the presence of anticoagulation does not affect outcome or mortality in patients with cirrhosis and upper GI bleeding [41]. In multiple studies evaluating therapeutic anticoagulation for treatment of portal vein thrombosis (PVT), AC has been demonstrated to be both effective and safe [36, 38, 42, 44, 45, 54, 55]. In one meta-analysis that reviewed 16 studies using primarily VKA or LMWH, the pooled rate of bleeding related to AC was only 3.3% (95% CI 1.1–6.7.) [54]. There are no studies evaluating the efficacy of DOAC for non-splanchnic VTE. Several small series have demonstrated that the rate of bleeding associated with DOAC in patients with cirrhosis is comparable to that of traditional AC [46, 47, 49]. Expert guidelines recommend treatment of VTE in patients with cirrhosis in the absence of contraindication [5]. The IMPROVE RAM may be useful to estimate bleeding risk prior to initiation of AC [72].

Portal Vein Thrombosis in Cirrhosis

Risk

Portal vein thromboses (PVT) are common in patients with cirrhosis with prevalence reported from 0.6% to 16% depending on severity of liver disease and population cohort [6]. Patients with cirrhosis are at high risk of PVT due to both slow flow in the portal vein and hypercoagulability associated with liver disease [75, 76]. Given the dual blood supply of the liver, PVT are often asymptomatic, but PVT microthrombi and consequent long-term reduction of blood flow to the liver have been proposed as a driver of fibrosis [77]. PVT have been associated with increased mortality, decreased survival post-transplant, and worse liver transplant outcomes [78–80]. Prevention of PVT in liver transplant candidates is critical as physiologic anastomoses improve post-transplant outcomes [81, 82].

Outside of the context of liver transplant there are observational data to suggest that recanalization of the portal vein is associated with improved transplant-free survival and reduction in portal-hypertension-related events [50]. However, debate persists as to whether PVT are merely a result of the progression of cirrhosis and portal hypertension or instead a direct cause of hepatic decompensation [83]. One landmark randomized controlled trial showed decreased mortality and rates of hepatic decompensation when PVT formation was prevented with administration of LMWH [37]. These findings potentially support a causal role of PVT producing

hepatic decompensation. Alternatively, some authors argue that PVT are a consequence from progression of liver disease and portal hypertension rather than a contributor to decompensation. In one large, longitudinal study of 1243 patients with cirrhosis, development of PVT was not independently associated with progression of liver disease or decompensation [83]. Furthermore, a significant proportion of PVT observed in this study spontaneously recanalized without treatment. Authors concluded that PVT likely occurred in the setting of severe liver disease due to reduction in portal vein flow but that there was no evidence to suggest development of PVT worsened liver function per se.

Therapy

Both anticoagulation and transjugular intrahepatic portosystemic shunting (TIPS) have been used successfully in the management of PVT [84, 85]. Prior to therapy, detailed characterization of PVT with cross-sectional imaging is essential to rule out malignancy and define the extent of the thrombus. Therapeutic decisions often depend on the extent and chronicity of PVT, as well as the presence or absence of liver disease (Fig. 12.3). It should be stressed that patients without cirrhosis and acute PVT require urgent anticoagulation, and management of these patients is discussed elsewhere [84]. However, in patients with cirrhosis, development of acute PVT is more common and rarely requires urgent anticoagulation. Exceptions to this include situations with concern for mesenteric ischemia, rapidly progressive thrombus into the proximal mesenteric veins, and post-liver transplant recipients. In cirrhosis, the presence of portosystemic collaterals may protect against mesenteric ischemia by allowing for alternative venous drainage. In patients with cirrhosis, PVT are most commonly discovered incidentally in an asymptomatic patient. In other cases, patients may present with vague abdominal pain or worsening of ascites. Prior to the initiation of treatment, risk assessment for bleeding should be performed with serial variceal ligation and non-selective beta blockade as needed.

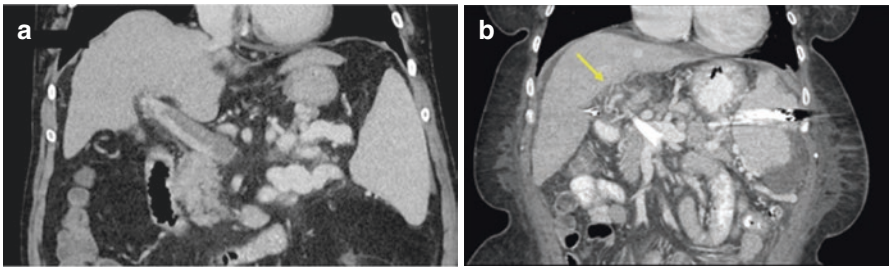

Fig. 12.3 Cross-sectional imaging of acute (panel a) and chronic (panel b) portal vein thrombosis. Collateral vessels suggesting chronicity are seen (yellow arrow)

Expert guidelines currently recommend consideration of therapeutic AC of acute and advanced non-malignant PVT in patients who are liver transplant candidates [5, 52, 84]. In patients who are not considered liver transplant candidates, current recommendations advise consideration of AC on individual basis. When to initiate anticoagulation is unclear and controversial. Importantly, up to 40% of PVT spontaneously recanalize in patients with cirrhosis without intervention [86]. In most cases, serial imaging early on in asymptomatic, low grade PVT prior to consideration of treatment is a reasonable approach [84, 85]. It should be acknowledged, however, that success of recanalization is dependent on timely diagnosis as rates of recanalization are higher in patients who are treated within 6 months [55].

If it is determined that anticoagulation is indicated, unfractionated heparin is usually the initial agent in the hospitalized setting given the potential for gastrointestinal bleeding and need to stop prior to procedures. For long-term anticoagulation, LMWH and VKA are often chosen due to clinical experience [84]. Direct oral anticoagulants are emerging options but data remain very sparse. The treatment duration is unclear, but experts recommend interval monitoring with cross-sectional imaging and consideration of a minimal of 6 months of therapy [84, 87].

In patients with both significant portal hypertension complications (e.g., refractory ascites) and advanced PVT, TIPS may be an alternative to AC. TIPS promotes portal vein recanalization by increasing portal vein flow and is effective in patients with severe portal hypertension and extensive PVT [5]. While PVT as a primary indication for TIPS alone is not currently recommended, the use of TIPS for advanced PVT, including chronic cavernomas, to recanalize the portal vein to then allow transplantation has recently been described [82]. TIPS should be approached with caution in patients at risk of portosystemic encephalopathy or high MELD.

Hepatic Vein Thrombosis

Risk

Budd-Chiari syndrome (BCS), or hepatic vein obstruction, can be asymptomatic or present with fulminant hepatic failure, depending on the extent of collateral hepatic drainage present [88]. Classically, BCS presents with hepatomegaly, right upper quadrant pain, and ascites in the setting of acute liver injury or failure. Primary BCS is caused by thrombotic disease of the hepatic vein, whereas secondary BCS is obstruction of the hepatic vein from invasion or external compression [85]. A significant majority of patients with primary BCS have thrombotic risk factors and should undergo thrombophilia testing (concurrent malignancy, particularly myeloproliferative disorders, pregnancy, and thrombophilia) [85]. Primary BCS is relatively rare with an estimated incidence of 2 per million individuals [89]. Untreated, it is highly morbid with one historical series reporting death of >90% of patients within 3 years [90].

Therapy

Suspected hepatic vein obstruction (HVO) identified on ultrasound should be further evaluated by cross-sectional imaging with magnetic resonance imaging or computed tomography [91, 92]. Venography is the gold standard for diagnosis but may be avoided if adequate cross-sectional imaging is obtained. Therapeutic options include medical therapy with AC, interventional therapy with thrombolysis, and/or stenting including TIPS and liver transplant [84]. Current societal guidelines recommend a stepwise approach with AC first, then directed therapy with thrombolysis or stenting if AC is ineffective [84, 93]. If thrombolysis is unsuccessful, TIPS should be considered and then, ultimately, liver transplant. Rates of bleeding with AC for BCS were high in older series, with up to 50% of patients developing bleeding [94]. In a more modern series, bleeding was only reported in 17% of patients [93]. There are no randomized controlled trials of AC for BCS, but observational studies have supported a survival benefit [95] and a beneficial effect post-transplant in preventing re-occlusion of the hepatic vein [40, 96]. Furthermore, one study of patients who underwent angioplasty noted that lack of at least 6 months of AC was a risk factor for re-occlusion [97]. When possible, portal hypertensive bleeding prophylaxis should be provided prior to initiation of AC to minimize bleeding risk. AC should be continued indefinitely, including post-transplant, as BCS can recur in these patients. Female patients with BCS should be screened for pregnancy as this increases the risk of BCS and affects choice of AC agent. As above, all patients with BCS should be screened for prothrombotic states as these are common in primary BCS [85].

Atrial Fibrillation

Risk

Historically atrial fibrillation was thought to be uncommon in patients with cirrhosis [98]. Recent studies, however, demonstrate the prevalence of atrial fibrillation in patients with cirrhosis is 5%, similar to patients without cirrhosis [99, 100]. Patients with cirrhosis, particularly critically ill patients, commonly have left atrial dilation in the setting of volume overload and frequent electrolyte disturbances that are known to increase risk of atrial fibrillation [99]. One observational cohort study suggested that the risk of stroke and intracranial hemorrhage in patients with atrial fibrillation is higher in patients with cirrhosis than those without liver disease (HR 1.10, $p = 0.046$ and 1.20, $p = 0.043$, respectively) [101]. Atrial fibrillation is associated with increased risk of mortality in patients with cirrhosis (OR 1.44, 95% CI 1.36–1.53) [99].

Therapy

The HAS-BLED and CHA_2DS_2-VASc scores have been used in the general population to determine the risks and benefits of AC for stroke prevention in patients with atrial fibrillation [102, 103]. These scores have not been validated in cirrhosis. A large number of patients with cirrhosis and atrial fibrillation have CHA_2DS_2-VASc scores ≥2, the cutoff at which AC is felt to be beneficial for stroke reduction in the general population [101]. One analysis of net clinical benefit suggests that AC but not anti-platelet therapy is beneficial in this population [101]. There are no prospective data explicitly evaluating the efficacy and safety of anticoagulation in patients with cirrhosis specifically for stroke prevention in the setting of atrial fibrillation. One observational study comparing 173 patients with cirrhosis and atrial fibrillation on VKA to 148 patients not on VKA showed a reduction in the incidence of ischemic strokes (1.8%/year vs. 4.7%/year, $p = 0.01$) but an increased incidence of major bleeding (9.6%.year vs. 6.2%/year) [51]. Subgroup analysis suggested the risk to benefit ratio may be more favorable in patients with Child-Turcotte-Pugh (CTP) A cirrhosis rather than CTP B or C cirrhosis patients [51]. Another observational study comparing 113 patients on VKA to 352 patients not on VKA also demonstrated increased incidence of major bleeding (5.9% vs. 2.6%, $p < 0.05$) among VKA users but did not show a reduction in the incidence of ischemic stroke (0.9%/person-year in users vs. 1.2%/person-year in non-users) [43]. Application of these results is limited as both are retrospective and used VKA for AC. Again, our understanding of the safety of AC with LMWH or DOAC is mainly extrapolated from studies evaluating the use of AC for treatment of PVT [36, 38, 42, 44, 45, 54, 55]. Until further evidence is generated, decisions regarding the use of therapeutic AC for stroke prevention in atrial fibrillation in cirrhosis must be made on an individualized basis.

Arterial Thrombosis

Risk

Historically, autopsy studies suggested a low prevalence of myocardial infarction in patients with cirrhosis compared to the general population [29]. More recently, a population-based cohort study found an incidence of acute coronary syndrome (ACS) of 2.81/1000 person-years and an incidence of peripheral arterial disease (PAD) of 2.97/1000 person-years in patients with cirrhosis [104]. In this study, cirrhosis actually increased the adjusted subhazard ratio of both ACS (1.12, 95% CI 1.03–1.22) and PAD (1.11, 95% CI 1.02–1.21) [104]. This discrepancy with earlier autopsy studies may be due to the increasing proportion of cirrhosis due to non-alcoholic steatohepatitis (NASH) cirrhosis, which is associated with an elevated cardiovascular risk [30]. With the rising prevalence of

NASH cirrhosis, the prevalence of comorbid coronary artery disease (CAD) in patients with cirrhosis will continue to increase [105]. One prospective study of 228 liver transplant candidates aged ≥50 or with CAD risk factors who underwent coronary angiography found CAD in 37% of patients and 53% of patients with NASH cirrhosis [106]. Cardiovascular disease is a significant cause of mortality in patients with cirrhosis and in-hospital mortality in patients with cirrhosis and ST elevation myocardial infarction is high, around 17% in one retrospective study [107].

Therapy

In patients with acute coronary syndrome (ACS) in the general population, there are data to support both revascularization and the use of medical therapy with anti-platelet agents and statins [108, 109]. There are no prospective trials evaluating the safety and efficacy of medical or interventional therapy for ACS specifically in patients with cirrhosis, but limited observational data are available. Cardiac catheterization has an acceptable risk profile in patients with cirrhosis [110–113]. Data evaluating coronary artery bypass grafting (CABG) and/or percutaneous coronary intervention (PCI) in patients with cirrhosis suggests PCI is better tolerated [114]. Authors from one retrospective Japanese study recommend consideration of PCI over CABG even in complex occlusive disease given the high morbidity and mortality associated with CABG in cirrhosis and numerous competing non-cardiac causes of death in patients with cirrhosis [114]. Available data suggest aspirin and statin therapies are underutilized in patients with cirrhosis, perhaps related to fears of increased bleeding risk or risk of hepatic decompensation or renal injury [115]. As above, the safety of use of statins and aspirin to reduce cardiovascular mortality in patients with cirrhosis has not been evaluated prospectively, however, these appear safe [115, 116]. Data evaluating dual anti-platelet therapy after PCI in patients with cirrhosis are lacking. One retrospective case control series demonstrated comparable rates of variceal bleeding and intra-operative transfusion requirements during liver transplantation between patients who received cardiac stents (and anti-platelet therapy) and controls [117]. In that series, high-risk varices were treated with EVL and beta blockade prior to cardiac catheterization. Due to earlier data demonstrating higher risk of first variceal bleeding episode on aspirin [118], some authors have suggested that the risk-benefit ratio of aspirin as primary or secondary prophylaxis may depend on the presence or absence of varices [119]. In summary bleeding risk associated with anti-platelet therapy may be elevated in patients with cirrhosis compared to patients without cirrhosis due to baseline thrombocytopenia and portal hypertension. Irrespective of these risks, given the benefits of prophylaxis, particularly secondary prophylaxis, interventional and medical therapies are likely warranted in high-risk patients, such as those who present with ACS.

Conclusion

Current understanding of "rebalanced" hemostasis in patients with cirrhosis supports clinical observations that patients with cirrhosis are at high risk of thrombotic events. Venous thromboembolism, portal vein thrombosis, acute coronary syndrome, and atrial fibrillation are all clinical scenarios that will be encountered in critical care of patients with cirrhosis (Fig. 12.2). Given the association of NASH with a prothrombotic state [28], the prevalence of thrombotic events in patients with cirrhosis is likely to continue to rise. Studies evaluating the efficacy and safety of anticoagulation in patients with cirrhosis are largely observational. Patients with decompensated cirrhosis are at a relatively higher risk of bleeding given abnormalities of hemostasis and underlying portal hypertension. Despite this increased bleeding risk, anticoagulation should not be withheld automatically from patients with cirrhosis. Rather, evaluation of the individualized clinical scenario is necessary to accurately weigh the risks and benefits of each approach [5, 84, 85]. As the field continues to grow and our understanding of the pathophysiology of hemostasis in cirrhosis expands, approaches to these complex clinical scenarios should improve.

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Chapter 13
The Management of Hepatocellular Carcinoma

Robert R. McMillan and Vatche G. Agopian

Epidemiology

Hepatocellular carcinoma (HCC), the most common primary malignancy of the liver, is the fifth most common neoplasm and the second leading cause of cancer death worldwide, resulting in approximately 800,000 deaths per year [1, 2]. The case fatality ratio of HCC is 0.8, with the number of new cases nearly similar to the number of deaths each year, equivalent to pancreatic cancer [3]. The highest incidence areas worldwide are in East Asia and sub-Saharan Africa, with incidences of 24.2/100,000 and 35.5/100,000, respectively [4].

Unlike most common cancers, which have seen a reduction in death rates, the incidence and number of deaths due to HCC have increased in the United States. Between 2000 and 2012, the age-adjusted incidence of HCC in the United States increased from 4.4/100,000 to 6.7/100,000, more than four times the incidence of 1.6/100,000 in 1976 [5, 6]. In parallel to the rising incidence, there has been a two-fold increase in deaths due to HCC between 1999 and 2016 [7]. These trends are driven by the high rate of hepatitis C virus (HCV) in the "Baby Boomers" birth cohort from 1945 to 1964, where researchers estimate HCC cases due to HCV will peak in 2020 [8], as well as the epidemic of nonalcoholic fatty liver disease (NAFLD).

HCC is unique in that >90% of cases are associated with some form of underlying chronic liver disease and/or cirrhosis. Risk factors for developing HCC include chronic viral hepatitides (hepatitis B virus [HBV] and HCV), alcoholic liver disease, diabetes, NAFLD, and less common causes of cirrhosis such as hereditary hemochromatosis [8]. Worldwide, over 50% of cases of HCC are due to HBV, followed by

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HCV, which accounts for approximately 20% [9]. While chronic viral hepatitis is implicated as the etiologic factor in the development of the majority of HCC, these risks are now modifiable in light of both vaccination efforts and antiviral therapies. Efforts to reduce HBV rates with universal vaccination efforts have been effective in reducing HCC mortality in high incidence areas, such as Taiwan and East Asia [10]. Furthermore, the recognition that the risk of HCC in patients with HBV is higher in patients who have higher HBV DNA viral load [11] underscores the importance of aggressive HBV antiviral therapy, which results in a 50–60% risk reduction of HCC following successful treatment [12, 13]. However, inactive carriers with no viral load (HbcAb positive, HbsAb negative) remain at higher risk than patients without HBV, with an annual incidence of 0.06% versus 0.02% [14]. Regarding HCV, the risk of HCC in patients achieving a sustained virologic response (SVR), which is considered a virologic cure, is lower than patients who do not achieve SVR, whether SVR is achieved by interferon or directly acting antivirals (DAAs) [15–17]. Even after achieving SVR, patients with HCV who have cirrhosis will develop HCC with an incidence of approximately 1% per year [18, 19]. DAAs for HCV may lead to a reduction in HCC over the next 1–2 decades, with the degree of this impact depending on the availability of these medications [17].

NAFLD, an increasingly important etiologic factor in the development of HCC, warrants specific discussion. NAFLD has become the most common cause of chronic liver disease in the developed world, and it is a rising cause of HCC-related liver transplant in the United States [20]. The prevalence of NAFLD is higher among Latinos compared to other ethnic groups in the United States [21]. Diabetes mellitus is commonly found in patients with NAFLD and is itself associated with a two- to threefold increase in the risk of developing HCC [22]. Perhaps most alarmingly, HCC has been found to arise in NAFLD patients without established cirrhosis, complicating surveillance recommendations for this specific group of patients. Recently, Mittal and coworkers reviewed a national cohort of VA patients with HCC and found 13% of patients with HCC did not have cirrhosis, with NALFD accounting for approximately 1/3 of patients with noncirrhotic HCC [23]. Additional research is required to define high-risk subgroups with NAFLD to facilitate surveillance and early disease detection.

Pathophysiology

HCC most commonly forms in the setting of liver injury, whereby hepatocyte damage results in genomic instability and transformation into HCC. The great majority of HCC, approximately 80–90%, develops in the context of cirrhosis. Among patients with established cirrhosis, the annual incidence of HCC is 3–8% [24].

The common denominator for the development of HCC is thought to be the ongoing inflammation and cell turnover in patients with cirrhosis and can be due to viral hepatitis, alcoholic or nonalcoholic steatohepatitis (NASH), or other disease processes that lead to injury and repair. In this setting, patients develop precancer-

ous dysplastic nodules which may be low or high grade, based on degree of cellular atypia. The presence of stromal invasion differentiates HCC from dysplastic nodules [25]. In patients without cirrhosis, there are discrete alternate pathways for the development of HCC. The DNA virus HBV integrates its DNA randomly into the host hepatocyte genome and may directly contribute to the development of HCC via activation of oncogenes or inactivation of tumor suppressor genes. The viral regulatory protein HBx causes cell cycle dysregulation via chromatin remodeling and abnormal transcription activity, leading to cell proliferation [26]. Aflatoxins, carcinogens produced by Aspergillus molds, contaminate agricultural crops in developing nations and can lead to HCC. Aflatoxin directly binds to DNA, forming DNA adducts that cause DNA strand breakage and mutations in the *p53* tumor suppressor gene [27, 28]. Malignant transformation of hepatic adenomas into HCC has been associated with mutations *TERT* and *CTNNB1* genes [29].

More recently, there have been numerous studies detailing the genetic landscape of HCC using next-generation sequencing methodologies that have allowed for detailed genomic and transcriptomic molecular analyses of HCC. HCC lesions carry numerous somatic mutations, with an average of 40–60 alterations in protein-coding areas of the genome [29]. Study of recurrent mutations has shown common mutations in pathways for telomere maintenance, cell cycle signaling, WNT-β-catenin signaling, epigenetic chromatin modification, receptor kinases, and oxidative stress [29–32]. At present, a minority of HCC tumors harbor potentially targetable mutations with available agents [33]. As the molecular landscape of HCC becomes better defined, HCC treatment may become more individualized, with personalized treatments targeting patient-specific aberrations.

Diagnosis and Staging

Surveillance and Diagnosis

The majority of patients diagnosed with HCC present with advanced disease, with 60–70% presenting with disease not amenable to surgical resection (SR) or liver-directed therapies [34]. Because 80–90% of HCC develops in patients with underlying advanced liver disease, there is an opportunity to impact mortality with early detection. The very purpose of HCC surveillance is to reduce mortality by detecting disease at a treatable stage. The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) have promulgated guidelines for surveillance for HCC, which inform the discussion of surveillance in this chapter [35, 36] (Table 13.1).

A requirement for effective surveillance is first identifying high-risk patient groups who are appropriate for testing. Cost-effectiveness studies have defined an appropriate incidence for surveillance at 1.5%/year [37]. High-risk groups meeting these criteria include patients with established cirrhosis due to any underlying etiology. Other high-risk groups include noncirrhotic patients with HBV who have

Table 13.1 AASLD and EASL surveillance guidelines

	AASLD	EASL
Target patient groups	Cirrhotic patients[a]	Cirrhotic patients[a]
		Chronic HBV infection[b]
		Chronic HCV with bridging fibrosis
Surveillance testing	US +/− AFP, every 6 months	US every 6 months
Diagnostic testing	CT or MRI, using LI-RADS criteria, for cirrhotic patients	CT or MRI, using li-RADS criteria, for cirrhotic patients
	Biopsy for noncirrhotic patients or cirrhotic patients with nondiagnostic imaging	Biopsy for noncirrhotic patients or cirrhotic patients with nondiagnostic imaging

[a]Patients with decompensated cirrhosis who are ineligible for curative therapies are excluded from surveillance

[b]High-risk factors to consider for screening include PAGE-B score ≥10, active viral replication, geographic origin (e.g., Asia and Africa), increased age, and male gender

specific features. Noncirrhotic HBV patients from Asia or Africa and patients with higher levels of HBV replication or active hepatitis are appropriate for surveillance [38, 39]. The Platelet, Age, Gender, Hepatitis B (PAGE-B) system may help define which patients with HBV are intermediate or high risk and merit surveillance. PAGE-B scores are based on a decade of age, gender, and platelet count, and scores 10–17, and ≥18, correspond to intermediate and high risk [40]. Patients with chronic HCV and bridging fibrosis without cirrhosis have also been recommended for surveillance, due to the difficulty identifying progression from fibrosis to cirrhosis, as well as the possibility of understaging liver disease [41]. Lastly, patients with chronic HCV with advanced disease who have achieved SVR merit surveillance as they continue to be at risk for HCC. Because advanced liver failure prevents the use of many HCC therapies due to debility, surveillance is not recommended for patients with decompensated Child-Pugh B or C cirrhosis who cannot tolerate liver-directed or systemic therapies [35, 36].

An evolving area of particular concern is the appropriate recommendation for surveillance in patients without cirrhosis who have NAFLD. There is an increasing surge of NAFLD-related HCC cases occurring in patients without cirrhosis. However, due to the high prevalence of NAFLD and lack of specific high-risk NAFLD features, recommending universal surveillance is challenging [42]. Furthermore, ultrasound has lower sensitivity to detect tumor in patients with obesity, and routine surveillance using computed tomography (CT) or magnetic resonance imaging (MRI) would make health costs prohibitive [35]. At present, neither AASLD nor EASL recommends surveillance for noncirrhotic NAFLD. Research to define high-risk subgroups among patients with noncirrhotic NAFLD could make targeted surveillance more cost-efficient and effective.

Surveillance testing incorporates imaging and serologic studies. The most common imaging test for HCC surveillance is ultrasound (US). Studies investigating the effectiveness of US have found sensitivity ranging from 58% to 89% and specificity

higher than 90% [43]. The coarse echotexture of the cirrhotic liver presents a challenge to the ultrasonographer, and technician experience and quality of equipment impact US efficacy. Though more sensitive than US, CT and MRI are not recommended as surveillance due to their increased cost and a higher rates of false positive findings [44]. Both EASL and AALD recommend biannual US for high-risk groups. For lesions ≥1 cm discovered on ultrasound, further characterization with multiphase CT or MRI is recommended [36]. Lesions <1 cm are followed with ultrasound or other diagnostic imaging in 3-month intervals.

Serologic studies used to detect HCC include serum alpha-fetoprotein (AFP), the lectin-binding subfraction of AFP (AFP-L3), and des gamma carboxyl prothrombin (DCP), also known as protein induced by vitamin K absence/antagonist-II (PIVKA II). AFP is the most common serologic study used for surveillance, and some studies have shown an added sensitivity when AFP is used in addition to ultrasound [45, 46]. AASLD guidelines permit the inclusion of AFP in surveillance programs, but the guidelines do not go so far as to recommend universal AFP testing. AASLD guidelines recommend an AFP cut-off of 20 ng/mL for high-risk patients when it is used, which provides sensitivity of ~60% and specificity of ~90% [47]. EASL does not recommend inclusion of AFP in surveillance, citing studies that report a limited improvement in disease detection of only 6–8% of cases not already detected by US [48]. AFP-L3 and PIVKAII are novel biomarkers produced by HCC with promising predictive value. The Gender, Age, AFP-L3, AFP, and DCP (GALAD) model incorporates both AFP-L3 and PIVKAII, along with AFP to predict the risk of HCC development with a c-statistic of 0.88 [49]. These biomarkers are considered investigational until they are validated in larger study groups.

The diagnosis of HCC can be made with imaging studies or tissue biopsy. Imaging alone is sufficient to make the diagnosis of HCC in the vast majority of patients with underlying cirrhosis. The Liver Imaging Reporting and Data System (LI-RADS) has standardized the interpretation and reporting of liver lesions among patients with cirrhosis, providing a uniform method to diagnose HCC [50] (Table 13.2). For cirrhotic patients who undergo dynamic contrast-enhanced CT or MRI imaging, liver lesions meet the diagnostic criteria for HCC, a LI-RADS 5 lesion, if they exhibit nonrim-like arterial hyperenhancement and one of the following characteristics: nonperipheral "washout" in the venous phase of imaging, a ≥50% size increase in less than 6 months, and if the lesion size is ≥20 mm with an enhancing capsule [43]. The LI-RADS system is not validated to make the diagnosis of HCC in noncirrhotic patients. For noncirrhotic patients, EASL recommends tissue pathology to make the diagnosis of HCC. Biopsy is also an option to make a diagnosis in cirrhotic patients with nondiagnostic imaging. The risks of biopsy include bleeding and seeding of tumor along the biopsy needle tract. Historical rates of tumor seeding range from 0.6% to 5.1%. Due to these risks, AASLD guidelines recommend against routine biopsy of all indeterminate lesions. However, centers using new coaxial biopsy techniques have reported series with zero cases of tumor seeding after biopsy [51]. At present, biopsy represents a viable option for patients with lesions concerning for HCC, whose imaging remains nondiagnostic.

Table 13.2 LIi-RADS criteria (liver imaging reporting and data system)

Category	Significance	Examples	Enhancement criteria	Size criteria and presence of additional major criteria	Pathologic correlation	Natural history of lesions in 12 months
LR-1	Definitely benign	Cyst, hemangioma, hepatic fat deposition, confluent fibrosis or scar			0% are HCC or malignant	
LR-2	Probably benign	Cyst, hemangioma, hepatic fat deposition, confluent fibrosis or scar		<20 mm	8–22% are HCC or malignant	0–6% progress to LR-5
LR-3	Intermediate probability of malignancy	Hepatocellular adenoma	Nonrim arterial phase hyperenhancement	<20 mm	31–50% are HCC or malignant	3–11% progress to LR-5
			Arterial phase hypo- or isoenhancement	<20 mm with ≥1 additional major feature or >20 mm with no additional major features		
LR-4	High probability of HCC		Nonrim arterial phase hyperenhancement	<10 mm with ≥1 additional major feature; 10–19 mm with "capsule" as the only major feature; or ≥20 mm with no additional major features	67–95% are HCC or malignant	36–47% progress to LR-5
			Arterial phase hypo- or isoenhancement	<20 mm with ≥2 additional major features or ≥20 mm with ≥1 additional major feature		
LR-5	Definitely HCC		Nonrim arterial phase hyperenhancement	10–19 mm with nonperipheral "washout" or threshold growth or ≥20 mm with ≥1 additional major feature	92–99% are HCC or malignant	

Additional major features:

Nonperipheral "washout"—Temporal reduction in enhancement, relative to adjacent liver tissue, in venous phase of imaging

Enhancing "capsule"—Uniform, sharp border around most or all of lesions

Threshold growth—Size increase of ≥50% in ≤6 months or ≥100% in >6 months

Clinical Presentation and Staging

The clinical presentation of HCC can be quite variable, depending on a patient's degree of medical follow-up and the natural history of the disease at the time of diagnosis. Patients who undergo surveillance may be asymptomatic at the time of diagnosis, while patients with advanced HCC tumors may have local or systemic symptoms. Unfortunately, up to 60–70% of patients present with advanced disease [34]. Among patients with advanced disease, 75–90% have right upper quadrant abdominal pain, weight loss, and palpable mass [52]. Jaundice occurs in 19–44% of patients with HCC. The majority of cases with jaundice result from liver decompensation in the cirrhotic patient, and 1–12% are due to obstruction of the biliary system [53]. The most radical presentation of HCC is tumor rupture. Spontaneous rupture is life-threatening and accounts for 6–10% of patient deaths from HCC. The best treatment of rupture is transarterial embolization, as emergency hepatic surgery carries increased risk of mortality [54, 55].

