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Editors

Complications of Cirrhosis

Evaluation and Management

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Preface

The field of hepatology has never been so dynamic as it is today, with advances in the understanding of disease pathogenesis, imaging, and therapeutics all providing an unparalleled opportunity to treat patients who suffer from the complications of cirrhosis. However, such treatments require careful assessment for efficacy and value. Moreover, some interventions such as liver transplantation are only available to a select group of patients. Determining disease prognosis, who should be considered for transplant, and how to manage patients that are terminally ill with cirrhosis are challenges faced by practitioners on a daily basis.

Cirrhosis is the twelfth leading cause of mortality in the USA accounting for more than 30,000 deaths per year. In addition, it accounts for 4–5 % of deaths of people between the ages of 45 and 54 years in the USA. These numbers are driven by the complications patients with cirrhosis suffer. In addition, the economic burden of cirrhosis and its complications are considerable as the estimated national average cost in the USA for treatment ranges from $14 million to $2 billion, depending on disease etiology. Thus a thorough understanding of the diagnosis and management of cirrhosis and its complications are mandatory for the practicing physician.

In this book, we have assembled an outstanding international group of experts that provide insights into the management of the most common complications of cirrhosis. We would like to thank them for their exceptional contributions that summarize the currently available management options and review increasingly important topics surrounding delivery of care to patients with cirrhosis.

We acknowledge Mr. Andy Kwan and Ms. Portia Wong from Springer, whose support for this project was invaluable to its development and successful completion.

We would like to thank our families, Gurmeet and Thomas Keaveny, Maria Luisa and Luis Cardenas, for their forbearance during the book's preparation.

Finally, we remember the countless patients and families who we have cared for over the years—it is our sincere wish that the information so generously provided by this book's contributors will provide comfort and hope, prolong life, and alleviate suffering to current and future patients.

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Part I

Diagnosing and Prediction—Getting It Right Now, Predicting It Right in the Future

Pathogenesis and Evolution of Liver Fibrosis: Cirrhosis or Cirrhoses?

1

Francesca Saffioti and Massimo Pinzani

"Cirrhosis" identifies the morphologic alterations observed in the end stage of a variety of chronic liver diseases (CLD), characterized by a deranged hepatic angio-architecture, in which regenerative parenchymal nodules are encapsulated and separated by fibrotic septa. Key morphological features of cirrhosis include: diffuse fibrosis, regenerative nodules, altered lobular architecture, and establishment of intrahepatic vascular shunts between afferent (portal vein and hepatic artery) and efferent (hepatic vein) vessels of the liver [1]. The vascular shunts are determined by the topography of the vascularised fibrotic septa and represent an essential feature of cirrhosis [2]. Other relevant characteristics include: capillarisation of sinusoids and perisinusoidal fibrosis, vascular thrombosis, and derangement of the vascular network in portal tracts, and under-perfusion of lobular parenchyma with consequent tissue hypoxia [3, 4]. Altogether, these changes are responsible for the development of portal hypertension (PH) and its related complications. PH is indeed the principal mechanism leading to the death of cirrhotic patients. In addition, the constant attempt of hepatocyte regeneration which takes place in a fibro-inflammatory tissue microenvironment leads to the possilble occurrence of hepatocellular carcinoma (HCC).

The term "cirrhosis" was introduced almost two centuries ago and traditionally implies an adverse prognosis related to the complications of PH, HCC, and liver failure typical of advanced stage CLD. However, with the increasing knowledge about the pathophysiological mechanisms and the advances in clinical management achieved in the past 30–40 years, the use of the name "cirrhosis", indicating a static and irreversible end-stage condition, appears more and more inappropriate to describe the advanced stage of chronic fibrogenic liver diseases. The current distinction between compensated and decompensated cirrhosis, based on the degree of portal pressure and the occurrence of clinical complications, but not on other potentially relevant biological events such as altered tissue regeneration and the progressive loss of specific liver functions, does not reflect the spectrum of different stages with a range of feasible and stage-related therapeutic options (e.g. antiviral treatments in patients with hepatitis B virus (HBV) and hepatitis C virus (HCV) cirrhosis and promising antifibrotic agents) [5]. In this context, the definition of favourable or unfavourable endpoints and the need of an integrated clinical–pathological assessment, which should include etiology, grade of activity, comorbidity, risk factors for malignancy,

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and features potentially suggestive of progressive disease have clearly emerged [6].

In 2012, a group of liver pathologists belonging to the International Liver Pathology Study Group suggested that it is time to find a more rational and clinically useful approach to identify different stages of the evolution of advanced-stage CLD which better describe the dynamic development of the disease [7]. A key concept emerging from this proposal is the different fibrotic evolution of diverse CLD which leads to different types of cirrhosis, implying the concept of "etiology-driven cirrhosis". This entails the consideration of different predominant mechanisms and fibrogenic cell types in the progression of CLDs.

Mechanisms of Hepatic Fibrogenesis

The reiterated liver tissue damage due to infective (mainly hepatitis B and C viruses), toxic (in particular alcohol) drug induced, metabolic (iron and copper overload, non-alcoholic liver disease), and autoimmune causes (autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC)), activates a series of pro-fibrogenic mechanisms leading to the progressive accumulation of fibrillar extracellular matrix (ECM) [8–10]. Essential features of hepatic fibrogenesis are: the cellular damage consistent in a variable degree of necrosis and apoptosis of hepatocytes and/or cholangiocytes surrounded by a composite inflammatory infiltrate including mononuclear cells and lymphocytes, the perpetual activation of different highly proliferative, hyperplasic and contractile types of ECM-producing cells. In biological terms, fibrogenesis is a dynamic process characterized by continuous accumulation of fibrillar ECM associated with continuous degradation and remodelling in a context of chronic tissue damage. Fibrosis emerges as an apparently static result when degradation is not sufficient [9]. The principal mechanism leading to liver fibrosis is the chronic activation of the wound-healing reaction. The wound-healing process is normally characterized by an ordered cascade of biological events involving cells and soluble factors aimed at resolving a single tissue injury. In general terms, these events and effectors are disposed in a logical sequence with activation of the next step preceded by the resolution of the previous phase (for review see [11]). This process, which is highly efficient in the presence of a single acute tissue insult, leads to progressive scarring when tissue damage is chronic. In other terms, deposition of fibrillar matrix rather than organized tissue regeneration becomes the best option in order to maintain tissue continuity. The modification in ECM composition (predominantly collagen types I and III) has not only obvious mechanical and physical but also biochemical implications, thus contributing to the modulation of several cellular functions (growth, migration, gene expression) through a direct interaction between ECM components and cell adhesion molecules and by functioning as reservoir for pro-inflammatory and pro-fibrogenic mediators [8, 10, 11].

The reference fibrogenic cell type in the liver is represented by the hepatic stellate cell (HSC). HSCs are characterized by the physiological ability to store retiny-esters in intracytoplasmic lipid droplets and by ultrastructural features of vascular pericytes possibly contributing to the regulation of sinusoidal blood flow [12]. The process of HSC activation and phenotypical transformation into myofibroblasts, as well as their pro-fibrogenic role have been extensively clarified and represent an important basis for the understanding of the hepatic fibrogenic process. It is now evident that distinct ECM-producing cells, each with a distinct localization and a characteristic immunohistochemical and/or electron microscopic phenotype, are likely to contribute to liver fibrosis [8–10]. These include: fibroblasts and myofibroblasts of the portal tract, smooth muscle cells localized in vessel walls and myofibroblasts localized around the centrolobular vein. It is also evident that the relative participation of these different cell types is dependent on the development of distinct patterns of fibrosis. In addition to resident mesenchymal cells, myofibroblasts may derive from a population of unique circulating fibroblast-like cells derived from bone marrow

stem cells, commonly termed "fibrocytes", which has been identified and characterized in recent years [13, 14]. Depending on the pattern of fibrosis evolution, different ECM-producing cells may have a predominant role. For instance, HSC are likely to be more involved when hepatocellular damage is located within the liver lobule, whereas portal fibroblasts and myofibroblasts play a major role when the damaged zones are the periportal areas. In the more advanced stages of the process, it is likely that all those cell type are involved in ECM production and contribute to fibrogenesis.

While much of the attention has been directed at myofibroblast-like cells as the effectors of fibrillar ECM synthesis, increasing evidence suggests that the effective drive towards a fibrogenic evolution of CLD is due to a concerted action between activated myofibroblasts and other cells and biological events involved in the chronic wound-healing reaction. Platelet aggregation/degranulation and the activation of complement and of the coagulation cascade represent the initial events of the wound-healing reaction. Accordingly, several studies, mostly based on animal models, demonstrate that anticoagulants or antiplatelet agents prevent fibrosis by acting on HSCs [15]. The role of macrophages is an area of intensive investigation at present. Macrophages have been shown to be indispensable for both fibrosis progression and regression [16–18]. The modulation of macrophage activity in one sense or the other is conditioned by the features of the network of cytokines and other soluble factors dictated by the direction taken by the wound-healing reaction, i.e. progression if the cause of damage is persistent or resolution if the causative agent has been successfully removed. In CLD characterized by damage, proliferation, and activation of the biliary epithelium, cholangiocytes tend to express a wide array of profibrogenic molecules, thus contributing to the peribiliary fibrogenic process [19, 20]. Indeed, "activated" cholangiocytes play an active role in stimulating fibrogenic, apoptotic, and proliferative response, through an intense crosstalk with portal fibroblasts/myofibroblasts and HSC mediated by proinflammatory and chemotactic cytokines (such as interleukin (IL)-6, tumour necrosis factor alpha (TNF-α), IL-8, and monocyte chemoattractant protein-1 (MCP-1)). Several growth factors (endothelin-1 (ET-1), platelet-derived growth factor-BB (PDGF-BB), transforming growth factor (TGF-2), connective tissue growth factor (CTGF)), released in the portal spaces by immune cells, macrophages, and mesenchymal cells, or produced by the epithelium itself, contribute to promote the synthesis of ECM and may have relevant effects on epithelial cell function. This mechanism, which has been recently highlighted in the genesis of cholangiocarcinoma [21], is likely to play an important role in PSC.

The involvement of oxidative stress has been documented in all fibrogenic disorders characterized by chronic tissue damage and the overexpression of critical genes related to extracellular matrix remodelling and inflammation (for review see [22]). Oxidative stress resulting from the presence of free radicals as well as by a decreased efficiency of antioxidant defences, does not represent simply a potentially toxic consequence of chronic tissue injury but actively contributes to excessive tissue remodelling and fibrogenesis. Accordingly, reactive oxygen species (ROS) or reactive aldehydes (in particular 4-hydroxy-2,3-nonenal, HNE) released by damaged or activated neighbouring cells can directly affect the behaviour of myofibroblasts by an up-regulation of pro-fibrogenic genes including procollagen type I, MCP-1, and tissue inhibitor of metallopeptidase-1 (TIMP1) [22]. Along these lines, oxidative stress likely represents a predominant pro-fibrogenic mechanism in conditions such as chronic alcoholic hepatitis and non-alcoholic steatohepatitis (NASH). In these settings, perisinusoidal fibrosis may develop independently of evident tissue necrosis and inflammation due to the direct pro-fibrogenic action of ROS, HNE, and several acetaldehydes in the case of chronic alcohol abuse [23].

In the past decade, more and more attention has been given to the alterations of mechanisms of innate immunity in the establishment of a systemic pro-inflammatory and pro-fibrogenic environment affecting the progression of CLD.

The symbiotic relationship existing between gut microflora and human host plays an important role in modulating immunological homeostasis and is integral to health. In CLD, a combination of dysbiosis (e.g. an imbalance between pathogenic and non-pathogenic bacterial species), increased intestinal permeability, altered gut defences, and reduced immunological surveillance leads to increased migration of bacteria or bacterial products from the intestinal lumen to mesenteric lymph nodes or other extraintestinal organs or sites [24]. Multiple lines of investigation suggest that bacterial translocation contributes to CLDs, particularly in NASH [25]. In particular, the attention is focused on bacterial by-products termed pathogen-associated molecular patterns (PAMPs). PAMPs are lipoproteins, bacterial DNA, and double-stranded RNA, which are recognized by pattern recognition receptors (PRRs) present on a wide variety of cells, including fibroblasts [26]. The interaction between PAMPs and PRRs serves as a first line of defence during infection and activates numerous pro-inflammatory cytokine and chemokine responses. In this context, it is particularly relevant that fibroblasts, myofibroblasts, and vascular pericytes express a variety of PRRs, including toll-like receptors (TLRs), and that their ligands can directly activate these cell types and promote their differentiation into collagen-producing myofibroblasts [27, 28]. In addition, upon stimulation with the TLR4 ligand lipopolysaccharide (LPS) or the TLR2 ligand lipoteichoic acid, fibroblasts activate mitogen-activated protein kinase (MAPK) pathways, translocate NF-κB and secrete substantial amounts of pro-inflammatory cytokines and chemokines [29]. The interaction between PAMPs and PRRs, particularly TLRs, is in addition important for the establishment of a pro-inflammatory/pro-fibrogenic condition in a defined vascular district, i.e. the portal circulation, with activation of HSC expressing TLRs by an excessive amount of PAMPs reaching the liver as a consequence of abnormal intestinal permeability in conditions such as chronic alcohol abuse, diabetes, and obesity [30, 31].

Neo-Angiogenesis: A Key Mechanism Towards Cirrhosis

The progression of CLD towards cirrhosis is not only characterized by fibrogenesis. The formation of new vessels (angiogenesis) and the establishment of an abnormal angioarchitecture of the liver is a process strictly related to the progressive fibrogenesis leading to cirrhosis and liver cancer. Established evidence clearly indicate that CLD are characterized by intrahepatic vascular remodelling with capillarisation of sinusoids, and the development of intrahepatic shunts, which would lead to increased hepatic resistance (and hence to increased portal pressure) and decreased effective hepatocyte perfusion (and hence to liver failure) [32, 33]. The development of neoformed vessels tends to follow the progression of fibrosis within the liver parenchyma. The effort of tissue revascularisation is indeed chaotic with the formation of many "blind end" vascular structures and a minority of attempts resulting in portal-central anastomoses (shunts between afferent and efferent hepatic vessels). These anastomoses follow irregular patterns and are embedded in the fibrotic tissue which contains contractile cells such as activated hepatic stellate cells and myofibroblasts. As a consequence, the development of intrahepatic shunts leads to increased hepatic resistance and to a further reduction of the effective perfusion of hepatocytes, thus reiterating the hypoxic stimulus to angiogenesis and fibrogenesis. In this context, a key interplay and/or association between fibrogenesis and angiogenesis in CLD is suggested and supported by several findings: (a) angiogenesis and upregulation of vascular endothelium growth factor (VEGF) expression have been documented in different models of acute and chronic liver injury [34, 35] as well as in specimens from human fibrotic/cirrhotic liver and hepatocellular carcinoma [36–38]. Following their activation and phenotypical modulation, HSC tend to acquire a generic "pro-angiogenic" phenotype. In aggregate, the available experimental evidence suggests that HSC may represent a cellular crossroad connecting neo-angiogenesis to inflammation and fibrogenesis. Indeed, these cells represent a target for the multiple actions

of VEGF and angiopoietin 1 (Ang-1), including stimulation of proliferation, collagen type I synthesis, and recruitment of HSC [39]. At the same time, activated HSC are a significant source of these angiogenic cytokines under conditions of hypoxia, acute and chronic liver injury, possibly through the contribution of a number of growth factors, pro-inflammatory cytokines, and conditions of altered metabolic control, as recently suggested by data indicating that leptin is able to up-regulate VEGF and Ang-1 [40].