Extrahepatic disease often occurs in cases of advanced HCC. The most common sites of extrahepatic disease are the lung (38–55%), abdominal lymph nodes (20–41%), and the bone (25–38%). Other less common sites of disease include the adrenal gland (8%) and the brain (1%) [56–59]. Large primary tumor size, vascular invasion by tumor (e.g., portal vein thrombus), and elevated serum AFP >1000 ng/dL have been associated with the presence of extrahepatic disease [60, 61]. Extrahepatic lesions may be detected by cross-sectional imaging during surveillance or by studies ordered for signs and symptoms such as bone pain, lymphadenopathy, and elevated AFP. Appropriate testing to detect extrahepatic disease include CT of the chest, nuclear medicine bone scintigraphy, and 18F-fluorodeoxyglucose positron emission tomography (PET scan) [62]. Metastatic disease is the direct cause of patient death in a minority of patients. In their series of 324 patients with extrahepatic disease, Uchino and colleagues found 23 (7.6%) patients expired as a direct result of extrahepatic disease, with the majority of patients succumbing due to their primary HCC (273 patients, 90.7%) or liver failure (13 patients, 4.3%). The median survival for patients with metastatic disease is 7–8 months [61].

Compared to other GI malignancies, treatment recommendations for HCC are particularly nuanced because the patient's underlying liver function weighs heavily in determining the most appropriate treatment. Numerous clinical staging systems have focused on assigning a treatment algorithm based on incorporation of both the extent of tumor involvement and measures of underlying liver function such as Child-Pugh status, performance status, and laboratory evaluations, with two of the more popular algorithms being the Okuda and Barcelona Clinic Liver Cancer (BCLC) staging systems.

The Okuda staging system was proposed in 1984, as the first staging system to incorporate tumor extent and liver function [63]. The Okuda system includes tumor size (≤50% or >50% of the entire liver), the presence or absence of ascites, albumin level ≤3 or >3 g/dL, and serum bilirubin level ≤3 or >3 mg/dL. Depending on how

many factors are present, clinicians categorize patients by Okuda stage: Stage I: not advanced; Stage II: moderately advanced; and Stage III: very advanced. The Okuda stages accurately discriminated survival in a validation cohort, with median survival of Stage I patients at 11.5 months, Stage II patients at 3 months, and Stage III patients at 0.9 months. Hepatic failure and gastrointestinal bleeding accounted for the majority of deaths in the series, rather than direct complications of malignancy.

The BCLC system is the most commonly used treatment algorithm-based staging system. BCLC was proposed in 1999, and it takes into account extent of tumor, liver function, physical status, and cancer-related symptoms [64] (Fig. 13.1). BCLC stages patients into five categories— very early stage (0), early stage (A), intermediate stage (B), advanced stage (C), and terminal stage (D). Unique among staging systems, BCLC offers treatment recommendations by stage. EASL guidelines endorse BCLC as the preferred staging system because it has been externally validated in different clinical settings and it has been shown to be adaptable with the addition of new clinical data [65, 66]. Since its original iteration, BCLC researchers have added Stage 0 (very early HCC) and new additional treatment modalities with transarterial chemoembolization (TACE) for intermediate HCC and sorafenib for advanced disease [67]. Current areas of further refinement for the BCLC include efforts to improve the discrimination and stratification of patients with BCLC-B and BCLC-C diseases, as the current categories include a wide range of patients with different liver function and tumor burden.

For HCC patients eligible for surgical resection or liver transplantation, pathologic staging is performed using the American Joint Committee on Cancer (AJCC) Tumor, Node, and Metastasis (TNM) staging system. The AJCC published the most recent iteration of the TNM staging system in 2017 (eighth edition), which featured changes to the primary tumor (T) classification [68] (Table 13.3). In their multi-institutional, retrospective study of 1109 patients, Shindoh and coworkers found tumors ≤2 cm with MVI did not have worse survival than tumors ≤2 cm without MVI ($p = 0.8$), although MVI was associated with worse survival in larger tumors [69]. As a result, The AJCC eighth edition of the HCC TNM staging system subdivides T1 and T2 staging to account for these data. The TNM staging system is the only staging system validated to predict outcome after resection and transplantation [69–71].

Locoregional Therapy

Locoregional therapy (LRT) refers to nonsurgical treatment of HCC that aims to destroy tumors and includes ablative and transarterial therapies, as well as external beam radiation therapy. The indications for LRT include definitive curative-intent therapy for very small HCC, “bridging” therapy for patients wait-listed for liver transplantation (LT) to mitigate tumor progression and wait-list dropout, “down-staging” therapy for patients whose extent of disease is outside of criteria for surgical resection or LT, and destination therapy to prolong survival in patients with

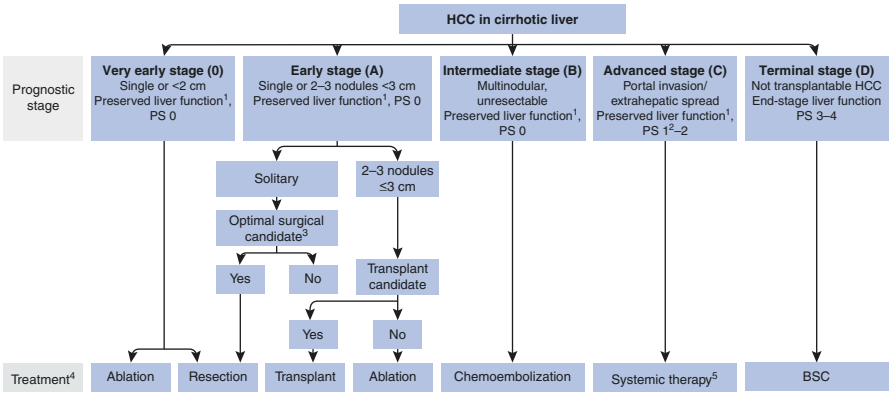


Fig. 13.1 BCLC Staging Systems. (From Galle et al. [35])

locally advanced disease who are not candidates for surgical resection or LT. Patient selection for LRT is guided by the extent of disease and the patient's hepatic reserve. General contraindications to LRT include decompensated cirrhosis (e.g., ascites, encephalopathy, or other symptoms of portal hypertension), MELD>20, and elevated total bilirubin >3 mg/dL [72–74]. Tumor location and the presence of portal vein thrombosis (PVT) affect treatment decisions regarding treatment modality.

Ablative Therapies

Methods of ablative therapy include percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), and microwave ablation (MWA). Ablative techniques require the placement of an electrode or applicator, which is performed percutaneously or intraoperatively. Laparoscopic ablation may be employed for tumors in difficult locations, such as for subcapsular tumors. For accurate percutaneous placement of the ablation device, operators may use US or CT, according to personal experience and preference.

PEI was the first established ablative technique. It causes coagulative necrosis in the tumor, with outcomes of complete necrosis in 90% of tumors <2 cm [75, 76]. Disadvantages of PEI include unequal distribution of ethanol within the tumor and poor tissue diffusion of ethanol in the cirrhotic liver, limiting the zone of necrosis. Meta-analyses of randomized controlled trials (RCTs) have compared PEI to RFA, and RFA has been shown to be superior to PEI for overall survival (OS), disease-free survival, and recurrence [77, 78]. In one representative study, Germani and coauthors found the hazard ratio (HR) of death was 0.53 for RFA versus PEI, with the odds ratio for local recurrence strongly favoring RFA (0.27 for RFA compared to PEI) [79].

Table 13.3 AJCC staging system (eighth ed.)

		Stage	T	N	M
T category	*N category*	IA	T1a	N0	M0
T1a—Single tumor ≤2 cm	N0—No lymph node metastasis	IB	T1b	N0	M0
T1b—Single tumor >2 cm without vascular invasion	N1—Any lymph node metastasis	II	T2	N0	M0
T2—Single tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm	*M category*	IIIA	T3	N0	M0
T3—Multiple tumors, at least one of which is >5 cm	M0—No distant metastasis	IIIB	T4	N0	M0
T4—Tumor involving major branch of PV or HV or direct invasion of adjacent organs	M1—Distant metastasis	IVA	Any T	N1	M0
		IVB	Any T	N0	M1

RFA achieves coagulative necrosis and tumor death by generating frictional heat through high-frequency alternating current. A zone of necrosis forms around the tumors, which may explain the lower rate of local recurrence for RFA over PEI. RFA has been used as definitive therapy for early stage HCC (BCLC 0 and BCLC A), with 5-year overall survival (OS) and recurrence-free survival of 67.9% and 25.9%, respectively [80]. There have been meta-analyses comparing RFA to surgery for solitary, small HCC. A recent Cochrane review showed no difference in overall mortality between surgery and RFA (HR 0.80, CI 0.60–1.08) but improved cancer-related mortality at maximal follow-up for patients who had surgery (or 0.35, CI 0.19–0.65) [81]. At present, EASL guidelines state RFA offers "competitive results" with respect to surgery for HCC lesions ≤2 cm [35]. Furthermore, EASL guidelines state surgery is acceptable for any size lesion, and AASLD guidelines recommend surgery over RFA for patients who are resectable (*see* section "Surgical Resection") [35, 36]. The risk of tumor progression after RFA increases with increasing tumor size, with an increased risk of local tumor recurrence/progression for tumors >2 cm compared to those which are ≤2 cm (3-year rate 17.6% vs. 5.1%, $p < 0.001$) [76, 82, 83]. These larger tumors present a challenge to RFA. LRT treatment strategies for tumors that are 3–5 cm have been developed to address this, including multi-polar RFA and combination of RFA with transarterial chemoembolization (TACE; *see* section "Transarterial therapies") [84–86]. Meta-analyses of combination RFA and TACE show improved OS compared to RFA alone, with a statistically significantly higher or of survival at 1, 2, and 3 years of 2.96, 3.72, and 2.65, respectively [86].

MWA has emerged as a new ablative technique to treat HCC. MWA uses electromagnetic energy to heat tissue and destroy tissue. Compared to RFA, MWA is less affected by the "heat sink" effect of adjacent vasculature. Studies have compared MWA to RFA, though no RCTs exist at this point. All studies to date have found no statistically significant difference in OS between the two modalities [87, 88].

Transarterial Therapies

Transarterial therapies for LRT include bland transarterial embolization (TAE), transarterial chemoembolization (TACE), and transarterial radioembolization (TARE) with yttrium-90 (Y90) microspheres. General indications for transarterial therapy include BCLC-B patients or patients with multifocal or large tumors >2 cm. Contraindications to transarterial therapy are similar to those listed above for ablative therapy. An additional consideration arises in patients with PVT. Because the liver relies on dual blood supply from the portal vein and hepatic artery, patients with HCC who have PVT are contraindicated to undergo TACE and TAE to prevent damaging liver ischemia. In contrast, TARE with Y90 uses smaller particles for embolization and causes less arterial ischemia. TARE with Y90 has been shown to be safe when used in patients with PVT. [89]

TACE is the EASL recommended therapy for patients with BCLC-B stage HCC [35]. TACE takes advantage of the neo-angiogenesis of HCC tumor development by allowing targeted intra-arterial administration of chemotherapy, followed by embolization of arterial vessels feeding the tumor, causing a cytotoxic and ischemic injury to the tumor. The most common chemotherapeutic drugs used in TACE are doxorubicin and cisplatin. A newer modification of TACE uses drug-eluting beads (DEB), which may reduce systemic exposure to chemotherapy. The survival benefit of TACE compared to best supportive care has been shown in two RCTs [90, 91]. Patients with unresectable HCC who received TACE achieved a 2-year survival that ranged from 31% to 63%, compared to 11–27% among the control group. Modern series have achieved a median survival of 40–50 months using more stringent selection of patients with asymptomatic Child Class A or B cirrhosis, uni- or paucinodular disease, and no vascular invasion or metastases [92–94]. Complications of TACE include postembolization syndrome (PES; affecting 60–80%), liver failure (7.5%), hepatic abscess (2%), gastroduodenal ulceration (3–5%), renal dysfunction (2%), and rare complications such as pulmonary and cerebral embolization, interstitial pneumonia, and access-related complications [73, 95, 96]. PES, the most common complication, occurs due to a complex pathogenesis involving the direct effects of chemotherapy, tumor necrosis, and effects of hypoxia on normal liver parenchyma. Manifestations of PES include liver enzyme abnormalities, fever, hematological/bone marrow toxicity, pain, and vomiting, which may persist for 7–10 days but are otherwise self-limiting.

TARE employs techniques similar to TACE but uses microspheres containing radioactive substances like Y90 to emit high-energy radiation directly to HCC tumors. The TARE therapy requires coordination with interventional radiologists, nuclear medicine specialists, radiopharmacists, and physicists. In its current iteration, TARE requires a pretreatment session of angiography with the injection of 99Tc macroaggregated albumin to calculate the dose to the HCC tumor and the amount of affected adjacent liver tissue and degree of hepatopulmonary shunting. Severe pulmonary shunting may contraindicate TARE in some patients. Studies of

long-term outcomes have shown median survival times for patients with intermediate-stage disease of 16–17 months and 10–12 months for patients with advanced disease [74, 97, 98]. At present, RCTs comparing TARE and TACE do not exist; however, retrospective studies comparing TARE and TACE have shown longer time to tumor progression (26 vs. 6 months) and improved quality of life with TARE [99–101].

External Beam Radiation Therapy

Historically, external beam radiation therapy (XRT) has not played a major role in the treatment of HCC. However, with technological advances allowing focal administration of ablative doses of radiation, termed stereotactic body radiation therapy (SBRT), radiation therapy has become an effective LRT modality for HCC.

Early use of XRT for liver cancer required large fields, which resulted in rates of radiation-induced liver disease (RILD), a progressive veno-occlusive disorder often resulting in mortality or serious morbidity, of >40% [102]. The development of three-dimensional conformal radiation therapy has allowed high doses of radiation to smaller fields with resultant lower rates of RILD. Several phase I/II trials have shown 1- and 2-year local control rates of 82–99% for HCC cases treated with SBRT, with low rates of RILD [103–106]. Clinicians have also studied SBRT in the neoadjuvant setting before LT. Mannina et al. reported results of 38 patients treated with SBRT who went on to LT with 1-, 3-, and 5-year survival of 92%, 77%, and 73%, respectively. Explant pathology showed a complete response in 45% of lesions and a partial response in 23% [107]. Furthermore, particle-based radiation therapy in the form of proton beam and carbon-based therapy has been used for HCC. In a prospective phase II study at Loma Linda University, clinicians treated 76 patients with proton beam therapy, of whom 47% had Child Class B cirrhosis, with a mean tumor size of 5.5 cm. Progression-free survival at 3 years was 60%, and local control was 80% [108]. At present, no RCTs exist comparing radiation-based therapy to other forms of LRT; however, retrospective studies have shown SBRT to have comparable efficacy to RFA and TACE, with some studies showing superior local control with the use of SBRT [109, 110].

LRT for Bridging and Downstaging Before Liver Transplantation

LRT is commonly used for "bridging" patients who are waiting for LT or to "downstage" patients who are outside criteria for LT so that they may have tumor reduction and become eligible for LT. AASLD and EASL guidelines recommend the use of LRT before LT for both bridging and downstaging [35, 36]. Several meta-analyses have demonstrated reduced dropout risk in patients who have a response to bridging

therapy [111, 112]. Mehta and coworkers studied 398 patients with HCC awaiting LT and found that a complete response to LRT, along with single tumor 2–3 cm, and AFP level <20 ng/mL was associated with a 1- and 2-year dropout risk of 1.3% and 1.6%, respectively, compared to 21.6% and 26.5% for all other patients [111]. Patient responses to pre-LT downstaging have been shown to predict post-LT tumor recurrence [113–116]. In their most recent published guidelines, neither society gives specific recommendations regarding the specific type of LRT to use for pre-LT treatment, and such decisions should be based on individual patient and tumor characteristics.

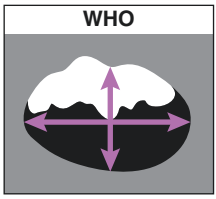
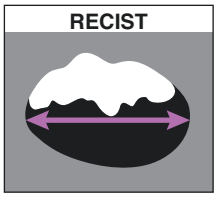
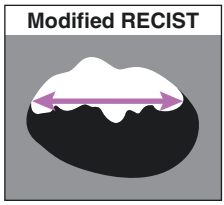
Assessing Response to Treatment

Patients treated with LRT undergo assessments with imaging and serologic tests to determine their response to treatment. Typically, patients have CT or MRI imaging at 4–6 weeks post-LRT and then every 3–6 months. Patients with elevated AFP before treatment may also undergo serial serologic testing to assess for an appropriate reduction in the serum AFP level.

Criteria to assess imaging response after treatment have been developed for HCC. The World Health Organization (WHO), Response Evaluation Criteria In Solid Tumors (RECIST) 1.0, and RECIST 1.1 report tumor size as the longest dimension of the tumor, and they are commonly used for solid tumors [117, 118]. Each system measures the change in tumor size after LRT and grades treatment response as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). (*See* Table 13.4 *for specific criteria*.) However, the treatment effect of LRT causes tumor necrosis with a resulting absence of arterial flow within the lesion. The imaging finding after treatment will therefore show a smaller area of arterial enhancement within the lesion, while the nonviable tumor remains in situ without necessarily a reduction in its overall size. Neither WHO nor RECIST 1.1 criteria limit the area of measurement to the part of the tumor with arterial enhancement or the viable portion of the tumor. To account for this, the modified RECIST (mRECIST) criteria has been developed to specifically evaluate the amount of viable tumor. These criteria measure the single longest dimension of the part of the tumor with arterial enhancement [119]. The mRECIST system also grades the response of tumor to treatment, similarly to the systems listed above. EASL and AASLD guidelines recommend mRECIST as the preferred method for assessing treatment response for HCC to LRT. Exceptions which are not eligible for the mRECIST system include infiltrative HCC lesions and other lesions with atypical enhancement.

Additionally, the LI-RADS system has put forth criteria to grade treatment response, the LR-TR Response Algorithm. In this treatment assessment paradigm, treatment response is graded as LR-TR Nonviable, LR-TR Equivocal, and LR-TR Viable. Tumors with treatment responses graded as Nonviable show no enhancement within the lesion or only a treatment-specific, expected enhancement pattern. Viable lesions show nodular, mass-like, or irregular tissue along the treated tumor with enhancement similar to the pretreatment state, arterial phase hyperenhance-

Table 13.4 Assessment of treatment response: Comparison of WHO, RECIST 1.1, and mRECIST

	WHO	RECIST 1.1	mRECIST
Measured dimension(s)	Product of longest dimension and greatest perpendicular diameter	Sum of the longest unidirectional diameter of all lesions	Sum of the longest unidirectional diameter of all arterially enhancing, viable lesions
Area measured			
Complete response (CR)	Disappearance of all lesions	Disappearance of all lesions	Disappearance of all intratumoral arterial enhancement
Partial response (PR)	≥50% decrease in the sum of the area of all lesions	≥30% decrease in the sum of diameters of all lesions	≥30% decrease in the sum of diameters of all arterial enhancing, viable lesions
Stable disease (SD)	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD
Progressive disease (PD)	≥25% increase in the sum of the area of all lesions	≥20% increase in the sum of diameters of all lesions	≥20% increase in the sum of diameters of all arterially enhancing, viable lesions

Figures from Fig. 13.1: Imaging response criteria used in evaluation of HCC after treatment, Graphic 99,552 Version 1.0, from "Assessment of tumor response in patients receiving systemic and nonsurgical locoregional treatment of hepatocellular carcinoma
Authors: Iqbal and Stuart, UpToDate 2019

ment, or venous phase washout. Equivocal lesions have enhancement that is atypical for the expected treatment effect or enhancement that does not definitely meet criteria to be graded as viable.

Surgical Resection

Surgical resection (SR) is the gold-standard curative-intent therapy for well-compensated cirrhotic patients with HCC. EASL and AASLD guidelines recommend SR when HCC is deemed resectable and the patient's liver function permits the intervention. However, there is no consensus or universally accepted criteria for resectability, with further challenges posed by the myriad of factors a surgeon must consider when evaluating a patient's liver function for surgery. EASL and AASLD guidelines both include morphometric tumor characteristics when defining resectability [35, 36]. EASL guidelines allow surgery for single HCC lesions of any size and for multiple HCC lesions that lie within Milan criteria, if the amount of liver remaining after surgery is of sufficient size. AASLD guidelines define resectability

as T1 or T2 HCC (one to three unilobar lesions, less than 5 cm for single lesions and 3 cm for multiple lesions). Additional considerations include the presence of macrovascular tumor involvement, typically of the portal or hepatic veins. Any macrovascular involvement with tumor has traditionally been considered a contraindication to surgery; however, some centers in the East have reported success with resection for highly selected patients with HCC involving segmental branches of the portal vein. The Liver Cancer Study Group of Japan reported a median survival of 2.87 years for patients with portal vein invasion who had SR versus 1.10 for patients in the non-SR group [120]. The same group reported superior outcomes for patients with hepatic vein invasion who had SR, with median survival of 4.47 years versus 1.58 years for patients in the non-SR group [120].

A patient's liver function, as determined by the degree of portal hypertension and the amount of functional liver remaining after surgery, determines whether a patient will tolerate resection. SR is contraindicated for decompensated patients with clinically significant portal hypertension or advanced liver disease, as signified by Child Class B or C patients with jaundice, encephalopathy, ascites, or varices. In otherwise well-compensated Child A cirrhotic patients, an assessment of the degree of underlying portal hypertension is critical. Signs of significant portal hypertension include platelet count <100,000 platelets/μL and the presence of splenomegaly and varices on imaging. Clinically relevant portal hypertension can also be defined by a hepatic vein pressure gradient >10 mm Hg [121]. Furthermore, liver function can be assessed by measuring indocyanine green retention at 15 minutes (ICG_{15}) after administration. Patients with poor liver function retain a greater amount of ICG. Various groups have set ICG_{15} parameters for liver resection, with most advocating an ICG_{15} retention of <15–20% for patients to undergo hepatic resections safely [122, 123].

The functional liver remnant (FLR), defined as the volume of the liver remnant divided by the entire liver volume, will provide the hepatic reserve for the patient after surgery. FLR may be calculated before surgery using CT or MRI volumetrics, and the planned resection must provide a FLR of >30–40%, to reduce the risk of post-resection liver failure. For patients with inadequate FLR, clinicians may employ portal vein embolization (PVE) to increase the size of the FLR. Patients typically undergo PVE and then surgery 4–6 weeks afterwards, allowing for FLR hypertrophy in the intervening time period. The rate of growth of the liver remnant after PVE itself provides prognostic information. In a large single-center series, no patients with growth rate >2.66%/week after PVE developed liver failure after hepatectomy [124].

The technical conduct of SR has been shown to affect patient outcomes. To reduce bleeding from hepatic veins, surgeons employ low central venous pressure (CVP) during surgery. Components of low CVP surgery include the selective use of central venous catheters to guide resuscitation and limit the volume of intravenous infusions during surgery to prevent hepatic congestion and back-bleeding from transected hepatic veins. A minimally invasive approach to SR using laparoscopic or robotic surgery may be considered for small lesions, as well as lesions which are superficial or located on the periphery of the liver. Studies of minimally invasive

hepatectomies have reported equivalent overall and disease-free survival between open and minimally invasive surgery, with one large study showing statistically significantly less blood loss (158 g vs. 400 g, $p < 0.001$), shorter hospital length of stay (13 days vs. 16 days, $p < 0.001$), and a lower complication rate (6.7% vs. 13.0%, $p = 0.003$) in the laparoscopic resection group [125, 126]. However, it is important to note that since such studies are not prospectively randomized, inherent selection bias may be present that makes it difficult to draw definitive conclusions regarding the superiority of either technique.

The extent of surgical resection and surgical margins have also been studied. Historically, preference has been given to anatomic resections for lesions >2 cm. However, recent literature has reported equivalent outcomes for nonanatomic resection [127]. Similarly, the importance of wide tumor-free margins >1 cm has been studied with differing outcomes reported. An early Japanese series reported improved 3-year survival (77% vs. 21%) for patients with >1 cm margins, while more recent reports have shown no difference in outcomes for patients with tumor-free margins <1 cm [128, 129].

Contemporary outcomes following SR for HCC have improved dramatically, largely due to better patient selection, improved surgical techniques, and better anesthetic and perioperative management that have significantly reduced postoperative mortality and complications. EASL guidelines propose a benchmark perioperative mortality rate of <3%, as a standard for cirrhotic patients undergoing resection for HCC [35]. The most common cause of death after SR is posthepatectomy liver failure (PHLF), which is often progressive, occurring outside a traditional 30-day postoperative period. The International Study Group of Liver Surgery (ISGLS) offered a consensus definition of PHLF in 2013, as an increased INR (≥1.5 for Grades A and B and ≥2.0 for Grade C PHLF) and hyperbilirubinemia after postoperative day 5 [130]. Clinicians grade the severity of PHLF from Grade A to Grade C (most severe). For Grade A PHLF, there is no required change in clinical management. For Grade B PHLF, patients require a deviation from normal postoperative management in the form of intermediate or ICU level of care, plasma transfusion, albumin infusion, diuretics, and other noninvasive interventions. Lastly, for Grade C PHLF, patients require interventions in the form of intubation, hemodialysis, transplantation, and other invasive treatments. The ISGLS definition was validated in a test group of 835 patients undergoing liver resection, of which 65 (11%) developed PHLF. The ISGLS PHLF definition discriminated postoperative mortality accurately, with mortality rates of 0%, 12%, and 54% for patients with Grade A, B, and C PHLF, respectively [131]. Fukushima and coworkers assessed the ISGLS PHLF definition in their study of 210 HCC patients undergoing curative hepatectomy. They found major hepatectomy (>1 segment), blood loss >1000 mL, and liver fibrosis stage ≥3, were independently associated with PHLF [132].

Common complications following hepatic resection include hemorrhage, bile leak, pleural effusion, and infection. To standardize the reporting of postoperative complications, ISGLS has offered definitions of posthepatectomy hemorrhage (PHH) and bile leak [133]. The criteria for ISGLS PHH are met by a drop in hemoglobin >3 g/dL (compared to preoperative levels) and/or the need to trans-

fuse PRBCs and/or the need for invasive intervention to stop bleeding. PHH is further categorized as Grades A to C, with C being the most severe. Grade A PHH includes transfusion up to 2 units of PRBCs; Grade B PHH indicates a transfusion >2 units of PRBCs, without the need for invasive intervention; and Grade C PHH requires intervention (e.g., embolization or laparotomy). In a validation group, postoperative mortality corresponded to PHH grade, with mortality rates of 0%, 17%, and 50%, for patients with Grade A, B, and C PHH, respectively. The ISGLS has also defined posthepatectomy biliary leak as a bilirubin concentration in surgical drain fluid exceeding three times the serum bilirubin, on or after postoperative day 3 [134]. Similar to other ISGLS definitions, biliary leaks are graded from A to C, with C being the most severe. Grade A biliary leaks persist ≤1 week and have little or no impact on a patient's clinical management. Grade B leaks require a change in patient management and include leaks persisting ≥1 week, leaks causing infection and needing antibiotic therapy, and leaks requiring percutaneous drain placement, endoscopic therapy (e.g., ERCP and sphincterotomy), or transhepatic biliary drain placement and stenting. Severe Grade C biliary leaks often require reoperation to control the complication, many times with reconstruction of a bilioenteric anastomosis. Altogether, postoperative complications occur in as many as 47% of patients undergoing SR. Therefore, an evaluation of a patient's fitness for surgery includes an assessment of their ability to tolerate postoperative morbidity [131].

The efficacy of SR has been demonstrated with 5-year overall survival ranging from 60% to 80%. However, recurrence of HCC following SR remains a significant issue, in part because the diseased liver left behind after resection is prone to de novo lesions. Clinicians distinguish early recurrences, which occur within 2 years of SR, versus late recurrence, arising more than 2 years after SR, because late recurrence often represent new lesions instead of true local recurrences from the primary lesion [135]. Risk factors of early recurrence have included nonanatomic resection, the presence of microscopic vascular invasion, and elevated AFP; whereas risk factors of late recurrence include higher hepatitis activity and the presence of multiple tumors [136]. The overall 5-year recurrence rate after SR is about 70%. In their large series of 661 patients undergoing SR, Tabrizian and coworkers reported 1- and 5-year recurrence rates of 35% and 70% [137]. Of the patients who had recurrences, the authors reported the different strategies used to treat each recurrence and their efficacy. Sixty-eight patients (19%) were eligible for re-resection and underwent repeat surgery with a median survival after treatment of 56 months. Additionally, 56 patients (16%) were listed for transplant and 35 patients underwent transplant, with median survival of 47 months; and 145 patients (40%) underwent ablation or embolization with median survival of 27 and 19 months, respectively. The remaining patients not eligible for treatment with curative intent were mostly treated with sorafenib or best supportive care and had median survival of <8 months. Thus, in this representative study, many patients undergoing SR remain eligible for treatment with curative intent after tumor recurrence.

Given that recurrence following SR is a significant concern, a unique option that has been espoused for patients with post-resection recurrent HCC is the

so-called salvage LT (SLT). In this setting, patients undergo surgery and then are listed for LT if they recur. The advantages of this approach for individual patients include immediate treatment without waiting for organ allocation and the avoidance of a more intensive intervention (i.e., LT), immunosuppression, and the attendant risks of the immunosuppressed state. Potential societal advantages of SLT include a more efficient allocation of organs and possible cost savings.

In practice, the main challenges to the SLT strategy have been identifying patients at high-risk for recurrence outside of transplant criteria who may have lost their opportunity for cure and the development of post-resection liver failure requiring urgent LT. One of the earliest studies looking at SLT was reported by Belghiti et al. in 2003, where they showed that HCC patients undergoing SLT who had similar characteristics to SR patients had equivalent perioperative complications and similar survival [138]. More recently, De Haas and colleagues reported their outcomes of SLT using an intention to treat analysis in 110 patients who underwent SR. [139] In their group, 63 patients (57%) recurred with 47 patients (42.7%) listed for LT and 30 patients (27.2%) undergoing SLT. The intention-to-treat overall and disease-free survival was 69% and 60%, respectively. The patients who had a successful outcome with this strategy, defined by SR patients who either did not develop recurrence or developed recurrence and underwent LT, had an 83% disease-free survival at 5 years, while not surprisingly, patients failing the strategy and developing untransplantable disease following resection had a dismal 7% survival. Overall, the ITT SLT strategy was successful in 55% of the patients. In a different study, a head-to-head comparison of an intention-to-treat SLT strategy to primary LT was reported by Bhangui et al. [140] While the overall (73% vs. 58% at 5 years) and recurrence-free (69% vs. 27% at 5 years) survival of primary transplant patients was superior to patients enrolled in a SLT strategy, the best outcomes at 5 years were observed in resection patients who went on to undergo salvage liver transplantation (87% disease-free at 5 years), highlighting that the most important factor is to identify patients who are best suited for salvage LT.