Etiology-Driven Fibrogenetic Mechanisms and Patterns

Although cirrhosis is the common result of progressive fibrogenesis, there are distinct patterns of fibrotic development, related to the underlying disorders causing the fibrosis [41]. Biliary fibrosis, due to the co-proliferation of reactive bile ductules and periductular myofibroblast-like cells at the portal–parenchymal interface, tends to follow a portal-to-portal direction (Fig. 1.1b). This leads to the formation of portal–portal septa surrounding liver nodules, where the central vein and its connections with the portal tract are preserved until late stages. In contrast, the chronic viral hepatitis pattern of fibrosis is considered the results of portal-central (vein) bridging necrosis, thus originating portal-central septa (Fig. 1.1a). In addition, this form of fibrogenic evolution is characterized by the presence of "interface" hepatitis and development of portal-to-portal septa and septa ending blind in the parenchyma, and by rapid derangement of the vascular connections with the portal system (early portal hypertension). The so-called central to central (vein) form of fibrogenic evolution is in general secondary to venous outflow problems (e.g. chronic heart failure) and is characterized by the development of central-to-central septa and "reversed lobulation". Finally, a peculiar type of fibrosis development (pericellular/sinusoidal) is observed in alcoholic

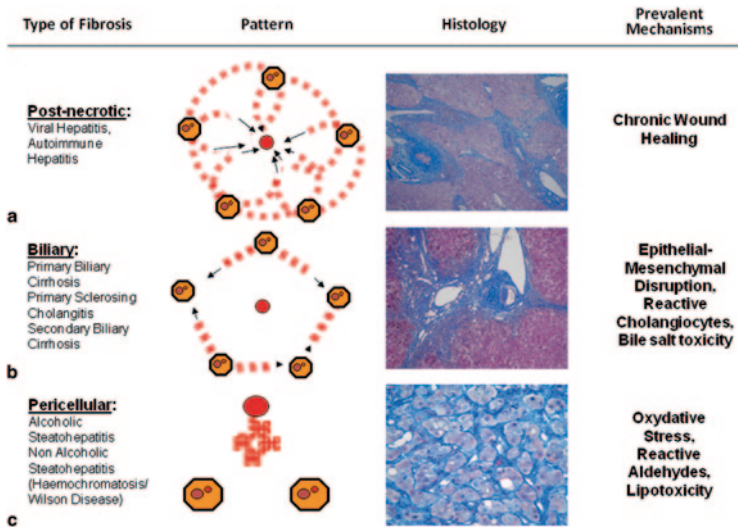

Fig. 1.1 Different patterns of etiology-driven fibrosis. **a** *Postnecrotic fibrosis*. Low magnification picture of a section of liver from a patient with chronic HBV infection (chromotrope aniline *blue* stain). Collagen is stained *blue*. Inflamed, expanded portal tracts are linked by fibrous tissue (*short arrows*). A slender fibrous bridge connects a portal tract and an outflow venule in the *middle* of the picture (*long arrow*). **b** *Biliary fibrosis*. Low magnification picture of a section of liver from a patient with primary sclerosing cholangitis (chromotrope aniline *blue* stain). Collagen is stained *blue*. Inflamed, expanded portal tracts are linked by fibrous tissue. A rounded scar (*arrow*) is present at the site of a destroyed bile duct, and there is fibrous thickening of the adjacent blood vessel wall. **c** *Pericellular fibrosis*. High magnification picture of a section of the liver from a patient with alcoholic hepatitis (chromotrope aniline *blue* stain). Collagen is stained *blue*. A fibrous lattice surrounds individual and small groups of hepatocytes. *Pale blue* intracytoplasmic Mallory material and associated inflammation can also be seen

and metabolic liver diseases (e.g. NASH), in which the deposition of fibrillar matrix is concentrated around the sinusoids (capillarisation) and around groups of hepatocytes (chicken-wire pattern) (Fig. 1.1c). These different patterns of fibrogenic evolution are related to different factors and particularly: (1) the topographic localization of tissue damage, (2) the relative concentration of pro-fibrogenic factors, and (3) the prevalent profibrogenic mechanism(s). In addition, these different patterns imply the participation of different cellular effectors of the fibrogenic process.

The knowledge of these aspects of the pathophysiology of CLD provides important insights on the correlation between times to progression of liver disease, the etiology agents, the dynamics of the necro-inflammatory infiltrate, the distribution of fibrosis, and the onset and progression of PH, depending on the etiology agent leading to cirrhosis. A proof of concept of these considerations derives from a recent study aimed at quantifying the amount of fibrosis present in cirrhotic livers of different aetiologies explanted from patients undergoing liver transplantation presenting with compatible model for end-stage liver disease (MELD) scores [42]. Remarkably, the amount of fibrosis, determined by means of the collagen-proportionate area (CPA) method [43] in cirrhotic liver due to chronic alcohol intake is, on average, double that observed in cirrhotic liver due to chronic HCV or HBV infection. These observations lead to the concept that there are several types of cirrhosis depending on the etiology of CLD. Along these lines, considering that the development of PH is the net result of several pathophysiological features of advanced CLD that ultimately results in increased intrahepatic resistance to portal flow due to static (tissue fibrosis, changes in hepatic angio-architecture) and dynamic (scar tissue contraction, endothelial dysfunction) mechanisms, it is plausible that different pattern of fibrosis progression can influence the development of PH. For example, as mentioned above, bridging fibrosis developing with portal to central septa, typical of chronic viral hepatitis, is characterized by an earlier involvement of the centrolobular vein with the establishment of a rapid derangement of the vascular connections with the portal system and leads to what is defined "sinusoidal PH". Instead, in fibrosis secondary to cholestatic diseases, which develop with a portal to portal pattern, the involvement of the centrolobular vein usually occurs later, with a more evident development of pre-sinusoidal resistance to portal flow.

Fibrosis and Portal Hypertension

Portal hypertension results from an increased intrahepatic resistance combined with increased portal (and hepatic arterial) blood flow. The increased intrahepatic resistance is the result of architectural distortion (fibrous tissue, regenerative nodules), endothelial dysfunction leading to intrahepatic vasoconstriction, and intrahepatic vascular shunts between afferent and efferent vessels of the liver [44, 45]. These portal-central anastomoses, although representing direct connections between the portal and the systemic circulation, follow irregular patterns and are embedded in a developing scar tissue characterized by the presence of contractile cells (e.g. activated HSC and myofibroblasts). In clinical practice, the hepatic venous pressure gradient (HVPG), an indirect measure of portal pressure, is the best predictor of the development of PH [46–50]. Since all cirrhotic patients are identified by the highest value of the currently used scoring systems, the histological features of disease progression within the stage of cirrhosis have not been traditionally linked to clinical outcomes. However, progressive increases in HVPG correlate with increasing severity of liver disease (normal, chronic hepatitis, pre-cirrhosis and cirrhosis) both in alcoholic [51] and in non-alcoholic liver disease [52]. In addition, the analysis of gross histologic features may also have important prognostic implications in cirrhotic liver biopsies: the thickness of fibrous septa correlates with HVPG and is an independent predictor of both clinically significant portal hypertension (e.g. HVPG >10 mmHg) [53] and clinical decompensation [54]. A more precise definition of the relationship between the fibrogenic evolution occurring within cirrhotic liver and the worsening of PH has been established

with the use of a new histological marker, the collagen proportionate area (CPA), obtained by digital video imaging analysis [55]. Additional work by the same authors suggests that CPA is indeed a histological variable that scores cirrhosis with a continuous scale and is able to predict relevant clinical outcomes [56].

Reversibility of Fibrosis and Cirrhosis

Although a regression has been shown in animal models of cirrhosis, this possibility is not yet fully substantiated in humans. Evidence of either fibrotic or cirrhotic regression has now been reported in CLD of different aetiologies, including viral hepatitis [57–63], autoimmune hepatitis [64], alcoholic and non-alcoholic steatohepatitis [65–67]. However, when these results were examined by experienced liver pathologists, there was agreement only for a variable degree of fibrosis regression in cirrhosis but not for a reversal of cirrhosis in most cases [68, 69]. Along these lines, there is no convincing evidence that the abnormalities of the intrahepatic vasculature revert in the human cirrhotic liver. Actually, the available evidence suggests that the so-called veno-portal adhesions persist even in cases of extensive fibrosis regression, and evident "arterialized" sinusoids appear in the context of intrahepatic arteriovenous shunts [70].

The most obvious problem when discussing the issue of fibrosis regression in cirrhosis or even cirrhosis reversal is the lack of a clear and common language in the precise distinction of advanced fibrosis ("pre-cirrhosis") from true cirrhosis and the staging of cirrhosis. The problem is fundamentally based on the use of semi-quantitative scoring systems for staging fibrosis and the fact that cirrhosis is always represented by the highest score and considered as the end stage of CLD [69, 71]. Indeed, cirrhosis appears in a very broad spectrum of variants (early, fully developed, "active" and "inactive") and more than one study has documented the transition from micronodular to macronodular cirrhosis following the discontinuation of the causative agent [72, 73]. While it is doubtful than an accurately defined cirrhosis is able to reverse to normal, there is sound evidence concerning the capacity of the healing liver to reabsorb scar tissue following an effective causative treatment (e.g. sustained viral response, abstinence from alcohol, etc.). However, scar tissue in the liver of patients with CLD lasting 30 or more years is likely characterized by different stages of biochemical and biological evolution. Indeed, fibrotic deposition related to recent disease and characterized by the presence of thin reticulin fibres, often in the presence of a diffuse inflammatory infiltrate, is likely fully reversible, whereas long-standing fibrosis, branded by extensive collagen cross-linking by tissue transglutaminase, presence of elastin, dense acellular/paucicellular ECM and decreased expression and/or activity of specific metalloproteinases, is not [74, 75]. In other words, within the same liver there are different types of scar tissue with different potential and dynamics of reversibility once the etiology agent is eradicated and/or anti-fibrogenic strategy is established. In addition, substantial experimental evidence suggests that long-term fibrogenesis occurring in human CLD is characterized by a progressive resistance to apoptosis of hepatic stellate cells/myofibroblasts with the consequent immovability of a critical mass of pro-fibrogenic cells [76].

Conclusions

The different aspects of the fibrogenic evolution towards the advanced stage of CLD illustrated in this chapter should invite to an open discussion and most importantly, to active research to address the question: "cirrhosis or cirrhoses?" Indeed, at least in the pre-clinical phase of cirrhosis, when there are no evident clinical manifestations, it is likely that the disease is sustained by different prevalent mechanisms depending on disease etiology. This potentially calls for different morphological classifications, different non-invasive diagnostic and prognostic indicators, different etiology-driven and/or antifibrotic therapies and, most importantly, different expectations on the effective reversibility of fibrosis and cirrhosis.

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Natural History of Cirrhosis

2

Guadalupe Garcia-Tsao

Cirrhosis is considered the end stage of chronic liver disease of any etiology with a broad spectrum of clinical manifestations that are due to portal hypertension and/or liver insufficiency. The gold standard in the diagnosis of cirrhosis is considered histological and is characterized by a disrupted liver architecture secondary to regenerative nodules surrounded by fibrous septa. Once cirrhosis is established, it has been considered that the process is progressive and irreversible with an inevitable progression to death unless liver transplantation (LT) is performed. Cirrhosis had also been considered a single entity with a continuum of increasing degrees of severity and common predictors of death. These paradigms have shifted in recent years [1] as described in the following paragraphs.

Is Cirrhosis the Same Irrespective of Etiology?

The pathophysiological process that leads to cirrhosis is complex but, at its core, consists of progressive fibrogenesis. However, as recently pointed out, different types of chronic liver disease lead to different patterns of fibrosis and may therefore lead to different clinical manifestations [2]. For example, in primary biliary cirrhosis, where the process is predominantly portal and therefore fibrosis is mainly portal to portal, the initial clinical complications may be secondary to presinusoidal portal hypertension (varices and variceal hemorrhage without liver insufficiency or ascites) while in alcoholic cirrhosis, where fibrosis is sinusoidal, initial complications will be secondary to sinusoidal portal hypertension and liver insufficiency (ascites, in addition to varices and variceal hemorrhage). Therefore, although cirrhosis is the end stage of any chronic liver disease, its natural history may vary depending on its etiology.

Is Liver Biopsy the Gold Standard in the Diagnosis of Cirrhosis?

Even though liver biopsy remains the gold standard in the diagnosis of cirrhosis, it is an imperfect test. It is an invasive procedure with potential complications, including death, along with sampling errors that can lead to a missed diagnosis of cirrhosis. It has been shown that measurement of hepatic venous pressure gradient (HVPG), an indirect measure of sinusoidal pressure obtained through catheterization of the hepatic vein, has a greater diagnostic accuracy than liver biopsy in the diagnosis of cirrhosis. In a study of 116 patients with recurrent hepatitis C post-LT, HVPG was very accurate in predicting the development of disease progression (with an area under the curve [AUC] of 0.96), more so than the presence of significant fibrosis on liver biopsy (AUC

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0.80) [3]. An HVPG measurement of 6 mmHg or greater indicates the presence of cirrhosis. HVPG addresses a larger area of hepatic parenchyma than liver biopsy, since the pressure obtained is the average pressure of many sinusoids, thus reducing the possibility of sampling error due to the presence of fibrosis heterogeneity within the diseased liver. More recently, noninvasive tests including serum markers, ultrasound, and liver and/or spleen stiffness measurements have become important tools in ruling in or excluding cirrhosis with a high diagnostic accuracy and may substitute for liver biopsy in the diagnosis of cirrhosis.

Nevertheless, the extent of liver fibrosis (by semiquantitative or quantitative assessment of liver biopsy) correlates with different prognostic strata in the cirrhotic liver and histological features (thickness of fibrous septae or fibrosis area) in a liver biopsy may have a prognostic/stratifying role [4–7].

Is Cirrhosis Irreversible?

The advent of effective therapies, specifically antivirals, has shown that cirrhosis is a dynamic and potentially reversible process. Several recent studies performed in patients with chronic hepatitis B infection have shown that histological regression (by at least one stage) of advanced fibrosis/cirrhosis occurs in at least 50% of patients receiving antiviral therapy [8]. Likewise, in studies performed in patients with hepatitis C infection, sustained virological response (i.e., viral elimination) to specific antiviral therapy has led to histological regression of cirrhosis in about 62% of patients [8].

The assessment of regression of fibrosis by liver biopsy is also subject to sampling variability and therefore the rate of regression may be overestimated. A better way to assess such reversibility would be by the application of HVPG measurements (or noninvasive surrogates) because of its higher diagnostic accuracy. It is probable that the likelihood of reversibility will depend on the amount of fibrosis deposited in an already cirrhotic liver [1].

Is Cirrhosis a Single Entity?

Numerous prognostic studies over the years have demonstrated that cirrhosis is not a single entity. In a systematic review evaluating 116 of such studies, the median survival of patients with cirrhosis ranged widely, from 1 to 186 months [9], indicating that cirrhosis is a heterogeneous disease.

When patients were divided in two stages depending on the presence or absence of clinically evident decompensating events (specifically ascites, variceal hemorrhage, hepatic encephalopathy [HE] and jaundice), 1-year survival in those who were compensated, that is, those who had no clinical decompensating events was 95% (interquartile range 91–98%) while in decompensated patients, it was 61% (interquartile range 56–70%) [9]. Analysis of individual patient data from two prospective Italian cohort studies that included over 1600 patients demonstrated a median survival of greater than 12 years in patients with compensated cirrhosis, while patients with decompensated cirrhosis had a median survival of 1.8 years [9]. Compensated patients have a very low probability of death (10% in 20 years) before becoming decompensated [10]. Importantly, the systematic review revealed that predictors of death were different in patients with compensated versus those with decompensated cirrhosis [9].

These results have been confirmed in a recent prospective study that analyzed a concurrent cohort of patients with cirrhosis (both compensated and decompensated) and showed that decompensation was the strongest predictor of death [11]. Furthermore, both stages had different prognostic indicators (age for compensated; model for end-stage liver disease (MELD) score for decompensated), and that those predictors that were common to both stages (albumin, platelet count) had different strengths of association [11].

All these findings support considering the natural history of cirrhosis not as a continuum of a single entity but as a progression across different *prognostic stages*, with the compensated and decompensated stages being the most important. Sub-stages within these two main stages

are being increasingly described and are summarized below. An additional terminal stage in cirrhosis characterized by multi-organ failure has been designated "acute-on-chronic liver failure" (ACLF) and is also discussed. Hepatocellular carcinoma (HCC), although strictly a complication of cirrhosis, is not considered a separate stage of cirrhosis as it may occur in both compensated and decompensated cirrhosis and, when it develops in the compensated patient it can lead to decompensation. Therefore, HCC will not be considered further in this chapter.

1 Compensated Stage of Cirrhosis

Compensated cirrhosis is defined as cirrhosis in the absence of ascites, variceal hemorrhage, HE or jaundice. It is asymptomatic. Importantly, patients in whom ascites is controlled through the use of diuretics or in those with HE that is controlled with specific medications are not compensated patients. Even though therapy may initially resolve some of the clinical complications, the pathogenic mechanisms that led to their development are still in place and, in general, prognosis is not improved by therapy.