In order to define which patients might benefit from the SLT strategy, researchers have sought to identify risk factors for unsalvageable recurrence after SR, for example, tumor recurrence beyond criteria for transplant. Lee et al. studied 320 patients undergoing SR for HCC, of which 183 patients (62.5%) had recurrence within 5 years [141]. Factors associated with unsalvageable recurrence were preoperative disease beyond Milan criteria, the presence of microsatellite lesions or multiple tumors, and lymphovascular invasion. An international collaborative subsequently analyzed 1023 patients and validated these findings. Features associated with recurrence beyond criteria for LT included preoperative disease beyond Milan criteria (HR 1.95), the presence of multiple nodules or satellite lesions (HR 1.51), and microvascular invasion (HR 2.12) [142]. Despite its challenges, SLT remains a viable option for patients with HCC, and improvements in patient selection for SR versus up-front LT will further refine its implementation in the future.

Liver Transplantation

History and Organ Allocation

Liver transplantation is unequivocally the gold-standard treatment for cirrhotic patients with surgically unresectable HCC meeting specified criteria. However, the early experiences with liver transplant for HCC were met with dismal results, with recurrence rates as high as 80% within 1 year and >70% mortality within 2 years, largely due to a lack selection criteria based on tumor burden [143–145]. In 1996, Mazzafero and colleagues published outcomes of liver transplant for HCC which is now widely known as the Milan criteria. Their group transplanted 48 patients diagnosed with either a single tumor of ≤5 cm or up to three tumors each ≤3 cm. Overall actuarial 4-year survival was 75 percent, and 4-year recurrence-free survival was 83 percent [146]. The Milan criteria have subsequently been validated in numerous other studies and have become ubiquitously accepted as the gold-standard size and number criteria for the selection of HCC patients for LT [147, 148].

Given the successful outcomes when utilizing the Milan criteria, LT for HCC has increased dramatically over the last two decades, and HCC has now become a leading indication for LT in the United States, accounting for nearly 25% of all transplants performed on a yearly basis [149]. This increase has largely been driven by a Model for End-Stage Liver Disease (MELD) exception policy that allows allocation of organs to HCC recipients who typically have lower physiologic MELD scores. Since HCC patients often do not have physiologically decompensated liver disease, clinicians intended the MELD exception points to balance the risk of wait-list dropout due to tumor progression and allow access to LT. The first iteration of the MELD exception policy was instituted in 2002. Patients with T1 tumors (1 lesion <2 cm) were assigned a MELD of 24, and patients with T2 tumors (one tumor >2 cm but <5 cm or three tumors each <3 cm) were designated a MELD of 29. One additional point was awarded for each 3 months the patients remained on the list without progression beyond Milan [150]. However, it soon became evident that patients with HCC were being overprioritized, receiving transplants at a higher rate than non-HCC patients. Consequently, there have since been numerous iterations of the HCC MELD exception policy to better balance this risk of wait-list dropout between HCC and non-HCC listed patients. In 2003, MELD exception prioritization decreased to 20 points for T1 lesions and 24 for T2 lesions, with another revision in 2004 not granting MELD exception points for the T1 lesions. In 2005, MELD exception points were once again reduced to 22 points for T2 lesions. In 2019, ongoing discussions are being considered to potentially change the priority of MELD exception points in patients with HCC once again; however no definitive guidelines have yet to be set.

Despite these refinements in the allocation of MELD exception points in 2005, LT for HCC continued to increase over the subsequent decade, and HCC patients continued to remain overprioritized with lower rates of wait-list dropout and higher transplant rates despite inferior survival [151–153]. During this time period, it also became apparent that patients expedited to transplant in regions with “short waiting

times" had greater post-LT recurrence and inferior post-LT outcomes compared to HCC-listed patients from "long wait time" regions [154, 155]. Subsequently, MELD exception policy was once again revised in 2015, with institution of a 6-month delay for patients with T2 lesions prior to being granted 28 exception points and with capping of the MELD at 34—which is the current policy in the United States [156].

Pretransplant Models to Expand Eligibility Criteria to Beyond Milan

While the tumor size and number paradigm of the Milan criteria remain the gold standard for the selection of HCC candidates for LT, there have been concerns they may be too restrictive, excluding some patients beyond criteria with an otherwise acceptable posttransplant recurrence risk. Over the past two decades since the establishment of the Milan criteria, there have been numerous expanded criteria proposed that allow for recipients with tumors beyond Milan to receive LT. In 2001, Yao and colleagues defined the UCSF criteria, which allowed inclusion of patients with a single tumor ≤6.5 cm and up to three lesions ≤4.5 cm, with total tumor diameter ≤8 cm. Patients who met these UCSF criteria and underwent LT had survival rates of 90% and 75.2% at 1 and 5 years, respectively [157]. These results were validated by Yao and colleagues in 2007 in a series of 168 patients with disease exceeding Milan but meeting UCSF criteria, with 1- and 5-year survival without recurrence of 92.1% and 80.7%, respectively [158].

In addition to the UCSF criteria, numerous other expanded criteria have been proposed and externally validated to result in outcomes similar to Milan criteria. These include the Up-to-7 criteria (i.e., criteria using 7 as the sum of the size (cm) of the largest tumor and the number of tumor nodules; total tumor volume (TTV) criteria and alpha-fetoprotein (AFP) (i.e., TTV <115cm^3 and AFP <400 ng/ml)); and the AFP-French model (i.e., points system using tumor size, number of tumors, and an AFP cut-off at 100 ng/ml and 1000 ng/ml) [159–161]. Selected pretransplant models based on morphometric and serum biomarkers are summarized in Table 13.5.

Wait-List Management: Surveillance and Bridging Therapy

Patients with HCC listed for liver transplant undergo baseline imaging and lab testing at the time of diagnosis, commonly with dynamic CT or MRI of the abdomen, CT of the chest, and serologic AFP testing. Additional metastatic workup may include nuclear medicine bone scanning and MRI of the brain to rule out distant disease. After placement on the LT waiting list, patients require quarterly CT or MRI to continue to receive MELD exception points in the United States [162].

While remaining on the transplant wait list, patients with HCC are at risk for tumor progression. To ameliorate this risk, AASLD and EASL guidelines recommend "bridging" treatment with LRT, especially if patients are expected to remain

Table 13.5 Pretransplant models defining HCC eligibility criteria

Lead author	Morphometric criteria	Biomarker criteria	Donor type	Year	Patient outcomes
Mazzaferro (Milan) [146]	One lesion ≤5 cm or ≤3 lesions ≤3 cm each		Cadaveric	1996	4-year OS, 85%; 4-year RFS, 92%
Yao (UCSF) [157]	One lesion ≤6.5 cm or 2–3 lesions ≤4.5 cm each. Total tumor diameter ≤8 cm		Cadaveric	2001	5-year OS, 72.4%
Herrero [194]	One lesion ≤6 cm or 2–3 lesions ≤5 cm each		Cadaveric	2001	5-year OS, 79%
Roayaie [195]	Any number of lesions 5–7 cm each		Cadaveric	2002	5-year RFS, 55%
Keneteman [196]	One lesion <7.5 cm or multiple lesions <5 cm each		Cadaveric	2004	4-year OS, 82.9%; 4-year RFS, 76.8%
Onaca (Baylor criteria) [197]	One lesion ≤6 cm or 2–4 lesions ≤5 cm each		Cadaveric	2007	5-year RFS, 63.9–64.6%
Soejima [198]	Any number of lesions ≤5 cm each		Living	2007	3-year OS, 68.6%
Jonas [199]	Any number of lesions ≤6 cm each. Total tumor diameter ≤15 cm		Living	2007	3–year OS, 53%
Sugawara (5–5 rule) [200]	≤5 lesions ≤5 cm each		Living	2007	3-year RFS, 94%
Kwon [201]	Any number of lesions ≤5 cm each	AFP ≤400 ng/mL	Living	2007	5-year OS, 79.9%
Takada [202]	≤10 lesions ≤5 cm each	PIVKA-II 400 mAU/mL	Living	2007	5-year OS, 87%
Silva [203]	≤3 lesions ≤5 cm each. Total tumor diameter ≤10 cm		Cadaveric	2008	5-year OS, 67%
Zheng (Hangzhou criteria) [204]	Total tumor diameter ≤8 cm or <8 cm if grade I or II	AFP ≤400 ng/mL if tumor diameter >8 cm	Living	2008	5-year OS, 70.7%; 5-year RFS, 62.4%
Mazzaferro (up-to-7) [159]	The sum of the number of lesions and the size of the lesions (in cm) ≤7		Both	2009	5-year OS, 71.2%
Fujiki [205]	≤10 lesions ≤5 cm each	DCP ≤400 mAU/mL	Living	2009	5-year OS, 89%
Lai [206]	Total tumor diameter 8 cm	AFP ≤400 ng/mL	Cadaveric	2012	5-year RFS, 74.4%
Grat [207]	UCSF or up-to-7 criteria	AFP <100 ng/mL	Cadaveric	2014	5-year OS, 100%
Toso [160]	Total tumor volume ≤115 cm^3	AFP ≤400 ng/mL if tumor diameter >8 cm	Cadaveric	2015	4-year OS, 74.6%
Lee [208]	Total tumor diameter ≤10 cm	PET negative uptake	Living	2015	5-year OS, 73.4%; 5-year RFS, 80.4%

on the waiting list for more than 6 months [35, 36]. Neither society prescribes the exact type of LRT to be used, and these decisions are made based on individual patient factors. Several studies have supported reduced dropout risk with the use of LRT and response to treatment [111, 112]. Mehta and colleagues reviewed the experience of 398 patients listed for LT for HCC, and they found the risk of wait-list dropout correlated with degree of response to LRT as assessed by mRECIST, with risk of dropout of 9.3% for patients with complete response, 19.2% for partial response, 39.5% for stable disease, and 85% for progressive disease [111].

Living Donor LT for HCC

Clinicians have used living donor liver transplant (LDLT) for HCC in areas where cadaveric organs are less available (e.g., East Asia) and as a way to bring HCC patients to transplant earlier, reducing the risk of disease progression. In an intention to treat analysis comparing LDLT and deceased donor liver transplant (DDLT), Bhangui and colleagues found a shorter mean waiting time for LDLT than DDLT (2.6 vs. 7.9 months) and similar recurrence rates for the two groups (12.9% and 12.7%). [163] Other studies have compared LDLT to DDLT using decision analysis and cost-effectiveness analysis, with findings that showed an improved life expectancy with LDLT (4.5 years longer compared to DDLT) and decreased health costs if patients spent greater than 7 months on the wait list [164, 165].

Notably, some centers have offered LDLT for patients outside of Milan criteria. Hong and colleagues from the Seoul National University reported their experience with LDLT for HCC, including >30% of patients receiving LDLT beyond Milan. They reported excellent outcomes for low-risk patients (AFP <200 ng/mL with no FDG avidity on PET) who were inside and outside Milan criteria, with 5-year disease-free survival of 88.4% and 80.3%, respectively [166]. However, the Adult to Adult Living Donor Transplantation Cohort Study (A2ALL) has reported an increased risk of disease recurrence for patients receiving LDLT, compared to DDLT (HR = 2.34; $p = 0.04$). The authors have attributed this difference to a foreshortened wait time as well as greater tumor burden and serum AFP in the group undergoing LDLT [167]. Undoubtedly, LDLT will remain a treatment option for patients with HCC. Because the living donor recipient does not remove a cadaveric organ from the limited donor pool, there will likely remain a tendency for these transplants to "push the envelope" beyond traditional criteria.

HCC Recurrence After Liver Transplantation

Modern series of post-LT outcomes report recurrence rates ranging from 8% to 21%, with median times to post-LT recurrence of 13–15 months [168–172]. Researchers have sought to identify prognostic factors to predict which patients will

have recurrence to improve post-LT surveillance and inform organ allocation criteria. In the largest reported single-center experience of LT for HCC, Agopian and coauthors analyzed the UCLA experience with 865 patients undergoing LT for HCC, 117 (13.5%) of whom suffered recurrence. A novel clinicopathologic nomogram was developed to allow for the individualized prediction of post-LT HCC recurrence, with independent factors including tumor grade, the presence of macrovascular or microvascular invasion, tumors outside Milan criteria, radiological maximum tumor diameter >5 cm, and increased pretransplant AFP and neutrophil-to-lymphocyte ratio [170]. Additional predictive models include the Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score, which uses explant pathologic features such as the size of viable tumor and presence of microvascular invasion, as well as serum AFP levels, to calculate a risk of recurrence at 1 and 5 years [171], and the Model of Recurrence After Liver Transplantation (MoRAL) score includes neutrophil-lymphocyte ratio and histologic grade to calculate a risk of tumor recurrence [172]. As newer therapies become available that have efficacy in the adjuvant setting, models that allow for individualized prediction of post-LT HCC recurrence will become all the more valuable.

Unfortunately, recurrence of HCC following LT has a far worse prognosis compared to recurrence following SR, where numerous treatment options including salvage LT exist. In a large series examining outcomes of HCC recurrence following LT, Bodzin and colleagues reported a median post-recurrence survival of only 10.6 months, which is in line with a median survival of only 13 months reported in a systematic review of 61 studies examining 1021 LT patients with post-LT recurrence [173, 174]. However, several studies have now established that a subset of patients with HCC recurrence following LT may have improved survival, with median survivals ranging from 28 to 32 months for select patients whose recurrences were amenable to surgical resection or curative-intent ablation [173, 175]. Optimizing the identification of such patients who stand to benefit from more aggressive treatment of their recurrence is necessary.

Systemic Therapy

Systemic therapy is an option for locally advanced or metastatic HCC patients who have adequate liver function but who are not candidates for resection, LT, or LRT due to their tumor burden. Traditional cytotoxic systemic therapy has been ineffective in HCC, largely due to inherent chemotherapy resistance of HCC, as well as the concomitant underlying hepatic dysfunction in patients with HCC, limiting the applicability of drug therapy. After years of failed trials of cytotoxic chemotherapy, sorafenib, a tyrosine kinase inhibitor (TKI) which targets multiple kinases, was the first agent discovered to provide a survival benefit in a prospective randomized controlled trial in 2007 [176]. This initial positive trial with sorafenib was followed by a drought of 10 years, during which time no additional targeted therapies were found to be efficacious. During this time, multiple, large, prospective randomized

controlled trials investigating the kinase inhibitors sunitinib, brivanib, linifanib, and erlotinib each failed to show an improvement in survival for patients with HCC compared to sorafenib [177–180]. However, since 2017, there have been numerous new drug approvals for HCC in both the first and second lines, including the targeted therapies lenvatinib, regorafenib, and cabozantinib and the checkpoint inhibitors nivolumab and pembrolizumab.

In 2007, sorafenib was established as the gold-standard treatment for advanced HCC on the basis of the SHARP trial, a prospective RCT. Patients receiving sorafenib had a median overall survival of 10.7 months compared to 7.9 months in the placebo group [176]. Sorafenib is a small molecule that inhibits Raf-1 and B-Raf, vascular endothelial growth factor receptors (VEGFR 1, 2, and 3), and platelet-derived growth factor receptor-β (PDGFR-β). These pathways play an important role in the pathogenesis of HCC [181, 182]. Additional analyses have suggested sorafenib provides a greater survival for patients with HCC due to HCV, compared to HCC due to HBV or alcohol. Although sorafenib is FDA-approved for all stages of cirrhosis, data consistently shows worse outcomes for treated patients with greater than Child A cirrhosis [183–185]. Side effects of sorafenib include diarrhea and hand-foot skin reaction. Combination treatment with sorafenib and doxorubicin has been attempted, but the only randomized phase III trial was terminated by the data monitoring safety board due to futility at planned interim analysis [186]. Sorafenib in the neoadjuvant and adjuvant setting for LT is being investigated, and results from trials are pending. The largest trial to date of sorafenib in the adjuvant setting after SR is the STORM trial. This RCT tested sorafenib versus placebo in patients who underwent successful SR; however, the authors found an improvement in recurrence-free survival for the sorafenib group [187].

Lenvatinib is a small molecule that inhibits VEGFR, PDGFR, RET, KIT, and fibroblast growth factor receptors (FGFR). Lenvatinib was compared to sorafenib in patients with unresectable HCC and Child A cirrhosis in a non-inferiority trial. The authors reported a median survival of 13.6 months for lenvatinib and 12.3 months for sorafenib, and they concluded lenvatinib was non-inferior [188]. Lenvatinib has since been FDA approved in August 2018, and it is being used as frontline systemic treatment, in addition to sorafenib.

Clinicians offer second-line therapy to patients who have progression of disease while on first-line therapy and can tolerate additional systemic treatment. Progression of disease manifests as radiographic progression and an increase in serum AFP. Since 2017, numerous new drugs have been approved for HCC in the second line, including the tyrosine kinase inhibitors regorafenib and cabozantinib, as well as the immune checkpoint inhibitors nivolumab and pembrolizumab.

Regorafenib is a small molecule inhibitor of VEGFR and tyrosine kinase inhibitor (TKI). It is similar in structure and function to sorafenib. The RESORCE trial studied patients who progressed on first-line treatment with sorafenib and were treated with regorafenib. Patients who were randomized to regorafenib had significantly increased median survival (10.6 vs. 7.8 months) and higher rates of disease control (65% vs. 36%) compared to placebo [189]. Cabozantinib is another small molecular kinase inhibitor, which has been studied in patients previously treated

with sorafenib. The phase III CELESTIAL trial included patients who received cabozantinib versus placebo as second- or third-line treatment after receiving sorafenib. Results showed increased median survival for patients treated with cabozantinib (10.2 months) versus the placebo group (8.0 months), resulting in its approval by the FDA in 2019 [190].

Nivolumab is a human monoclonal antibody to programmed cell death 1 receptor (PD-1), which functions to restore T cell activity against tumor cells. The CheckMate 040 trial studied nivolumab as a second-line treatment for patients with HCC and Child A or B cirrhosis who had disease progression on sorafenib. In the study and follow-up reports, patients had an overall response rate of 18%, significantly greater than the 2% historically reported for sorafenib. Most notably, the patients who did respond demonstrated durable responses to treatment with some reports of complete tumor response [191, 192]. Pembrolizumab is also a monoclonal antibody and PD-1 inhibitor. The Keynote-224 trial supports the efficacy of pembrolizumab as second-line treatment following sorafenib failure with similar rate of objective responses and stable disease (17 and 44 percent, respectively) compared to nivolumab [193]. Pembrolizumab was FDA approved in November 2018 for patients with HCC who were previously treated with sorafenib. Currently, there are numerous ongoing prospective, randomized controlled trials evaluating both single-agent and combination therapies in HCC in both frontline and second line. Further development and validation of radiologic, serologic, and molecular biomarkers will greatly improve the ability to allow for personalized treatment decisions for advanced HCC.

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Chapter 14
Liver Transplantation

Michael Sean Bleszynski and Peter T. W. Kim

Introduction

For a critically ill cirrhotic patient, liver transplant is the only treatment that can provide a chance at long-term survival. In patients who meet the criteria for transplant listing, the current allocation system is designed to direct the next available donor liver to the sickest patient on the list to reduce wait-list mortality. Liver allocation was originally based on overall wait times, the Child-Turcotte-Pugh (CTP) score, and ABO blood type compatibility [1]. However, this allocation scheme had limitations in that longer waiting times on the transplant list did not correspond with increased patient mortality and the CTP score did not adequately represent the general transplant population [1]. The CTP score is based on three laboratory values (prothrombin time, bilirubin, albumin) and two subjective clinical variables (ascites and encephalopathy). Despite the CTP scoring model initially being utilized as part of an organ allocation system, it has never been validated for estimating survival in patients with chronic liver disease [1]. The CTP score is rather reflective of complications of portal hypertension, and its lack of objectivity limited its application to transplant organ allocation [2].

The model for end-stage liver disease (MELD) score was initially developed to determine risk of mortality for the transjugular intrahepatic portosystemic shunt (TIPS) procedure within a 3-month period [3]. The MELD score has subsequently been validated as a severity of liver disease scoring system and predictive mortality tool independent of etiology or occurrence of portal hypertensive complications [1,

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2]. Baseline MELD scores have been shown to be significantly associated with wait-list mortality [4]. Since its approval in 2002, the MELD score helps determine liver allocation for patients awaiting transplantation by providing 3-month predictive mortality [5] and has become the most commonly utilized liver organ allocation tool worldwide. Sicker patients are represented by a higher MELD score and therefore are assigned a higher priority on transplant waiting lists. The main advantage of the MELD score is that it is objective in that it is based on three laboratory values (serum INR, bilirubin, and creatinine). It is not a perfect system in that it doesn't always reflect the urgency in patients with relatively low physiologic MELD score but who have clear indications for liver transplantation (e.g., hepatocellular carcinoma, hepatopulmonary syndrome, metabolic disorders) [6]. These patients are usually granted MELD exception points that would help them to be competitive for transplants depending on their region of residence. More recently, the MELD-Na has been introduced to provide a more accurate assessment of wait-list mortality and to take into account the complications of portal hypertension [7].

Despite the advancements within transplantation over the last 20 years, several challenges remain, as organ shortages persist and patients remain on wait-lists for extended periods of time. Due to the current allocation system based on MELD, transplant programs are often offering liver transplants for patients with high MELD scores. This raises new challenges and questions in today's practice. This chapter aims to outline current evidence for transplantation of patients with high MELD scores, discuss transplant futility, address simultaneous multi-organ transplantation, discuss surgical techniques for complications of cirrhosis at the time of transplantation, discuss postoperative management, and outline the role of living-related transplantation in today's environment.

Liver Transplantation in High MELD Patients

The MELD score has been validated as a scoring tool to prioritize patients on liver transplantation (LT) waiting lists by predicting 3-month mortality risk based on a scale from low scores of 6 to high scores capped at 40, with 83–87% accuracy [1]. Wait-list mortality is directly proportional to the MELD score, where a MELD score of <9 is associated with an approximate mortality of 2% and a MELD score $\geq$ 40 is associated with a wait-list mortality of 71% [1]. In general, for the patients with MELD scores $\leq$15, the risks of LT likely outweigh the benefit. In low MELD patients, the risk of mortality from LT is greater than remaining on the transplant wait-list [8]. These patients are therefore allocated to the bottom of the list and, depending on the program, often not listed until their MELD score increases. Application of the MELD score has reduced the number of patients awaiting LT and lowered peri-transplant mortality [6]. The MELD score has not been able to improve the shortage of available organs. Organ distribution is based on medical urgency, rather than expected posttransplant outcomes. Patients with MELD scores >35 are typically admitted to the ICU, potentially on dialysis, receive hemodynamic or

respiratory support [9], and are potential candidates for urgent LT. In such situations, it may seem that sick patients would not benefit from operative intervention. However, based on a 5-year time frame, the higher the MELD score, the greater the benefit of LT [10]. Survival benefit posttransplantation is seen in MELD scores >40 because this population has the greatest risk of mortality while awaiting LT [11].

Patients with MELD scores >40 were previously thought to be "too sick" to undergo LT. It was believed that organ allocation to this higher risk population was futile and not beneficial for individual patient outcomes or for appropriate resource utilization. Currently, the pretransplant MELD score has not been able to reliably predict posttransplant outcomes [12, 13]. As patients linger on waiting lists, MELD scores continue to increase. It is common to see patients with MELD scores >40 awaiting LT. Low-MELD-score patients may also spend a prolonged amount of time on wait-lists, deteriorate, and become part of the sickest quartile of individuals awaiting LT. Interest lies in assessing which critically ill patients with high MELD scores derive the most benefit from LT. In patients with MELD scores >40, are there additional factors not captured by the MELD score that can predict successful or futile transplantation outcomes? In order to reduce wait times, in 2013, the United Sates adopted the Share 35 policy, which mandated that there would be an increase in regional sharing of organs to patients with MELD scores ≥35 [14].

A Canadian retrospective review assessed the outcomes of 198 critically ill ICU cirrhotic patients undergoing LT with a median MELD score of 34 on ICU admission [15]. The 90-day and 3-year survival were 84 and 62.5%, respectively, despite the fact that 88% of patients received vasopressors, 56% received renal replacement therapy, and 87% were mechanically ventilated prior to transplantation [15]. The same study found that patients >60 years of age had a significantly higher 90-day mortality (27% vs 13%) [15]. A multivariate analysis of 8070 transplant patients aged ≥60 identified that recipient albumin levels <2.5 mg/dL, serum creatine ≥1.6 mg/dL, hospitalization at the time of organ offer, ventilator dependence, presence of diabetes, and recent hepatitis C virus (HCV) positivity were independent predictors of poor patient survival [16]. In this study, the strongest prognostic factor was a recipient and donor age combination equal to or greater than 120 years [16]. Asrani et al. [17] retrospectively reviewed non-HCV cirrhotic LT recipients and identified that patients who had a survival of <50% at 5 years were above 60 years old with median MELD scores of 40. These patients also had multiple medical comorbidities and were on life support at the time of LT. Age > 60 in patients with elevated MELD scores has consistently been shown to be associated with worse posttransplantation survival compared to those patients with MELD scores >40 and age < 60.

Patients with MELD scores >40 have increased wait-list mortality compared to patients with lower MELD scores [1]; however, an elevated MELD score is no longer a contraindication to LT [18]. Studies have shown contradictory results for high MELD score patients and postoperative mortality. Retrospective analysis has demonstrated that cirrhotic patients with MELD scores ≥40 do benefit from LT and have similar 5-year cumulative survival posttransplantation compared to patients with MELD scores <40. However, these patients confer a higher burden of health-care

costs [19]. In 2014, the University of California, Los Angeles, group showed similar findings, in which patients with MELD score > 40 LT was deemed beneficial with a 5-year patient survival rate above 50% [20]. The same group also identified that a subgroup of patients with MELD scores >40 did not benefit from transplantation. Patients with MELD scores >40 who had septic shock, cardiac risk factors, and other significant comorbidities, were found to have a predicted futility of LT of >75% [20]. Prospective analysis has confirmed the association of elevated healthcare costs with MELD scores ≥28 is due to longer hospital and ICU admissions, despite no differences seen in postoperative survival or complications when compared to MELD scores <28 [18].

Panchal et al. [21] retrospectively reviewed a nationwide transplant database and found that the overall mortality was statistically higher in patients with MELD scores ≥40, compared to patients with a MELD score < 30 (30 versus 26%). Despite the significant difference in mortality, the MELD >40 group had a lower mortality rate than initially predicted, which was thought to be secondary to younger age of recipients, lower prevalence of diabetes, portal vein thrombosis (PVT), HCV, Epstein-Barr virus, TIPS, or prior upper abdominal surgery [21]. This group utilized greater hospital resources (longer pretransplant hospitalization, ICU admission, required mechanical ventilation, and longer hospital length of stay) [21]. Within the same study, MELD patients with a score of >40 and recipient age > 60, BMI > 30, pretransplant hospitalization, or use of extended criteria donors predicted LT futility. The risk of mortality increased by 95%, and graft failure was 60% higher when compared to patients with a MELD <30. Despite the significantly increased risk, there is a perceived benefit to transplanting such sick patients because they have expected survival of >50% at 5 years (64% graft and 69% patient survival) [21]. In recipients with satisfactory graft function, MELD scores >30 are significantly associated with prolonged ICU stay (defined as ≥3 days) which is associated with poor patient and graft survival at 3, 12, and 60 months [22]. However, good LT outcomes can be seen in patients with MELD scores ≥40, where overall 1-, 3-, 5-, and 8-year survival of 89, 79, 75, and 69% can be seen when futile deaths are excluded [20]. There is a definite subgroup of patients in this high-risk category in whom LT becomes futile despite optimal management. Michard et al. performed a single-center retrospective review and identified that in patients awaiting LT with MELD scores >40, those admitted to the ICU had elevated lactate (>5 mmol/L) or developed acute respiratory distress syndrome (ARDS) and had a poor 3-year survival rate of 29% [23]. In this subpopulation, LT is clearly not beneficial. A comparison of several studies with high MELD scores and associated variables predicting poor patient survival is summarized in Table 14.1.

There are several challenges of offering transplants to patients with high MELD scores. Selecting the most appropriate donor organ for the most appropriate recipient in order to provide the best postoperative survival can be challenging. Single-center experience has demonstrated that high-risk donor organs transplanted in low MELD patients has resulted in lower recipient transplant survival [26, 27]. Furthermore, the quality of the donor organ has not impacted recipient survival in recipients with MELD scores >30 [28]. The complexity of organ allocation systems

Table 14.1 High MELD score and variables associated with poor survival

Study	Year, study type	Total number of patients	MELD	Overall patient survival	Recipient factors associated with poor survival
Nekrasov et al. [24]	2017 Retrospective single center	207	≥40	86% at 1 year 79% at 3 years 73% at 5 years	DM RRT prior to transplant Pretransplant PVT
Nekrasov et al. [25]	2016 Retrospective UNOS database	5002	≥40	80% at 1 year 72% at 3 years 67% at 5 years 53% at 10 years	Age > 60 Hospitalization time Previous liver transplant Previous abdominal surgery Ventilator dependence HCV DM
Karvellas et al. [15]	2013 Retrospective multicenter	198	34 (median)	84% at 90 days 74% at 1 year 62.5% at 3 years	Age > 60
Aloia et al. [16]	2010 Retrospective UNOS/OPTN database	8070 (92% of patients between age 60 and 69)	MELD score available for 40% of cohort	MELD >23 75% at 1 year 72% at 3 years MELD 16–23 83% at 1 year 77% at 3 years MELD <16 87% at 1 year 77% at 3 years	Albumin <2.5 mg/dL Hospitalization Ventilator dependence DM + HCV Cr ≥ 1.6 mg/dL Combined recipient/donor age of ≥120 years
[a]Asrani et al. [17]	2018 Retrospective SRTR/OPTN database	31,829	23 (median)	79.1% at 5 years Survival ≤50% at 5 years for; age > 60, median MELD 40, and on life support	Ventilator support Age > 60 HD Cr ≥ 1.5 mg/dL without HD DM
Petrowsky et al. [20]	2014, Single-center retrospective	169	42.2 (mean)	72% at 1 year 64% at 3 years 60% at 5 years 56% at 8 years	[b]Cardiac risk Age-adjusted CCI ≥ 6 Life support treatment Pretransplant septic shock

(continued)

Table 14.1 (continued)

[c]Panchal HJ et al. [21]	2015 Retrospective UNOS database	33,398	MELD ≥40 = 2610 patients MELD 30–39 = 5984 patients MELD <30 = 24804 patients	MELD ≥40 80% at 1 year 73% at 3 years 69% at 5 years	Age > 60 BMI > 30 ICU or ventilation Multiple comorbidities Obese or extended criteria donors

Legend: SRTR (Scientific Registry of Transplant Recipients), OPTN (Organ Procurement and Transplantation Network), HD (hemodialysis), Cr (Creatinine), HCV (hepatitis C virus), CCI (Charlson comorbidity index), RRT (renal replacement therapy), PVT (portal vein thrombosis)
[a]Recipient factors associated with graft failure, rather than poor survival
[b]Cardiac risk defined as severe valvular disease, coronary artery disease with 70% stenosis or previous revascularization, history of myocardial infarction, history of ventricular/atrial arrhythmias, increased pretransplant troponin, new wall motion abnormality on echocardiography
[c]Factors associated with poor survival were analyzed in a subpopulation of patients with MELD ≥40, in order to assess predictors of futility

in individual countries can further complicate organ allocation. In 2013, the Share 35 policy was implemented in order to enhance distribution of organs in the United States for patients with MELD scores ≥35 [29]. Since its implementation, there has been a 36% reduction of organ offers accepted for patients with MELD scores ≥35, while there was no change in organ acceptance for MELD scores <35 [29]. The most common reasons for declining an organ offer were "patient transplanted, transplant in progress, or other offer being considered," indicating that programs had several offers to choose from and were selectively choosing donors that were deemed to be more optimal [29].