In patients with compensated cirrhosis, liver insufficiency is minimal or absent and **portal hypertension** is the predominant pathogenic mechanism (Fig. 2.1).

Portal hypertension is the initial consequence of cirrhosis. An HVPG ≥ 6 mmHg defines portal hypertension, and therefore, as discussed previously, the presence of cirrhosis. This is true in diseases in which the resistance to portal flow is located at the sinusoids, such as alcoholic and/or viral-related cirrhosis [12], as well as cirrhosis secondary to nonalcoholic steatohepatitis. In portal-based diseases (cholestatic liver diseases), there will be an important presinusoidal component of portal hypertension that is not reflected by the HVPG which, at least initially, will underestimate the actual portal pressure. Therefore, patients with cholestatic liver disease have been routinely excluded from therapeutic or prognostic studies using HVPG. Once a threshold HVPG of 10 mmHg has been reached/surpassed, patients are at a higher risk of developing gastroesophageal varices [13]. Patients in whom varices are present have an HVPG of 12 mmHg or greater [14].

Different prognostic sub-stages have been identified in patients with compensated cirrhosis based on the following stratifying factors:

a. Gastroesophageal varices

The initial mechanism leading to portal hypertension is an increase in intrahepatic vascular resistance to portal flow. One of the early consequences of portal hypertension is the formation of porto-systemic collaterals, the most important being those that form via the coronary or the short gastric veins and constitute gastroesophageal varices. Although varices are a complication of cirrhosis, they are asymptomatic (unless they rupture) and are only diagnosed by endoscopy. About a third to half of patients with compensated cirrhosis have varices when first diagnosed [10, 13]. Patients with varices (without ascites, HE or jaundice) that have not bled are still in the low-mortality compensated stage, although studies have shown that rates of mortality and evolution to decompensation are higher in these patients than in those without varices [10, 15, 16]. This has led to the classification of compensated cirrhosis into two sub-stages: stage 1 are patients with compensated cirrhosis who do not have varices (the very compensated patient) while patients with varices are designated as being at stage 2 [9, 10].

One may assume that visualization of porto-systemic collaterals on imaging studies may have the same prognostic significance as the presence of endoscopically-proven gastroesophageal varices, but this remains to be determined.

b. Clinically significant portal hypertension

As mentioned above, in patients with compensated cirrhosis *without varices*, the main predictor of the development of varices is the HVPG. The cutoff that best predicts variceal development is 10 mmHg. While the probability of developing varices at 2 and 5 years in patients with an HVPG ≥ 10 mmHg was 18 and 45 %, respectively, these probabilities were 7 and 30 % in those with an HVPG < 10 mmHg

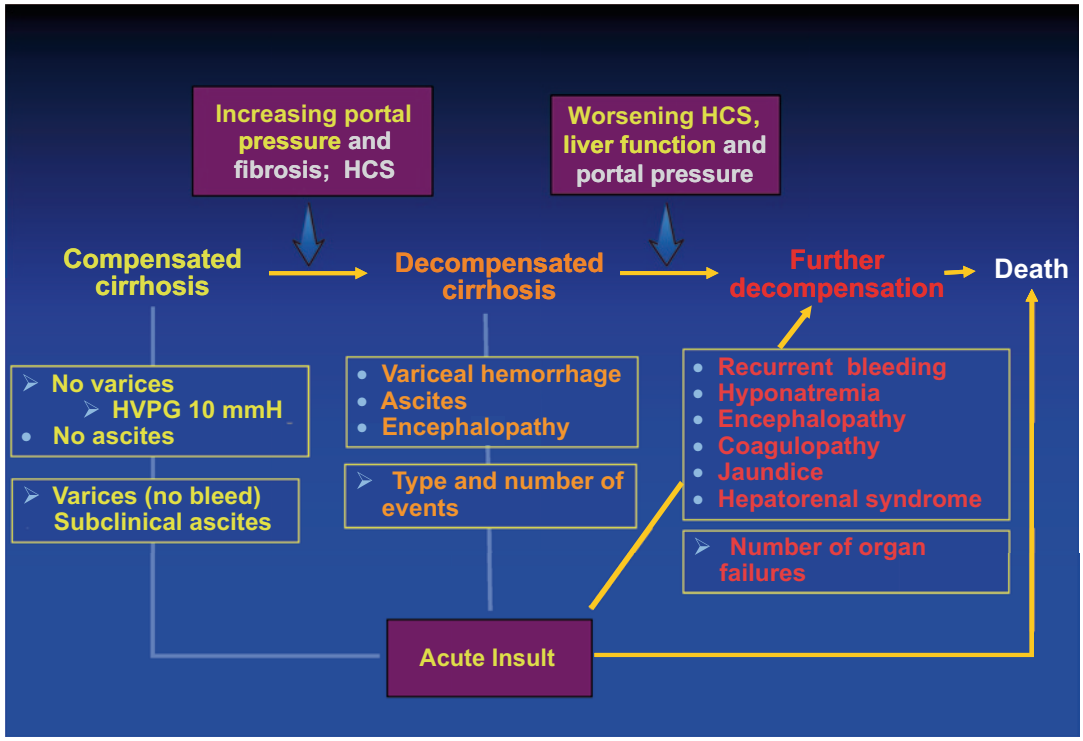

Fig. 2.1 Schematic diagram of the stages of cirrhosis. The compensated patient has no ascites, variceal hemorrhage, encephalopathy or jaundice. The main stratifying factors are the presence or absence gastroesophageal varices, although the presence or absence of subclinical ascites may also be a useful stratifying factor. In patients without varices, an hepatic venous pressure gradient (HVPG)> or <10 mmHg is the main stratifying factor. The principal mechanism in the development of decompensation is increasing portal pressure. Decompensation is defined by the presence of clinically evident events, specifically variceal hemorrhage, ascites and hepatic encephalopathy. The lowest mortality is associated with variceal hemorrhage as the initial event, followed by an isolated nonbleeding event (mostly ascites) and highest mortality with a second decompensating event. A stage of "further decompensation" occurs with worsening of the hyperdynamic circulatory state (*HCS*) and liver dysfunction and usually follows an acute insult (infection). The highest mortality is associated with renal failure. The number of organ failures is proportional with mortality

[13]. In fact, an HVPG≥10 mmHg is also the best predictor of the development clinical decompensation [17] and HCC [18]. The probability of developing decompensation at 2 and 5 years in patients with an HVPG≥10 mmHg was 13 and 29%, respectively, while in patients with an HVPG<10 mmHg, it was 6 and 15%, respectively [17]. An HVPG≥10 mmHg has been termed "clinically significant portal hypertension" (CSPH).

Therefore, it can be proposed that patients without varices could be stratified into those with an HVPG<10 mmHg (without CSPH), that would be the extremely compensated patients (a redefined stage 1), and those with an HVPG≥10 mmHg (with CSPH). The staging system in cirrhosis is clearly in evolution and at this point, simply describing the populations at risk (e.g., patients with compensated cirrhosis with varices or patients with compensated cirrhosis without varices and an HVPG<10 mmHg) is recommended.

Of note, patients with varices have, by definition, CSPH because all patients with gastroesophageal varices have an HVPG of at least 11–12 mmHg [14, 19].

c. Ascites detectable only by ultrasound
Patients who have ascites detectable only by ultrasound have no symptoms or signs referable to ascites and therefore are still compensated. However, a recent study evaluated the prognostic significance of subclinical ascites ($n=38$) in a population of patients with predominantly alcoholic cirrhosis and compared them to patients without ascites ($n=153$) and to patients with clinically-evident ascites ($n=252$) [20]. Patients with subclinical ascites had a survival that was intermediate between patients with overt ascites and those without ascites. This situation would be akin that of the patient with cirrhosis (without ascites or HE) and varices that have never bled who is considered compensated because the presence of varices cannot be established by physical examination. Therefore, as for nonbleeding varices, patients with subclinical ascites should be considered compensated, albeit at a higher risk of death and clinical decompensation than those without any ascites.

d. Portosystemic encephalopathy without liver insufficiency
Perhaps one exception to the definition of decompensation is the case of HE that presents in patients with compensated cirrhosis (no variceal hemorrhage, no ascites) and essentially normal liver synthetic function, in whom HE is the result of a large spontaneous portosystemic shunt [21]. It has been shown that patients with a MELD score less than 11 (i.e., compensated) are more likely to respond to occlusion of the spontaneous shunt, without changes in MELD score in the short-term [22]. The long-term course of patients with HE due to these shunts (and the effect of their occlusion) needs to be further evaluated to determine their prognostic significance. Until then, these (rare) patients could be considered compensated.

2. Decompensated Stage of Cirrhosis
This is the symptomatic stage of cirrhosis and is defined by the presence of ascites, variceal hemorrhage, HE or liver insufficiency (jaundice). The main pathogenic mechanisms are **portal hypertension** and the **hyperdynamic circulatory state** [23]. This hemodynamic abnormality is the result of splanchnic and systemic vasodilatation that increases as HVPG surpasses 10 mmHg and portosystemic collaterals develop. The vasodilatation (manifested clinically as arterial hypotension) leads to activation of the neurohumoral systems, sodium and water retention, increased blood volume and increased cardiac output, that is, a hyperdynamic circulatory state.
Of the decompensating events, overt ascites is clearly the most common, accounting for 60–80% of initial clinical events, followed by gastrointestinal hemorrhage, while HE and jaundice occur as the first clinical event in only a minority of patients [10, 24].
Sub-staging of patients with decompensated cirrhosis is not as well-defined as compensated cirrhosis and requires further investigation. The following are different proposed prognostic sub-stages based on the following stratifying factors:

a. Type and number of decompensating clinical events
Even though each of the individual complications of cirrhosis has an impact on survival in patients with cirrhosis, the magnitude of the impact is different. The Baveno IV consensus conference, based on results from a large Italian cohort, had stratified patients with decompensated cirrhosis into two sub-stages based on the type of initial decompensating event: (1) patients with ascites with or without varices (stage 3) and (2) patients with gastrointestinal bleeding with or without ascites (stage 4) [25]. However, it was shown in another cohort that decompensated patients with ascites have a significantly poorer outcome than those presenting with variceal hemorrhage as the only decompensating event [16]. This led to a re-staging of cirrhosis, based on an Italian prospective inception cohort study of 464 patients in which patient flow across stages was assessed by competing risk analysis [10]. In this re-staging, decompensated patients would be placed in three strata: (1) bleeding without other complications; (2) first nonbleeding decompensation (mainly ascites); and

(3) patients with any second decompensating event [10]. Five-year mortality rates for each of these three stages was 20, 30, and 88%, respectively. The mortality rate difference between patients who present with variceal hemorrhage (no other complication) and those that presented with one nonbleeding complication was not large, similar to findings in another cohort followed for a median of 33 months in which a poor outcome (death or LT) was 20% in patients with variceal hemorrhage and 36% in those with ascites [24]. It is not unexpected that patients that develop more than one complication have the highest mortality. The higher mortality in the different sub-stages was confirmed in a retrospective study of patients on a transplant list with a MELD score < 20 that combined patients with compensated and decompensated cirrhosis [26].

b. Complications of the initial complication or "further" decompensation

Patients who die of decompensated cirrhosis often do so after development of "further decompensation"—worsening of the pathophysiological mechanisms (portal hypertension, hyperdynamic circulatory state and/or liver insufficiency) lead to a subsequent complication after the initial event. Specifically, patients with ascites would develop diuretic-refractory ascites, hyponatremia or hepatorenal syndrome (HRS) as a result of worsening vasodilatation (and decreasing mean arterial pressure) and activation of neurohumoral systems [27]; patients with variceal hemorrhage would develop recurrent variceal hemorrhage as a result of worsening portal pressure and/or worsening of the hyperdynamic circulatory state [28–30]; and patients would develop recurrent/persistent HE, coagulopathy and jaundice as a result of further impairment in liver function. The development of these added decompensating events may have a trigger that is not clinically evident (e.g., overt bacterial infection versus bacterial translocation). Bacterial infections occur in both compensated and decompensated cirrhosis and are a frequent precipitant for acute decompensation (see below) and therefore do not represent a separate stage.

There is evidence demonstrating that refractory ascites has a higher mortality than diuretic-responsive ascites [31], that the presence of hyponatremia is associated with a significantly poorer survival in patients on the liver transplant waiting list, independent of MELD score [32] and that HRS type 1 (acute renal failure in cirrhosis) has a higher mortality than HRS type 2 (renal failure associated mostly with refractory ascites), which in turn has a higher mortality than refractory ascites [33]. In fact, while the median survival in compensated cirrhosis is greater than 12 years (as long as the patient remains compensated), the median survival in decompensated cirrhosis, refractory ascites and in patients with untreated HRS type 1 is approximately 2 years, 7 months and 1 month, respectively. Therefore, another way to stratify patients with decompensated cirrhosis would be to divide them into those who are decompensated by virtue of the development of ascites, variceal hemorrhage or HE and those that have other complications that denote a more advanced liver disease: refractory ascites, hyponatremia, HRS, recurrent/persistent HE, and jaundice.

c. Organ failures

Most of the complications of the "further" decompensated stage represent an "organ failure" with HRS representing the kidney, hypotension (resulting from extreme vasodilatation) representing the circulatory system, encephalopathy representing the nervous system, coagulopathy and jaundice representing liver failure. The presence of multiorgan failure in cirrhosis has recently been termed ACLF. Many definitions of this entity have been proposed in recent years. Most of them, particularly those developed in the West, have in common the presence of acute deterioration of pre-existing cirrhosis [34]. Results of a large multinational European consortium demonstrate that ACLF is distinct from "mere" decompensated cirrhosis [35]. The consortium built a substaging of ACLF based on a modification of the sequential organ failure assess-

ment (SOFA) score, the SOFA-CLIF score. It divides ACLF into 5 grades with progressively greater 28-day mortality: grade 0 (no organ failure, 2 % mortality); grade 1 (one nonrenal failure, 6 % mortality); grade 2 (renal failure alone or an extra-renal failure with added criteria, 22 % mortality); grade 2 (two organ failures, 32 % mortality); and grade 3 (three organ failures, 77 % mortality). Similar results relating organ failures with survival were found in hospitalized patients with cirrhosis and bacterial infections in another Western consortium, the North American Consortium for the Study of End-Stage Liver Disease, in which two extra-hepatic organ failures were associated with a significant increase in mortality compared with patients with only one or no organ failures [34].

An entity that requires further study is the ACLF that presents in a patient with compensated cirrhosis. These patients represent a minority of patients presenting with ACLF but, quite interestingly, their mortality (42 %) is significantly greater than patients who were decompensated and developed further decompensation (30 %) [35].

Summary

Cirrhosis is a dynamic and potentially reversible disease. Large cohort studies looking at predictors of death in cirrhosis have determined that the natural history of cirrhosis is not the continuum of a single entity but is a progression across different *prognostic stages*, with the compensated and decompensated stages being the most important. Patients in these two stages of cirrhosis should be managed differently both clinically and in research. Within the compensated stage, different prognostic strata have been identified, the main one based on the presence or absence of varices. In patients without varices, the main stratifying marker is an HVPG of 10 mmHg. Within decompensated cirrhosis, the different complications and their coexistence (or not) add to the prognostic granularity of the stage (with ascites having a worse prognosis, more so when associated with variceal hemorrhage). However, a stage of "further" decompensation as defined by the presence of complications of the complications (specifically refractory ascites, HRS, recurrent variceal hemorrhage and recurrent/persistent HE) is likely to provide a larger prognostic differential among patients with decompensated cirrhosis. A final stage characterized by multi-organ failure and that has been termed ACLF has the worst prognosis; however, it can occur in both compensated and decompensated patients and requires further evaluation.

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Prediction of Complications of Cirrhosis: Molecular Biomarkers

3

Mar Coll, Elsa Solà and Pau Sancho-Bru

Cirrhosis is no longer viewed as a static end stage in the progression of liver disease. Instead, it is considered as an advanced phase of liver disease that can be stratified based on clinical, histological, and/or pathophysiological findings [1]. Accurate stratification of cirrhotic patients with correct prediction of the development of complications is of utmost importance in order to improve the management and prognosis of these patients.

A molecular biomarker is any biological product or marker that can be measured and is indicative of the presence, stage, or progression of a disease. In cirrhosis, a good biomarker should be able to predict or detect the presence of a particular complication of cirrhosis with a high sensitivity and accuracy. In addition, it must be specific for a particular complication and/or be able to discriminate among these. Moreover, a good biomarker should ideally be detected non-invasively and be cost effective. However, there are no stand-alone biomarkers for cirrhosis with predictive value that are currently available and ready for use in the clinical practice. Nonetheless, a number of biomarkers in this area have been identified and are being considered as predictors of complications or are used in combination with clinical prognostic models for the management of cirrhotic patients.

In this chapter, we describe the efforts that have been made to identify new molecular markers of complications of cirrhosis. This chapter does not include an exhaustive enumeration of molecular markers of liver disease, but rather reviews the existing knowledge on molecular markers associated with complications of cirrhosis and discusses their potential uses as predictive biomarkers for the development of cirrhosis-associated complications.

Molecular Biomarkers Associated with Complications of Cirrhosis

Portal Hypertension, Ascites, and Variceal Bleeding

Portal hypertension is one of the first clinical manifestations of severe architectural changes of the liver structure and function and associated with hemodynamic changes [2]. The hepatic venous pressure gradient (HVPG) greater than 5 mmHg defines portal hypertension and is perhaps the most reliable prognostic indicator of the formation of varices and ascites [3].

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A number of noninvasive methods may be useful in screening for esophageal varices. Platelet count or serum levels of albumin, prothrombin time, and serum bilirubin levels and the alanine transaminase (ALT)/aspartate transaminase (AST) ratio have been associated with the presence of esophageal varices or a higher risk of variceal progression [4–6]. In addition, a low platelet count and serum albumin have also been described as independent predictors of the presence of esophageal varices [4–6]. A recent study in a large series of patients with compensated cirrhosis evaluated the value of noninvasive methods for the prediction of clinically significant portal hypertension and the presence of esophageal varices [7]. This study evaluated liver stiffness, spleen size, and platelet count. Although liver stiffness was the best single noninvasive variable, the area under the curve increased with the combination of the three parameters [7]. Other studies have recently described the indocyanine green retention test (ICG-r15) to assess portal hypertension in compensated patients and as a tool to rule out esophageal varices. However, its usefulness for the prediction of complications related to portal hypertension has not been evaluated [8].

Several serum markers have been described to identify patients who are at risk for significant hepatic fibrosis. Among these, one of the most widely used and validated is the FibroTest [9]. Indeed, a significant correlation has been reported between FibroTest values and HVPG values, occurrence of esophageal varices, and variceal bleeding [10, 11]. However, additional studies are needed to confirm its prognostic value, especially in patients with compensated cirrhosis [12]. Lower baseline levels of hyaluronic acid have also been associated to the likelihood of developing varices in hepatitis C virus patients [13–15].

Biomarkers of endothelial dysfunction have been shown to be useful in the prediction of decompensations and death among cirrhotic patients. Peripheral and hepatic levels of von Willebrand factor correlate with liver function and HVPG in patients with cirrhosis and portal hypertension and distinguish patients with cirrhosis with a different probability of survival free of portal hypertension-related complications [16].

Bacterial infection is frequently associated with upper gastrointestinal bleeding, which may appear in up to 60% of patients. Gut permeability, serum levels of lipopolysaccharide (LPS)-binding protein (LBP) and interleukin-6 (IL-6) were reported higher in patients at high risk of variceal bleeding with portal hypertension. Importantly, both markers were significantly correlated with the degree of portal pressure and clearly decreased under nonselective beta-blocker treatment [17].

Serum inflammatory biomarkers have also been investigated. In a study of a cohort of patients with compensated cirrhosis there was significant correlation of HVPG with IL-1b, IL-1a, Fas-R, and vascular cell adhesion molecule-1(VCAM1) serum levels [18]. The authors of the study also developed a diagnostic test composed of four variables (tumor necrosis factor (TNF)-β, heat shock protein (HSP)-70, at-risk alcohol use, and child class B that allowed the identification of compensated cirrhotic patients with a HVPG≥12 mmHg [18]. In addition, plasma soluble CD163 (sCD163) has also been correlated with the HVPG and with the risk of variceal bleeding [20, 21]. Levels of sCD163 were also higher in patients with ascites [20, 21]. The association between ascites formation and elevated levels of serum cancer antigen 125 (CA-125) could also mean that this antigen may be a highly sensitive serum marker for detection and quantification of ascites. However, it is not currently used in the clinical practice and its usefulness as a predictive biomarker still needs to be confirmed [22].

Bacterial Translocation and Infections

Cirrhotic patients are at risk of developing bacterial infections due to gut barrier dysfunction, increased bacterial translocation, and reduced immune competence [23]. Bacterial infections are known to induce the systemic inflammatory response syndrome (SIRS) in cirrhotic patients and are predictors of complications such as acute kidney injury (AKI), variceal bleeding, or encephalopathy [24–26]. SIRS is associated with a poor outcome and development of complications and may develop in both infected and noninfected pa-

tients precluding the use of SIRS as being used as indicative of infection [24, 27].Therefore, there is a need for potential biomarkers that predict gut barrier dysfunction and bacterial infections and also have the ability to discriminate between infected versus noninfected patients with SIRS.

Increased translocation of bacteria or bacterial products has been described to be predictive of infections and be correlated with the development of complications [23, 28]. The detection of bacterial fragments LPS or bacterial DNA in blood or fluids is correlated with bacterial translocation and spontaneous bacterial peritonitis (SBP), systemic hemodynamic abnormalities, and poor outcome in decompensated cirrhotic patients [23, 28]. Accordingly, a prospective, observational multicenter study has shown that the presence of bacterial DNA in blood and in ascitic fluid is an independent predictor of mortality in patients with cirrhosis [29]. However, bacterial DNA levels are not consistently correlated with the severity of liver disease and have not shown to be good predictors of complications [29, 30]. Moreover, a clear limitation of LPS as a predictive biomarker is the fact that it is mainly expressed in gram-negative bacteria populations, which may underestimate bacterial translocation.

Acute phase proteins are commonly used as clinical markers of infection in the general population [31]. However, a number of confounding factors may alter the expression and circulating levels of acute phase proteins in end-stage liver disease, such as underlying viral liver infection, the local sterile inflammatory response, bacterial translocation, or hepatocellular carcinoma. Despite these limitations, the levels of C-reactive protein (CRP) [32] or high sensitive-CRP [33], LBP [34, 35], and other proteins such as procalcitonin (PCT) [36] or soluble CD14 (sCD14) [34, 35] have been found to be elevated in infected cirrhotic patients and some of them predict mortality [36–38]. Moreover, CRP levels are able to predict the likelihood of clinically significant bacterial infections in patients without overt infections [37].

Serum or ascites levels of inflammatory response markers such as IL-6, IL-8, IL-10, TNF, interferon (IFN)-γ, and monocyte human leukocyte antigen among others have been shown to be early markers of inflammation in cirrhotic patients [39–42]. Although some of these markers may correlate with the outcome of sepsis in these patients, their predictive value for future infections is unclear [39–42].

Hepatorenal Syndrome and Acute Kidney Injury

Hepatorenal syndrome (HRS) is a unique cause of kidney failure of functional origin that occurs in patients with cirrhosis. However, besides HRS, patients with cirrhosis may develop AKI due to other causes, such as prerenal azotemia (PRA), intrinsic AKI (iAKI), bacterial infections, nephrotoxicity, and parenchymal nephropathy [43, 44]. These causes of kidney failure have a completely different treatment approach and prognosis. In this context, biomarkers are of particular interest in order to help categorize the type of renal failure and predict or stage renal dysfunction.

Several prognostic and predictive markers of functional and structural changes of the kidney have been described in the setting of other diseases, and are now being investigated as potential biomarkers in the context of cirrhosis. Kidney biomarkers can be divided into two groups: those that are differentially expressed in the kidney as a result of an injury and can be detected in urine or blood (i.e., kidney injury marker (KIM)-1, IL-18, serum urea, creatinine, among others) [43, 45] and those that may or may not change their expression but can be detected in urine due to a dysfunction in their reabsorption (i.e., neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (CysC), b2-microglobulin, α1-microglobulin, liver-type fatty acid binding protein (L-FABP), albumin, fractional urinary sodium excretion (FENa), among others [43, 45].

NGAL is a 21-KDa protein detected in tubular kidney injury. A number of studies have reported the potential of NGAL as an early marker of AKI in non-liver diseases. Recent studies have shown that urinary NGAL (uNGAL) is useful in the differential diagnosis of AKI in cirrhosis [46]. Patients with cirrhosis and AKI had higher uNGAL levels compared to patients without AKI. Moreover, patients with iAKI had significantly higher

uNGAL levels compared to patients with PRA, HRS, and parenchymal nephropathy [47, 48]. NGAL is also useful in the prognosis in patients with bacterial infections. In a recent study in this group of patients, uNGAL levels were significantly higher in those who developed persistent AKI compared to those with transient AKI. Moreover, in patients with persistent AKI, uNGAL levels were able to distinguish between HRS and other causes of AKI. Finally, baseline values of uNGAL were also able to predict clinical outcomes such as the development of a new infection and survival [49, 50].

CysC is a non-glycosilated protein produced at a constant rate by all nucleated body cells. Almost all CysC filtered by the glomerulus is reabsorbed. CysC is thought to be a more reliable marker of glomerular filtration rate (GFR) as it is less influenced by age, sex, muscle mass, or serum bilirubin levels than serum creatinine [51]. CysC has been used in the field of nephrology. However, results in patients with cirrhosis are limited and nonconclusive. Therefore, more studies are needed to evaluate its usefulness in this setting [52].

Multiple biomarkers have been used to address the differential diagnosis of AKI in cirrhosis. In one study, uNGAL, IL-8, KIM-1, L-FABP, and albumin were found to be significantly increased in patients with iAKI with respect to non-iAKI. The study concluded that a combination of uNGAL, IL-8, KIM-1, L-FABP was able to distinguish iAKI from other causes in patients with cirrhosis and AKI. Moreover, the higher the number of these markers found increased in urine, the higher the probability of structural tubular damage as an underlining kidney dysfunction [53].

Hepatic Encephalopathy

The pathogenesis of hepatic encephalopathy (HE) in chronic liver failure is multifactorial and still not completely understood [54]. Ammonia is considered to be an important factor in the pathogenesis of HE. Indeed, blood ammonia levels are increased in most patients with HE and are strongly correlated with the severity of HE in patients with chronic liver failure [56, 57].

Between 30 and50% of the cirrhotic patients who do not show symptoms of clinical HE present minimal HE (MHE). MHE predicts the development of clinically relevant HE and has an important impact on patients' quality of life [58]. The determination of 3-nitro-tyrosine in serum may be useful to identify patients with MHE. However, its value to predict the subsequent development of HE has not been evaluated [59].

Induced hyperammonemia in cirrhosis causes a deterioration of neurophysiological tests during the inflammatory state but not after its resolution, suggesting that inflammation and its mediators may exacerbate the cerebral alterations induced by ammonia in cirrhosis [60]. This synergy between hyperammonemia and inflammation has been confirmed by other groups. In one study, a positive correlation was found between pro-inflammatory cytokines (TNFα, IL-6, IL-18), arterial ammonia, and serum endotoxin with different grades of HE in patients with cirrhosis [61]. Moreover, inflammatory markers may be of value in discriminating cirrhotic patients with and without MHE, since patients with MHE show higher levels of IL-6 and IL-18 which correlate with psychometric HE score [62]. There is also a significant correlation between serum levels of TNFα and the severity of HE in patients with chronic liver failure [63]. Despite the clear link between inflammatory mediators and the development of HE, their predictive value as biomarkers of HE has not been specifically evaluated.

Magnetic resonance spectroscopy studies in patients with cirrhosis and HE has allowed the identification of early changes in brain metabolites and potential diagnostic biomarkers of HE [64]. There is increase in glutamine and a reduction in myoinositol and choline derivates in patients with HE [65]. Moreover, these changes are associated with the severity of HE and already detected in MHE, indicating that these metabolites may become useful early biomarkers for the diagnosis of the HE in patients with cirrhosis [65]. Indirect noninvasive molecular tests will need to be developed in order to evaluate the suitability of early changes of brain me-

tabolites or circulating inflammatory mediators in cirrhotic patients and their ability to predict the development of HE.

Summary

In recent years, an important number of studies have attempted to identify clinical and molecular markers in order to stage liver cirrhosis or episodes of specific complications. In this regard, a number of molecular markers have been described that accurately reflect the progression of liver disease and presence of complications (Table 3.1). However, few studies have considered predicting the development of complications. Although several biomarkers reflect the existence of a complication, in most cases their utility for the predictive assessment of complications is limited or has not been specifically evaluated. The majority of complications from cirrhosis are the result of a multifactorial situation comprising impaired liver function, fibrosis, local and systemic inflammation, vascular disturbances, and altered gut permeability among other pathophysiological factors. Thus, it is plausible that a number of molecular biomarkers may not be specific for a particular complication, but may be common to a number of complications thereby reflecting the underlying clinical situation. Currently, no single molecular biomarker is used to predict cirrhosis-associated complications in clinical practice. The usefulness of the biomarkers described above as well as others to predict complications must be assessed to allow the development of appropriate indirect noninvasive tests for the prognostic evaluation and prediction of complications associated with cirrhosis.

Table 3.1 Molecular biomarkers associated with complications of cirrhosis

Cirrhosis complication	Biomarker	Potential clinical applicability	Reference
Portal hypertension	FibroTest^{TM}	Correlates with HVPG degree	[12]
–	Hyaluronic acid	Predicts risk of variceal bleeding	[13]
–	Von Willebrand factor	Correlates with HVPG	[16]
–	IL-1β, IL-1α, Fas-R, and VCAM1	Correlates with HVPG	[18]
–	sCD163	Correlates with HVPG and variceal bleeding risk	[19]
–	CA-125	Correlates with ascites detection and quantification	[22]
Bacterial translocation-infections	Bacterial DNA, LPS	Correlates with bacterial translocation and SBP	[28]
–	C-reactive protein	Likelihood of bacterial infection	[33]
Hepatorenal syndrome	Urinary NGAL	Early marker of AKI	[49]
–	Urinary NGAL, IL-8, KIM-1, L-FABP	Marker of AKI due to iAKI	[53]
Hepatic encephalopathy	NH_4	Correlation HE severity	[55]
–	TNFα	Correlation HE severity	[63]
–	lL-6 and IL-18	Minimal HE marker	[62]
–	3-nitro-tyrosine	Minimal HE marker	[59]

HVPG hepatic venous pressure gradient, *LPS* lipopolysaccharide, *SBP* spontaneous bacterial peritonitis, *AKI* acute kidney injury, *TNFα* tumor necrosis factor α, *IL* interleukin, *VCAM* vascular cell adhesion molecule-1, *CA-125* cancer antigen-125, *NGAL* neutrophil gelatinase-associated lipocalin, *KIM-1* kidney injury molecule-1, *L-FABP* liver-type fatty acid-binding protein, *HE* hepatic encephalopathy

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Predictors of Clinical Complications of Cirrhosis

4

Joel P Wedd, Avash Kalra and Scott W. Biggins

The predominant clinical complications of cirrhosis can be classified as either portal hypertensive or malignant. The portal hypertensive complications include ascites, varices and variceal bleeding, hepatic encephalopathy, and hepatic hydrothorax, while the principal malignant complication is hepatocellular carcinoma (HCC). In addition, cirrhotic patients are at risk for malnutrition, sarcopenia, and psychiatric comorbidities. Ultimately, death can result from any of these complications, and practitioners frequently employ clinical or biochemical tools to predict complications or prognosticate on their repercussions. This chapter will discuss the complications of cirrhosis and introduce predictors applicable to the management of patients with cirrhosis.

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Complications of Cirrhosis

For a list of cirrhosis complications covered in this chapter, see Table 4.1.

Portal Hypertensive Complications of Cirrhosis

Cirrhosis was responsible for approximately 49,500 deaths in the USA in 2010 and resulted in more years of life lost due to premature mortality than breast cancer, HIV/AIDS, or cardiomyopathy [1]. In cirrhotic patients, the development of clinical complications such as ascites, encephalopathy, or variceal bleeding signifies "decompensated disease" and portends a worse prognosis. The rate of decompensation in previously compensated patients is about 5–7 % per year [2].