As high-MELD-score patients continue to be transplanted, ongoing study is required to assess how a multidisciplinary approach with surgeons, hepatologists, and anesthesiologists can continue to enhance perioperative care in order to improve short and long outcomes. It is imperative to establish a consensus of independently successful and futile predictors of transplant outcomes in patients with MELD scores ≥35, in order to optimize outcomes in high-risk patients and prevent futile LT.

Liver Transplantation and Futility

Medical futility can divided into four major types: physiological, imminent demise, lethal condition, and qualitative [30]. When LT was in its surgical infancy prior to becoming recognized as a life-altering treatment that should be offered to patients with end-stage liver disease (ESLD), the procedure was associated with physiologic futility. Physiologic futility is defined as a proposed treatment that cannot lead to its intended physiologic effect [31] such as the case if a patient with ESLD undergoes LT and the patient does not survive the operation.

Imminent demise futility is closely associated to physiologic futility. In imminent futility, a performed action may have prolonged an individual's life, however, only for the very short term. For example, a patient with ESLD undergoes LT, and a few days or weeks later pass without being discharged from hospital. The intent of the transplant was to extend the patient's life by years, and the result was below this expectation. In this situation there is a subjective perceived benefit; the patient's life was prolonged; however, the patient may or may not have believed that the short extension of life was of benefit to them. Lethal condition futility is an extension of imminent demise where the expectation is that a patient will pass away in the near term regardless of receiving or undergoing an intervention; however, the short extension on life is deemed appropriate. For example, biliary stent placement in patients with advanced incurable biliary tree tumors does not reduce mortality but provides symptom reduction thus enhancing remaining quality of life. A controversial definition of futility is qualitative futility, because it requires the scientific assessment of the probability of success for a given treatment [32].

Quantitative futility is defined by Schneiderman et al. [33], "where a treatment should be considered futile is if it has been useless in the last 100 cases, only preserves permanent unconsciousness, or fails to end total dependence on intensive medical care." Qualitative futility addresses the end result of the intervention performed and whether the functional outcome is acceptable or not [32]. How do we as a society universally agree on what is considered acceptable? Within today's society there are diversely held cultural and religious beliefs on what defines an acceptable quality of life outcome after an intervention in the setting of potential imminent death. A consensus definition in such a setting would be a milestone achievement. Qualitative futility encompasses the current and future ethical ambiguity surrounding transplantation of very sick, physiologically deranged patients. In today's environment, the ethical questions and dilemmas are typically no longer dominated by the technical aspects of "can it be done?" but have transitioned to "should it be done?" Performing a highly complicated anastomosis, transplanting a patient with a MELD score > 40 with adverse prognostic indicators, or re-transplanting a patient several times, is no longer technically impossible. The ability to withdraw from aggressive medical treatment in the setting of limitless options should propagate reflection on what we consider optimal versus futile care.

How can we identify what is currently considered futile but will no longer be considered futile in the next decade of LT? Identification and stratification of patients with MELD scores >40 with associated poor predictors of outcome is necessary in order to establish a consensus of specific conditions that independently provide significant postoperative challenges that may be insurmountable to the patient. In such situations, the focus should be on the application of qualitative futility: enhancing remaining quality of life, reducing hospital resource utilization, and preserving organs that might be of a more long-term benefit to other recipients. A consensus on how we define poor outcomes in situations of ESLD and imminent death is required. How do we determine what an acceptable survival rate is, and should it be based on being better than 50%, the flip of a coin? Should there be an objective evaluation, assessing success on a minimum 5-year survival and predetermined cost? We cannot

solely focus on what is best for an individual patient. Consideration must also be given to what is best for the next patient awaiting LT. Unfortunately, resource utilization and medical costs are also a mandatory part of the conversation.

Many scoring systems predicting post-LT outcomes are available, and specific definitions of futility have been created by several groups. Petrowsky et al. [20] and Panchal et al. [21] defined futility as a 90-day mortality or in-hospital mortality in patients with MELD scores ≥40. Petrowsky et al. [20] also identified that in patients with MELD scores ≥40 who underwent LT, futility was significantly associated with greater pretransplant morbidity, higher cardiac risk, age-adjusted Charlson comorbidity index of ≥6, life support treatment, and pretransplant septic shock. In this population, cardiac and septic causes of death were significantly higher compared to patients without futility-associated risk factors and MELD scores ≥40. Based on their observed findings, Petrowsky and his group state that despite high medical acuity, patients with high MELD >40 without associated futile risk factors have successful long-term survival, and therefore such patients should be transplanted. Asrani et al. [17], on the other hand, defined futility as any adult recipient with a >50% mortality at 5 years posttransplant. Rana et al. [34] state that LT in any patient with MELD score > 40 is likely futile because the predicted posttransplant mortality is greater than any wait-list mortality as predicted by the MELD score. However, based on previously discussed data, there are subsets of patients with MELD scores >40 that have good posttransplant outcomes, and a general policy of no LT for MELD scores >40 would not be appropriate.

Despite multiple proposed definitions for transplant futility, there are no global consensus criteria that clearly define transplant futility or provide a consensus on LT futility-associated criteria. No guidelines currently propose delisting patients deemed futile for transplantation from wait-lists. Delisting may provide a benefit by optimizing remaining quality of life, rather than proceeding with LT despite poor expected outcomes. For example, should a patient with a MELD score > 40, age > 60 with extensive cardiac risk factors undergoing dialysis, be delisted in order to optimize organ reallocation to another individual? Would family consent be required? What body of governance would make such a decision, and would this be considered too paternalistic of an approach? In North America, institutions review these unfortunate patient situations on a case-by-case basis. Multidisciplinary conferences, where decisions regarding high-risk cases are reviewed, play an important role in assessing not only the recipient but also the potential donor. The Baylor College of Medicine established the Houston City-Wide Task Force on Medical Futility, where a committee was created to preserve and protect patient rights while establishing a fair procedural process for potentially futile clinical situations [30].

With the limited supply of organs, objective evaluation of a patient's transplant candidacy should also take place and assessment if optimal allocation of organs is indeed to those critically ill patients at the top of the transplant list. Establishing a clear set of defined criteria that warrants a patient from being delisted from a transplant waiting list may help optimize organ allocation and globally improve outcomes. Linecker et al. [35] provide general definitions of futility and propose the

concept of "potentially inappropriate" LT by risk profiling a patient's clinical situation and probability of not surviving the early posttransplant recovery phase. If a predictive post-mortality score could be validated to accurately prognosticate post-transplant mortality risk and incorporate donor characteristics, enhanced allocation and minimization of futile transplants could occur.

Preoperative Preparation of a Sick Patient for Liver Transplantation

Hepatorenal Syndrome

Please refer to Chaps. 2 and 5 on this topic.

Porto-pulmonary Hypertension

Porto-pulmonary hypertension (POPH) is a disease where secondary pulmonary hypertension develops in the setting of portal hypertension with or without cirrhosis [36]. POPH occurs in 2–10% of all patients with cirrhosis, with approximately 1% of all patients with POPH demonstrating severe symptomatic disease [37]. The diagnosis of POPH is based on right heart catheterization findings and requires a mean pulmonary artery pressure of ≥25 at rest, an elevated pulmonary vascular resistance >240 dyne s/cm^{-5}, and a normal pulmonary capillary wedge pressure (PCWP) <15 mmHg [38]. Classification of mild, moderate, and severe disease is based on mean pulmonary artery pressures of >25 to <35, ≥ 35 to <45, and ≥45, respectively [39].

Untreated POPH is considered to be a relative contraindication for LT, and mean pulmonary pressures >35 is an absolute contraindication to proceed with LT. After reperfusion of transplanted liver, the increased venous return will exert the volume and pressure to the right heart against high pulmonary resistance resulting in right heart failure and likely death. All the potential liver transplant patients are screened with transthoracic echocardiogram where right ventricular systolic pressure (RVSP) is estimated based on the tricuspid jets. If the RVSP is found to be elevated, these patients undergo further testing with a right heart catherization. It is important to distinguish between primary pulmonary hypertension and volume overload which can commonly occur in patients with cirrhosis. In centers that use Swann-Ganz catheters routinely in LT, this simple measurement can identify undiagnosed pulmonary hypertension prior to starting the operation, allowing the transplant team to abort the case if the pulmonary pressure is found to be too high (>35 mm Hg).

Pharmaceutical vasodilators such as prostacyclin analogues, phosphodiesterase inhibitors, and endothelin receptor antagonists lower mean pulmonary artery pressures and allow for clinical stability evidenced by improved pulmonary hemodynamics [38,

40, 41]. However, medically treated POPH patients' 5-year survival is only 40–45% [42, 43], while pretreatment with prostacyclin therapy with LT can improve survival up to 67% [43].

Patients with mean pulmonary artery pressure ≤ 35 and peripheral vascular resistance <400 dynes/sec/cm^{-5} can be considered transplant candidates and can receive an exception MELD score of 22 points [44]. If patients do not meet transplant criteria, they can be medically treated to a mean pulmonary artery pressure < 35 mmHg and peripheral vascular resistance <400 dynes/sec/cm^{-5}; then MELD exception points can be provided and increased by 10% every 3 months if there is continued hemodynamic improvements [45]. POPH patients who are transplant eligible also have significant mortality potential. It has been shown that wait-list mortality or removal from the wait-list secondary to clinical decompensation is 23.2% with a median wait-list time of 344 days [46]. Age, initial MELD score, and pulmonary vascular resistance are independent risk factors for wait-list mortality [46]. Patients with the lowest wait-list mortality are those with MELD score ≤ 12 and initial pulmonary vascular resistance of ≤450 dynes/s/cm^{-5} [46].

Data from the Scientific Registry of Transplant Recipients between 2002 and 2010 was retrospectively reviewed by Salgia et al., and they identified 78 out of 34,318 patients who underwent cadaveric transplantation for POHP with MELD exception points [38]. The unadjusted 1- and 3-year patient survival for recipients with POPH was 85 and 81%, while graft survival was 82 and 78% respectively. After adjusting for donor and recipient factors, POPH recipients have a significantly higher adjusted risk of death and graft failure within the first posttransplant year compared to non-POPH transplants [38]. DuBrock et al. have reported an unadjusted 1-year posttransplant mortality rate of 14% similar to Salgia et al. [46]. Rajaram et al. performed a 10-year retrospective review between 2005 and 2015 with the objective to compare posttransplant outcomes of patients diagnosed with POPH and pulmonary venous hypertension versus patients without pulmonary hypertension [47]. The authors identified 28 patients with POPH, 13 of which underwent LT with an average MELD score of 21 [47]. One patient passed away intraoperatively; 30-day survival was 92.3%, and 1-year survival was 69.2% compared to a 1-year survival of 100% in the non-pulmonary hypertension group [47]. A recent systematic review demonstrated a 1-year posttransplant mortality rate of 26% for POPH compared to 12.7% in non-POPH patients [48]. A retrospective national cohort study of 110 POPH patients in the United Kingdom identified no difference in survival between cirrhotic and non-cirrhotic patients, and the overall survival rate at 1, 2, 3, and 5 years was 85, 73, 60, and 35% [49].

Renal Failure and Liver Transplantation

Please refer to Chap. 5 on this specific topic.

An alternate treatment strategy for liver transplant candidates with renal insufficiency is to proceed with LT and assess for the development of postoperative renal

insufficiency [51]. In high MELD patients undergoing SLKT, there is a high risk of renal allograft failure. As such, it has been suggested that liver-alone transplantation should be performed with assessment at 3 months posttransplant for potential prioritization for kidney allocation [53]. Fong et al. reported that renal allograft and patient survival were significantly lower in patients undergoing SLKT compared to isolated kidney transplantation [54].

The potential benefits of SLKT has been an ongoing debate, as there is no high-quality evidence demonstrating which patients benefit most from SLKT. A cited benefit of SLKT is immune protection of the renal allograft with lower rates of acute and chronic rejection compared to sequential kidney transplant [55]. The potential drawback of SLKT is that liver recipients receive a donor kidney when their native kidney might in fact recover, resulting in a lost organ for a patient waiting for kidney-only transplantation [53]. The ultimate goal in selecting patients for SLKT is to identify which ESLD transplant candidates will develop or have irreversible kidney damage at the time of transplantation and therefore will ultimately benefit from a single operation. The difficulty lies in that there is no reliable method to identify which liver transplant candidates with concurrent kidney injury will recover renal function or eventually require a renal transplant post LT [52]. Currently, there is no universal policy for SLKT. In 2015, Puri and Eason summarized the evolution of recommendations and guidelines for SLKT outlined below [56] [Table 14.2].

Combined Liver and Thoracic Transplantation

Combined liver thoracic transplantation is a rare phenomenon. From 1995 to 2016, there have been 17 single-center published reports [58]. Combined heart and liver transplant (CHLT) is only performed at a few select high-volume centers. From 1988 to 2015, there have been 192 CHLTs performed in the United States [59]. The rate of CHLTs being performed in the United States is rapidly increasing. A retrospective review of the UNOS database between 1987 and 2010 identified 97 reported cases of CHLTs [60]. The two most common primary cardiac diagnoses were amyloidosis (26.8%) and idiopathic dilated cardiomyopathy (14.4%), while the two most common primary liver diagnoses were amyloidosis (27.8%) and cardiac cirrhosis (17.5%) [60]. Other common indications for CHLT are for patients with heart and liver failure secondary to hemochromatosis and familial hypercholesterolemia and for patients with ESLD who have severe heart disease and are unfit for liver-alone transplantation [61]. Beal et al. summarized the following number of CHLTs performed at high-volume centers within the United States: Mayo clinic (n = 33), Hospital of the University of Pennsylvania (n = 31), University of Pittsburgh Medical Center (n = 14), University of Chicago Medical Center (n = 13), Methodist Hospital (n = 13), and Cedars-Sinai Medical Center (n = 9), with the remaining centers performing ≤7 CHLT each [59].

Cannon et al. reported that liver graft survival in 97 CHLT was 83.4, 72.8, and 71% at 1, 5, and 10 years, while cardiac graft survival was 83.5%, 73.2, and 71.5%,

Table 14.2 Evolution of recommendations and guidelines for SLKT [56]

Study	Recommendations for SLKT
Nadim et al. [50] 2012	1. Candidates with persistent AKI ≥ 4 weeks with one of the following: (a) Stage 3 AKI as defined by modified RIFLE, i.e., a threefold increase in serum creatinine (Scr) from baseline, Scr ≥ 4.0 mg/dL with an acute increase of ≥0.5 mg/dL or on renal replacement therapy (b) Glomerular filtration rate (GFR) ≤35 mL/min (MDRD-6 equation) or GFR ≤ 25 ml/min (iothalamate clearance)
	2. Candidates with CKD, as defined by the National Kidney Foundation for 3 months with one of the following: (a) eGFR ≤40 ml/min (MDRD-6 equation) or GFR ≤ 30 ml/min (iothalamate clearance) (b) Proteinuria ≥2 g a day (c) Kidney biopsy showing ≥30% global glomerulosclerosis or ≥30% interstitial fibrosis (d) Metabolic disease
OPTN Kidney Transplantation Committee and the Liver and Intestinal Organ Transplantation Committee (OPTN Policy 3.5.10)	(a) CKD requiring dialysis with documentation of the CMS form 2728 (b) CKD (GFR ≤ 30 ml/min) by MDRD-6 or iothalamate measurement and proteinuria >3 g/day (c) Sustained AKI requiring dialysis for 6 weeks or more (defined as dialysis at least twice per week for 6 consecutive weeks) (d) Sustained AKI (≤ 25 ml/min) for 6 weeks or more by MDRD6 or direct measurement not requiring dialysis (e) Sustained AKI: Patients may also qualify for SLK listing with a combination of time in categories (c) and (d) above for a total of 6 weeks (f) Metabolic disease
Eason et al. [51] 2008	(a) Patients with ESRD with cirrhosis and symptomatic portal hypertension or hepatic vein wedge pressure gradient ≥10 mmHg (b) Patients with CKD with GFR ≤ 30 ml/min (c) Patients with AKI/HRS with Scr ≥ 2 mg/dL and dialysis ≥8 weeks (d) Patients with evidence of CKD and kidney biopsy demonstrating >30% glomerulosclerosis or 30% fibrosis Other criteria recommend are the presence of comorbidities such as diabetes, hypertension, age > 65 years, other preexisting renal disease along with proteinuria, renal size, and duration of elevated serum creatinine
Davis et al. [57] 2007	(a) Patients with CKD with a measured creatinine clearance (or preferentially an iothalamate clearance) of ≤30 ml/min (b) Patients with AKI and/or HRS on dialysis for ≥6 weeks (c) Patients with prolonged AKI with kidney biopsy showing fixed renal damage (d) SLK not recommended in patients with AKI not requiring dialysis

respectively [60]. An interesting observation was that patients who received CHLT had lower rates of acute rejection compared to patients undergoing isolated heart transplantation [60]. A retrospective study from Mayo Clinic demonstrated that the incidence of T-cell-mediated rejection was 31.8% in CHLT recipients compared to 84.8% in isolated heart transplant recipients with similar overall incidence of antibody-mediated rejection [62]. Cannon et al. note that the average MELD score at time the time of CHLT was 13.8; however, the wait-list mortality for these patients would have been higher compared to patients with isolated hepatic failure with similar MELD scores [60]. Between January 1997 and February 2004, there were 110 patients wait-listed for CHLT within the United States; 33 patients (30%) underwent CHLT, 30 patients (27%) died, 11 patients (10%) were still wait-listed, and 34 patients received single-organ, sequential organ transplant or were awaiting transplant of the second organ [59]. A large single-center case series from the University of Bologna reported on 14 patients with combined heart and liver failure where 13 patients underwent CHLT and 1 underwent combined heart-liver-kidney transplantation. The 1-month, 1-year, and 5-year survival rates were 93, 93, and 82%, respectively, while graft free rejection at 1, 5, and 10 years for the heart was 100, 91, 36, and 100% and 91 and 86% for the liver [61].

Patients with end-stage pulmonary disease and ESLD who are not expected to survive with only a single-organ transplant can be considered for combined lung and liver transplantation (CLLT).

Isolated lung transplantation should be considered if there is a >50% risk of mortality secondarily to the primary lung disease within 2 years if a lung transplant is not performed, >80% chance of survival at 90 days after lung transplantation, and a >80% chance of 5-year post transplant survival with adequate graft function [63]. In addition to the lung transplant indications mentioned, if there is biopsy proven cirrhosis with a portal pressure gradient >10 mmHg, a CLLT can be considered [63]. Contraindications to CLLT include albumin <2.0 g/dL, INR > 1.8, presence of severe ascites, or encephalopathy [63].

Similar to CHLT, CLLT is rarely performed, and experience is limited to single-center or multicenter case reports. Double lung transplant is most often performed during CLLT instead of single lung transplant. The most common indication for CLLT is cystic fibrosis with pulmonary and liver involvement. Other indications include POPH with ESLD, hepatopulmonary fibrosis, alpha-1 antitrypsin deficiency with advanced lung and liver involvement, and sarcoidosis [64]. As with CHLT, there is a postulated immunological benefit for combined transplant, where LT is immune protective [65, 66]. There are no standardized recommendations available for CLLT, and candidacy is evaluated at each center with a multidisciplinary board committee review [64]. Potential CLLT candidates need to be placed on individual organ wait-lists. Prior to 2005, the United States and the Euro transplant region donated lungs based on patient waiting time [67]. In May 2005, the lung allocation score (LAS) was introduced, which is comprised of several patient clinical and laboratory parameters, and in the United States the LAS has replaced waiting time for determining priority of donor lungs [67]. Other European countries have followed suit over the years.

Patients undergoing CLLT derive a significant survival benefit from CLLT; however, there is a higher risk of wait-list mortality compared to single-organ transplantation [64, 68]. Survival rates are improving for CLLT. In 2008, Grannas et al. reported the largest published single-center cohort of CLLT with 1- and 5-year mortality rates of 69 and 49% [69]. Retrospective review of 14 consecutive patients who underwent simultaneous liver and thoracic transplantation included 10 patients who underwent CLLT [58]. In seven CLLT patients, the lung was transplanted prior to the liver, and three patients underwent a liver first principle while the lungs were perfused ex vivo [58]. One hundred percent of the CLLT patients were alive at 1 and 5 years with 10% suffering acute liver rejection, 40% acute lung rejection, and 10% chronic liver/lung rejection [58]. One of the largest single-center American series included 8 patients who underwent CLLT with reported patient and graft survival of 87.5, 75, and 71% at 30 days, 90 days, and 1 year [70].

CLLT can be performed with a liver first, then lung transplant approach or alternatively with a lung-first approach. Theoretical advantages of the liver first principle include reduced complications of hepatic reperfusion, potentially reduced need for blood products, reduced incidence of donor pulmonary edema, and reduced incidence of biliary strictures [58]. Advances are continuing to evolve for CLLT in critically ill patients. Extracorporeal membrane oxygenation with central cannulation has successfully been implemented after lung transplantation and prior to orthotopic LT in order to manage extensive pulmonary reperfusion edema and right heart insufficiency [71].

Intraoperative Preparation of a Critically Ill Recipient for Liver Transplant

Historically, adult orthotopic LT has been associated with massive hemorrhage with median red blood cell (RBC) transfusion rates of 28.5 units per case [72]. With improved surgical technique, intraoperative anesthetic management, transfusion medicine, and improved understanding of coagulation abnormalities [73] associated with cirrhosis, intraoperative transfusion rates have been steadily decreasing over the last 20 years [74]. Patients with low MELD scores can undergo transplantation with 0.3 units of packed RBCs without plasma, platelet, or cryoprecipitate transfusion [75], while increased INR and presence of ascites have been independently correlated with increased intraoperative blood product utilization [76, 77].

With reduced blood product transfusions, survival posttransplantation has improved [78–80]. In fact, transfusion of one or more units of plasma has been shown to have a 5.1 increased mortality risk compared to no plasma received [81]. A retrospective analysis of 286 transplant recipients found that the strongest predictor of overall survival was the number of blood transfusions after a mean follow-up of 32 months [77]. In order to identify which transplant recipients are at an increased risk of requiring intraoperative blood products, McCluskey et al. developed a risk index score for massive blood transfusion and identified 7 preoperative variables

including age > 40 years, hemoglobin ≤10 g/dL, INR 1.2–1.99 and >2, platelet count $\leq 70 \times 10^9$/L, creatinine >110 umol/L (females) and >120 umol/L (for males), and repeat LT [82].

Normal hemostasis requires a balance between the coagulation and the fibrinolytic systems. One of the pathophysiologic complications of end-stage cirrhosis is the reduced ability or inability of the liver to synthesize new or clear activated coagulation factors [83]. During technically challenging cases, surgical bleeding can be magnified by the inability of the recipient liver to produce coagulation factors and platelets for necessary clot formation. A majority of cirrhotic patients will exhibit some form of thrombocytopenia, which is secondary to increased platelet activation, consumption, and splenic sequestration of platelets associated with portal hypertension [84]. Although total number of platelets are reduced, it has been shown that in the remaining platelets, there is increased activity secondary to increased levels of von Willebrand factor and decreased levels of ADAMTS 13 [85]. All the coagulation factors are synthesized by the liver, the only exception being factor 8. In cirrhotic patients the levels of vitamin K-dependent factors fall by 25–70% [86].

Cirrhosis induced thrombocytopenia in conjunction with prolonged prothrombin time (PT), and activated partial thromboplastin time (aPPT) was previously thought to be indicative of an increased bleeding risk [85, 86]. However, cirrhotic patients have a "rebalanced" homeostasis of anticoagulant and procoagulant cascades [85]. Furthermore, the etiology of cirrhosis can impact the balance between coagulopathy and thrombosis [83]. In the critically ill cirrhotic recipient prior to LT, superimposed infections, renal injury, endotoxins, and imbalances of coagulation factors [87] contribute to the coagulopathy seen intraoperatively. Understanding the coagulopathic profile of severely cirrhotic patients and the impact of the phases of LT is important in order to anticipate intraoperative challenges.

The initial abdominal incision made is based on surgeon preference. Commonly utilized incisions for opening the abdomen include a bilateral subcostal incision with upper midline laparotomy (Mercedes incision) or an upper midline laparotomy with a right lateral extension (Cheney incision). Table-mounted Thompson, Omni, or Bookwalter retractors are used to help facilitate intra-abdominal exposure, and choice of retractor is typically also dependent on surgeon preference. When the abdomen is opened, it is important to be cognizant of patients with ascites. Quick removal of large-volume ascites upon entering the abdomen can potentially result in a rapid shift of recipient hemodynamics.

The general steps of LT are divided into pre-anhepatic, anhepatic, and neohepatic/reperfusion phases. The pre-anhepatic phase refers to recipient hepatectomy and is completed once the vascular inflow/outflow has been controlled and clamped. Once vascular inflow and outflow have been clamped, the anhepatic phase begins, and the recipient liver is removed. The anhepatic phase continues with implantation of the new donor liver and subsequent IVC and portal vein anastomosis. The neohepatic/ reperfusion phase begins with unclamping of the venous inflow and outflow, perfusion of the donor liver, and venous return to the heart. Subsequently the hepatic arterial and biliary anastomoses are performed, and the neohepatic phase is complete. Recipient warm ischemia time generally refers to the time that the recipient

liver has been explanted to the time that the donor liver has been implanted and flow through the donor graft has been established.

During the pre-anhepatic phase, the recipient liver is completely mobilized by taking down the falciform, triangular, and coronary ligaments of the liver. Once the liver has been mobilized, portal dissection is performed in order to identify and isolate the common bile duct, right/left and common hepatic arteries, and the portal vein. Dissection of the gastrohepatic ligament provides access to the portal structures. The common bile duct, right and left hepatic arteries, and portal vein are subsequently ligated. The common bile duct should be resected just distal to the cystic duct. The gastroduodenal artery should be identified; however, it does not routinely need to be ligated.

In severely cirrhotic patients with portal hypertension, the pre-anhepatic phase is usually associated with the greatest amount of bleeding. The surgeon may encounter several potentially large portosystemic collaterals in the setting of the previously described hyperdynamic circulation [88], complicating mobilization, and dissection of the recipient liver. Adhesions secondary to prior upper abdominal surgery can further complicate the hepatectomy phase [89], and previous abdominal surgery has been found to be an independent risk factor for blood transfusion requirements [90]. Reduced availability of coagulation factors and platelets inhibits the liver's normal ability to deal with surgical bleeding.

During the recipient hepatectomy measurement and prophylactic treatment of abnormal laboratory bleeding time (BT), PT, INR, and aPTT have been common practice in order to help control anticipated surgical bleeding. However, as early as 1997, it was identified that aggressively correcting laboratory coagulation abnormalities prior to the anhepatic phase of transplantation is not required and that over-resuscitation during the pre-anhepatic phase may lead to extensive blood loss [91]. Prophylactic administration of FFP and RBCs contributes to blood loss by increasing splanchnic pressure in an already hyperdynamic circulatory state. Infusion of additional volume will eventually circulate back to the heart during the neohepatic phase [92]. As such, the utility of prophylactic treatment of abnormal laboratory values in cirrhotic patients has been questioned [84, 87, 93]. An evolving trend is the minimization of blood product transfusions during LT.

In general, there are two anhepatic techniques of LT: caval interposition and caval sparing (i.e., piggyback technique). The classic caval interposition technique begins with a retrohepatic caval dissection with cross-clamping of both the suprahepatic and infrahepatic inferior vena cava (IVC). This is followed by removal of the recipient liver, interposition and anastomosis of the donor IVC, and liver graft to the recipient suprahepatic and infrahepatic IVC. Suprahepatic and infrahepatic IVC reconstruction is performed with 3-0 or 4-0 Prolene sutures in a running fashion. Prior to completion of the infrahepatic caval anastomosis, the donor portal vein is flushed with a preservation solution in order to rid the liver of accumulated toxins that may contribute to reperfusion syndrome. Once flushing is complete, the donor portal vein is reconstructed to the recipient portal vein in an end-to-end fashion with 6-0 Prolene sutures. Typically, a shorter portal vein reconstruction is preferred over

a longer donor/recipient portal vein reconstruction with the hope of reducing kinking or development of postoperative portal vein thrombosis.

Re-establishment of blood flow with unclamping of the IVC and portal anastomosis completes the anhepatic phase, and reperfusion of the liver begins. There are alternative flushing techniques described and are based on surgeon preference. Historically, venovenous bypass was used in conjunction with classic caval reconstruction. The purpose was to provide venous return when the usual caval venous return to the heart is interrupted [94]. Nowadays, it would be commonplace to perform caval interposition technique without venovenous bypass.

Alternate caval reconstruction techniques such as the piggyback [95] or side-to-side [96] caval anastomosis only require partial occlusion of the recipient suprahepatic IVC. The recipient liver is mobilized off of the recipient IVC, while the IVC is left intact. Care must be taken while dissecting the liver off the IVC as retrohepatic veins may easily tear, cause further bleeding, and potentially damage the IVC.

In the piggyback technique, the donor hepatic vein can be anastomosed to two or three recipient hepatic veins. If only two hepatic veins are used, then the right hepatic vein is ligated. The piggyback technique with partial IVC occlusion provides a theoretical advantage of maintaining venous blood flow from the infrahepatic IVC to the heart. Maintaining cardiac preload is believed to stabilize hemodynamic stability and therefore avoids large intraoperative fluid infusions and potential need for vasopressors. Additional suggested advantages of partial caval occlusion include shorter anhepatic phase and possible decreased incidence of renal injury [97]. Moreno-Gonzalez et al. retrospectively identified that the piggyback technique was associated with longer operative times but also with less intraoperative hemodynamic instability, RBC transfusions, pressors, and fluid administration [98]. Graft outflow obstruction and increased incidence of bleeding from the caval anastomosis are recognized potential complications of the piggyback technique [97]. Caval obstruction associated with the piggyback technique is thought to be secondary to a large donor graft causing compression or an inadequate graft size that can result in twisting of the caval anastomosis, ultimately leading to hepatic venous outflow obstruction [99].