Ascites Ascites is the most common complication of cirrhosis, as approximately 50 % of cirrhotic patients develop ascites within a decade of being diagnosed with cirrhosis [3]. Ascites results from complex vascular consequences of sinusoidal portal hypertension, including endogenous vasoconstriction, renal vasoconstriction, and sodium and water retention. It has been shown to develop when the portal pressure is greater than 12 mmHg [4], and reducing the portal pressure below this threshold is the goal when treating refractory ascites with a transjugular intrahepatic portosystemic shunt (TIPS). The development of ascites is associated with

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Table 4.1 Complications of cirrhosis

Portal hypertensive	Malignant	Systemic
Ascites	Hepatocellular carcinoma	Sarcopenia
Varices	–	Cachexia
Hepatorenal syndrome	–	Fatigue
Hepatic hydrothorax	–	Psychological distress
Portopulmonary hypertension	–	–
Hepatopumonary syndrome	–	–
Hepatic encephalopathy	–	–

a 50 % mortality within 2 years [5], and ascites refractory to medical therapy is associated with a 50 % mortality within only 6 months [6]. The model for end-stage liver disease (MELD) score underestimates the mortality risk of about 25 % of patients with moderate ascites by roughly 4–5 MELD points [7].

Cirrhotic patients carry an increased susceptibility to infection due to serum complement deficiency and reduced neutrophil and macrophage function [8–10]. With this baseline immunodeficiency, proposed mechanisms such as bacterial overgrowth, increased intestinal permeability, and bacterial translocation [11–13] lead to infection of the ascitic fluid, called spontaneous bacterial peritonitis (SBP). SBP demands early recognition, warrants specific evidence-based antibiotic and supportive treatment, and necessitates subsequent antibiotic prophylaxis.

Varices Elevated portal pressure typically above 12 mmHg leads to the development of varices, formed by portosystemic collaterals commonly in the esophagus, stomach, and rectum. At such high portal pressures, varices are at risk for rupture and hemorrhage, which occurs in 25–40 % of patients with cirrhosis [14]. Each episode of variceal hemorrhage is associated with a 15–20 % mortality at 30 days [15].

Hepatorenal Syndrome (HRS) Vasoconstriction of the renal circulation and portal hypertension-induced arterial vasodilatation in the splanchnic vascular bed can result in decreased renal perfusion. The consequence of these vascular changes is HRS, characterized by a rise in the serum creatinine in the absence of other causes of acute kidney injury. HRS is classified as type 1 (a twofold increase in creatinine to over 2.5 mg/dL over 2 weeks) or type 2 (renal insufficiency that progresses less rapidly than type 1). Additional features that are typical of HRS include a low rate of urine sodium excretion, a normal urine sediment with minimal proteinuria, and oliguria. The diagnosis of HRS requires deterioration in renal function after withdrawal of diuretics and administration of a weight-based volume expansion challenge with intravenous albumin [16, 17]. HRS is a common complication of advanced cirrhosis and is associated with a poor prognosis, especially for patients with type 1 HRS. HRS develops in as many as 18 % of patients with cirrhosis, and in 39 % of patients with ascites [18]. The prognosis for patients who develop type 1 HRS is grave and is associated with a median survival of less than 1 month without therapy. By 6 months, type 1 HRS is almost universally fatal [18].

Hepatic Hydrothorax Fluid can accumulate in cirrhotic patients' thoracic cavity as it does in the peritoneal cavity. Hepatic hydrothorax develops in an estimated 5–10 % of cirrhotic patients in the absence of cardiopulmonary disease. Hepatic hydrothorax results from direct movement of ascitic fluid from the peritoneal cavity into the pleural space through small diaphragmatic defects. It involves the right hemithorax in approximately 85 % of cases [19].

The clinical sequelae of hepatic hydrothorax include cough, dyspnea, and hypoxia, and roughly 20 % of cases are refractory [20]. Infection of the pleural fluid, called spontaneous bacterial empyema, occurs in approximately 15 % of patients with hepatic hydrothorax [21]. The prog-

nosis associated with hepatic hydrothorax has not been well-defined, although infectious complications such as spontaneous bacterial empyema are associated with a mortality as high as 20% despite treatment [21].

Portopulmonary Hypertension Portopulmonary hypertension is present in up to 16% of patients with severe liver disease [22]. It is defined as the presence of portal hypertension in addition to increased pulmonary arterial pressure or pulmonary vascular resistance, with no other identifiable cause for pulmonary hypertension. It typically presents with dyspnea on exertion [23] and can be diagnosed by echocardiography or right-heart catheterization [24]. The mechanisms for the development of portopulmonary hypertension remain incompletely understood, with genetic predisposition, a hyperdynamic circulation, and endogenous humoral substances and cytokines all potentially contributing [25–27]. Reports regarding prognosis vary widely, with 5 year survival rates ranging from 10 to 50% [28].

Hepatopulmonary Syndrome In contrast to portopulmonary hypertension, hepatopulmonary syndrome (HPS) is a better defined cause of hypoxemia. It is the result of abnormal intrapulmonary vascular dilation combined with increased pulmonary blood flow, leading to anatomical shunting and a diffusion–perfusion abnormality that is correctable by oxygen supplementation [28]. The pulmonary vascular shunts seen in HPS are preferentially perfuse when the patient is upright, leading to the characteristic symptoms of platypnea and orthodeoxia [29]. Estimates of HPS prevalence vary widely, but the presence of HPS worsens prognosis among patients with cirrhosis [30]. Among cirrhotic patients, HPS is an independent risk factor for mortality, with median survival time of roughly 11 months compared to 41 months in cirrhotic patients without HPS [30], and more severe hypoxemia predicts higher posttransplant mortality [31].

Hepatic Encephalopathy Hepatic encephalopathy (HE) encompasses all the neuropsychiatric abnormalities that develop in the setting of portal hypertension. Overt HE develops in 30–45% of patients with cirrhosis [32]. Subclinical HE is more subtle and characterized by psychomotor slowing, visuoconstructive disabilities, and attention deficits. It is present in up to 80% of cirrhotics [33]. HE is precipitated by neurotoxins normally cleared by the liver, but that are shunted around the liver in the presence of portal hypertension-induced portosystemic collaterals, allowing them to influence the central nervous system. Patients hospitalized with HE experience mortality rates of 42% at 1 year and 23% at 3 years [34].

Malignant Complications of Cirrhosis

Patients with cirrhosis are at increased risk of developing HCC. Those at the highest risk are patients with chronic hepatitis B and C, which together contribute to approximately 80% of HCC cases worldwide [35]. Metabolic diseases, rapidly growing in incidence in western populations, are also independent risk factors for the development of HCC [36, 37]. The annual incidence of HCC varies by etiology of liver disease, as well as geography. In the USA in 2005, the annual incidence was 4.9 per 100,000 people [38]. Staging and prognosis of HCC are discussed later in this chapter.

Systemic Complications of Cirrhosis

While portal hypertensive and malignant complications are easily recognized, sarcopenia is the most common systemic complication. Sarcopenia is a loss of skeletal muscle mass and is present in up to 40% of patients undergoing evaluation for liver transplant (LT) [39]. Its presence adversely affects quality of life and posttransplant outcomes and is an independent predictive risk factor for mortality [39].

Cachexia, in contrast to sarcopenia, is a loss of muscle and fat mass. It is also common among cirrhotic patients. The loss of both muscle and fat mass in cirrhosis is caused in part by complex

metabolic dysregulation processes at the cellular and muscular level [40].

In addition to the nutritional consequences of cirrhosis, patients' disease course is typically complicated by multifactorial fatigue. Psychological distress with anxiety and depression is common, estimated at 23 % of patients undergoing evaluation for LT [41].

Existing Predictors/Prognostic Scores of Complications and Outcomes of Cirrhosis

Child–Turcotte–Pugh Score

The Child–Turcotte–Pugh (CTP) score was originally conceived to predict surgical mortality in patients with portal hypertension [42, 43]. It was subsequently applied to mortality prediction in cirrhotic patients [44]. It organizes five variables [serum total bilirubin, serum albumin, international normalized ratio (INR), ascites grade, and encephalopathy grade] each into three severity categories with different point values (1–3, with 3 representing the most severe derangement). The total points from each variable are added to determine if a patient is in class A, B, or C, each being associated with an increasingly poor prognosis.

The criticisms of the CTP score include its subjective grading of ascites and encephalopathy. In addition, the CTP score's discriminatory power is diminished by its few categories, which limits its consideration as a priority score for LT [45].

Model for End-Stage Liver Disease Score

The MELD score is the backbone of the LT allocation system in the USA. It was developed to predict mortality in patients undergoing TIPS for complications of portal hypertension [46], then expanded to predict 3-month mortality in end-stage liver disease [47] and validated in patients on the LT wait list [48]. It uses serum creatinine, serum total bilirubin, and the INR in an equation producing values ranging from 6 to 40. Despite its merits of objective variables and wide discrimination of mortality risks, the MELD score has been scrutinized for its lack of specificity for individual liver diseases and for its sensitivity to laboratory variation [49]. Nonetheless, the MELD score revolutionized the USA LT allocation system.

Hepatic Venous Pressure Gradient

The hepatic venous pressure gradient (HVPG) measurement requires an invasive procedure to directly measure hepatic vein pressure and indirectly measure the portal pressure. The HVPG is used to diagnose portal hypertension, differentiate between portal hypertension secondary to liver disease versus heart disease, and prognosticate on the risk of complications from cirrhosis. It is also used to assess risk of postsurgical hepatic decompensation or death after liver resection [50].

Staging Systems for Hepatocellular Carcinoma and Predictors of Post-Transplant Recurrence

There are two staging systems for HCC: the Barcelona Clinic Liver Cancer (BCLC) system and the American Joint Committee on Cancer (AJCC) system. The BCLC is the most used worldwide and combines tumor characteristics, liver function (CTP score), and patient functionality to describe five stages [51], while the AJCC system uses the traditional TNM (tumor size, regional nodes, and presence of distant metastases) terminology. Details of the AJCC TNM staging system can be found in the AJCC's cancer staging manual [52].

The Milan criteria are used to define a pretransplant threshold that predicts acceptable posttransplant HCC recurrence rates. The tumor burden threshold defined by the Milan Criteria as acceptable for LT is one intrahepatic tumor no larger than 5 cm, or no more than three tumors each measuring 3 cm or less. The Milan criteria predict posttransplant 4-year overall survival of

Table 4.2 Comparison of hepatocellular carcinoma liver transplant criteria

	Milan criteria	UCSF[a] criteria	Up-to-seven criteria
Tumor threshold	1 lesion: 5 cm 2–3 lesions: ≤3 cm each	1 lesion: 6.5 cm 3–4 lesions: ≤4.5 cm each Total tumor burden: ≤8 cm	Sum of total number of lesions and size (cm) of largest lesion ≤7
Post-transplant disease-free survival	92% 4-year disease-free survival [53]	91% 5-year disease-free survival [55]	Not given
Post-transplant overall survival	85% 4-year survival [53]	81% 5-year survival [55]	71% 5-year survival [57][b]

[a] *UCSF* University of California San Francisco
[b] For patients beyond the Milan criteria but within the up-to-seven criteria

85% and disease survival of 92% [53]. Patients with HCC within the Milan criteria can be awarded MELD score exceptions in the US LT allocation system. Modest extension of tumor number and size criteria beyond the Milan criteria has resulted in acceptable posttransplant outcomes [54–57]. Two of these expanded criteria, which are not currently used in formal transplant policy for standard priority points, are compared to the Milan Criteria in Table 4.2.

Emerging Predictors/Prognostic Scores of Complications and Outcomes of Cirrhosis

Alterations to the MELD Score

The MELD score cannot perform equally for all patients because of the pathophysiological variation in liver diseases. Furthermore, its prognostic ability worsens in its lower range [7, 58]. To address these issues, adjustments to the MELD score have been proposed.

MELDNa is the addition of serum sodium to the MELD score. It predicts mortality better than the MELD score, particularly in the lower range of scores [59, 60]. Criticisms of MELDNa include sensitivity of serum sodium to laboratory processes and variation dependent upon management strategies often employed in patients with cirrhosis [61]. Nonetheless, a similar score incorporating serum sodium, UKELD, is used for LT prioritization in the UK [62].

MELD-XI was developed to address concerns regarding unfair prioritization of patients on vitamin K antagonists because of their nonhepatic INR elevation. In MELD-XI, the INR is removed from the score and resulted in predictive ability for 30-, 60-, 90-, and 180-day mortality similar to that of the MELD score [63]. While MELD-XI may mitigate concerns about INR variability in patients on vitamin K antagonists, for other patients, it could sacrifice any extra value of using the INR.

New Predictors of Hepatocellular Carcinoma Post-Transplant Recurrence—Other Scoring Systems, Biomarkers

There is uncertainty about the best way to predict posttransplant recurrence of HCC. All the current models for prognosticating on posttransplant recurrence use tumor size and number, both of which are poor surrogates for tumor biology. Furthermore, most use a dichotomous threshold, which does not account for heterogeneity of tumor behavior, e.g., large tumors that are beyond the threshold for transplantation but which have "good" biology and lower risk for posttransplant recurrence.

An ideal prognostic tool would be a noninvasive serum or radiographic marker that better approximates tumor biology and predicts outcomes with accuracy. Such a tool could be used to drive management strategies and improve prioritization of HCC patients for LT. As more is learned about oncogenic pathways and genome alterations in HCC patients, the ongoing research in this area shows promise [64].

There are also continuous prognostic models for HCC that include variables other than size

and number, such as the MELD score, age, alpha-fetoprotein, and liver disease etiology [65, 66]. To date, continuous HCC models have not impacted clinical practice or allocation policy.

Acute-on-Chronic Liver Failure

Acute-on-chronic liver failure (ACLF) is a recently recognized clinical state wherein acute decompensation of liver disease is associated with liver and/or other organ failure. Consensus definitions are lacking, but a recent study created definitions for ACLF and validated a prognostic tool [67]. The chronic liver failure sequential organ failure assessment (CLIF-SOFA) score was an independent predictor of development of ACLF as well as mortality.

Comorbidity Scoring

The Charlson comorbidity index was developed to predict mortality based on comorbidities in a generic population [68]. Patients with cirrhosis frequently have comorbidities that affect their mortality risk [69, 70]. This Index has been updated, adapted, and validated for patients with cirrhosis to create a liver-specific comorbidity scoring system [71] resulting in a simpler tool specific for patients with liver disease with improved prognostic ability in liver patients.

Functional and Anthropometric Measurements

The 6-min walk distance (6MWD) predicts death in patients with cardiac and pulmonary diseases [72, 73]. It is a global measure of submaximal exercise capacity. Because cirrhotic patients suffer from sarcopenia, weakness, and decreased exercise capacity, 6MWD is an interesting potential prognostic tool. It is defined as the distance walked on a flat surface in 6 min at a patient-determined pace [74]. In LT candidates, a 6MWD less than 250 m is associated with an increased risk of death after adjustment for the MELD score [75].

Anthropometric measurements of body composition other than body mass index (BMI) are worth evaluating because of the BMI's imperfect measurement of adiposity. Measures investigated include waist circumference, hip circumference, and arm circumference, among others, but none of these have proven clearly superior to BMI as prognostic tools in cirrhotic populations [76].

Conclusion

Cirrhosis, the common end state of a variety of chronic liver diseases, is associated with high mortality due to portal hypertensive, malignant, and systemic complications. Management of patients with cirrhosis therefore requires careful attention to these complications. Several clinical and biochemical prognostic tools are useful for assessing outcomes and predicting complications, which are key components of patient care.

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

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Noninvasive Markers of Fibrosis in the Assessment of Cirrhosis

5

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The assessment of the extent of fibrosis in liver disease has long been a topic of interest because it plays a central role in the management of many disease processes. As the field of hepatology is quickly evolving with the introduction of novel treatments for various conditions, there is a critical need for an accurate assessment of the degree of liver fibrosis. Liver biopsy has long been regarded as the gold standard for evaluation of liver fibrosis and cirrhosis. However, this invasive procedure has its inherent shortcomings. The search for an alternative to liver biopsy has led to the development of noninvasive markers for hepatic fibrosis [1].

In this chapter, we describe how noninvasive liver fibrosis markers and liver biopsy assess for the presence of cirrhosis. Significant progress has been made in identifying both nonspecific and specific biomarkers of fibrosis. Nonspecific markers include age, gender, laboratory markers of liver injury or dysfunction including aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transferase (GGT), bilirubin, haptoglobin, platelet count, and prothrombin time. Metabolic markers also fall under the category of nonspecific markers; these include cholesterol, apoprotein A1, and α-2 macroglobulin (A2M) [2].

We will review the successful application of biomarkers that are more specific for fibrosis. These markers incorporate extracellular matrix proteins such as hyaluronic acid (HA), matrix metalloproteinase-2, tissue inhibitor of matrix metalloproteinase-1, and amino-terminal peptide of type III procollagen [3–5].

We will provide data on the nonspecific liver fibrosis markers FIB-4, APRI, and FibroTest, as well as the specific markers HepaScore, enhanced liver fibrosis (ELF), and FibroMeter. For each of the noninvasive markers, we will assess their area under the receiver operating curve (AUROC), sensitivity and specificity in cirrhosis (F4 fibrosis) due to hepatitis B (HBV), hepatitis C (HCV), nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH), and alcohol-related liver disease (ALD).

Liver Biopsy

The first liver aspirate was performed by Dr. Paul Ehrlich in 1883. Percutaneous liver biopsy was first reported in the 1920s [6]. For the next 70 years, the diagnosis and treatment of acute and chronic liver disease was dependent on the histologic evaluation of the liver [1, 7, 8]. With the introduction of treatments such as interferon for hepatitis C, establishing the stage of fibrosis assumed greater importance in patient management. Liver biopsy was regarded as the "gold standard" for this assessment. Although liver biopsy remains essential in the practice of

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hepatology, physicians and patients may now be reluctant to proceed with it because of its associated risks, patient preference, and other diagnostic options [1, 7, 8].

The American Association for the Study of Liver Disease (AASLD) guidelines state that liver biopsy currently has three major roles: (1) for diagnosis, (2) for the assessment of prognosis (disease staging), and/or (3) to assist in making therapeutic management decisions [1]. There are multiple drawbacks to traditional biopsy. It is associated with significant patient discomfort, with up to 25% of patients experiencing right upper quadrant or referred right shoulder pain after biopsy. More serious complications are infrequent, but include significant bleeding, with rates varying from 0.05 to 5.3% and a mortality rate of less than 0.15% [8].

The performance of liver biopsy for fibrosis staging has also been called into question, due to concerns regarding possible sampling error and significant intra- and interobserver variability. Since a biopsy sample represents 1/50,000th of the liver, the heterogeneity of liver fibrosis and inadequacy of sample size can cause considerable bias in the assessment of hepatic histology [9, 10]. A study which included 124 patients with chronic HCV infection who underwent simultaneous laparoscopic-guided biopsies of the right and left hepatic lobes showed that 33.1% of the subjects had a difference of at least one stage between the two lobes [9, 11]. Similarly, a study on virtual liver biopsy indicated that a nonfragmented specimen of at least 25 mm in length would be necessary to correctly evaluate fibrosis with a semiquantitative score, a goal not always achieved in daily practice [9, 12].

The workup and treatment of viral hepatitis are rapidly changing with the advent of all oral drug regimens. The well-documented toxicity of interferon-based therapy for HCV infection in patients with cirrhosis will likely be of historical interest only given the efficacy and side-effect profile of the direct acting antiviral (DAA) regimens [13]. Prior nonresponders to interferon including a protease inhibitor regimen are now experiencing 94–99% sustained viral response rates (SVR) with new combinations of DAA that are very safe. The potential for disease progression due to chronic HCV infection will be markedly altered because of the high SVR rates [14, 15].

As newer all oral, well tolerated, and highly efficacious HCV therapies become available, the need for staging of liver disease in predefined categories such as the METAVIR score is not as clinically relevant [1]. The major need for staging is to identify patients with advanced fibrosis and more importantly cirrhosis. In the remainder of this chapter, we will focus on the role of biomarkers in identifying cirrhosis.

Noninvasive Liver Fibrosis Markers

Over the past few years, several noninvasive markers have been proposed to assess the extent of liver fibrosis. Besides the clear advantage of being noninvasive, a more objective interpretation of test results may overcome the inter- and intra-observer variability of liver biopsy. In addition, these tests can theoretically offer a more accurate view of fibrogenic events occurring throughout the entire liver, providing frequent fibrosis evaluation without additional risk, as currently liver biopsy provides a static view of a dynamic disease process [7, 8].

Noninvasive methods to assess cirrhosis are based on two distinct approaches: a "biological" approach (quantifying biomarkers in serum samples) or a "physical" approach (measuring liver stiffness). While these methods are complementary, they take different pathways to assess the extent of fibrosis. Serum biomarkers indicate several specific and nonspecific features in the blood that have been associated with the biological stage of fibrosis. Liver stiffness corresponds to an intrinsic physical property of the liver parenchyma [16].This chapter focuses on the biological approach in quantifying serum markers.

The practical advantages of analyzing serum biomarkers to measure fibrosis include their high applicability (>95%) and inter-laboratory reproducibility, as well as their widespread availability [16, 17].

Table 5.1 Ideal features of a noninvasive liver fibrosis marker

Highly sensitive and specific to identify different stages of fibrosis
Applicable to the monitoring of disease progression or regression as part of the natural history of liver disease or treatment process
Readily available and inexpensive
Reproducible
Not susceptible to false positive results

The ideal characteristics of a noninvasive liver fibrosis marker are summarized in Table 5.1. The marker should be highly sensitive and specific to identify different stages of fibrosis, as we are interested in cirrhosis specifically. The marker should also be applicable to the monitoring of disease progression or regression as part of the natural history of liver disease or treatment process. The marker should also be readily available, safe, inexpensive, and reproducible. It should not be susceptible to false positive and negative results [18].The potential for such results reflect the fact that the process of fibrogenesis is also a component of the normal healing response to injury, invasion by pathogens, and many other etiologic factors [1]. In addition, most studies evaluating biomarkers have only been in patients with liver disease primarily. In practice, patients may have other confounding fibrotic and inflammatory processes which need to be considered when determining the validity of a "liver" biomarker.

In the following section, we review the markers that have been validated in METAVIR F4 fibrosis/cirrhosis stage for patients with HCV/HBV/NAFLD and ALD (Table 5.2).

Table 5.2 Specific and nonspecific liver fibrosis markers in cirrhosis

Test	Variables	Median AUROC	Median sensitivity (%)	Median specificity (%)
APRI	AST and platelet count	HCV0.83	HCV 76	HCV 72
		HBV 0.75	HBV 45[a]	HBV 88[a]
		EtOH 0.65	EtOH 44	EtOH 94
		NASH (??)	NASH 77	NASH 71
FIB-4	Age, AST, ALT, and platelet count	HCV 0.87	HCV 90	HCV 92
		HBV 0.89	HBV	HBV
		EtOH 0.80	EtOH --	EtOH --
		NASH 0.802	NASH 73	NASH 89
FibroTest	A2M, Haptogloben, GGT, TBil, apoprotein A1	HCV 0.87	HCV 74	HCV 82
		HBV 0.87	HBV 72	HBV 87
		EtOH 0.94	–	–
		NASH 0.860	NASH 73	NASH 92
ELF Score	Age, TIMP-1, PIIINP, and hyaluronic acid	HCV 0.94	HCV 93	HCV 86
		HBV	HBV	HBV
		EtOH	EtOH	EtOH
		NASH 0.89	NASH 91	NASH 69
FibroMeter	Hyaluronic acid, Platelet, PT, AST, A2M, urea, Age	HCV 0.92	HCV 72	HCV 90
		HBV 0.87	HBV 79	HBV 83
		EtOH 0.96[a]		
		NASH 0.94		
HepaScore	Age, sex, TBil, A2M, hyaluronic acid, GGT	HCV 0.88	HCV 71	HCV 84
		HBV 0.91	HBV 87	HBV 86
		EtOH 0.91	EtOH 87	EtOH 89
		NASH 0.92	NASH 87	NASH 89

AUROC area under the receiver operating curve, *APRI* AST-to-platelet ratio index, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *EtOH* ethanol, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NASH* nonalcoholic steatohepatitis, *TBil* total bilirubin, *apoprotein A1* apolipoprotein-A1, *A2M* α-2-macroglobulin, *GGT* γ-glutamyl transpeptidase, *ELF* enhanced liver fibrosis, *TIMP-1* tissue inhibitor of matrix metalloproteinase-1, *PIIPNP* amino-terminal peptide of type III procollagen, *PT* prothrombin time

[a]Data available for cohort containing patients with hepatitis B or C

Indirect (Class II) Markers of Liver Fibrosis

AST-to-Platelet Ratio Index

The AST-to-platelet ratio index (APRI) score is the simplest nonspecific liver fibrosis marker for predicting fibrosis [7]. The APRI incorporates only AST and platelet count and can be calculated using the formula:

$$\text{APRI} = \text{AST}/\text{upper limit of normal}$$
$$\text{AST}/\text{platelet count}\left(10^9/\text{L}\right)\times 100.$$

The APRI is based on the premise that progression to cirrhosis and increasing portal pressure are associated with reduced production of thrombopoietin by hepatocytes, increased platelet sequestration within the spleen, and reduced clearance of AST [8].

HCV

The AUROC for APRI in cirrhosis was 0.83 with an optimal cutoff of 1.0, for a sensitivity and specificity of 76 and 72%, respectively. A threshold of 2.0 exhibited a specificity of 91% for diagnosing cirrhosis, but the sensitivity for this level was only 46%. A major advantage of APRI is that it has been validated in special populations such as HIV/HCV coinfection [8].

HBV

APRI is one of the most widely used and validated biomarkers in HBV. It is able to predict cirrhosis with more accuracy than advanced fibrosis. A meta-analysis of APRI in 1798 HBV patients found a mean AUROC value of 0.75 in diagnosing HBV cirrhosis [16]. Degos et al. reported an AUROC of 0.77 (95% CI, 0.73–0.81) with a sensitivity of 45% (95% CI, 39–52) and specificity of 88% (95% CI, 87–90.0) for APRI's performance in predicting cirrhosis in a cohort of patients with either hepatitis B or C [19]. A positive predictive value (PPV) of 39% (95% CI, 33–45) and negative predictive value (NPV) of 91% (95% CI, 89–92) were observed [19].

Alcohol

In assessing cirrhosis secondary to ALD, a cutoff of 1.10 yielded an AUROC 0.648 (95% CI, 0.43–0.87) with a sensitivity and specificity of 44 and 94%, respectively. A PPV of 0.44 and NPV of 0.94 were reported [20].

NASH

Adams et al. used a cutoff of 0.54 for assessing NASH cirrhosis with a sensitivity of 77%, specificity of 71%, PPV 22%, and NPV of 97%. Specific noninvasive serum models developed for the prediction of cirrhosis in HCV are more useful for the prediction of advanced fibrosis or cirrhosis in subjects with NAFLD when compared to APRI [21].

Limitations to the interpretation of APRI include the presence of acute hepatitis; AST elevation from nonliver origin, thrombocytopenia from other causes such as bone marrow suppression related to alcohol or HCV-induced thrombocytopenia.

FIB-4

FIB-4 is an inexpensive method for the evaluation of liver fibrosis based on simple variables such as age, AST, ALT, and platelet count that are routinely measured. The index is not influenced by a patient's body mass index [22]. It is calculated using the following formula:

$$\text{FIB-4} = \frac{\text{age}\times\text{AST}\left(\text{U/L}\right)}{\left[\text{PLT}\left(10^9/\text{L}\right)\times\text{ALT}\left(\text{U/L}\right)\right]^{1/2}}.$$

Although FIB4 is a useful and simple scoring system, which is more accurate than the APRI for the diagnosis of cirrhosis, the values and cutoffs differ for the various etiologies of cirrhosis.

HCV

The FIB-4 index enabled the correct identification of patients with cirrhosis (F4) with an AUROC of 0.91 (95% CI, 0.86–0.93). The FIB-4 index <1.45 had an NPV of 95% in excluding severe fibrosis, with a sensitivity of 74% [21]. For values outside 1.45–3.25, the FIB-4 index is a simple, accurate, and inexpensive method for assessing liver fibrosis and proved to be

concordant with FibroTest results. The test was validated in HCV-induced cirrhosis with an observed AUROC of 0.87, sensitivity of 90%, and specificity of 92% [23].

HBV

FIB-4 can predict the presence of cirrhosis due to chronic HBV with a high degree of accuracy. A FIB-4 score ≤1.58 identified mild to moderate fibrosis (F0–F2), while a score >5.17 predicted cirrhosis in CHB. The AUROC for HBV-induced cirrhosis was 0.89 [24].

NAFLD/NASH

When assessing the performance of FIB4 in NAFLD, the data were only provided for advanced F3/F4 fibrosis and not exclusively for cirrhosis. The AUROC was 0.802 (95% CI, 0.76–0.85). The predicative values of the FIB4 index for advanced fibrosis (F3–F4) identified the presence of advanced fibrosis with 89% accuracy, using a cutoff value of >2.67 [25].

Alcohol

When applied to ALD-induced cirrhosis, FIB-4 yielded an AUROC of 0.80 (95% CI, 0.72–0.86) [26].

FibroTest/FibroSure

FibroTest/FibroSure is a frequently used biomarker of liver fibrosis which was initially validated in patients with chronic HCV. It employs a patented calculation of a combination of five serum biochemical parameters [27]. These include α-2-macroglobulin, apolipoprotein A1, haptoglobin, L-glutamyltranspeptidase, and bilirubin. Advantages of FibroTest include widespread availability, high applicability (>95%), and inter-laboratory reproducibility [28]. It was developed using a linear scale from 0 to 1; cirrhosis is diagnosed when the FibroTest score is greater than 0.75. The higher the Fibrotest score, the more likely the diagnosis of cirrhosis is correct. A major cause of a false positive is the presence of hemolysis or Gilbert's disease.

HCV

There have been multiple studies in HCV along with significant validation in normal population studies. The assessment of cirrhosis in HCV with FibroTest has an AUROC of 0.87±0.04 (95% CI, 0.80–0.94). Using a cutoff of 0.63, there was an observed sensitivity of 0.74, specificity of 0.82 with NPV, and PPV of 0.96 and 0.53, respectively [29].

HBV

Multiple large studies have been conducted assessing the performance of FibroTest in HBV-induced cirrhosis. The results yielded an AUROC of 0.87 (95% CI, 62–79), with a sensitivity of 72% (95% CI, 62–79) and specificity of 87% (95% CI, 84–90%). FibroTest had an NPV of 92%, which established that it is an excellent test to rule out cirrhosis in this patient population [9]. Drawbacks to FibroTest include its cost, lack of external validation, and lack of specificity for liver disease as its results can be severely impaired by comorbidities, i.e., Gilbert's syndrome or hemolysis [9].

Alcohol

Applying FibroTest to assess cirrhosis in the setting of alcohol yielded an AUROC of 0.94±0.02 (95% CI, 0.87–0.97) [26].

NASH

When FibroTest was applied to patients with NASH/NAFLD, a cut-off value of 0.57 resulted in an AUROC of 0.86 (95% CI, 0.77–0.95) with a sensitivity of 73%, a specificity of 92%, PPV of 49%, and NPV of 97% for the diagnosis of cirrhosis [21].

Direct (Class I) Markers of Liver Fibrosis

Multiple etiologies of liver disease including HCV, HBV, NAFLD/NASH, and ALD can lead to liver fibrosis though integrated signaling networks that regulate the deposition of extracellular matrix [8, 30].This sequence of events drives the activation of hepatic stellate cells into a myofibroblast-like phenotype that is contractile,

proliferative, and fibrogenic. Collagen and other extracellular matrix (ECM) components are deposited as the liver generates a wound-healing response to encapsulate injury. The direct (or class I) markers of liver fibrosis are usually fragments of the liver matrix components produced by hepatic stellate cells during the process of ECM remodeling, usually reflecting the deposition or removal of ECM.

The most studied direct markers are hyaluronic acid (HA), YKL-40, laminin, fibronectin, α-2-macroglobulin, procollagen type I carboxy terminal peptide (PICP), procollagen type III amino-terminal peptide (PIIINP), N-terminal propeptide of type II collagen, metalloproteinases (MMPs), tissue inhibitors of matrix metalloproteinases (TIMPs), and transforming growth factor b1 (TGF-b1) [8].

HepaScore

The HepaScore is a patented model that combines age, sex, HA, total bilirubin, γ glutamyl transferase, and α-2-macroglobulin. It was devised in a cohort of chronic HCV patients and further validated in several studies. The HepaScore scoring system has a range of 0–1.0, with a higher score indicating the presence of increased fibrosis [8].