The transition from the anhepatic to neohepatic phase is critically important as there is no functioning liver during the anhepatic phase. No clotting factors are produced, and the concentration of tissue plasminogen activator increases, which contributes to fibrinolysis [100]. The accumulation of citrate leads to increased binding of ionized calcium, and calcium is an important cofactor for proper hemostasis [101]. Pooled systemic blood below the IVC clamp becomes cold and hyperkalemic as lactic acid, toxic metabolites, cytokines, and free radicals accumulate and cannot be removed [102]. When the IVC and portal vein clamps are removed, circulation is restored, and the donor liver receives the systemic blood and forwards it toward the recipient heart while the portal vein provides a fresh inflow of blood.

At this critical time, reperfusion syndrome can induce recipient hemodynamic instability as the pooled systemic blood is returned to the heart. Hilmi et al. classified postreperfusion syndrome (PRS) as mild or severe [102]. Mild PRS occurs when the decrease in blood pressure and or heart rate is <30% of the anhepatic

blood pressure levels, lasts for ≤5 minutes, and is responsive to a 1 g intravenous bolus of calcium chloride and or intravenous boluses of epinephrine (≤100ug) without requiring continuous infusion of vasopressor agents [102]. Severe PRS is defined as the presence of persistent hypotension >30% of the anhepatic level, asystole, significant arrhythmias, and requirement of intraoperative or postoperative vasopressor support [102]. Severe PRS is additionally defined as prolonged (>30 minutes) or recurrent fibrinolysis requiring treatment with antifibrinolytics. The three main categories that contribute to the development of PRS are donor/organ related, recipient related, and procedure related [103]. Prolonged warm ischemia time typically >90 minutes is a procedure related factor that can contribute to the increased risk of developing PRS.

The reality is that there is an interplay between many risk factors that contribute to PRS. In the setting of a technically straightforward transplant with an optimal donor, the new liver begins to produce coagulation factors immediately, and is able to metabolize systemic toxins, thus avoiding PRS and potential primary graft nonfunction. In the setting of a technically challenging transplant and higher donor risk index organ, the newly implanted liver may have difficulty in initially metabolizing the pooled systemic blood while simultaneously synthesizing necessary coagulation and antithrombotic factors.

During the neohepatic phase, the donor and recipient hepatic arteries are reconstructed with 6-0 to 7-0 Prolene sutures depending on size of the hepatic artery. Various arterial reconstruction techniques can be employed along with different recipient and donor arteries depending on donor and recipient anatomy [104]. Commonly, an end-to-end parachute technique (between donor and recipient common hepatic arteries) is performed. Alternatively, a Carrel patch of donor celiac artery can be anastomosed to the recipient common hepatic artery. A cholecystectomy and bile duct reconstruction are performed, and the abdomen is closed. If technically feasible, an end-to-end bile duct anastomosis is preferred. Alternatively, a Roux-en-Y hepaticojejunostomy can be performed. Intra-abdominal drains are placed at the surgeon's discretion.

Point-of-care coagulation monitoring with thromboelastography (TEG) or rotational thromboelastometry (ROTEM) has become commonly utilized within LT. Both TEG and ROTEM measure the viscoelastic properties of clot formation via whole blood assay tests that analyze the phases of clot formation [105] and fibrinolysis [106]. Both technologies can measure coagulopathy more accurately than standardized laboratory tests. Additionally, TEG and ROTEM have fast turnaround times. Standard laboratory tests measure coagulation in plasma, are associated with a 40–60-minute delay, and platelet function is not concurrently assessed [107].

Preoperative TEG has been shown prospectively to help predict which patients will require massive transfusion within 24 hours of surgery [108]. Preoperative ROTEM has also shown promise in predicting bleeding risk during LT [109]. A prospectively randomized trial of 28 patients undergoing orthotopic LT was performed utilizing intraoperative TEG compared to standard laboratory measures. Intraoperative TEG monitoring was shown to significantly reduce transfusion rates of plasma (12.8 U vs 12.5 U); however, 3-year survival was not affected [110].

Furthermore, intraoperative use of prothrombin complex and cryoprecipitate guided by ROTEM has shown to result in significantly less RBCs and FFP being transfused [111]. Overall, ROTEM and TEG have shown to help reduce perioperative blood loss and blood transfusions and are rapidly becoming indispensable adjuncts during LT [106].

With the wide adoption of tranexamic acid (TXA) to help reduce bleeding in trauma, there has been interest of adopting the use of TXA during LT. A large systematic review and meta-analysis of liver transplant recipient outcomes comparing the use of antifibrinolytics to placebo found that there was no increased risk for hepatic artery thrombosis, venous thromboembolic events, or perioperative mortality [112]. However, international recommendations advise against the prophylactic use of tranexamic acid [113], unless fibrinolysis is detected clinically or with point-of-care testing. ROTEM has also demonstrated to be helpful in guiding resuscitation in response to hyperfibrinolysis [114].

Postoperative Management After Liver Transplantation

Systemic and renal vascular changes associated with cirrhosis-induced hyperdynamic circulation have been demonstrated to return to normal after LT. However, several authors have also demonstrated that cirrhosis-induced hyperdynamic circulation persists for a long period of time post-LT despite normalization of liver function and portal pressure [115, 116]. Living donor liver transplant (LDLT) recipients with a good postoperative course have been found to have significantly higher portal venous velocity and volume compared to LDLT recipients with graft failure, while no significant differences were observed in absolute cardiac output, cardiac index, blood volume, mean arterial pressure, and hepatic arterial flow [116].

Postoperative LT complications can be divided into acute and chronic and further divided into vascular and nonvascular complications. The rates of the complications include hepatic artery stenosis (2–13%), portal vein stenosis (2–3%), arterial dissection, pseudoaneurysm (most commonly at the hepatic arterial anastomosis), or hepatic artery rupture (0.64%) [117]. Hepatic pseudoaneurysms typically appear in the second to third weeks post-LT with an incidence of 2.5% [118].

Hepatic artery thrombosis (HAT) is the most common acute vascular complication and is considered to be the most devastating as it contributes to bile duct necrosis, graft loss requiring re-transplantation, and overall mortality rates between 27 and 58% [119]. Early HAT is defined as occurring within 1 month of LT and has a higher reported mortality rate compared to late HAT (defined as >1 month post-LT [120]. Early HAT incidence can range from 0 to 12% [117]. A systematic review of 21,822 liver transplants identified 843 cases of early HAT with a mean incidence of 3.9% and without any significant difference between transplant centers worldwide [121]. Of note, this large review defined early HAT as occurring within 2 months of LT. The authors identified that low-volume centers (<30 transplants per year) had a higher incidence of early HAT compared to high-volume centers (5.8% vs 3.2%)

[121]. Furthermore, it was demonstrated that pediatric HATs occurred with significantly higher incidence compared to adults (8.3% vs 2.9%) [121]. There is also no significant difference in the incidence of HAT between deceased donor LT (4.6%) compared to LDLT (3.1%) [121]. The median time to diagnosis of early HAT is 6.9 days and of late HAT is 6 months [121, 122].

Risk factors for HAT include increased graft ischemia time, ABO incompatibility, CMV infection, acute rejection, and use of aortohepatic conduit anastomosis, although this can be overcome with experience [123]. Surgical causes for early HAT include retrieval injuries, technical failure, hepatic artery kinking, and small or multiple arteries requiring arterial reconstruction [118]. The type of arterial reconstruction impacts graft function likely secondary to kinking. Long-artery grafts are an independent risk factor for early HAT, and short-graft artery reconstruction is recommended [124].

A systematic review of 19 studies identified that when standard revascularization techniques were not feasible and arterial conduits were utilized, there was an independent increased risk for the development of HAT and increased risk of ischemic cholangiopathy and lower graft survival compared to LT without arterial conduits [125]. Schroering et al. performed a 10-year retrospective analysis of 1145 transplants and identified that nontraditional donor arterial anatomy did not result in any significant difference in HAT or 1-year graft survival [126]. Sixty-eight percent of livers had standard anatomy, 222 donor livers required back table reconstruction, and the most common reconstruction (161 cases) was of the accessory/replaced right hepatic artery to the gastroduodenal artery [126].

Routine early postoperative doppler ultrasonography (US) for the evaluation of HAT has been previously proposed [127], and it is routinely used in many centers for screening for postoperative vascular complications. It is common to obtain postoperative day 1 doppler US to rule out an obvious HAT as one can develop within a few hours of LT. Doppler US is also useful to establish baseline hepatic flows for future comparison. Protocols for postoperative US are variable from center to center. Typical symptoms of early HAT include fever, elevated WBC, elevated transaminases, and possible septic shock; however, patients are often asymptomatic [119]. Doppler US remains as the first-line imaging modality to detect vascular complications as it is relatively quick, inexpensive, and noninvasive [128].

A noncomplicated hepatic arterial anastomosis on US should demonstrate arterial waveforms with swift upstrokes lasting <0.08 seconds, continuous anterograde diastolic flow, and a normal resistive index (RI) of 0.5–0.8 [123]. Transient increases of RI > 0.8 are common within 48–72 hours posttransplantation and are typically due to edema, vasospasm, or the new graft's initial response to portal hyperperfusion [123]. Increased peak systolic velocities or absent diastolic flow can be seen on US within the first 72 hours and eventually return to normal; however, one must be suspicious of HAT when absent or reversed diastolic flow in combination with low or decreasing peak systolic velocity are present [123, 129]. Additionally, presence of low RI in the initial postoperative period is 100% sensitive for a vascular (arterial, portal, or hepatic) complication [119]. Marin-Gomez et al. identified that low

intraoperative hepatic artery blood flow of 93.3 ml/min was an independent risk factor for early HAT compared to an intraoperative blood flow of 187.7 ml/min without HAT [130].

The development of early HAT will require re-transplantation in approximately 50% of patients [131]. Re-transplantation has traditionally been the primary approach; however, surgical and endovascular revascularization are alternative options. Surgical revascularization has the benefit that the patient does not necessarily need to be re-listed if revascularization is successful. Especially in the current climate of limited organs, surgical revascularization with donor and recipient hepatic artery reconstruction is optimal. Scarinci et al. have reported that when revascularization is performed within the first week of LT, graft salvage approaches 81% [132]. However, successful surgical revascularization rates are variable across the literature [119]. In such situations where surgical revascularization fails, immediate re-listing and re-transplantation are required. In overtly symptomatic patients, with significant hepatic infarction or biliary necrosis, re-transplantation becomes the default primary option. Patients are eligible for immediate re-listing if they are diagnosed with HAT within 7 days of LT, along with an AST $\geq$ 3000 and/or an INR $\geq$ 2.5 or arterial pH of $\leq$7.30, venous pH of 7.25, and/or lactate $\geq$4 mmol/L [133].

Endovascular treatments for HAT include intra-arterial thrombolysis and percutaneous transluminal angioplasty with or without stent placement and have been used with increased frequency with some authors reporting high success rates [119, 133]. Endovascular approaches remain somewhat controversial, lack high-quality evidence, and require ongoing further study [117]. Late HAT has a reported incidence rate of 1.7%, and patients typically present with fever, jaundice, and hepatic abscesses [122]. Late HAT with evidence of arterial collateralization should be managed conservatively [118]. However, many patients with late HAT develop ischemic cholangiopathy which requires subsequent re-transplantation [120].

Hepatic artery stenosis (HAS) is defined as narrowing of the hepatic artery by >50% on angiogram with an RI of <0.5 and peak systolic velocity > 400 cm/s [117]. There has been an increasing trend for the management of HAS via interventional procedures. A meta-analysis of case series for HAS was performed by Rostambeigi et al., which identified that percutaneous balloon angioplasty and stent placement have similar success rates (89% and 98%), complications (16% and 19%), arterial patency (76% versus 68%), re-intervention (22% versus 25%), and re-transplantation (20% versus 24%) [134].

Vascular outflow complications include hepatic and IVC thrombosis. Patient symptoms/signs include the need for ongoing diuretic therapy, persistent ascites, or abnormal liver function tests. Persistent ascites has been found to be the most common symptom resulting in investigation for hepatic venous outflow obstruction [135]. Untreated hepatic venous outflow obstruction (HVOO) can lead to graft congestion, portal hypertension, and cirrhosis, which may ultimately compromise graft function and patient survival [136]. HVOO has been reported in about 1–3.5% of patients receiving full-sized grafts and found with increased frequency in re-transplanted patients [135, 137]. Doppler US is the initial radiographic investigation

of choice. Incidence of HVOO for orthotopic LT with partial grafts range from 5 to 13% and 12.5% in LDLT [136]. Early (within 1 month) HVOO is thought to occur secondary to kinking at the donor hepatic vein and recipient suprahepatic IVC anastomosis, technical factors resulting in a narrow anastomosis, or large graft compression of the IVC [137]. Delayed HVOO is related to fibrosis and intimal hyperplasia.

In order to evaluate the incidence of HVOO, a retrospective review of 777 consecutive liver transplants including 695 cadaveric transplants with a mean MELD score of 14, of which 88% underwent piggy back technique was performed [138]. Early hepatic vein outflow obstruction occurred in 1% (7/695) of cases with all occurrences in the piggyback technique with 2 hepatic veins [138]. Two of seven cases were successfully managed medically with diuretics, while five of seven cases required operative cavoplasty [138]. In patients with high-pressure gradients or hepatic vein stenosis at the anastomotic site, hepatic venoplasty alone has been used as the initial management strategy followed by hepatic vein stenting if symptoms or elevated pressure gradient persist [135]. Other centers have successfully performed venoplasty with stenting as a primary option rather than venoplasty alone [137, 139, 140]. Endovascular management for HVOO is preferred over surgical repair because of the increased morbidity and mortality associated with surgical repair [139]. In LDLT recipients diagnosed with early and late HVOO managed with stent placement, patency in the early HVOO group was 76, 46, and 46%, while late HVOO patency rates were 40, 20, and 20% at 1, 3, and 5 years, respectively [141].

Nonvascular complications are further subdivided into biliary complications, graft dysfunction/rejection, infectious, drug toxicity, and increased future risk of malignancy. Biliary complications are the most common complications post-LT, and duct ischemia is closely related to hepatic arterial complications. The biliary system is supplied only by the hepatic arterial system, and arterial anastomotic complications may lead to secondary biliary complications. Common biliary complications include strictures, leaks, stones, bile debris, and ischemia. Bile leaks and strictures occur in 2–25% of cases and comprise the majority of postoperative complications [142]. In a large American data set of 12,803 liver transplants, the incidence of bile duct complications was significantly higher in donation after cardiac death (DCD) recipients (23%) compared to neurologic death donor (NDD) recipients (19%) [143]. Within the same database, DCD recipients required more frequent diagnostic/therapeutic procedures (18.8% vs 14.4%), surgical revision of biliary anastomosis (4.1% vs 2.8%), and re-transplantation (9.1% vs 3.8%) when compared to NDD recipients [143]. A large meta-analysis also identified that biliary complications were significantly increased in DCD recipients compared to NDD recipients (26% versus 16%) [144]. Overall incidence of ischemic cholangiopathy was 16% in DCD recipients compared to 3% in NDD recipients [144].

Early bile leaks are defined as those occurring within 4 weeks of LT and usually occur at the site of the anastomosis. Patients may be asymptomatic or present with nonspecific symptoms such as fever and abdominal/shoulder pain and may develop peritonitis with or without superimposed infection. Elevated bilirubin is usually present along with elevations in lab values (GGT/ALP). Diagnosis can be made

with ultrasound, with CT scan, or with magnetic resonance cholangiopancreatography (MRCP) [144]. Several management options are available. Endoscopic retrograde cholangiopancreatography (ERCP) with or without stent placement is typically utilized. Radiographically guided percutaneous drainage can be effectively used in addition to ERCP to drain a biloma. ERCP has the advantage that it is simultaneously both diagnostic and therapeutic. If the bile duct is reconstructed in an end-to-end fashion, ERCP is technically feasible. When a hepaticojejunostomy has been performed; ERCP is more challenging, requiring a skilled endoscopist, and not always technically possible. If ERCP cannot be performed, or is unable to reach the area of concern, percutaneous transhepatic cholangiography (PTC) and drainage are required. If ERCP is unable to adequately stent or reach a leak at the biliary anastomosis, PTC can be additionally performed to control the leak. If a large biliary anastomotic defect or biliary necrosis is present early in the postoperative period, surgical revision with a redo end-to-end anastomosis, choledochojejunostomy, or hepaticojejunostomy is required. The biliary defect may be too large or degree of the biliary necrosis too significant to preserve enough bile duct length for a redo end-to-end anastomosis. Bile duct strictures mostly develop at the anastomotic site; however, non-anastomotic strictures may develop and are alternatively known as ischemic type strictures [145]. Non-anastomotic strictures can be caused by microangiopathic factors (prolonged cold/warm ischemia, hemodynamic instability) or secondary to HAT [145]. Extraction of the native recipient liver results in loss of arterial collateral circulation, and the newly implanted donor liver will not have arterial collateral circulation to supply the biliary system. Therefore, its blood supply is dependent on the hepatic arterial anastomosis. It takes approximately 2 weeks for collaterals to start to form. When blood flow is reduced to the biliary system, ischemic strictures may develop anywhere along the bile duct. Ischemic bile duct strictures are typically longer than anastomotic biliary strictures, are present in multiple locations, and are usually found at the hepatic hilum; however, they may be present throughout the intrahepatic biliary system [142].

Periportal edema, residual ascites, or fluid around the peri-hepatic space is expected and usually resolves within a few weeks. Normal postoperative US findings consist of periportal edema, reperfusion edema, and fluid stasis [129]. Periportal edema seen on ultrasound can be mistaken for biliary dilatation and was initially thought to correlate with rejection; this has since been disproved [129]. The incidence of acute graft rejection increases with time. Eighteen percent will experience acute rejection within the first 6 months, and this will increase to 33% by 24 months posttransplant [146].

Scoring Systems for Transplantation

The survival outcomes following liver transplant (SOFT) score is based on 4 donors, 13 recipient, and 1 operative factor [34]. It was designed in an attempt to improve organ allocation by avoiding transplantation of organs into patients when predicted

survival is below accepted levels. The SOFT score is composed of two components. There is the pre-allocation score to predict survival outcomes following LT (P-SOFT) and a SOFT score that is used to predict survival posttransplantation [34]. The SOFT score has additional variables with allotted points that can be added or subtracted from the P-SOFT score. The SOFT score can be used by the physician as an adjunct in deciding whether to accept a liver organ by estimating the 3-month postoperative mortality rate compared to a MELD estimated 3-month wait-list mortality rate. The SOFT score is the most accurate predictor of 3-month recipient survival and is also accurate for predicting 1-, 3-, and 5-year post-LT survival [34]. It was determined by the authors that the SOFT score was most accurate based on area under the curve analysis. Furthermore, the SOFT score can be used to improve donor-recipient matching [34].

The balance of risk (BAR) score was developed with a similar goal as the other prognostic scoring systems, and that was to assess post-LT recipient survival. Dutkowski et al. [147] wanted to develop a score based on donor, graft, and recipient factors that were readily available pretransplant and that would have a good correlation to 3-month posttransplant survivorship. Dutkowski et al. used the UNOS database and showed that receiver operator characteristic curves were 0.5, 0.6, 0.6, 0.7, and 0.7 for DRI, MELD, D-MELD, SOFT, and BAR for predicting 3-month patient survival [147]. The BAR score discriminated between survival and mortality with a score of 18. A cited advantage of the BAR score is that its included variables are collected in a standard method internationally and that with less variables compared to other scoring systems, it lends itself to quick and readily accessible calculations [147].

The UCLA group wanted to identify predictors of futility and long-term survival in adult recipients undergoing primary cadaveric orthotropic LT for patients with ESLD and MELD scores >40 [20]. They created a posttransplant futility risk score based entirely on independently verified recipient factors that predicted futility. The variables were MELD score, pretransplant septic shock, cardiac risk, and age-adjusted Charlson comorbidity index [20]. Various calibrated coefficients were added to the included recipient variables. A review of currently available scoring systems with associated variables and pertinent points regarding each scoring system is listed in Table 14.3.

Donor-Recipient Matching for a Sick Patient

Briceno et al. [151] summarize the historical and current realities of donor-recipient matching based on different organ allocation systems, from patient-based, donor-based, or combined donor-recipient-based policies. The higher the MELD score, the lower the mortality risk for deceased donor transplant recipients compared to wait-list candidates, as mortality was more likely to occur while awaiting LT, rather than from risk of mortality at 1 year posttransplantation [11]. Alternatively, deceased donor transplant recipients with MELD scores <15 had a higher risk of

Table 14.3 Posttransplant morbidity scoring systems

Scoring system	Incorporated variables	Pertinent points
Donor Risk Index (DRI) [148]	Donor characteristics Age Height Race Cause of death (CVA) Cardiac death Partial and split grafts Location Cold ischemia time	Donor age > 60 strongest risk factor for graft failure Split/partial thickness associated with >50% risk of graft failure compared to neurologic death donors Recipient factors are not included Poor predictive value for patient survival posttransplantation ECD are compared to an optimal reference donor with a DRI of 1.
Survival outcomes following liver transplant (SOFT) score [34]	Age > 60 BMI > 35 One previous transplant Two previous transplants Previous abdominal surgery Albumin <2.0 g/dL Dialysis prior to transplantation ICU pretransplant Admitted to hospital pretransplant MELD score > 30 Life support pretransplant Encephalopathy Portal vein thrombosis Ascites pretransplant P-SOFT (based on above variables) Portal bleed 48 h pretransplant Donor age 10–20 years Donor age > 60 Donor cause of death from CVA Donor creatinine >1.5 mg/dL National allocation Cold ischemia time 0–6 hours	Warm ischemia excluded Overlapping variables Provides a relative risk for 3-month survival <5 points, low risk 6–15 points, low-moderate risk 16–35 points, high-moderate risk 36–40 points, high risk
BAR score [147]	Recipient age Recipient MELD score Re-transplantation Recipient pretransplantation life support Cold ischemia time Donor age	Total score out of 27 Score > 18 considered futile, although this represents only 3% of liver transplants Recipient MELD score strongest predictor of 3-month mortality Less variables than SOFT Pretransplant variables removed from score: Dialysis Encephalopathy Ascites Portal bleeding

(continued)

Table 14.3 (continued)

D-MELD [149]	Recipient MELD score multiplied by donor age	Easily calculated Quick reference for high risk donor/recipient matches Score ranges between 40 and 3400 Score > 1600 found to have worse survival compared to <1600 Donor must be <54 years old for every MELD >30 recipient Patient and graft survival at 4 years
Delta-MELD [150]	Total change in MELD points from time of placement on waiting list to transplantation	Does not independently predict mortality after transplantation
UCLA-FRS [20]	Recipient MELD score Pre-OLT septic chock Cardiac risk Age-adjusted Charlson comorbidity index ≥6 (CCI)	Entirely based on recipient risk factors Recipient factors predicted futility rather than demographic, donor, or operative factors Cardiac and age-adjusted comorbidities associated with highest risk for futile outcome

post-LT mortality at 1 year compared to candidates (with MELD <15) awaiting transplantation. In this analysis, the quality of donor organ was not accounted for. When high MELD score patients receive high-risk or optimal organ donors, there is a survival benefit regardless of the DRI [10]; however, in patients with low MELD scores that received high DRI organs, there is an overall decrease in post-transplant survival [26].

As transplant wait-lists continue to increase along with patients accumulating higher MELD scores and limited organ supply, the use of extended donor criteria has increased. The importance of optimal donor-recipient matching has heightened. Recent data has revealed that 20-year survival for post-LT recipients is significantly influenced by the DRI (≤1.4 and >1.4) and donor age independently (<30 vs ≥30) [152]. It has been suggested that the ideal liver transplant recipient is a young woman with acute liver failure or cholestatic liver disease/autoimmune hepatitis, who has as BMI < 25, normal kidney function, and no dyslipidemia, while the optimal donor organ is <30 years old with an ET-DRI of <1.2 [152]. This optimal match is a rarity in today's clinical practice, and identifying donors that provide the best match for the sickest first or high MELD priority allocation system is paramount. An ideal match between donor and recipient would ensure that recipient survival and graft survival were optimized, where the probability of death on wait-lists, posttransplant survival, overall cost-effectiveness, and global survival benefit are all accounted for [151]. The question arises, should or shouldn't a liver be accepted for a particular patient while being cognizant of not just the immediate survival benefit of the particular recipient but also of the factors previously mentioned?

Table 14.4 Recipient-donor matching [34]

MELD score recipient	Proposed donor quality allocation via SOFT score
17–19	Low risk
30–39	Low, low-moderate, or high-moderate risk
>40	Low, low-moderate, high-moderate, high risk
Recommendations as per Rana et al. do not apply to patients with hepatic malignancy	

Previously, it was believed that high DRI organs should not be transplanted into patients with high MELD scores [27]. Further study revealed that in patients with high MELD scores, the donor organ quality measured by the DRI did not affect graft or patient outcomes, while in low to intermediate MELD score patients, the DRI did impacts graft/recipient survival [28]. Rana et al. [34] provide recommendations for donor-recipient matching according to recipient MELD score and donor quality as per SOFT score, displayed in Table 14.4.

Rauchfuss et al. [153] reviewed 45 patients who underwent LT with a MELD score of ≥36; their goal was to assess if DRI was associated with 1-year recipient survival post-LT. It was identified that the median duration of waiting time (2 days versus 4 days) was the only significant factor on univariate analysis that differentiated survivors from non-survivors. The overall survival in the group's study was 69.8% at 1 year. The DRI (median survivors 1.72 vs median non-survivors 1.89), mechanical ventilation status, use of vasopressors, renal replacement therapy prior to LT, or presence of the lethal triad (coagulopathy, hypothermia, acidosis) did not significantly differentiate between survivors and non-survivors [153]. The overall DRI was quite high; however, there was no significant difference between survivors and non-survivors for extended donor criteria. The definition of extended donor criteria included donor age > 65, donor BMI >30, ICU stay >7 days, histologic proven graft steatosis >40%, donor sodium >165 mmol/l, or more than three times increased AST, ALT or bilirubin, donor malignancy history, positive hepatitis serology, drug abuse, sepsis, or meningitis [153].

Liver Transplantation in Patients with Portal Vein Thrombosis

Portal vein thrombosis (PVT) is usually diagnosed incidentally in patients with underlying cirrhosis and may affect those with compensated or decompensated cirrhosis. PVT most commonly occurs in patients with cirrhosis with a prevalence of 1–16% [154]. PVT can also occur in patients with hepatocellular carcinoma (HCC) and other hepatobiliary malignancies. Different series report a 2.1–26% incidence of PVT in ESLD patients awaiting LT [155]. More recent data has reported that HCC and cirrhosis carry a 23–28% risk of PVT [156].

Cirrhosis is the clinical manifestation of derangements in the hepatic architecture secondary to fibrosis leading to an increased portal resistance, decreased velocity of blood flow, and subsequent development of collateral venous circulation. Reduced

flow and increased pressure within vessels create stasis and potential for clot formation. PVT in an underlying cirrhotic patient may contribute to further increase in venous pressures, leading to worsening portal hypertension and decreased synthetic liver function [157]. Cirrhotic patients with PVT have an increased association with factor 5 Leiden and prothrombin gene mutations. Mutation in the 20,210 gene has been shown to be an independent risk factor for the development of PVT [158].

Regardless of the underlying etiology of PVT, patients may present with an acute, subacute, or chronic PVT which may result in a partial or complete portal vein occlusion. PVT is further subdivided into benign versus malignant and intrahepatic versus extrahepatic thrombosis [159]. Extrahepatic PVT is exceedingly more common than intrahepatic PVT. For brevity, when discussing PVT, it will be inferred that it is an extrahepatic PVT unless stated otherwise. It is important to distinguish between acute versus chronic PVT and partial versus occlusive thrombus as management strategies, morbidity, and mortality vary accordingly.

Chronic PVT usually presents in an asymptomatic fashion and is incidentally found on imaging performed for other indications or during screening of cirrhotic patients awaiting LT. Chronic PVT in the setting of cirrhosis may eventually lead to accelerated sequala of portal hypertension manifested by ascites, variceal bleeding, ectopic varices, anemia, thrombocytopenia, or splenomegaly [160]. In the setting of a symptomatic PVT, gastrointestinal hemorrhage may be the first sign of underlying portal hypertension. Historically, there was an increased risk of death related to bleeding complications secondary to portal hypertension; however, improvements in prophylactic management of esophageal varices have reduced patient morbidity and mortality [161]. Malignant venous thrombus is diagnosed by an enhancement of the thrombus with direct contiguous extension of the tumor into the portal vein with disruption of the vessel continuity on CT, arterial pulsatile flow on doppler US, or by an increased uptake on PET scan [159]. Patients with malignant PVT are not candidates for LT, and therefore malignant PVT must be distinguished from nonmalignant PVT during the transplant evaluation.

Cirrhosis associated PVT treated with therapeutic LMWH has been shown to be safe and successful with complete or partial recanalization in 60% of patients [162]. Patients need to be continued on LMWH despite image documented recanalization. Patients who demonstrate complete recanalization and stop anticoagulation early have up to 38% re-thrombosis risk [163]. In cirrhotic patients, lifelong anticoagulation maybe required to maintain a patent portal vein post recanalization. A small randomized control trial of 70 outpatients with advanced cirrhosis randomized patients to receive 12 months of enoxaparin (dosed at 4000 IU/day) versus no treatment. Patients who received enoxaparin had a significantly lower rate of PVT development (8.8% versus 27.7%) at a 12-month follow-up [164]. An interesting finding of the study was that patients who received enoxaparin had a delayed occurrence of decompensated cirrhosis and improved survival compared to controls.

If a patient with PVT has a contraindication for systemic anticoagulation, a TIPS procedure, if technically feasible, should be considered. The advantages of a TIPS procedure over anticoagulation are a decreased risk of bleeding, possibility of utilizing catheter-based interventions, and risk reduction of recurrent PVT. TIPS has

shown to have a 98% technical success rate for PVT treatment pretransplant, with 92% patency rates until transplant or follow-up, without requiring post TIPS anticoagulation [165]. TIPS can also reduce complications of portal hypertension via portal bypass resulting in improved flow. However, there is high risk of hepatic encephalopathy (27% and 32% at 1 and 3 years) [165]. In a large series of nonmalignant PVT, TIPS resulted in complete recanalization in 57% of patients, 30% reduction in thrombus load, and 13% showed no improvement with an overall technical success rate of 100% [166]. It is important to note that the type of stent (bare versus covered) can impact TIPS dysfunction and the surgeon should be aware of which type of stents are available at their institution. Bare stents have been associated with increased TIPS dysfunction at 1 and 2 years (38% and 85%) compared to covered stents (21% and 29%) [166]. Thornberg et al. have also reported that portal venous recanalization TIPS is technically simpler and easier to perform via transsplenic access compared to transhepatic access [165]. Ultimately, treating PVT is important in reducing the risk of developing an occlusive PVT and also reduces the associated technical risks of PVT and LT.