HCV

The diagnostic performance score for HepaScore in cirrhosis due to HCV, as determined by AUROC, was 0.88. A cutoff point of 0.84 provided a sensitivity of 71% (95% CI, 63–80%) and specificity of 84% (95% CI, 77–90%) for the detection of cirrhosis [31]. A HepaScore >0.84 was 84–89% specific for the presence of cirrhosis. This may be useful to avoid liver biopsy in patients in whom occult cirrhosis is suspected, or to guide management decisions regarding screening for varices or hepatocellular carcinoma (HCC). A HepaScore <0.84 provided an NPV of 94% in some cohorts; however, Leon et al. observed that predictive values of a diagnostic test varied according to the underlying prevalence of a condition [31]. Applying a cutoff of ≥0.5, HepaScore has been used to determine treatment in the absence of a liver biopsy. In addition, Adams, et al. observed the exclusion of advanced fibrosis among patients who have a HepaScore <0.5 may be useful in providing prognostic information for patients who are reluctant to undergo biopsy [31, 32].

HBV

When HepaScore was used to assess cirrhosis due to HBV, an AUROC of 0.91 (95% CI 0.84–0.98) was observed. A cutoff of 0.88 yielded a sensitivity of 87% and specificity of 86% with a PPV and NPV of 36 and 99%, respectively [33]. Analysis of serial HepaScore values in a subset demonstrated that values were dynamic over time. HepaScore was able to determine the presence or absence of significant fibrosis in patients, thereby reassuring the physician regarding continued monitoring or providing additional data to support a decision to commence treatment [33].

NASH

Applying a cutoff HepaScore of 0.70 in patients with NASH/NALFD, resulted in an AUROC of 0.91 (95% CI, 0.83–0.99), with a sensitivity of 87%, specificity of 89%, and PPV and NPV of 45 and 99%, respectively [21].

Alcohol

When HepaScore was used to asses cirrhosis secondary to alcoholic liver disease, it yielded an AUROC of 0.92 ± (95% CI, 0.87–0.97) [26].

Enhanced Liver Fibrosis Score

The enhanced liver fibrosis (ELF) score provides a single value by an algorithm combining age as well as quantitative serum measurements of TIMP-1, PIIINP, and HA. Age was removed from the simplified ELF score [5].

HCV

When ELF was applied for the diagnosis of cirrhosis due to HCV, a cutoff value >9.3 provided a sensitivity of 93% and a specificity of 86%. The AUROC was 0.94 with a PPV of 75.6% and an NPV of 92.3% ($p<0.001$). ELF is a promising noninvasive method for assessing liver fibrosis in patients with chronic HCV as it can effectively diagnose cirrhosis [34].

HBV

In cirrhosis secondary to chronic HBV, the ELF cutoff value of 10.10 generated a sensitivity of 70%, a specificity of 79%, a PPV of 56%, and an NPV of 87% [35].

NASH

The ELF score was one of the first noninvasive markers to be validated in advanced fibrosis/cirrhosis in the setting of NASH/NAFLD. F3–F4 fibrosis stages were detectable using a threshold value of 0.375, with a sensitivity of 89% and specificity of 96%, PPV and NPV of 80 and 98%, respectively [5]. Rosenberg et al. observed an AUROC of 0.887 ($P<0.0001$), with a discriminant score threshold of.025 (95% CI, 0.666–1.000) with a sensitivity of 91%; and specificity of 69%. There are no data that validate the ELF score in F4 fibrosis alone for patients with NASH/NAFLD.

Alcohol

Applying a threshold ELF score of 0.431 resulted in a sensivitiy of 93%, specificity of 100%, PPV of 100%, and NPV of 86% for patients with F3–F4 fibrosis stages [5]. Similar to NASH, there are no data validating the ELF score in F4 fibrosis due to ALD.

FibroMeter

The FibroMeter is a combination of HA with prothrombin time, platelet count, AST, α-2-macroglobulin, urea, and age. The overall performance of FibroMeter has been validated in a number of chronic liver diseases, including HBV, HCB, ALD, and NAFLD. An important feature of the FibroMeter is that it presents the amount of liver fibrosis as a percentage of fibrous tissue within the liver. Another significant feature is that it validates the results through an expert system that detects erroneous results. FibroMeter has two main diagnostic targets—fibrosis stage corresponding to the histological staging system METAVIR and the amount of fibrosis, which corresponds to morphometric determinations of the fibrotic area [18].

HCV

When evaluating cirrhosis secondary to HCV, using a FibroMeter cutoff of 0.88 produced the following results: an AUROC of 0.92 ± 0.02 (95% CI, 0.87–0.96), with an observed sensitivity of 0.72, specificity of 0.90 with an NPV of 0.98, and a PPV of 0.46 [29].

HBV

When FibroMeter was used to assess cirrhosis in patients with HBV using a cutoff of 0.72, an AUROC of 0.87 ± 0.03 (95% CI, 0.81–0.93) was observed with a sensitivity of 0.79, specificity of 0.83, NPV and PPV of 0.94 and 0.45, respectively. Leroy, et al. observed that when cutoffs which had been validated in HCV were applied to HBV, FibroMeter was associated with a low but significant increased risk of underdiagnosing cirrhosis. Stringent cutoffs should be used along with a careful analysis of the patient's clinical condition and characteristics to avoid misdiagnosis of cirrhosis [29].

Alcohol

FibroMeter has been studied in advanced fibrosis (F2–F4) but not in patients with cirrhosis due to ALD. Using FibroMeter, Cales et al. found that F2–F4 fibrosis stages had an observed AUROC of 0.962 ± 0.018 (95% CI, 0.926–0.998). Additional studies are required to validate this test in cirrhotic patients [36].

NASH

FibroMeter testing in patients with NAFLD can easily be calculated from simple parameters and had good accuracy for the diagnosis of significant fibrosis. The reported AUROC for cirrhosis secondary to NASH was 0.942 [37–39].

The Role of Noninvasive Liver Fibrosis Markers and Prognosis of Liver Disease

Chronic liver disease results in progressive fibrosis and eventually cirrhosis that is associated with an increased risk of morbidity as well as mortality. A meta-analysis performed by Poynard et al assessed the 5-year prognostic value

of APRI, FIB-4 and FibroTest in HBV, HCV, and ALD as an alternative to liver biopsy. The meta-analysis included the three noninvasive markers from published prognostic studies: FibroTest (four studies; 2396 patients), APRI (five studies; 2422 patients), and FIB-4 (three studies; 1184 patients). The noninvasive tests were compared to liver biopsy for the prediction of survival without liver-related death. The AUROC for liver biopsy was 0.86 (95% CI, 0.77–0.95). For FibroTest, it was 0.88 (95% CI, 0.79–0.98), for FIB-4 the AUROC was 0.73 (95% CI, 0.62–0.85), and for APRI, the AUROC was 0.66 (95% CI, 0.57–0.75). FIB-4 and APRI had significant prognostic value in patients with chronic HCV infection; however, the values were lower than FibroTest [40]. FibroTest did not show a significant difference in prognostic value compared worth liver biopsy, with a mean difference in AUROCs of +0.02 (95% CI, −0.05 to +0.09; $P=0.85$). Additional studies are needed to confirm the prognostic value of other noninvasive biomarkers and to provide data for patients with NAFLD [40].

Conclusions

The clinician has multiple choices in using serum fibrosis markers to diagnose cirrhosis. We recommend that a combination of one indirect and one direct biomarker panel be used. When there is concordance for the diagnosis of cirrhosis, liver biopsy is not necessary and screening for varices, HCC, and appropriate therapy can be instituted. Where there is discordance, a confirmatory noninvasive test such as elastography can be used. Liver biopsy should be reserved for those in whom diagnosis and staging will add clinical value to patient management.

Despite significant advances in the past 10 years, serum fibrosis markers have not gained widespread acceptance amongst clinicians in the USA. In the near future, the incorporation of other methodologies such as genetic, proteomic, and metabolomic profiles will allow the diagnosis of fibrosis at earlier stages, even permitting the identification of stellate cell activation in prefibrotic stages.

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Diagnosis of Cirrhosis: Imaging

6

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Although liver biopsy is the gold standard for diagnosing cirrhosis, its invasive nature and associated complications limit its role as a screening method for cirrhosis [1, 2]. Results from liver biopsies are limited by interobserver variability with upwards of 25 % discordance in staging and sampling variability: As an example, a 25-mm biopsy correctly classifies stage of fibrosis in about 75 % of cases. Furthermore, given the heterogeneous distribution of cirrhosis, biopsies from the left and right lobe of the liver may yield disparate results [3–6]. Establishing the diagnosis of cirrhosis, especially at a compensated state has implications for the initiation of appropriate etiology-specific interventions and surveillance for hepatobiliary malignancies and complications of portal hypertension. The choice of imaging modality is based on multiple factors, including the diagnostic accuracy of the test, local availability, cost-effectiveness, and patient-related factors such as age, presence of renal failure or ascites, obesity, ability to hold one's breath, and a history of allergic reaction to contrast agents.

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Ultrasound

Abdominal ultrasound (US) can be used for morphologic characterization of liver parenchyma that may support a diagnosis of cirrhosis. Further, changes associated with portal hypertension and portal vein thrombosis can be identified which may serve as indirect evidence of advanced disease. Abdominal US is an easy-to-perform, quick and non-expensive test for the workup of liver disease. Its advantages include accessibility, high resolution, versatility, and real-time imaging capability without patient exposure to ionizing radiation. However, significant operator dependency and competency, substantial image degradation in obese patients, low tissue contrast, and limited field of view are major limitations of this modality [7].

A healthy liver measures approximately 12–15 cm in cranio-caudal dimension in the midaxillary line, is mildly echogenic/isoechoic in appearance (as compared to the normal right kidney), and homogeneous in echo texture [8]. Cirrhosis is typically characterized by irregularity of the liver surface, diffusely coarsened and heterogeneous echo pattern, increased parenchymal echogenicity, and increased sound attenuation. Surface nodularity along the deep surfaces of the liver is one of the more specific signs of cirrhosis [9]. There is lobar redistribution of atrophy and hypertrophy; cirrhosis may lead to atrophy of the right lobe of liver with relative enlargement of the caudate lobe. A ratio greater than 0.6 between the transverse diameter of the caudate lobe and the transverse diameter of the right lobe has a sensitivity of 84 %, specificity of 100 %, and

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a diagnostic accuracy of 94% for the diagnosis of cirrhosis [10]. Thickening of the gallbladder wall may be associated with cirrhosis [11]. US examination in obese patients or subjects with acute hepatitis (e.g., hepatitis B flares) may reveal sonographic evidence that overestimates the degree of underlying fibrosis. The appearance of cirrhosis can also be mimicked by other disorders affecting the liver such as:

- Congenital hepatic fibrosis
- Hepatic schistosomiasis
- Hepatic necrosis and regeneration after fulminant hepatitis
- Pseudocirrhosis
- Diffuse hepatic metastases
- Focal nodular regenerative hyperplasia

Another unique advantage of US is Doppler examination that allows visualization of blood flow and assessment of flow dynamics. *Doppler US* can be used for the assessment of vessel patency, direction of blood flow, flow velocity, and spectral waveforms within the portal system, hepatic veins, and arteries [7]. In healthy adults, the portal vein diameter is less than 13 mm, with the blood flow being monophasic and towards the liver (hepatopetal). However, in portal hypertension, there is dilatation of the portal vein with reversal of flow (hepatofugal), decreased velocity, and loss of fluctuation in portal vein pressure with respiration. Loss of the normal phasic waveform of the hepatic veins along with narrowing can also be seen. The presence of ascites, splenomegaly, and visualization of a prominent paraumbilical vein indicates the presence of portal hypertension and indirectly supports the diagnosis of cirrhosis. The hepatic artery resistive index and pulsatility index also increases secondary to increased blood flow through the hepatic artery [8].

The presence of anechoic to hyperechoic solid material within the portal vein lumen suggests that the presence of portal vein thrombosis seen on Doppler imaging as absent color flow or areas in the vessel that do not completely fill with color. Pulsatile arterial waveforms within the thrombus have 95% specificity for the diagnosis of malignant thrombus [12]. Multiple serpiginous vessels in the portal vein bed with hepatopetal flow and non-visualization of the main portal trunk indicate cavernous transformation of the portal vein [13].

Contrast-enhanced US is a useful adjunct to conventional US for the diagnosis of cirrhosis. Measurement of hepatic vein transit time, which is a measure of the time of onset of US contrast enhancement of the hepatic vein after intravenous (IV) injection of micro-bubble contrast medium, is highly sensitive for cirrhosis and decreases with progression of liver disease [14]. Enhancement of liver parenchyma in the late phase of contrast injection has also been found to negatively correlate with the severity of liver cirrhosis [15].

Computerized Tomography

Computerized tomography (CT) offers the added advantage of better image acquisition techniques coupled with short scan times (Fig. 6.1). Multiple detector CT provides thinner cross-sectional images allowing for a reduction in scan time and the capability of imaging to be performed during the different phases of parenchymal enhancement after IV contrast administration [16]. Disadvantages of CT scans include radiation exposure as

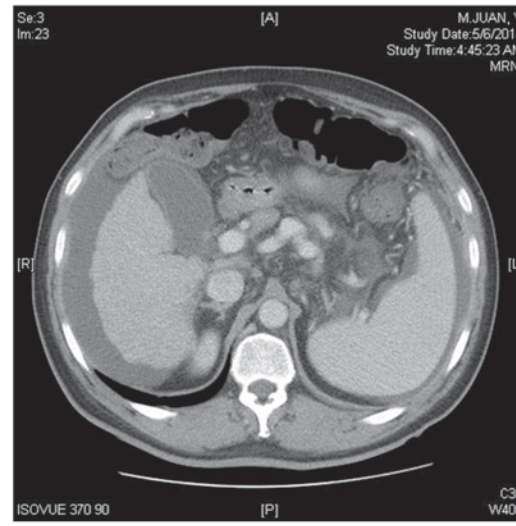

Fig. 6.1 Computerized tomography of the abdomen. This is an example of a cirrhotic appearing liver with ascites and splenomegaly by computed tomography

well as the need for preserved renal function for safe completion of examinations.

Morphological changes of cirrhosis are dependent on the severity of cirrhosis. In the early stages, enlargement of the hilar periportal space with increased fatty tissue in the porta hepatis may be seen. The typical features of non-contrast CT in advanced cirrhosis include a nodular hepatic outline, atrophy of right hepatic lobe and medial segments of left hepatic lobe, widening of the gallbladder fossa, hypertrophy of the lateral segments of the left hepatic and caudate lobes, widening of the interlobar fissures, and formation of regenerative nodules circumscribed by thick bands [17].

The attenuation value of the normal liver typically varies between 54 and 60 Hounsfield Units (HU). Non-contrast CT scan, which measures liver attenuation, can sometimes be used in determining the etiology of cirrhosis. Hemochromatosis, glycogen storage disease, and Wilson's disease are associated with increased attenuation whereas passive liver congestion and fat deposition show decreased attenuation [18]. CT is also helpful in characterizing other liver findings that are commonly encountered in cirrhosis, including peribiliary cysts, hemangiomas, and malignant lesions.

Administration of an iodinated contrast agent in hepatic CT not only allows the definition of the hepatic and portal vasculature but also helps in characterizing liver nodules in cirrhosis. After IV administration of a contrast agent, imaging is performed during the different phases of parenchymal enhancement namely the arterial, portal venous, and delayed phases [19].

In addition to confirming the findings of non-contrast CT, the injection of IV contrast can be used to confirm findings of portal hypertension by demonstrating the presence of: (a) esophageal and gastric varices, (b) patent paraumbilical veins and abdominal wall veins (c) splenorenal and gastrorenal shunts, (d) splenomegaly, and (e) ascites [20]. The presence of prominent mesenteric edema and stranding secondary to increased venous pressure and pseudo nodules surrounding mesenteric vessels which mimic enlarged lymph nodes can also be indirect evidence for cirrhosis.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the liver is performed to define focal liver lesions as well as to confirm and validate findings from other imaging studies. In contrast to CT, MRI has advantages of avoiding ionizing radiation and iodinated contrast, superior soft tissue contrast, ability to characterize smaller lesions (<2 cm), and lesions with fat and iron. Disadvantages of MRI include its high cost, lower spatial resolution, increased imaging time, risk of nephrogenic systemic fibrosis associated with gadolinium, and poor image quality in uncooperative patients.