The development of PVT in patients with ESLD awaiting LT was historically considered an absolute contraindication for proceeding with LT [167]. In the past, LT with surgical management of PVT was associated with increased blood loss, coagulopathy, and mortality [168]. It has been reported that cirrhotic patients undergoing transplant evaluation with occlusive PVT have a significantly lower survival compared to those without occlusive PVT ($p = 0.007$); and occlusive PVT is in itself an independent risk factor for perioperative death [154]. Identifying which patients with PVT benefit most from LT is paramount in order to minimize postoperative complications and optimize postoperative recovery.

Previously, the identification of PVT in patients awaiting LT was considered a relative indication for adding points to the MELD score in order to transplant patients with PVT earlier. A review of 46,530 patients from the Scientific Registry of Transplant Recipients (SRTR) database showed that the presence or absence of PVT in transplant candidates has no difference on survival while awaiting LT [169]. In the presence of PVT, transplant recipients with MELD scores <12 had significantly inferior postoperative survival with a more than fourfold increase in mortality compared to wait-list mortality. The benefit of LT was seen in MELD scores >13 regardless of presence or absence of PVT [169]. Doenecke et al. [170] retrospectively reviewed 170 liver transplant patients and identified that a MELD score < 15, and presence of PVT was associated with significantly higher perioperative mortality (33%) compared to patients with a patent portal vein (5%). Furthermore, 1-year survival was significantly lower in patients with MELD <15 and PVT compared to patients with a patent portal vein (57% versus 89%). In patients with MELD scores >15, there was no statistically significant difference in mortality between a patent portal vein or presence of PVT. An important observation from these studies is that patients with PVT and MELD scores <13 should not be transplanted. A watchful approach is most beneficial along with medical management of the PVT until MELD score increases to at least >13, which would then provide a survival benefit. If PVT patients with MELD scores <13 are diagnosed with porto-pulmonary hypertension

or hepatopulmonary syndrome, they may receive additional MELD score points and be considered for earlier LT.

Improvements in patient selection for LT, operative techniques, and perioperative management have resulted in PVT becoming a relative contraindication in proceeding with LT [171]. Molmenti et al. reported on 85 cases of PVT that were managed with thromboendovenectomy at the time of LT in comparison with a control group without PVT, and there were no significant differences in 1-, 3- and 6-year patient and graft survival rates between the groups [171]. Gimeno et al. [172] demonstrated that the anhepatic phase and transplant duration were only slightly longer in patients with PVT compared to patients without PVT ($p = 0.28$, =0.23). Llado et al. [173] showed that PVT at time of LT is not associated with an increase in overall morbidity and mortality. However, PVT is associated with longer operative times, hospital length of stay, and increased RBC transfusions [173].

Currently, the preferred grading system for PVT was established by Yerdel et al. [174] and has four grades, which are treated differently at the time of surgery.

1. PV minimal or partially thrombosed <50% of the vessel
2. >50% PV occlusion
3. Complete thrombosis of the PV and proximal SMV
4. Complete thrombosis of the PV as well as proximal and distal SMV

Commonly employed surgical techniques that are used for PVT Grades 1–4 are thrombectomy, thromboendvenectomy with venous reconstitution, and interposition of vein grafts. In rare circumstances, with extensive PVT, portocaval hemitransposition has been described. Thrombectomy and its technical variants, interposition grafts, and mesoportal jump grafts are techniques that restore physiologic portal flow. Nonphysiologic technical options are portocaval hemitransposition, renoportal anastomosis, and portal vein arterialization.

Grade 1 and Grade 2 PVT are more common than Grade 3 and 4 PVTs. When technically feasible, the procedure of choice for the management of PVT is considered to be thromboendovenectomy. Grade 1 and 2 PVT can be managed with end-to-end portal vein anastomosis with or without thrombectomy. Grade 1 and 2 PVT repaired with simple thrombectomy, eversion thrombectomy, or improved eversion thrombectomy have been associated with 0% in hospital mortality rate [175]. Furthermore, endovenetomy has been shown to successfully restore portal venous flow in 90% of cases of PVT at the time of LT [154]. It has also been shown that partial PVT patients have a similar incidence of postoperative complications to patients without postoperative PVT [176].

Grade 2 and 3 cases may be amendable to thrombectomy and end-to-end anastomosis; however, an anastomosis at the SMV confluence may be required instead of the proximal portal vein. When the distal SMV is not available for anastomosis, dilated branches of the recipient portal venous system (coronary vein or large collateral vein) may be utilized. Despite intraoperative technical advances in the management of PVT and reported equal survival between PVT and no PVT transplant patients, increased PVT grade is still reportedly associated with worse in hospital mortality, secondarily to increased technical difficultly of successful thrombectomy

techniques [175]. Specifically, Grade 2 or higher PVT has been associated with increased risk of perioperative complications, mortality, and decreased long-term survival [160].

Grade 4 PVT is the most technically challenging for the transplant surgeon. Grade 4 PVT can be operatively managed with anastomosis to the coronary vein or a dilated collateral vein, and eversion thrombectomy procedures are documented to have good outcomes [173, 175]. If the previously mentioned technical options are not feasible, portocaval hemitransposition is an alternative technique that is generally accepted as a last resort. Some authors state that the portocaval hemitransposition technique should be the standard surgical approach for Grade 4 PVT (ref).

Postoperative PVT rate in preoperative complete and partial PVT have reported to be 22.7% and 3.3% with a de novo postoperative PVT rate of 1.3% in patients with a preoperative patent portal vein [176]. Jia et al. [176] in 22 cases of complete PVT and 33 cases of partial PVT most commonly performed a PV reconstruction was an end-to-end PV anastomosis (47 cases), followed by 3 portocaval hemitranspositions, 1 PV to mesenteric vein anastomosis, and 1 PV to renal vein anastomosis, highlighting the use of portocaval hemitransposition as a salvage option in either complete or partial PVT. Additional options are available to the previously mentioned surgical alternatives when portal vein thrombectomy fails to re-establish adequate portal vein flow for extensive PVT. Quintini et al. [177] describe renoportal bypass using a venous conduit from the recipient renal vein anastomosed to donor portal vein. The left renal vein is dissected with a caudal mobilization of the soft tissue anterior to the inferior vena cava, until the left renal vein is identified at the insertion of the IVC. A caveat of the renoportal bypass procedure is that its success is also dependent on the presence of a patent splenorenal shunt.

Regardless of PVT grade, re-establishing physiological portal venous flow has a significant impact on reducing patient morbidity. Hibi et al. [178] retrospectively reviewed a large cohort examining 174 patients with PVT (48% occlusive, 52% partial thromboses) at the time of transplantation. They identified that 149 PVT patients had physiological portal inflow re-established and there was no significant difference in survival between patients with re-established physiological portal inflow compared to patients without PVT. Thrombectomy was performed in 123 cases, while 16 patients received interpositional vein grafts, and 10 patients underwent mesoportal jump grafts. The subsequent challenge is improving outcomes in PVT patients in whom physiological portal inflow cannot be re-established. The same study identified that when physiological portal inflow was not re-established, there was a significant increase in the incidence of re-thrombosis, gastrointestinal bleeding, and worse 10-year overall survival [178]. In the nonphysiologic PVT group, 18 underwent cavoportal hemitranspositions, 6 renoportal anastomoses, and 1 portal arterialization procedures.

In adults, post-orthotopic LT portal venous complications (stenosis or thrombus) occur at a rate of approximately 3%. In the pediatric population, portal vein complications are higher at approximately 8%. The increased complication rate in this population is secondary to the increased technical challenge of a shorter portal vein, the use of living-related donors, and split LT [179]. Generally, portal vein stenosis

occurs at the anastomotic site secondarily to donor/recipient portal vein diameter mismatch [162, 179]. Portal vein stenosis may occur in the immediate postoperative period or can be detected during long-term follow-up. Patients may be asymptomatic or present with signs of portal hypertension, similar to pretransplant PVT presentation.

Management of posttransplant portal vein stenosis differs from the management of posttransplant PVT. Portal vein stenosis management is dependent on whether the stenosis is deemed to be clinically significant or not. In asymptomatic patients with normal hepatic function, periodic observation with ultrasound has been described. However, in patients where portal venous stenosis is potentially contributing to worsening, portal hypertension intervention is required [179]. Interventional percutaneous portal vein dilatation with or without stent placement can be performed. Funaki et al. [180] and Shibata et al. [181] describe treatment of portal venous stenosis with balloon dilatation and stent insertion if pre- and post-portal vein dilatation pressure gradient is >5 mmHg or >3 mm Hg. Funaki et al. have had high success with interventional venoplasty and have eliminated the need for surgical revision, portacaval shunting or re-transplantation [180]. Management of PVT post-LT may differ between various institutions. Experience with percutaneous vein thrombolysis is limited, and few case reports have been published. For significant postoperative PVT that is not amendable to anticoagulation, portal vein angioplasty (with or without stent placement) remains as a first-line option, followed by TIPS, or re-transplantation, as a last resort.

Impact of Hepatic Flows in Liver Transplant

The liver weighs approximately 1.2–1.6 kg and is 2.5% of a human's total body weight, yet receives 25% of the cardiac output [182, 183]. Total hepatic flow ranges between 800 and 1200 mL/min [184]. The hepatic inflow is supplied both by the hepatic artery and portal vein. Twenty-five percent of the total hepatic flow comes from the hepatic artery, which provides 30–50% of hepatic oxygen requirements [185]. Seventy-five percent of the total hepatic flow is provided by the portal vein, which provides 50–70% of hepatic nutritional requirements [186]. Interplay between the portal and hepatic inflow has significant impact on hepatic regeneration [187]. This is especially true after orthotopic LT and even more so for LDLT. Forty percent of the hepatic blood is within large vessels, while 60% is held within the hepatic sinusoids. Hepatic sinusoids are very compliant and can accommodate a large volume of blood so that portal venous flow can be increased or decreased without disruption to the portal venous pressure in healthy livers [185]. Significant differences can be seen in portal venous blood flow between non-cirrhotic and cirrhotic patients especially if extensive portal hypertension or PVT is present. Cirrhotic-induced vascular changes impact intraoperative decision-making on whether to perform standard donor to recipient vascular anastomosis versus a modified restoration of physiologic or nonphysiologic inflow. The goal is to provide

optimal blood flow and tissue perfusion that are required for the metabolic activity of the liver [185].

The hepatic arterial system is a high-pressure, high-resistance system with an average flow of 400 mL/min that is controlled by an intrinsic autoregulatory system [188]. Norepinephrine and angiotensin can cause hepatic artery vasoconstriction without affecting the portal vein flow. Their effects can be reversed with high doses of intra-arterial adenosine [189], a well-known vasodilator. The main portal vein provides 50–70% of the liver's oxygen requirements with a flow of 700–850 mL/min and portal pressure ranging between 5 and 10 mm Hg in healthy subjects. The high-resistance arterial system ends at hepatic sinusoids and transitions to the portal venous system via sinusoidal capillaries [190]. Under normal conditions, the portal venous system is a low-pressure, low-resistance system. It is affected by venous drainage from visceral organs, regulated by splanchnic arteriole constriction and intrahepatic vascular resistance. The hepatic artery and portal vein flows in healthy individuals are typically proportional; however, in patients with cirrhosis, it is observed that the portal vein and hepatic artery flows are inversely related to each other [191].

Adenosine is secreted at a constant rate and is equal between the hepatic artery and portal vein [184]. When portal vein inflow increases, it causes the adenosine to be washed away with a resultant decrease in hepatic artery flow mediated by hepatic artery vasoconstriction [189]. When portal perfusion decreases via impeded or diverted portal inflow, the liver triggers adenosine to locally accumulate. Adenosine induces hepatic artery vasodilatation and increases hepatic artery blood flow in order to compensate for the reduced portal venous flow. In addition to adenosine, local nitric oxide, carbon monoxide, and a gaseous mediator known as H2S have been found to change in concentration depending on the portal venous pressure [189]. The ability of the hepatic artery to vasodilate in response to changes in portal pressure is an intrinsic autoregulatory mechanism of the liver that is known as the hepatic artery buffer response (HABR) [184]. Initial clamping of the splenic artery has shown to cause an increase in hepatic artery velocity followed by a quick and maintained decreased portal venous velocity [192]. Subsequent clamping of the splenic vein induces a significantly quick and maintained decrease in the portal venous flow, with an eventual increase in hepatic arterial flow [192]. The increase in hepatic arterial blood flow is able to compensate for up to a 25–60% reduction in portal flow [189]. The goal of the HABR is to maintain adequate oxygen supply to tissues and minimize the impact of portal venous flow changes on hepatic clearance [184].

Prior to the HABR theory, it was believed that the splenic artery was diverting blood away from the hepatic artery, and this was termed the splenic steal syndrome [193]. Splenic steal syndrome cannot be diagnosed in the presence of HAT, HAS, arterial kinking, or other hepatic arterial abnormality that may impede its flow [193]. The HABR has been shown to remain intact with human LT [190]. In partial donor liver grafts, there is a blunted HABR response where the hepatic artery inflow remains depressed compared to what would be expected in a whole-sized graft [190].

Doppler ultrasound is a very useful imaging modality to identify physiologic and pathophysiologic hepatic flow. Normal portal vein waveform normally shows gentle undulations with hepatopetal flow [194]. The normal waveform within the hepatic veins is triphasic with two hepatofugal phases related to the atrial and ventricular diastole. Cirrhotic changes in the liver can cause a large reduction in the visualization of hepatic veins that alters the normal waveform. The normal triphasic wave form can be replaced with a monophasic pattern that indicates high portal pressures [194]. Hepatic artery flows can be indirectly measured by the pulsatility index or estimations of the resistive index on doppler ultrasound which approximates the hepatic artery flow [191]. Portal inflow becomes partially reversed, and this is known at hepatofugal flow. Hepatofugal flow of the main portal vein is a known marker of portal hypertension, and it has been identified that a threshold velocity of 11 cm/s in the right portal vein and left portal vein velocity of <8 cm/s are associated with the development of main portal vein hepatofugal flow [195].

In cirrhosis, underlying fibrosis-induced architectural changes result in alterations of hepatic microvasculature, hepatic sinusoids, reduced blood supply, and increased total hepatic vascular resistance. Due to the increased hepatic vascular resistance, the intrahepatic endothelial cells produce less nitric oxide resulting in portal hypertension (mean intraluminal portal pressure > 12 mm Hg). In response, the extrahepatic mesenteric vascular beds cause progressive vasodilation of splanchnic vasculature secondary to increased release of nitric oxide. At baseline, the HABR in cirrhotic patients is continuously active; however, hepatic artery flow changes are blunted in response to sudden changes in portal venous flow [191, 196]. In a cirrhotic patient prior to LT, portal flow is approximately 1 L/min [188, 197]. The porto-splanchnic system attempts to redistribute the increased portal inflow; however, because of cirrhosis-induced fibrosis and increased intrahepatic vascular resistance, the liver is unable to accommodate for the increased incoming portal inflow. Preexisting and/or newly formed venous collaterals receive redistribution of hepatofugal portal flow. This leads to varices and further subsequent vascular remodeling with an overall reduction in portal venous blood flow, increased hepatic venous resistance, systemic hyperdynamic circulation, and increased cardiac output [198]. To compensate for increased intrahepatic resistance, the HABR increases hepatic arterial flow by a reduction in hepatic arterial resistance.

The hepatic artery can induce a compensatory vasoconstriction reducing arterial blood flow in response to portal hyperperfusion and therefore leads to a high resistivity index (RI). Unlike the portal vein patterns, the hepatic artery and the superior mesenteric artery RI do not correlate with the stage of cirrhosis [199]. Hyperdynamic cardiovascular changes can lead to significant obstacles at the time of LT. Sudden reduction in vascular preload and impaired cardiac contractility can impair cardiac output, while in the postoperative period, hypovolemia and hypervolemia can negatively impact cardiac contractility [200]. Hyperdynamic pretransplant cirrhotic pathophysiology persists posttransplantation for months to years, regardless of the underlying etiology of cirrhosis [200]. In patients with underlying viral cirrhosis, there is a rapid improvement with reduced cardiac output and increased systemic vascular resistance that is not present in alcoholic cirrhosis [200].

Obtaining optimal intraoperative hepatic artery and portal vein blood flow is necessary for a successful liver transplant in the short- and long term. However, optimal flows for the hepatic artery and portal vein are still unknown without strong quality evidence. Prior to LT, in the cirrhotic liver, portal flow is approximately 1–2 L/min [188, 197]. Mean hepatic artery flow has a range from 268 to 584 ml/min, with a resultant cardiac output of 10 L/ min. Spitzer et al. found that for full donor implanted grafts, a minimum hepatic artery flow of 250 ml/min is required for improved patient survival; however, flows of >400 ml/min are optimal [201].

Intraoperatively, different presentations of altered hepatic flow may present, namely, portal vein enlargement and splenomegaly, without significant collateral formation or reduced portal vein size with massive collateralization [185]. In the setting of a large portal vein without significant collateralization, improving portal venous and hepatic flow can be achieved with either splenectomy or splenic artery ligation [185]. Alternatively, if the portal vein is smaller than expected with large collateralization, spontaneous splenorenal shunting is likely to have occurred. Some authors report that ligation of major collaterals when portal venous flow is <1 L/min may help with preventing portal hypoperfusion [185]. Ligating large collateral coronary veins greater than 1 cm is thought to increase PV flow by 55–140%, depending on the size of the varix [202]. Common veins to ligate are the coronary vein, inferior mesenteric vein, gastroepiploic vein, splenorenal shunt, and retroperitoneal varices. Large splenorenal shunts can be embolized via percutaneous methods or via intraoperative ligation of the left renal vein. The main causes of decreased portal flow are unrecognized portal mesenteric/splenic vein thrombosis, inadequate portal vein thromboendvenectomy, or large portosystemic collaterals [188]. Once a new liver graft has been transplanted, a lower portal resistance within the new graft allows for improved portal flow, which has been measured to increase to 1.8–2.8 L/min after implantation. Minimum portal vein flow should be >1 L as portal vein flow >1 L mL/min is associated with improved graft survival at 30, 60, and 365 days post-LT in the deceased donor transplantation [188, 197, 201].

Decreased intraoperative hepatic artery flows are thought to be primarily due to technical issues with the anastomosis. However, arterial steal syndrome, celiac artery stenosis, or hypoperfusion secondary to under-resuscitation can contribute to decreased hepatic artery flows. Additionally, mechanical ventilation, hypercarbia, positive end expiratory pressure, hypotension, hemorrhage, and hypoxemia are other intraoperative factors that may reduce hepatic artery flow [203]. In patients who develop hepatic artery strictures, there are significantly lower intraoperative arterial and portal vein flows compared to patients who do not develop hepatic arterial strictures [204]. Low hepatic artery RI after deceased donor LT can be attributed to surgical edema, hepatic artery stenosis, severe aorto-celiac atherosclerotic disease, arteriovenous or arterial biliary fistula formation, hepatic vein, or portal vein thrombosis [199]. The hepatic artery is the sole blood supply to the bile duct. This is supported by evidence that lower measured hepatic flows have been associated with higher rates of biliary complications after LT [205]. Therefore, ensuring proper hepatic artery flow is imperative to obtaining optimal biliary anastomotic outcomes.

Dealing with Portosystemic Shunts to Prevent Portal Vein Steal

TIPS is primarily indicated in patients with refractory ascites and variceal hemorrhage, with less frequent indications being PVT and HVOO and can be utilized as a bridge to LT [206]. In 2015, a Consensus Conference on TIPS was held to provide recommendations for proper evaluation, technical considerations, patient selection, follow-up, contraindications, and management of complications [207]. TIPS placement as a bridge to LT may result in technical difficulties during the transplant with the shunt extending into the portal vein, hepatic vein, or right atrium; however, TIPS has not shown to have any significant negative impact on graft or patient survival [208]. Even in the setting of cirrhosis complicated by nonmalignant PVT, TIPS is technically feasible and is not associated with increased procedure related complications, stent occlusion, or mortality [166]. TIPS can be used to maintain and improve patency of the portal venous system and reduce the re-occurrence of PVT. It has also been used to decrease the effect of mesosystemic collaterals and shunting of blood away from the liver [166, 209].

Patients with portal hypertension and advanced cirrhosis have increased resistance to portal inflow and develop portosystemic shunts; as a result, blood flow is shunted away from the portal vein and liver via the mesosystemic collaterals, otherwise known as hepatofugal flow [210]. Splenorenal shunts form between the splenic and renal veins and are an example of such spontaneous mesosystemic collateral development. Portal steal syndrome develops after LT when the mesosystemic collaterals persist and continually divert flow away from the newly implanted graft [211]. After full-sized cadaveric orthotopic LT, hepatofugal flow usually resolves, portal vein flow becomes hepatopedal and results in a decreased intrahepatic resistance [210]. However, hepatofugal flow may only slightly decrease or persist post-LT, especially in the setting of partial graft transplantation, and contribute to the development of portal steal syndrome [212]. Hyperdynamic spontaneous portosystemic shunts are present in up to 19% of portal hypertensive patients awaiting LT [210]. The higher the flow from the splenic vein into the renal vein the greater likelihood of significant blood flow diverted away from the liver [209]. When a portosystemic shunt persists post-LT, it may reduce portal inflow/portal venous pressure and impact early hepatic regeneration and harm the new graft [212, 213]. This especially applies in small-for-size grafts after LDLT [211]. Risk factors for recipient portal steal phenomenon include portal hypertension with large varices and natural shunts, chronic liver failure, macrosteatosis, low liver donor mass, donation after cardiac death with prolonged warm ischemia time and receiving a LDLT [210].

It is imperative to detect portal flow steal as early as possible and to manage accordingly, to ensure survival of the newly transplanted liver graft. Large spontaneous splenorenal shunts (> 10 mm in diameter) have been shown to occur in 6.6% of adult LDLTs [211]. Splenorenal shunts <10 mm in diameter are thought to not require intervention as portal pressures post-LT normalizes, and the shunt will eventually collapse [209]. Lee et al. describe their technique of left renal vein

(LRV) ligation in 44 patients with large splenorenal shunt for portal steal syndrome during partial graft LDLT [211]. At the time of LT, intraoperative portal flow assessment of the ligated portal vein was performed when LRV was unclamped and subsequently clamped. If a large difference in portal vein flow was observed during LRV clamping, then ligation of the LRV was performed prior to hepatic arterial construction. The authors report that all 44 patients recovered well without re-transplantation at a median follow-up of 17 months, with 1 patient passing away secondarily to HCC [211].

In the presence of large spontaneous splenorenal shunts, Castillo et al. have used a portal vein flow threshold (after reperfusion) of ≤1200 ml/minute to perform LRV ligation, which successfully increased portal flow post-ligation without any consequence to renal function [214]. Tang et al. summarize eight case series of LRV ligation with Lee et al. having the largest series of LRV ligation to date [215]. A patent portal vein is required to proceed with LRV ligation which has been demonstrated to improve portal vein blood flow. This should not be performed in unresectable PVT, portal vein stenosis, or with large portal vein mismatch between donor and recipient [215]. Although LRV ligation has been shown to be safe and effective for dealing with portal vein steal syndrome, definitive consensus indications cannot be made based on size of splenorenal shunts or threshold portal vein flows. Larger multicenter prospective studies are required.

In 26 patients with hepatofugal flow detected on preoperative doppler US or weak flow identified at the time of transplant, direct ligation of large splenorenal shunts was performed intraoperatively with a 7.7% major complication rate and 96.2% survival rate [216]. Eleven of the 26 patients with splenorenal shunts had a preexisting PVT and underwent PV thrombectomy. In contrast to LRV ligation, PVT is not a contraindication for ligating the entire shunt. Splenectomy is an alternative option to ligation of the LRV at the time of LT; however, there is an increased risk of PVT, sepsis, and bleeding [215].

Use of Live Donors in Sick Patients and Impact of Portal Hypertension on Small-for-Size Syndrome

There is a universal shortage of available organs to meet demand of patients requiring transplantation. Currently, live donor liver transplantation (LDLT) comprises <5% of all liver transplants performed in the United States [217]. In an attempt to reduce LT wait times and increase the organ pool, LDLT was introduced as an alternative to cadaveric transplantation. LDLT was initially performed within the pediatric population; however, currently LDLT has been implemented for adult LT in high-volume centers. The left hepatic lobe has traditionally been used in the pediatric population for an appropriate donor to recipient size match, accounting for the smaller-sized pediatric population. In adults, left lobe implantation was initially utilized; however, initial results were poor due to small-for-size syndrome (SFSS) and early graft dysfunction. In the late 1990s, adult right hepatic lobe LDLT was

increasingly utilized in order to circumvent SFSS [218]. Recent studies have shown that left hepatic lobe donation is associated with favorable recipient and donor outcomes compared to right hepatic lobe LDLT [217]. Despite this, right LDLT remains the most commonly utilized lobe in adult LDLT due to the ability of the right lobe to provide consistently more reliable hepatic mass [219].

A major limitation for LDLT is the potential for donor death and postoperative donor complications. The risk of donor death from live liver donation (90 days within surgery) is reported to be 1.7 per 1000 donors (0.17%), which is in keeping with living kidney donor rates [220]. Minor donor complications are reported to occur in approximately 27% of donors, with the most common complications being biliary leaks (9%), bacterial infections (12%), and incisional hernias (6%) [221]. Several studies have shown that donor outcomes with left lobe LDLT is associated with lower complication rates, lower rates of serious complications, and identical 1-, 5-, 10-year recipient survival compared to right lobe LDLT [222–224]. Although donors are associated to have increased postoperative morbidity and mortality, in high-volume centers, donors are able to enjoy good postoperative health and return to preoperative baseline without serious complications [225].

Recipient LDLT complications arise from the donor graft having a reduced hepatic reserve and receiving portal flows that are higher than the donor graft would have received in its original state prior to LT; that would normally be reserved for a whole liver. The most pronounced hemodynamic changes are an increase in portal perfusion rate and cardiac output of the recipient secondary to the effects of cirrhosis [226]. Typically, a whole transplanted liver has a large vascular bed of hepatic sinusoids to accommodate for the increased portal flow and cardiac output [218]. The liver compensates for the increased portal vein flow and cardiac output by activating the HABR, which reduces hepatic artery inflow. The live partial donor graft must manage the hyperdynamic portal circulation secondary to high portal flow immediately after LT. With LDLT it is believed that within minutes of reperfusion, portal hyperperfusion can cause shear stress to hepatocytes, sinusoidal congestion, and hemorrhagic necrosis of peri-sinusoidal hepatocytes [227, 228].

In small-for-size syndrome (SFSS), a donor graft is significantly reduced in size and portal hyperperfusion in conjunction with a smaller graft's high portal resistance can cause further reduction of hepatic artery inflow via the HABR and resultant de-arteriolization [229]. Doppler studies have shown that hepatic artery vasoconstriction in response to portal hyperperfusion and an exaggerated HABR produce a high resistive index with poor arterial perfusion [199]. Additionally, excessive portal flow can lead to oxidative stress thereby activating the inflammatory cascade leading to further hepatocyte damage [230]. The major concern is for graft dysfunction and secondary biliary complications. The symptoms of SFSS manifest as a pattern of liver dysfunction with associated portal hypertension, diminished arterial inflow, delayed synthetic function, and prolonged cholestasis. In advanced cases of SFSS, patients can clinically decompensate with the development of sepsis, encephalopathy, and death [231]. SFSS is typically thought to occur when the donor graft to recipient weight ratio (GRWR) is <0.8% during the first postoperative week after excluding other causes of graft dysfunction [232].

However, studies have identified that GRWR of 0.6 in LDLT is safe [233, 234]. Others have shown that GRWR of 0.6% and 0.85% is safe in Child Pugh Class A recipients, while Child Pugh Class B and C recipients require GRWR >0.85% for appropriate outcomes [235]. The International Liver Transplantation Society Living Donor Liver Transplant Recipient Guidelines state that the safety limit for minimum GRWR can be less than 0.8% in the setting of improved center experience and patient selection; however, most centers consider GRWR of 0.8% as the lower limit [219].

Intraoperative doppler ultrasonography should be used post-hepatic arterial reconstruction to assess hepatic artery flow and portal vein flow [199]. Portal venous pressure has been considered the most important hemodynamic factor influencing the functional status of the liver and graft regeneration post-LT [199]. It has been demonstrated that portal venous pressure < 15 mm Hg results in improved 2-year survival compared to patients with portal venous pressures >15 mmHg [236]. Wu et al. have demonstrated that high portal venous flow was well-tolerated by right LDLT recipients postoperatively if initial portal pressure was <23 mm Hg and the postreperfusion portal venous pressure was <15 mm Hg [213]. Furthermore, when initial portal venous pressure is ≥23 mmHg, and after reperfusion ≥15 mmHg, patients developed significantly more ascites compared to patients with lower portal venous pressures [213]. Optimal portal venous flows and hepatic arterial inflow remain a topic of debate, dependent on right or left LDLT and the true impact of HABR [185, 188]. It has been shown that portal venous flows <180 ml/min/100 g of liver weight (LW) leads to lower survival [237] and experimental models have supported that optimal outcomes occur with portal venous flows <260 ml/min/100 g LW [238]. It is believed that in order to avoid SFSS, portal venous flows of <260 mL min per 100 g LW are recommended [239] and graft inflow modulation techniques should be employed if the portal venous flow is >250 ml/min/100 g LW [240].

Several techniques have been described to decrease or reduce the impact of SFSS via modulation of graft inflow [241] when portal venous pressures exceed 15 mmHg. Splenic artery ligation [242] is usually the first step in portal flow modulation; however, splenectomy [243], portacaval, mesocaval, and splenorenal shunts are alternative options. Splenic artery ligation reduces portal vein flow by 30% [240] by reducing resistance of the distal hepatic artery and subsequently reducing flow in the splenic circulation. The net effect of splenic artery ligation/embolization results in promotion of liver regeneration and overcoming the effects of portal hypertension and portal hyperperfusion [244]. If elevated portal pressures are identified postoperatively, splenic artery embolization can be performed via interventional radiological methods. Splenectomy is potentially life-threatening, and if splenic artery ligation is technically feasible, it should be a primary management option. Portocaval shunts are believed to be beneficial when lower portal venous flows of 190/mL/min/100 g LW are present compared to higher flows of 401 mL/min/100 g [245].

A group from Taiwan proposed a flowchart for when to perform graft inflow modulation according to the portal venous pressure and portal venous flows which is briefly described here; however, it is yet to be validated [185]. The group

performed splenectomy in the setting of PVF ≥ 250 mL/min/100 g LW, PVP ≥ 20 mmHg, and without outflow obstruction, or if PVF was ≤100 mL/min/100 g LW, PVP was 15–20 mmHg; hepatic arterial inflow (HAF) was <100 mL/min without anastomotic error. No graft inflow modifications were made if the PVF was ≥250 mL/min/100 g LW and the PVP was <15 mmHg or if PVF was ≥250 mL/min/100 g LW, PVP was 15–20 mmHg, and the HAF was >100 mL/min. International recommendations (class 1, level b) for preventing/treating graft injury and SFSS are to monitor the portal vein/hepatic artery hemodynamics and to use portal inflow modulation techniques [219].

In 2002, the New York State Committee on Quality Improvement recommended that patients awaiting LT with MELD scores >25 should not undergo LDLT [246]. However, LDLT has been demonstrated to have similar postoperative complication rates and survival outcomes compared to DDLT [146, 247]. An adult-to-adult LDLT cohort multicenter retrospective study reported a 13.2% graft failure rate in 385 ALDLT recipients in the first 90 days [248]. The group identified that older recipient age and length of cold ischemia were significant predictors of graft failure, while individual center experience greater than 20 ALDLT was associated with lower risk of graft failure. Also, recipient MELD score was not a significant predictor of graft failure, but this sub analysis was limited to a small percentage (4%) of patients with MELD scores >30. [248]. The same group reported a 90-day and 1-year recipient survival of 94% and 89%, respectively. This was a seminal paper, as this was the first multicenter study of donor and recipient LDLT outcomes. A follow-up study identified that adjusted long-term mortality risk between LDLT and DDT was similar (for recipient gender, age, diagnosis, dialysis, MELD, and donor age) [249].

With persistent limited access to organs and growing evidence identifying equivalent outcomes between LDLT and DDLT, focus should be directed to LDLT for patients with high MELD scores and sick patients awaiting LT. High MELD patients awaiting LT have a high wait-list mortality and, as discussed previously, demonstrate significant benefit from transplantation. If deceased donor organ is not available for sick/high MELD patients, consideration should be made to utilize LDLT. However, ethical issues arise regarding the benefit risk ratio for donors undergoing a significant life-transforming event for a potentially futile recipient transplant outcome. In 2006, at the Vancouver Forum on the Care of the Live Organ Donor LDLT was deemed appropriate for acutely ill and sick transplant candidates [250]. However, LDLT in patients with MELD scores >25 remains controversial. It has been shown that in patients with MELD scores >20 undergoing LDLT, preoperative renal dysfunction, severe hypoalbuminemia, and massive intraoperative RBC transfusion are independent risk factors for in-hospital mortality. In recipients with two or more risk factors, 3-month survival was 25% [251].

Recent 5-year recipient LDLT survival has been shown to be similar to DDLT among patients with MELD scores <20, and it has been postulated that LDLT is underutilized in patients with MELD scores above 20 [252]. Feng summarizes the findings of several authors from both Eastern and Western transplant centers that have demonstrated good survival in patients with elevated MELD scores undergoing LDLT [253]. Selzner et al. in a large series compared outcomes in patients with

MELD scores <25 and >25 in 271 consecutive adult-to-adult right lobe LDLT [246]. They demonstrated that there was no significant difference in the overall complication rate within 3 months of LT between MELD <25 and MELD >25 recipients (51% versus 45%, $p = 0.28$). Graft survival between MELD <25 and MELD >25 was not significantly different at 1 year (92% vs 83%), 3 years (86% versus 80%) and 5 years (78% versus 80%), and patient survival was similar between groups at 1 year (92% versus 83%), 3 years (86% versus 83%), and 5 years (82% versus 83%) [246]. Kaido et al. have also shown that overall recipient patient survival did differ between patients with MELD scores <25 and ≥25 who underwent LDLT [254]. Liu et al. found that LDLT for patients with acute on chronic HBV with mean MELD scores of 36 had similar patient survival compared to elective LDLT in patients with mean MELD scores of 17.8 with a median follow-up of 23 months (88% versus 84%) [255]. In 2013, Chok et al. displayed similar 1- and 5-year LDLT recipient survival for MELD ≥25 (95.9% and 93.2%) compared to MELD <25 (96.9% and 95.3%) [256].

For many of these studies, right hepatic lobe LDLT was utilized more often than left lobe LDLT, which highlights the general preference for right hepatic lobe donation, especially in the setting of sick and high MELD score patients. In experienced LDLT centers, transplantation of a high MELD recipient is technically feasible and is associated with good outcomes. With continued education, discussion, and supportive data, hopefully LDLT can aid in the challenge of tackling the sickest patients first and can help decrease the shortage of available organs.

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Chapter 15
Gender Disparities in Liver Transplantation

Trinidad Serrano and Marina Berenguer

One of the challenges of modern medicine is to focus on health disparities. In recent years, inequalities in the study of diseases between men and women have become apparent [1]. Traditionally, medical research was based on an androcentric model, and data obtained in studies conducted in men were systematically extrapolated to women. Only in the last few years, requirements have been made to obtain scientific data from both male and female individuals and to further extend this diversity in research in experimental animal or even cell cultures or alternative in vitro models. Overall, less than 40% of studies using experimental animals and only about a quarter of studies using cells in culture indicate the sex of the experimental material [2]. Although sex differences exist from biological and physiopathological perspectives, these have rarely been considered when proposing prognostic models or when applying and evaluating treatments. Awareness of the lack of knowledge about inequities in health care has generated great interest in recent years leading to recommendations regarding significant information that should be collected and spread to avoid maintaining gender disparities in medical care.

Gender inequities have been described in transplant medicine [3]. In this chapter, we will describe gender inequities in the setting of liver transplantation, including

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the type of liver diseases leading to the need of transplantation, the referral pattern to transplant centers, access to waiting lists, and transplantation itself as well as posttransplant outcome.

Gender Differences in Liver Diseases

At present, there is no national data collection system that provides an accurate estimate of the global epidemiology of liver diseases by sex. However, the differential prevalence of specific liver diseases by sex can be used as an indirect measurement. Autoimmune hepatitis, primary biliary cholangitis, and toxic hepatitis affect more frequently women than men. In contrast, viral hepatitis and hepatocellular carcinoma are more common in men. The main differences in liver diseases that typically result in an indication of liver transplantation are described below.

Alcohol-Related Liver Diseases (ALD)

Alcohol abuse represents a frequent cause of hepatic damage worldwide. An excessive consumption of alcohol may cause hepatic steatosis, alcoholic hepatitis, and cirrhosis. Although it varies from country to country, alcoholic cirrhosis represents approximately 40% of deaths due to cirrhosis. Several studies have demonstrated that alcohol-related liver damage develops faster in women than in men [4]. In case of heavy drinkers, the relative risk of developing ALD is 3.7 in men and 7.3 in women [5]. Under the same conditions and with equal doses of alcohol, women reach higher blood ethanol concentrations than men. In addition, the risk of progression from hepatitis to cirrhosis after abstaining from alcohol is greater in women [6]. Finally, women with ALD have significantly lower alcohol consumption than men with ALD despite a similar duration in years of alcohol consumption, which supports the concept of female propensity to ALD [8]. Ethnic differences may also contribute to gender disparities. A recent study explored ethnic differences in hospitalization and mortality of all liver diseases, ALD, and specific alcohol-related diseases (ARD), linking the Scottish NHS hospital admissions and mortality to the Scottish Census demonstrating substantial variations by ethnicity both in men and women; thus, the risk of ARD was almost twice as high in white Irish men and in women from any background compared to other groups [7].

The causes attributed to these gender differences include hormonal but also different corporal structures and enzymatic activities. At the gastric level, alcohol dehydrogenase (ADH) enzyme, linked to the first passage of alcoholic metabolism, is expressed less in women than in men. Therefore, in women a greater proportion of alcohol reaches the liver directly, potentially worsening liver damage [9]. Another cause of female vulnerability to the toxic effects of alcohol is the reduced content of corporal water leading to increased blood alcohol concentration when the ethanol is distributed in water [4].

Nonalcoholic Fatty Liver Disease (NAFLD)

NAFLD more often affects men than women [10], yet among older ages, this difference is no longer present. Premenopausal women seem to be protected from NAFLD development as well as from cardiovascular diseases (CVD) [11]. A multicenter study from northern Italy found that men with NAFLD were about 10 years younger than women with NAFLD [12], a finding compatible with the role of estrogens in preventing liver damage. Recent studies in the overnourished zebrafish model have shown that ovarian senescence facilitates the development of massive hepatic steatosis and fibrotic progression of liver disease [13]. A large Italian multicenter study on more than 5000 healthy hysterectomized women, randomly assigned to receive tamoxifen (an estrogen inhibitor) or placebo for 5 years, showed that tamoxifen was associated with a higher risk of development of NAFLD, especially in overweight or obese women [14]. Interestingly, a lower prevalence of NAFLD and metabolic syndrome has been reported in postmenopausal women receiving hormonal therapy suggesting that the latter probably protects from NAFLD [15].

In Asian population, age was shown to modulate the risk of incident NAFLD as a function of gender and reproductive status; age was independently predictive of NAFLD development only in females [16]. Furthermore, the longer the estrogen deficiency in postmenopausal status, the higher is the risk of fibrosis [17].

A recent multi-omic integrative approach tried to combine gene expression, functional genomics, and modeling of delineated gene networks, pathways, and specific tissue networks to analyze the sexual dimorphism of NAFLD. The results support the existence of specific pathogenic processes in both sexes. In the near future, identifying sex-specific mechanisms, to guide differential therapeutic options for NAFLD in men and women in a personalized manner, might become possible [18].

Autoimmune (AI) Liver Diseases

There are significant differences in the prevalence of AI liver diseases that may be related in part to the differences in the immune system of both sexes [19].

Primary biliary cholangitis (PBC) is one of the best examples of differences between sexes, with an incidence rate in women/male of 10:1 [20]. In addition, the disease develops earlier in women (≈51 years) than in men (≈62 years). The causes of these disparities are not well-understood, although genetic and epigenetic factors such as the inactivation of the X chromosome have been postulated [4]. The prevalence of concomitant AI diseases such as sicca syndrome, Raynaud's phenomenon, or scleroderma is lower in men than in women. No significant differences in the course of disease have been demonstrated, although hepatocellular carcinoma (HCC) development was recently shown to occur more frequently in men [21].

AI hepatitis is also characterized by predominantly affecting women. However, there are no differences in age and clinical presentation at onset or frequency of concomitant AI diseases. Regarding clinical outcome, men seem to have a better

long-term life than women [4]. Sex hormones may play a role. Indeed, the severity of AI hepatitis decreases during the second trimester of pregnancy, when estrogen secretion is greater and acute exacerbation is more likely to occur after delivery [22].

Hepatitis C Virus (HCV)

Although the availability of the new effective oral antiviral agents has resulted in a significant decrease in HCV-related liver disease, differences in disease progression and outcome have been reported both in immune-competent and immune-suppressed patients. Women with hepatitis C have less liver damage during their reproductive years. Postmenopausal women lose this advantage where fibrosis progression has been shown to accelerate. In a study from a cohort of women with hepatitis C classified by reproductive phase and compared with men of the same age, Villa et al. [23] demonstrated that the severity of fibrosis in women is strictly related to the levels of estradiol and the estradiol/ testosterone ratio. These findings may explain the discontinuous progression of fibrosis observed in women compared to the more linear and severe pattern in men. Together with other factors, such as concomitant alcohol intake, it may also explain the higher mean age of women listed for liver transplantation (LT) for an HCV indication.

From a social point of view, several studies around the world have reported disparities in access to therapy, with women less likely to receive treatment than men [24–26]. These findings were not confirmed in a recent study on an American cohort of veterans where access to therapy with direct antiviral agents (DAA) was found to be similar in men and women, yet young women were found to be particularly vulnerable to the under use of antiviral drugs [27].

Taken together, these findings suggest that in the future, HCV-infected women may progressively become higher contributors to the overall burden of cirrhosis and its related complications [28].

Drug-Related Hepatitis

Clinically, women have been reported to have a 1.5–1.7-fold greater risk than men of experiencing an adverse drug reaction [29]. Acute liver failure is a rare but very serious adverse event that occurs more frequently in women. In the USA, 74% of drug-induced acute liver failure occurs in women [30]. Paracetamol overdoses were the most frequent cause followed by idiosyncratic drug reactions.

This susceptibility has also been demonstrated experimentally by using human hepatocytes pooled from different donor groups. Significant differences were found in mitochondrial injury, nuclear condensation, and plasma membrane permeability between sexes with female cells showing higher susceptibility at certain exposure times, for some well-known hepatotoxic drugs [31].

Gap in Listing

There is not much data to elucidate whether there are disparities between genders in terms of patient referral to a transplant center for LT evaluation. In the field of kidney transplantation, multiple studies have found that female gender is associated with a lower probability of inclusion in waiting lists; these studies also suggest that this disparity is not due to fewer women seeking medical attention [32, 33]. In a national survey of nephrologists [34], men were more likely to be recommended for kidney transplant. Another study [35] showed that women were more likely to be considered unsuitable for kidney transplantation compared to their male counterparts, mainly due to age or medical contraindications.

Unfortunately, knowledge about referring patterns in LT is very limited. Bryce et al. [36], linking data from the Pennsylvania Health Care Cost Containment Council (PHC4), Liver transplant centers in Pennsylvania and UNOS, showed that socioeconomic factors play a role in access to the stages of transplant services in which there is no formal oversight. In their study, using competing risk models, the authors found few overall differences by sex, but both black patients and those insured by Medicare and Medicaid (combined) waited longer before being listed emphasizing the importance to address sex but also race disparities. Once patients were placed on the transplant waiting list, gender became significant, with women waiting longer to receive a transplant. In another subsequent study based on national liver transplant registration data and liver mortality data from the Scientific Registry of Transplant Recipients and the National Center for Healthcare Statistics from 1999 to 2006 in the USA [37], the authors found that female patients had greater access to the waiting lists with attenuation in this difference from the pre-MELD to the MELD era. The authors suggested that these findings could be related to differential access to health insurance, given than adult female subjects make up more than 60% of Medicaid enrollees, which likely facilitates access to specialty liver disease care. Delays in referring male subjects to transplant centers or termination of the evaluation process at the transplant center for medical, surgical, or psychosocial reasons could account for a proportion of the differences observed, but these hypotheses could not be measured in the study.

Gender Disparities in the Liver Transplantation Waiting List

The current system of organ allocation in the USA and many other countries is based on the severity of the disease measured by the MELD score. The introduction of MELD meant the implementation of a more objective and fair system, trying to minimize the subjectivity in establishing risk of death, and avoiding other factors such as waiting list time. Unfortunately, reduced access of women with liver disease to transplantation continues to exist under this new system [38]. In fact, an increasing rate of sex disparity in LT access was noted by Moylan et al. [39] after the implementation of MELD. Using a large national database of liver

transplantation from the Organ Procurement and Transplantation Network (OPTN), the authors found that women had a higher mortality while waiting for LT in the post-MELD era. Before the MELD era, black race was associated with a higher probability of death or being too sick for LT and a lower likelihood of liver transplant within 3 years after listing. After the introduction of the MELD allocation system, racial differences were no longer present while gender disparities persisted. Overall, this and other studies have shown that women are about 30% more likely to die or be too sick for LT compared to men. Such differences were not observed if HCC was the indication and were especially significant in females with MELD scores above 15 [40].

More recent studies have looked at potential causes. Difference in serum creatinine values between sexes despite similar renal function is likely one of the most relevant factors. Because serum creatinine overestimates renal function, women tend to have lower MELD scores than males despite similar risk of death. Dietary intake of creatine, tubular secretion of Cr from the kidneys, and the total pool of body creatine that depends on muscle mass are reasons for sex differences in serum creatinine values [41]. Interestingly, if individual females were considered as males and had their creatinine concentrations corrected using the Modification of Diet in Renal Disease (MDRD) formula for males, they had higher concentrations for the same glomerular filtration rate (GFR) and subsequently higher MELD scores. This effect was present irrespective of the creatinine method used for measurement. Nevertheless, substitution of serum creatinine with MDRD-derived eGFR did not improve discrimination or calibration for waiting list mortality [42].

Differences in transplant rates have also been reported for shorter individuals, so height may also contribute to gender disparities in access to LT once wait-listed [43]. Indeed, a recent UNOS study found that 48.8% of men and 52.3% of women had to decline an organ offer while placed in the first wait-list position. In multivariable models, women were significantly more likely than men to have an organ offer declined while in the first, second, or third position. UNOS refusal code for donor-recipient size mismatch was associated with female gender in those declined in first position. This disparity remained when adjusting for blood type, diagnosis, ethnicity/race, region, and donor-specific antibodies. Interestingly though, transplant rates remained lower among women, even after adjusting for height, with height accounting for only 5% of the disparity observed [44]. In the same line, Mindikoglu et al. [45] analyzed the liver size mismatch calculating the estimated liver volume (eLV) of the transplant candidate with different formulas. The median estimated liver volume (eLV) was significantly lower for women compared to men on the LT waiting list. Women had lower LT rates than men (0.29 vs. 0.39 per person-year, $P < 0.001$) in each liver size or volume stratum, but this disparity was greatest among those with the lowest liver size or volume. Multivariate models suggested that transplant candidate/donor liver size mismatch could be one of the factors behind the lower transplantation rates for women.

In another recent study, Cullaro et al. [46] analyzed patients delisted from US LT waitlist, focusing on removal codes of “too sick” or “medically unsuitable.” Women

were 10% more likely to be delisted than men. One possible explanation provided by the authors is the perception of frailty by attending physicians, possibly affecting more women than men, and thus resulting in higher delisting in women. Importantly though, no differences in survival were observed after being removed from the waitlist.

Another factor that likely influences LT disparities between men and women is the addition of MELD exception points. More men than women are included in waitlists with MELD exception points, and several studies have shown that patients listed with MELD exception points are transplanted at higher rates than those with equivalent calculated MELD. Allen et al. [47] noticed that women had similar calculated MELD and MELD Na scores at listing than men yet were less likely to receive MELD exception points (21% vs. 29%, $P < 0.0001$). These authors found that women had higher mortality and were 20% less likely to be transplanted. They also observed that differences in height and MELD exception points could explain most of the gender disparity in LT access. With the incidence of HCC increasing, the numbers of exception points granted to men on the waitlist is likely to grow, although modification of HCC MELD exception upgrades are currently being discussed and potential future modifications might ensue.

Gender Disparities in Outcome

Sex-based differences exist not only in wait-list but also in posttransplant outcomes. A German study [48] noted that female sex in the post-MELD era was a strong and independent risk factor for post-LT 90 days mortality (OR 3.2), particularly among women with high MELD score ≥20 (32.6% vs. 13.7%). The authors proposed a new index to predict mortality after LT by using five parameters including MELD ≥20, female gender, coronary heart disease, and donor risk index. All these parameters are available preoperatively and were identified to be independent predictive factors for postoperative 90-day and 1-year mortality.

Female patients have also been found to have slightly higher re-LT rates compared to men. In a US study (1999–2008) 1 liver in every 10.5 was utilized for retransplantation in females compared to 1 in 11.6 for males [49]. These results may have resulted from greater risk of graft loss for recurrent HCV in women before the DAA era [50]. In fact, the differences in the results of LT in specific liver diseases are not very well studied but have been noted only in HCV (as reviewed by Sarkar et al.; 50), but not in other diseases such as NASH, AI hepatitis, PBC, or alcohol-related diseases.

Donor selection may also be subject to gender bias. A study based on the US Registry of Transplant Recipients found higher donor risk rates in women than men. Women were 24% more likely to receive a low-quality graft than men (OR 1.24), but there were no differences in graft survival between women and men after adjustment for graft quality [51]. One explanation for this difference may be the need to wait for more offers and use of smaller grafts in women.

Conclusion

In summary, there are clear gender inequities in liver transplantation that span the whole process, from access to LT waitlists to posttransplant outcome (Fig. 15.1), although most differences exist in access to transplantation once wait-listed. Measures, such as calibration of MELD in women (by adding extra-points) or alternative type of donors such as live-donor organs and/or splits, should be encouraged in liver transplant programs. In addition, studies should be designed to understand all causes of gender disparity. Finally, incorporating a gender perspective in research whereby analysis by sex is performed in each clinical study in the liver transplant field is mandatory (Table 15.1).

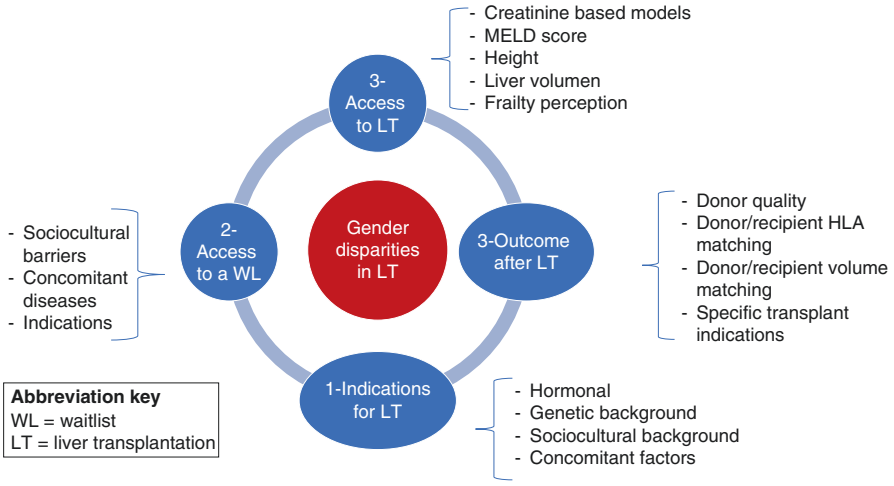

Fig. 15.1 Gender-based disparities in access to and outcomes of liver transplantation

Table 15.1 Strategies to address gender disparity in liver transplantation

Changes in allocation policy
Proposed strategies to date have not yielded improvement in prediction of 3-month mortality
Prospective evaluation: addition of 2 points to the MELD score in women
Consider greater utilization of live donation
Break down sociocultural barriers to utilization
Support oriented to the needs of women (assistance, e.g., childcare, etc.)
Greater use of split livers

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Chapter 16
The Role of Palliative Care in Cirrhosis

Robert L. Fine

Introduction

Although cirrhosis may improve or even reverse when detected early and the underlying cause can be treated, it is a significantly life-limiting disease [1]. Once a cirrhotic patient has decompensated into critical illness with hospitalization and MELD scores ≥21, annual mortality rates become quite high with median survival ≤6 months [2]. 2016 data from the Centers for Disease Control revealed chronic liver disease and cirrhosis to be the 12th leading cause of death in the United States [3]. This chapter will provide an overview of palliative care, whether provided by the specialist or nonspecialist, in management of more advanced and end-stage liver disease due to cirrhosis. The modern field of palliative care is often referred to as a specialty serving patients and families facing serious illness, but many palliative care services and tasks are delivered by non-palliative care specialists providing what might be best described as primary palliative care. This chapter will thus further focus on the essential tasks of palliative care whether provided by the hepatologist, gastroenterologist, or other professionals who might serve patients with cirrhosis or provided by the interdisciplinary palliative care specialist team.

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What Is Palliative Care?

When many persons hear or read the words *palliative care*, the first image that pops into their mind is that of the Grim Reaper, death. Palliative care is frequently misunderstood by health-care professionals and the public alike as equivalent to "end-of-life" care and is further often misunderstood to be synonymous with hospice. This misunderstanding prevents patients and families facing serious though not necessarily terminal illness from gaining appropriate access to palliative care services at the earliest moment when the services could be of benefit.

Although palliative care frequently serves dying patients, especially in the acute care hospital, on any given day, most palliative care teams are serving far more patients living in the face of mortality than those actively dying. Furthermore, for a variety of reasons, not the least of which is a shortage of board-certified palliative care professionals, most palliative care tasks must be met by non-palliative care health-care professionals, including primary care doctors, hospitalists, gastroenterologists, hepatologists, and transplant surgeons. Indeed, one purpose of this chapter is to help non-palliative care specialists caring for critically ill cirrhotic patients to best serve their patients via primary palliative care whenever possible and via calling in specialty palliative care professionals when necessary.

Health-care professionals need a robust understanding of palliative care to best serve their seriously ill patients. Such an understanding begins by conceptualizing palliative care as having two stages. The first and ideally earlier stage is best referred to as *supportive palliative care* (SPC). Bringing the term *supportive* into the palliative care lexicon reminds the listener that this field is not only about dying. The second, later stage, is *hospice palliative care*, or more simply *hospice*, a service focused strictly on the dying patient who has chosen to forgo any further attempts at remission or cure. Think of hospice as a subset of the larger field of palliative care. Supportive palliative care is needed by and serves the sickest 5–10% of patients, while hospice palliative care serves the less than 1% of the population dying in any given year (Fig. 16.1). Most SPC patients eventually become hospice patients. Another way to think of the distinction is that although all hospice care is palliative in nature, most supportive palliative care is not hospice! In the remainder of this chapter, I will refer to supportive palliative care as SPC and will refer to hospice palliative care simply as hospice.

Supportive palliative care is appropriate at any stage of serious illness, but how might serious illness be defined? A serious illness is "a condition that carries a high risk of mortality, negatively impacts quality of life and daily function, and/or is burdensome in symptoms, treatments, or caregiver stress" [4]. It typically shortens the patient's life expectancy to a few years or less. Many patients with advanced liver diseases of all sorts will fall into this definition and time frame of illness and, at some point, in the absence of liver transplant, will become hospice-appropriate.

One way to recognize a serious illness is to see it as one from which the doctor *would not be surprised if the patient died in the next year.* I refer to such patients as "surprise question positive" as opposed to patients whom the doctor would in fact

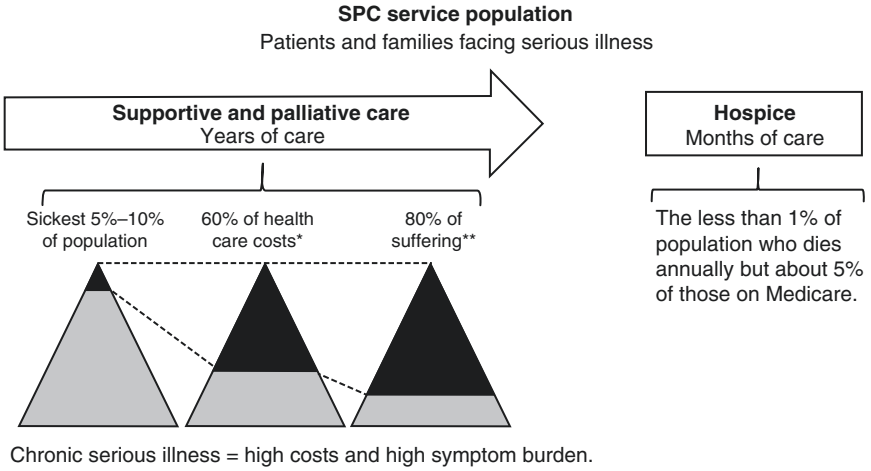

Fig. 16.1 SPC service population

be quite surprised if the patient died in the next year (surprise question negative). The utility of this question has been studied in a number of disease types, though admittedly not in chronic liver disease to my knowledge. When a nephrologist would not be surprised if a chronic hemodialysis patient died in the next 12 months, mortality is 3.5-fold higher than if the physician would be surprised [5]. If an oncologist would not be surprised if a metastatic cancer patient died in the next 12 months, mortality is almost eight times higher than if the physician would be surprised [6]. A 2017 meta-analysis of the surprise question suggested an overall predictive accuracy of about 75% [7]. Finally, in my personal experience, again mostly with cancer patients, surprise question positive patients typically have an annual mortality rate around 50%. A patient with such a mortality rate is not hospice-appropriate, but such a patient is very appropriate to have the tasks of palliative care (outlined below) completed. On the other hand, hospice is appropriate for patients whose *death is expected in the next 6 months* if the disease follows its normal course and the patient accepts treatments solely intended to promote comfort. Data from the National Hospice and Palliative Care Organization indicated greater than a 90% mortality rate among patients enrolled in hospice in 2017 [8].

Those who treat chronic liver disease are often providing supportive palliative treatments, hoping to prolong life and even hoping for a chance at cure. Consider the patient with progressive cirrhosis on a transplant waiting list who suffers with hepatic encephalopathy. The hepatologist will seek to "palliate" the encephalopathy perhaps with rifaximin and lactulose. Neither agent is curative, and both can lessen

the symptoms of encephalopathy. Of course, the physician may even treat an acute crisis such as infection while hoping for the curative intervention of a successful liver transplant. This sort of care plan can be seen as primary palliative care. In contrast, hospice is appropriate when in reasonable medical judgment the patient is expected to die within the next 6 months and the patient is either not a transplant candidate and/or the patient prefers to stop attempts at modifying the course of disease and focus on interventions intended to provide comfort only.

Multiple organizations including Centers for Medicare and Medicaid Services (CMS), the American Cancer Society, the Institute of Medicine, and more have offered definitions of palliative care. At Baylor Scott and White Health, we have drawn on many of those to define palliative care as *a multidisciplinary team-based process to relieve total suffering and improve quality of life for patients and families facing serious illness*. Obviously, such a definition requires further clarification, starting with the unit of treatment as the patient and family.

The welfare of the patient should be every physician's first concern, but family members should come in as a close second focus of concern. Families are likely to become more involved in the patient's care as the patient's condition worsens such as when the cirrhotic patient becomes encephalopathic and critically ill. Family members not only participate in supporting the patient; they often become the patient's decision-maker, subjecting them to significant emotional distress that may complicate their function in that role. Early attention by the hepatologist to the family's journey may not only lessen family grief and posttraumatic stress disorder but through trust building over time can help the hepatologist by making it easier to guide the family to acceptance of hospice and/or "comfort care only" when appropriate.

Note that the focus of palliative care is not upon cure or even remission but upon relief of suffering and improving quality of life. This should certainly resonate with physicians caring for the critically ill cirrhotic as such patients, even if they can temporarily improve, will not be cured short of liver transplantation. An aspect of palliative care that liver specialists might not be so familiar with is the notion of total suffering. Total suffering, whether attended to by the hepatologist or the palliative care specialist, has four major components: physical suffering (pain, dyspnea, nausea, fatigue, etc.), emotional suffering (depression, anxiety), social suffering (suffering of both the patient and the family as accustomed relationships and roles are disrupted by serious illness), and spiritual suffering (questions and concerns about meaning and purpose in life which often come to the fore in numinous, life-and-death situations).

Why Did Palliative Care Develop?

Modern hospice services first came to England in the mid-1960s under the leadership Dr. Cicely Saunders and then subsequently to the United States in the mid-1970s. The Medicare hospice benefit was established in 1981, requiring patients

who wished to receive hospice services to forgo attempts at remission or cure. It should perhaps not be a surprise that in the decade after establishment of the American hospice movement, evidence began to mount that such a service requiring the abandonment of disease directed interventions in order to receive comfort directed services was inadequate in meeting four major deficits in end-of-life care: excessive non-beneficial treatment prior to death, unnecessary suffering, unsustainable costs to individual families and society, and a lack of concordance between what patients wanted at the end of life and what the medical profession actually delivered. As you read the further explanation of those deficits, think about how they apply to serious liver disease.

The best early evidence demonstrating the failure of hospice alone to meet patient needs in the setting of serious illness came from the SUPPORT Trial. This trial involved 9000 seriously ill patients with a projected 6-month mortality of 50% (i.e., not appropriate for hospice) treated at five major teaching hospitals. It revealed major misunderstandings between physicians, patients, and surrogates about goals and preferences for treatment, that almost 50% of the patients had severe pain after more than 8 days in the hospital, and over 50% of those who died had severe pain during last 3 days of life [9]. The branch of medicine that might have otherwise been able to help manage the pain and suffering of such patients, hospice, could not typically be consulted because these patients were neither ready to transition to a comfort only plan of care nor was the predicted mortality of 50% appropriate for hospice care.

Meanwhile, researchers at Dartmouth documented that among Medicare beneficiaries who died, some spent up to three times as many days in the hospital or six times as many days in the ICU prior to death as others who died from the same conditions, yet these patients who received more intervention were not clearly sicker and did not have a better outcome. Hospice use varied fourfold across the country, but this was not due to hospice availability nor patient preference. Significant amounts of extra, high intensity treatment were not associated with better survival among Medicare patients who died. Regional differences and even differences within the same community were noted. Some clinicians, especially those who practiced at high treatment intensity, high costs institutions, claimed that because the Dartmouth researchers were only studying patients who died, they could not detect patients for whom high intensity treatment led to better survival. Barnato and colleagues however studied that claim and found it lacking as outcomes were not meaningfully better at high intensity, high-cost hospitals compared to lower intensity of treatment hospitals [10]. The reasons for treatment variation are certainly complex, involve both supply and preference sensitive factors, and are not appropriate for this chapter. However, I believe physician behaviors drive much of this treatment variation with attendant non-beneficial treatment, and I urge the reader to visit the Dartmouth Atlas for Healthcare at www.dartmouthatlas.org for further exploration.

It is not hard to imagine that non-beneficial treatment and high suffering were being purchased at great cost. In the SUPPORT trial, 31% of families lost most of their life savings. This should not have been a surprise given that for many years,

those who studied Medicare expenditures and concluded that somewhere between 25% and 30% of Medicare expenditures accrued in the last year of life with about half of that in the last 2 months of life – a time frame that should be very familiar to those taking care of the critically ill cirrhotic [11]. More recent data that may be of significant interest to physicians managing serious chronic illnesses like liver disease suggest that among Medicare patients who die, 43% have expenditures in the last 5 years of life exceeding their nonhousing assets, and 25% lose all their assets including the value of their home prior to death [12]. This last 5 years of life, time frame should resonate with hepatologists when considering the natural progression of cirrhosis.

Finally, researchers have demonstrated that seriously ill patients have goals beyond cure when cure is no longer possible, yet physicians frequently do not understand patient desires in this circumstance. Faced with a hypothetical terminal illness, 40% of patients fear receiving too little treatment, while 45% fear receiving too much! Obviously, a patient who fears receiving too little treatment is less likely to enroll in hospice. Still, even those persons have limits on what they are willing to endure to extent life. For example, 86% of persons considering a hypothetical terminal illness state that they prefer to spend their last days at home, 87% prefer to avoid mechanical ventilation to extend life by 1 week, and 77% prefer to avoid mechanical ventilation to extend life by only 1 month [13]. Steinhauser, Christakis, and others demonstrated that although patients and physicians rated freedom from pain as an important attribute of quality of treatment near the end of life, there was a significant disconnect between patient and physician ratings of the importance of other attributes of quality care near the end of life. For example, 85% of patients agreed that the ability to pray is very important at the end of life, yet only 55% of physicians felt the same way. In 89% of patients, only 58% of physicians agreed it is very important to not be a burden to family at the end of life. Finally, 92% of patients, but only 65% of physicians agreed a very important attribute of quality care at the end of life was maintenance of mental clarity [14]. Think about that issue in the treatment of the critically ill cirrhotic!

What Are the Benefits of Palliative Care?

Over the past 20 years, a substantial body of evidence has established multiple benefits to palliative care in the setting of serious illness. Patients endure less pain and other suffering with fewer hospital readmissions [15–18]. Palliative care in the medical ICU, a frequent site of care for the critically ill cirrhotic, has been associated with shorter ICU length of stay and less non-beneficial or futile treatment at the end of life [19, 20]. Better treatment concordance with patient preferences, less PTSD, less depression, and better bereavement among families have been documented [21–23].

In a medical reimbursement world increasingly focused on value-based rather than fee for service-based payment, these significant patient and family benefits accrue at significantly lower cost than customary care [24–28]. These financial benefits were again recently demonstrated in a large meta-analysis of the impact of palliative care for hospitalized adults with serious illness [29]. Finally, although this has not been demonstrated in the setting of advanced liver disease, early palliative care referral in the setting of metastatic solid tumors is associated with improved survival [30, 31]. This finding, in combination with the other benefits of palliative care, has led the American Society of Clinical Oncology to recommend early palliative care services for all metastatic cancer patients within 8 weeks of diagnosis [32]. Similar data and recommendations do not yet specifically exist in the world of serious liver disease, but it would not be a surprise if supporting data and recommendations were to come to fruition in the decade ahead.

What Are the Tasks of Palliative Care?

Whether provided by a non-palliative care specialist performing primary palliative care, or provided by the palliative care specialist, the specific tasks of palliative care can be divided into six basic areas as shown in Table 16.1 and reviewed below.

Table 16.1 Clinical tasks of palliative care

PC clinical tasks	Considerations for primary and/or specialty palliative care
Medical assessment and prognostication	Initial assessment and periodic reassessment of prognosis and total suffering. Consider medical, emotional, social, spiritual factors.
Communication	Serious illness communication, including patient/family understanding, information desires, prognosis sharing, goals, hopes, fears, essential abilities, trade offs.
Advance care plans or "Plan B" thinking	*What* are minimum QOL needs to make life worth it? *Who* speaks for the patient? Does *who* know *what*? Complete advance directives such as Living Will.
Treatment/support	Is primary Rx with curative intent? Palliative intent? Does patient understand?
	Focus of SPC professionals is on total suffering.
	Palliative treatments: medical, psycho-social-spiritual.
	Family support, including children of seriously ill adults.
Transitional care planning	Would you be surprised if patient died in the next year or some shorter time frame? If not surprised, then create or update serious illness conversation. Consider SPC consultation. Update or establish advance directives. Encourage legacy work, address anticipatory grief, and practical issues.
Admission to hospice	Ideally as an outpatient months prior to death. If patient is never a candidate for transplant then hospice referral may come earlier with maintenance of basic symptom management medications.

Medical Symptom Assessment and Prognostication

The first task involves medical assessment and prognostication. Beyond traditional medical assessment of the cirrhotic patient, a basic assessment of the symptom burden should be undertaken. Just as we can't treat hyperkalemia if we don't measure or assess potassium, so too we cannot treat the major symptoms associated with any disease if we do not specifically assess for those symptoms. Among the common symptoms of serious liver disease are physical and mental fatigue, abdominal pain and bloating, spontaneous bruising, pruritis, GI bleeding, muscle cramps, and confusion. One study from the palliative medicine literature focused on liver disease identified fatigue, distention, peripheral edema, and muscle cramps as the symptoms patients most wanted help with [33], and another study added irritability, depression, and pain as significant symptoms [34]. Depression was present in 50% of cirrhotics when screened for using a depression tool [35]. Of course, as liver disease progresses, symptom burdens worsen. It is not surprising that the quality of life experienced by end-stage liver disease (ESLD) patients is like that of end-stage heart failure patients [36]. ESLD patients have pain levels similar to patients with metastatic lung or colon cancer, and 60% of hospitalized ESLD patient experience pain [37, 38]. Most symptom management will be provided by the hepatologist, and this will be covered later.

Prognostication is another important task. Patients may of course live with cirrhosis for years, but once an episode of decompensation has occurred, median survival falls to 2 years. Median survival further declines to 1 year with chronic encephalopathy and 6 months with refractory ascites. Infections increase mortality fourfold with 30% dying within 30 days [39], and hepatorenal syndrome implies the direst prognosis. The other point I would urge the reader to consider is that in addition to prognostic markers such as those I have just listed, one must consider emotional, social, and spiritual factors. Depressed patients or those with poor social support are less likely to maintain compliance with complex treatment regimens. In my experience, patients at spiritual peace are more accepting of mortality, while those experiencing the greatest spiritual conflict are often most likely to wish to pursue non-beneficial interventions. Pastoral care and social work professionals play a major role in both supportive palliative care and hospice, and input from such professionals can be helpful in both prognostication and support of the patient and family.

Communication

Bernacki and Block, writing for the American College of Physicians High Value Care Task Force, have succinctly summarized multiple studies demonstrating that communication in the face of serious illness is a low-risk high-value intervention associated with improved patient outcomes, including better quality of life, better treatment alignment with patient preferences, longer life in some circumstances,

reduction in non-beneficial treatment at the end of life, improved family outcomes, and reduced costs [40]. They go on to propose best practices for serious illness conversations. These best practices are based upon solid evidence, including that patients want the truth about prognosis [41–44], and will not be harmed or lose hope by talking about end-of-life issues [45, 46]; anxiety is common for all parties involved in such discussions – patients, families, and physicians [47]; and patients and families have goals and priorities besides living longer [14]. Most importantly, these practices should be initiated before a crisis – a crisis such as sudden critical illness in a cirrhotic patient. These best practices include but are not limited to the following four practices:

- Training clinicians in communication skills including the uses of a conversation guide directing the trained physician to ask the right questions in the right order at the right time, delivering prognostic information in the best manner possible.
- Identifying seriously ill patients who will most benefit from a structured serious illness conversation and whenever possible doing so in the outpatient setting. (See previous comments on prognosis and the surprise question.)
- Initiate serious illness conversations earlier in the outpatient setting, before a crisis develops. (I note, however, that the same communication principles may be used in the setting of a crisis; however, at this point the advantages of early communication have been lost, and the physician may be communicating with family rather than patient due to the frequency of encephalopathy in critically ill cirrhotics.)
- Documenting communication in the electronic medical record in an easily retrievable format so that all members of the treatment team may easily see the information communicated by the physician, the patient's and/or family's values, goals, and treatment preferences, and any recommendations made and/or accepted.

The basic elements of an effective structured serious illness conversation, and the order in which they should be utilized are listed below.

- Obtain permission. Most patients want to discuss with their physician what they have already been through and what might be likely in the future; however, on any given day, a patient may not yet be ready. Thus, it is important to obtain permission before further embarking on a serious illness conversation. If the patient does not wish to discuss when first recommended, ask the patient when an appropriate time might be.
- Assess the patients understanding of their illness. Do not divulge prognostic information until you have knowledge of what the patient already understands and believes about their condition.
- Share prognostic information using "hope-worry" or "wish-worry" language. For example, the hepatologist might say in the office setting, "I hope you do well for a very long time, but I worry that things could change suddenly and without warning in the future. It is important to prepare for that possibility." Later in the course of the illness, the hepatologist might say, "I wish we were not in this situation, but things have not been going as well as we have hoped, and I am worried

that your time could be as short as …" When offering a time-based prognosis, I recommend offering a range such as hours to days, days to weeks, weeks to months, or months to a year or a little more. For some physicians and patients, offering a functional prognosis is more appropriate, for example, "I wish this was not the case, but I am worried that this is the best you are going to feel and I'm worried that you are likely to become weaker and more confused, that you are likely to get worse in the not too distant future."

- Assess the patient/family emotional response to this serious news before moving on to next questions. If you are not certain, simply ask the patient, "Would you mind sharing with me what you are feeling about the serious news I've just shared with you?"
- Explore patient goals in the setting of this serious news. If in fact things get worse, what other goals besides living longer might the patient have?
- What are the patient's biggest fears and worries about the present and future with their illness?
- What abilities are so important that it is hard for the patient to imagine living without them? For many patients these abilities will include such basics as the ability to participate in caring for self and to interact meaningfully and/or purposefully with the world around them.
- What trade-offs might the patient be willing to make to gain more time? Most patients are willing to endure short-term aggressive interventions to restore them to a life they can participate in and enjoy. On the other hand, most patients are not interested in aggressive interventions that only serve to prolong their dying in an institutional setting.
- How aware is the family of the patient's condition, goals, fears, important abilities, and trade-offs? Remember that as liver disease progresses, encephalopathy often worsens to the point the patient loses decision-making capacity and the family becomes the primary decision-maker. In my experience, failure to engage the family early in serious illness communication is a recipe for chaos near the end of life!
- Finally, make clear treatment recommendations. I strongly recommend against giving the patient an array of treatment choices as if they are all equal. The physician should recommend the steps he or she believes will best serve the patient based upon the patient's values as previously and/or currently expressed and what is known about the patient's medical condition, including reasonable medical judgment about the benefits, risks, burdens, and alternatives to various medical or surgical interventions.

Advance Care Planning

Advance care planning is a process for directing treatment preferences at a time in the future when the patient is no longer able to effectively communicate. Think of it as a "Plan B" for a time in the future when the Plan A of remission or cure is no

longer working. It is a sort of preparedness planning for a future that no one wants but ultimately happens to every mortal being. I think of it as the equivalent of putting on one's seat belt before driving. After all, once an accident occurs, it is too late to put on the seat belt!

Advance care planning (ACP) is ideally a universal preventive care intervention for all persons, including healthy persons, before a serious illness even develops. It should be an ongoing periodic dialogue between patient, family, and physician. This dialogue may be further aided by nurses, chaplains, social workers, and, if trained, lay persons. However, even when there is a prior advance directive, advance care planning should be revisited in the setting of a serious illness, ideally only after completion of a serious illness conversation as noted above. Although this process may be aided by nonphysicians, I believe it as a fundamental responsibility of the physician. Consider the most basic steps of assessing patient and/or family understanding and the sharing of prognosis. Part of assessing patient understanding involves assessment of patient decision-making capacity. This is a medical judgment and may be difficult in the setting of a condition like hepatic encephalopathy. Likewise, prognostication and the sharing of prognosis involve both science and art best integrated into practice by the skilled physician.

Advance care planning may be memorialized in the EMR in various forms of structured notes built into many EMRs and may be further memorialized into written advance directives unique to laws where each patient lives. The most common advance directives are the Living Will and the Medical Power of Attorney documents. Physicians should familiarize themselves with the specifics of such documents where they practice medicine. I will offer only a few comments in general on these two different types of documents.

A living will is the most direct expression of a patient's preference for intensity of treatment in the circumstance of a terminal or irreversible illness leaving the patient unable to communicate. A living will is completed at time when the patient has decision-making capacity and expresses treatment preferences for a time in the future when the patient has lost decision-making capacity and the patient has been declared terminally or irreversibly ill. Most living wills are documents that simply allow the patient to refuse life-sustaining treatment in such circumstances. However, a few states have living wills allowing a patient to express a preference to either maintain life-sustaining treatment or to withdraw or withhold life-sustaining treatment. It is thus important for each physician to understand the specifics of local state law and to review the contents of the living will personally. Assistance in understanding such information is often available from supportive palliative care professionals, social workers, chaplains, and hospital legal departments.

The second common legal document related to ACP work is the Medical Power of Attorney (MPOA). The patient, when of sound mind, appoints a surrogate to make medical decisions for the patient at a time in the future when the patient is no longer able to make decisions. The patient need not be considered terminally or irreversibly ill. This may sound very attractive to physicians caring for patients with progressive liver disease given the frequency of hepatic encephalopathy. However, I believe extreme caution should be used in recommending the completion of such

documents for the following reasons. Surrogates are not particularly accurate at predicting patient treatment preferences [48]. Surrogates face considerable emotional burdens, both immediate and long term, when making life-and-death decisions [49]. Surrogate decisions are typically delayed [50]. I believe this is a natural response to what I refer to as decision-making burden. Finally, compared to other forms of advance care planning, having an MPOA with an appointed surrogate is least likely to limit non-beneficial treatment at life's end. A 12-year longitudinal study of the impact of various ACP strategies indicated that having a physician-patient conversation about end-of-life decisions decreased the odds of non-beneficial interventions by a factor of 1.93 and completing a living will decreased odds of non-beneficial interventions by a factor of 2.51, however, having only a MPOA had no impact on non-beneficial interventions [51]. The ethical standard of care for a MPOA agent is to follow the known wishes of the patient; however, in some jurisdictions, the agent may be legally empowered to overrule the wishes the patient expressed in the living will.

Treatment and Support

Hepatologists and transplantation specialists are of course the experts in treatment of serious liver disease, including the critically ill cirrhotic, even though multiple other specialties may participate in the care of such patients. From the perspective of palliative care, there are two areas to focus on. The first has to do with clarity about whether interventions being proposed are of curative intent, for example, transplantation, or palliative intent only. In my experience, too many ESLD patients and families make decisions based upon an expectation that liver transplantation will be forthcoming, when for a variety of reasons, the patient will not receive the desired potential lifesaving liver transplant. Utilizing evidence based serious illness conversation techniques as outlined above can give clarity to this issue, and this should be performed sooner rather than later in the course of illness when possible. It is also essential to document that the patient and/or family clearly understand when liver transplantation is no longer an option.

The second area of comment regarding treatment and support is a specific focus on palliation of symptom burdens and total suffering as part of providing the best treatment or best care possible. Treatment of symptoms such as pruritis, depression, anxiety, and encephalopathy is certainly part and parcel of primary hepatology. The treatment of pain and the use of opioids are more challenging in serious liver disease, as is the assessment and treatment of total suffering.

Most symptom management in severe liver disease will be provided by the hepatologist with additional expertise available, at least in most major medical centers, from palliative medicine and/or pain management specialists. As previously mentioned, ESLD patients may have pain levels similar to patients with metastatic lung or colon cancer, and 60% of hospitalized ESLD patients experience pain [37, 38]. When the pain is severe enough, opioids will be needed, even though there is known

risk of increased sedation, constipation, and precipitation of hepatic encephalopathy. A brief review of basic opioid pharmacology can be useful in mitigating these risks while helping the physician find the "right dose," i.e., one that balances adequate pain relief in conjunction with an acceptable side effect profile.

Opioids are primarily metabolized in the liver via two basic pathways or phases: [1] changes in the structure of the drug via oxidation, reduction, or hydrolysis catalyzed largely by the cytochrome P450 enzyme system, especially CYP2D6 and CYP3A4 and [2] conjugation with glucuronide, promoting renal excretion [52, 53]. The first pathway is impacted not only by severe liver disease but by significant genetic polymorphism in the activity of these enzymes from one person to the next and by other drugs, including drugs that may be used in patients with severe liver disease. The second major pathway is less affected in hepatic disease due to glucuronidation enzyme preservation in the liver and extrahepatic glucuronidation processes present in other organs. At the simplest level when considering opioids in serious liver disease, one must realize that opioid clearance is reduced and opioid bioavailability is generally increased. Thus, compared to patients without liver disease, opioid doses should be smaller, and dosing intervals should be longer.

When further examining the two distinct phases of opioid metabolism, it is important to be aware of which opioids are primarily metabolized by which pathway. The opioids subject to metabolism via CYP2D6 and CYP3A4 may be remembered as Fentanyl plus the "D" opioids, that is, opioids with the letter "d" in their generic name. These "D" opioids are co*d*eine, hydroco*d*one, oxyco*d*one, trama*d*ol, and metha*d*one. Opioids generally metabolized by glucuronidation are the "PH" opioids, mor*ph*ine and hydromor*ph*one.

When considering metabolism of the "D" opioids, whether in normal liver function or impaired liver function, it is also important to know if the opioid in question is a prodrug. A prodrug is administered in an inactive form that is then metabolized into an active form to yield the desired effect [54, 55]. Among the "D" opioids, there are three prodrugs: [1] codeine, metabolized to morphine; [2] hydrocodone, metabolized to hydromorphone; and [3] tramadol, metabolized to O-desmethyltramadol. Now consider the issue of genetic polymorphism among CYP3A4 and CYP2D6. It is believed that approximately 7% of Caucasians and up to 30% of Blacks are rapid metabolizers through these pathways and 10%of Caucasians are slow metabolizers. Using codeine as an example, one can begin to see the challenges of prescribing this opioid to any patient given the polymorphism in its metabolic pathway noted above and in liver disease. Rapid metabolizers of codeine are at risk of excess morphine effect, leading to risk of overdose. On the other hand, slow metabolizers and those with liver failure will not convert codeine to morphine and will thus not achieve pain relief. Such a patient may even be misperceived as having drug-seeking behavior when asking for more pain medicine, when in fact, they simply do not metabolize to active form what they have been given. Also note that other drugs may either inhibit or induce various CYP isoenzymes. For example, the antidepressant fluoxetine inhibits both CYP3A4 and CYP2D6. In so doing these drugs can lessen the conversion of a drug like tramadol (which has no mu-opioid receptor activity) to O-desmethyltramadol which has some mu-opioid effect. On the other hand, if oxy-

codone is given, the inhibition of its metabolism via CYP3A4 and CYP2D6 can lead to markedly elevated levels of the opioid. Fentanyl is the one common opioid metabolized primarily via the cytochrome P450 pathways that doesn't have the letter "D" in it. It is active in its native form – that is, it is not a prodrug, but it is still subject to the other precautions of prescribing opioids metabolized via the same pathways. A safe habit in general when prescribing multiple drugs, but in particular when prescribing opioids, is to utilize a drug interaction checker, many versions of which are available and are sometimes even built into various EMR platforms.

Glucuronidation is the primary metabolic pathway for morphine and hydromorphone. There is likely less genetic variability in metabolism via this pathway and less potential for other drugs to impact metabolism of these opioids. Remember that morphine is metabolized to M6G (morphine-6-glucuronide, an active metabolite more potent than morphine) and M3G (morphine-3-glucuronide, a metabolite lacking analgesic effects but with significant neuroexcitatory effects). Both of these metabolites will build up in renal failure, so morphine should be avoided in patients at risk of or who already have some degree of renal failure or hepatorenal syndrome.

With the above in mind and based upon clinical experience, formal SPC consultation is strongly encouraged for ESLD patients with significant pain. If such consultation is not available, the hepatologist should try to limit opioid use to the following if possible. Patients with intermittent pain impacting them only a couple of times a day should use short-acting opioids, *if an opioid is needed at all*. There is nothing wrong with standard daily doses of acetaminophen, although a maximum of 2 g in a 24-hour period (half the normal recommended bottle dosage label) in cirrhotic patients is safe. If a short-acting opioid is needed, hydromorphone at a 50% dose reduction and at least double the typical dosing interval is a good first choice. Because hydromorphone is metabolized via glucuronidation, one need not worry about other drugs that might affect its metabolism, and as mentioned above, glucuronidation is preserved relatively well in liver failure. If one feels that one of the "D" opioids must be used in liver disease, oxycodone is a reasonable first choice because it has good mu-receptor activity in its native form as do its active metabolites noroxycodone and oxymorphone, although one must be careful about the impact of other drugs that might impact its metabolic pathway. As with hydromorphone, oxycodone should be started at half the dose one would expect if there was no liver disease and only offered at twice the customary interval.

What about the cirrhotic patient with around-the-clock pain, even pain causing nocturnal awakening? Such patients will best be served in most cases with an around-the-clock long-acting opioid rather than multiple short-acting agents. If a long-acting opioid is needed in liver failure, I have had the best experience with generally low doses of transdermal fentanyl as have others in the field of palliative medicine [56]. Methadone is another opioid that may be used as a long-acting opioid, but I recommend this only be prescribed by physicians experienced in its use when other agents prove ineffective. Although I have seen some utilize tramadol in severe liver disease because it is considered a weaker opioid, I avoid it. As mentioned above, it is inactive as a pain reliever until converted to O-desmethyltramadol.

This has lower affinity for mu-receptors and thus less sedation but also less analgesia. Constipation still occurs due to anticholinergic effects. It is a partial serotonin and norepinephrine reuptake inhibitor that may both lower the seizure threshold and increase the risk of serotonin syndrome, although rare.

There are of course other aspects to total suffering than only physical symptoms. Physicians caring for severe liver disease patients, including the critically ill cirrhotic, should be cognizant of the potential for emotional, social, and spiritual suffering and should be proactive in addressing these elements of the human condition. When alcoholism has been the sole cause or only one of many contributors to cirrhosis, issues of codependency, guilt, and anger may come to fore within the family structure, significantly impacting the family decision-maker for the encephalopathic cirrhotic. Social work and pastoral care providers, whether members of a supportive palliative care team or not, may be especially helpful in assessing and helping manage these problems. The advantage of utilizing social workers and pastoral care providers who are part a SPC team, however, is they have not only the extra expertise that comes from full-time work with the seriously ill; they usually meet with the entire interdisciplinary team on a daily basis, enhancing coordination of care.

Transitional Care Planning

Transitional care planning typically involves a shorter future time horizon than advance care planning. One may have an advance care plan such as a living will years or even decades before it might become active. On the other hand, transitional care planning typically occurs at a point in time when transition from supportive palliative care to hospice is considered because anticipated survival is measured in weeks to months or days to weeks and the physician would not be surprised if the patient died suddenly at any point. To give some very practical examples, consider the end-stage liver disease patient with spontaneous bacterial peritonitis. This common complication will normally be treated with the disease directed therapy of intravenous antibiotics in the supportive palliative care model, but antibiotics would not normally be given in the hospice model of care. Similarly, the patient with recurrent GI bleeding will normally be treated with interventions directed at hemostasis and transfusion in the SPC model but not in the hospice model of care.

But transitional care planning is more than just about a particular time frame. For example, if the hepatologist has engaged in successful serious illness conversations and care planning at an earlier point in time and learned that among the patient's most important goals was maintenance of ambulatory independence or reasonable mental clarity, then at the point those have been lost and are not likely to be restored, it is time to explore hospice enrollment.

There are some very specific tasks that should be addressed during this time frame if they have not been addressed at an earlier point in time. Among these tasks are legacy work, facing anticipatory grief, and practical planning. The hepatologist will not likely be the professional directing these tasks but is rather the treatment

team leader who recommends such tasks be completed, especially if SPC consultation is not available.

Legacy work involves connecting the terminally ill patient to the future via conversations and projects creating meaning for both the terminally ill patient and surviving family and community. Legacy work provides ongoing meaning and remembrance to those living after loss. But, in my experience, it also provides meaning and purpose for the terminally ill patient living in the face of mortality. For the patient who has had to give up an important social role such as being the family breadwinner or homemaker, it can provide a daily sense of purpose and meaning. It may be accomplished through a variety of tasks ranging from creating memory boxes, preparing "future" letters or presents to be opened at a particular point during the life of a surviving family member (e.g., a child's future graduation), video testimonials, or utilization of the Dignity Therapy framework [57–59].

Anticipatory grief is a grief reaction in anticipation of an impending loss – in essence a grief that occurs before death. It may include cognitive, affective, social, or cultural reactions to expected death felt by the patient and/or the family. The terminally ill patient or family may grieve the loss of a particular ability slipping away due to illness or the general loss of vitality that accompanies almost all dying, other than sudden death. Honesty by the physician about the sorrow of loss is important and can actually be healing in the long run, even though in the short run it may produce tears or even anger. The multidisciplinary team approach of both SPC and hospice care can be quite effective in helping all face the challenges of anticipatory grief as well as grief after death. Although the hepatologist is not expected to deal with this challenging aspect of mortality alone, neither should the hepatologist be allowed to ignore the challenge. A general familiarity with grief assessment and management is a reasonable skill to aspire to and practical consensus-based guidelines for facing grief are available in the general medicine literature [60].

Finally, there are practical aspects to dying and death that must be faced sooner or later and are typically faced better when addressed sooner. These can include such basic tasks as getting one's legal affairs in order, making provisions for the transmission of physical or financial assets, bill paying during illness or after death, and funeral arrangements. Again, the hepatologist is not expected to take the lead in such issues but rather should be able to make referrals as needed to those who are trained and equipped to help.

Hospice Enrollment

Compared to terminally ill persons without chronic liver disease, those dying from chronic liver disease have longer hospitalizations (19.4 vs 13.0 days), higher costs ($175,000 vs $109,000) prior to hospice enrollment, and shorter hospice lengths of stay (13.7 vs 17.7 days) [61]. One can think of these longer hospital stays and higher costs prior to death as non-beneficial. They did not lead to a meaningful prolongation of survival, and given the high symptom burden of end-stage liver disease,

these non-beneficial treatments were almost certainly associated with increased suffering. I believe that every liver specialist has an obligation to help improve this problem but also admit it is not an easy problem to solve! The reasons are complex, not the least of which is the potential for definitive cure via transplantation. In 2016 the number of candidates on the adult liver transplant waiting list was 11,340, and the number of transplants was 7,841. Of adult wait-list registrants in 2013, the 3-year cumulative transplant incidence was 55% – varying significantly by geography from 29% to 86%, with 13% dying on the wait-list and another 19% removed from the list [62]. Life is precious. Few persons want to forgo the possibility of longer life offered by transplant, yet few want to endure suffering without benefit. The sooner transplantation teams conclude a patient will never be a candidate for liver transplantation, the more likely the patient will be able to avoid non-beneficial treatment and suffering at life's end. On the other hand, if even the most remote possibility of transplant is dangled in front of the patient and family, most will want to pursue that remote possibility.

Conclusion

My hope is that this chapter will prove helpful to the hepatologist in best treating the total suffering of the advanced cirrhotic. This total suffering from cirrhosis and its complications is best eliminated by liver transplantation, yet the majority of advance liver patients will live for some time uncertain as to whether a transplant will be received, a substantial portion of patients will never receive the desired transplant, and those who receive transplantation remain mortal beings – as do we all. Supportive palliative care does not require eschewing the possibility of transplant in the same manner that hospice does. As with other serious illnesses in the modern era such as metastatic cancer or advanced heart failure, earlier integration of palliative care principles and specialty consultation as available into the management of advanced liver disease should be strongly considered. Finally, both the hepatologist and the palliativist will do well to reflect daily on the ancient Hippocratic wisdom: *Ars longa, vita brevis, occasio praeceps, experimentum periculosum, iudicium difficile*. Life is short, the art (craft) is long, opportunity fleeting, experiment treacherous, judgment difficult.

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