Several MRI protocols, modalities, and sequences are available, a combination of which allows for the evaluation of fat and iron content, detection and characterization of liver lesions, and also allows for accurate assessment of the biliary and vascular tree [21]. Accurate timing of the different vascular phases is essential for good quality imaging studies [22].

MRI can detect moderate to severe cirrhosis by identification of fibrotic septa, which are seen as subtle parenchymal reticulations with low T1 and high T2 signal intensity. These septa become more conspicuous on T1-weighted gadolinium-enhanced images acquired during the delayed phase due to delayed washout of fibrotic tissue compared to the surrounding liver. Enlargement of the hilar periportal space and the gallbladder fossa has been shown to be a helpful sign at MRI in the diagnosis of early cirrhosis [23]. Findings on MRI may also have prognostic value. A study of MRI in patients with compensated cirrhosis suggested that, a large spleen, the presence of varices or collaterals, and a higher volume index of caudate lobe to right lobe correlate well with clinical progression to decompensated cirrhosis [24].

Several iterations of MRI-based imaging have been investigated and aid in the diagnosis of cirrhosis. For example, *diffusion-weighted imaging* avoids the need for IV contrast and produces images of tissues weighted with the local structural properties of water diffusion. It can be used to characterize focal hepatic masses and assess liver

fibrosis. Several studies have described lower apparent diffusion coefficient value in patients with varying degrees of cirrhosis as compared with healthy individuals undergoing diffusion-weighted MRI [25].

Progressive liver fibrosis gradually obliterates normal intrahepatic vessels and sinusoids. Once portal hypertension is established, the portal venous flow to the liver decreases, hepatic arterial flow increases, and intrahepatic shunts form. These perfusion changes in the liver can be detected by *magnetic resonance perfusion imaging,* which can determine absolute arterial and venous blood flow, absolute total liver blood flow, portal venous and arterial fraction, distribution volume, and mean transit time and correlate with presence of advanced fibrosis.

Ultrasound-Based Elastography

Elastography is a relatively novel method to assess the intrinsic property of the liver parenchyma, or liver stiffness, with elevated stiffness associated with presence of advanced fibrosis. Three specific US techniques include transient elastography (TE), acoustic radiation force impulse imaging (ARFI), and shear wave elastography (SWE) [26].

Ultrasound-based TE is a single dimension-based technique that measures the velocity of a low frequency 50-Hz elastic shear wave propagating through the liver. This propagation is directly related to tissue stiffness, called the elastic modulus (E). This is expressed as $E = 3pv2$, where v is the velocity and p is the density of tissue that is assumed to be constant. Shear waves propagate faster in stiffer tissue. The volume that is measured is 10 mm × 40 mm long, lying 26–65 mm below the skin surface. Results are expressed in kilopascals and range from 2.5 to 75 kPa with a normal value of approximately 5 kPa and a value generally above 12–14 kPa implying the presence of cirrhosis.

ARFI is based on the measurement of the velocity of short-duration acoustic pulses generated by mechanically exciting liver tissue through manual compression by the US probe. The shear wave velocity is measured in a smaller region. Mechanical excitation of tissue using short-duration acoustic pulses propagates shear waves and generates localized u-scale displacement in tissue. Displacement results in short shear-wave propagation away from the region of excitation are tracked. The shear wave velocity is examined and increases with increasing severity of fibrosis. The median value for a cirrhotic liver is ~1.8 m/s.

SWE, a newer technique has the ability to image liver stiffness in real time and allows the operator to choose the size and location of the region of interest. Series of push pulses create plane shear waves that propagate over a region of interest (ROI). The speed is estimated by Doppler-like acquisition. Color-coded two-dimensional quantitative SWE images of tissue stiffness are obtained in real time. A circular ROI is defined to measure stiffness. Values are approximately 12–14 kPa for cirrhosis (Fig. 6.2).

US-based techniques have the advantage of being an outpatient procedure that takes a few minutes. TE has excellent reproducibility for interobserver and intraobserver agreement. Limitations of this technique include incomplete examinations (approximately 20%), mostly driven by obesity, ascites, and operator experience. Fibrosis may be overestimated in cases of acute hepatitis, cholestasis, and passive congestion.

MRI-Based Elastography

Magnetic resonance elastography (MRE) is an MRI-based technique to evaluate the mechanical properties of tissue (Fig. 6.3) [27]. Mechanical shear waves are generated within the liver and the propagating waves are imaged using special MRI sequences. An active driver sends 60 Hz acoustic vibrations through a connected 7.6-m-long plastic tube to a passive pneumatic driver that is placed against the chest and upper abdomen of the patient. Measurements of liver stiffness are obtained. Based on previous studies, normal liver stiffness ranges between 1.5

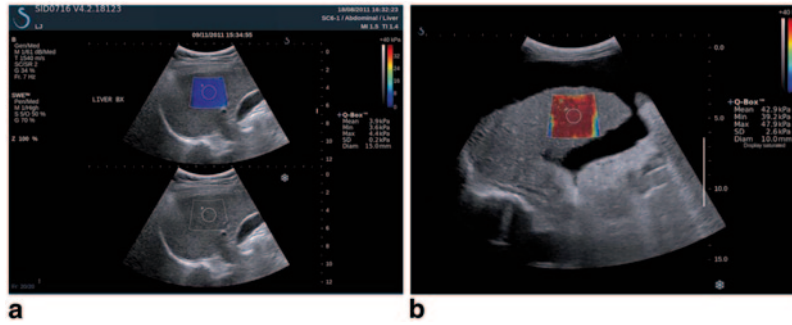

Fig. 6.2 Shear wave elastography (SWE). (**a**) A patient with hepatitis B infection and a liver stiffness measurement of 3.9 kPa by SWE. (**b**) A patient with hepatitis B infection and a liver stiffness measurement of 42.9 kPa (cirrhosis) by SWE

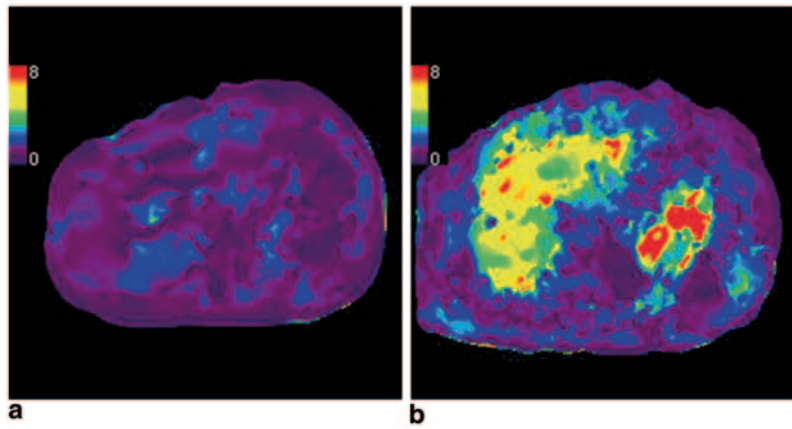

Fig. 6.3 Magnetic resonance elastography (MRE). (**a**) A normal liver with a liver stiffness measurement of 2.1 kPa by MRE. (**b**) A patient with primary biliary cirrhosis with a liver stiffness measurement of 5.8 kPa by MRE, indicating the presence of advanced fibrosis

and 2.9 kPa. Cirrhosis is often seen in persons with values greater than 5.2 kPa. Contraindications to performing MRE include cardiac pacemaker and severe claustrophobia. MRE performs well in pediatric patients, obese patients, and those with ascites as well as post-transplant patients. Other advantages include a lower rate of incomplete examinations as compared to US-based elastography. MRE allows for evaluation of morphological changes (MRI component) as well as provides a map of liver stiffness over the entire liver surface. Causes of elevated stiffness may include acute biliary obstruction and passive congestion due to congestive heart failure or elevated central venous pressure [27, 28]. Disadvantages of MRE include its inability to be successfully performed in patients with high iron overload because of signal-to-noise-limitations, cost, and longer examination time.

Table 6.1 outlines the results of some of the studies that have examined the various techniques used for diagnosing cirrhosis [29–34].

Table 6.1 Summary of selected meta-analysis and studies looking at the performance characteristics on noninvasive methodologies in prediction of cirrhosis

	Diagnosis of cirrhosis		
Methods	AUROC	Sensitivity (%)	Specificity (%)
TE	0.93	83–87	87–89
ARFI	0.92	88–89	83–87
SWE	0.98	88	97
MRE	0.97	92–93	91–96

AUROC area under the receiver operating curve, *TE* transient elastography, *ARFI* acoustic radiation force impulse imaging, *SWE* shear wave elastography, *MRE* magnetic resonance elastography

Summary

Cirrhosis is the end result of most chronic liver diseases and carries with it the risk of developing significant morbidity and mortality. The limitations of liver biopsy and ability of imaging tests to not only provide noninvasive clues for the diagnosis of cirrhosis but also detect its complications make the latter an attractive clinical tool for the practicing hepatologist. Conventional imaging techniques such as US, CT, and MRI have their respective advantages and disadvantages but are not very sensitive. The development of liver stiffness-based techniques over the past decade has emerged as a promising modality for early diagnosis of cirrhosis in patients who may still be asymptomatic.

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Measurement of Portal Pressure and Transjugular Liver Biopsy

7

Juan G. Abraldes, Philippe Sarlieve and Puneeta Tandon

Portal hypertension is the major source of complications in patients with cirrhosis. Therefore, it would be expected that portal pressure measurements hold prognostic information in these patients. Indeed, several cross-sectional and longitudinal studies have shown that the degree of portal hypertension and the portal pressure response to pharmacological and non-pharmacological interventions can reliably predict several outcomes in cirrhosis.

Hepatic vein catheterization with measurement of the hepatic venous pressure gradient (HVPG) is currently the gold standard technique for determining portal pressure in clinical practice. It is calculated as the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP; Fig. 7.1) [1]. The WHVP is measured by occluding a main hepatic vein; stopping the blood flow causes the static column of blood to transmit the pressure that is present in the preceding vascular territory—in this case, the hepatic sinusoids. This, in the absence of pre-sinusoidal obstruction, reflects portal pressure [2]. The hepatic vein can be occluded either by "wedging" the catheter into a small branch of a hepatic vein or by inflating a balloon at the tip of the catheter [2]. The latter is preferred, as the volume of the liver circulation transmitting portal pressure is much larger [3] (Fig. 7.2), thereby reducing the variability of the measurements [4]. It has been shown that the WHVP gives an accurate estimate of portal pressure in alcoholic and viral cirrhosis [5]. The FHVP, as its name suggests, is a measure of the pressure of the unoccluded hepatic vein. The FHVP should be used preferentially over the right atrial pressure to calculate the HVPG, since the latter shows a worse correlation with clinical outcomes [6]. In addition to portal pressure measurements, a transjugular liver biopsy (TJLB) can also be carried out during the liver catheterization.

Since HVPG reflects portal pressure, changes in HVPG sense changes in the factors that determine portal pressure, namely hepatic vascular resistance, collateral resistance or portal blood flow inflow, or their combination [3]. Changes in hepatic resistance can be caused by changes in fibrosis, regenerative nodules or appearance of thrombosis (mechanical factors) or by a change in hepatic vascular tone (dynamic factors). In this sense, HVPG can be a reliable surrogate of the degree of liver fibrosis, but it also integrates many other pathogenic aspects occurring in liver diseases.

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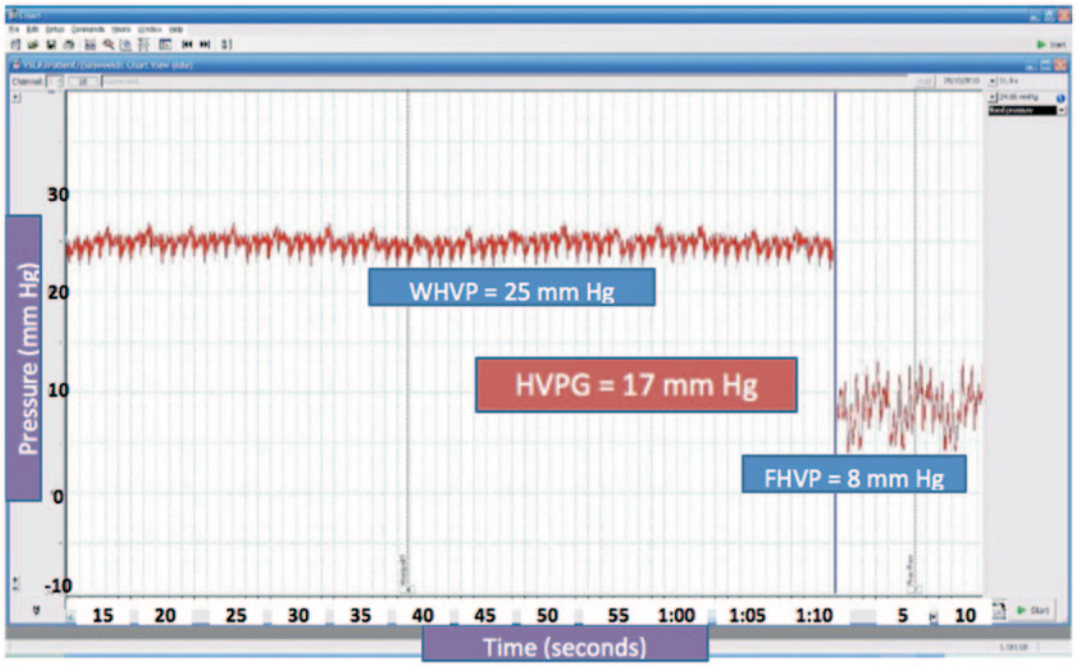

Fig. 7.1 A typical tracing of a hepatic venous pressure gradient (HVPG). Equilibration of WHVP requires over 20 s. The HVPG is calculated as the difference between WHVP and free hepatic venous pressure (FHVP). WHVP wedged hepatic venous pressure

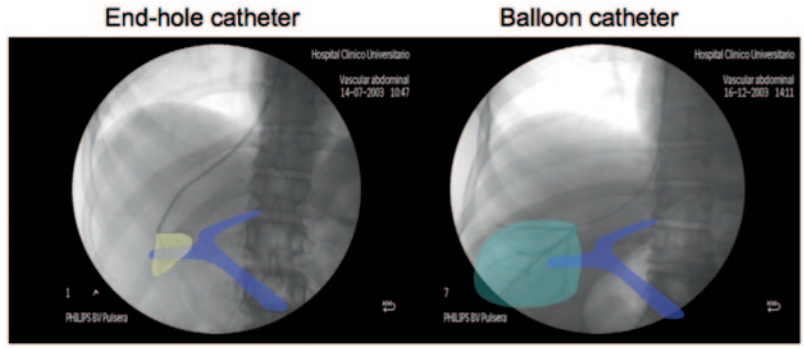

Fig. 7.2 Hepatic venous pressure gradient (HVPG) measurement with the "wedged" end-hole catheter (*left panel*) and the balloon catheter (*right panel*). After occluding the hepatic vein, the static column of blood transmits the pressure of the preceding vascular territory: the hepatic sinusoids. In the absence of a presinusoidal obstruction, this reflects the pressure of the portal vein. The volume of liver transmitting pressure is much larger (and thus less prone to artifacts) with the balloon catheter

HVPG: The Procedure

Guidelines for reliable HVPG measurements have been recently published by hepatologists interested in the procedure [1, 7], but it still lacks widespread standardization across radiology units. A technical summary of the procedure is provided below. Catheterization of the hepatic vein can be carried out under light sedation (Midazolam, up to 0.02 mg/Kg) [8], and is generally well tolerated [9]. Higher doses of midazolam or deep sedation significantly alter pressure measurements [10].

Hepatic Venous Pressure Gradient Procedure

1. The procedure should be performed in fasting conditions
2. Sedation: Midazolam, up to 0.02 mg/kg, does not alter HVPG measurements. Higher doses or the use of deep sedation (propofol/remifentanil) alter pressure measurements. Sedation might be intensified after completing the HVPG measurements, before the biopsy procedure.
3. Monitoring: continuous electrocardiography, arterial blood pressure, and pulse oximetry.
4. Calibration: Nowadays most transducers come precalibrated. If not precalibrated, it should be calibrated against known external pressures before starting measurements (e.g., 13.6 cmH_2O should read 10 mmHg, 27.2 cm H_2O should read 20 mmHg, and 40.8 cmH_2O should read 30 mmHg).
5. Zeroing: Place the transducer at the level of the right atrium (midaxillary line). With transducer open to air (zero pressure), adjust the recorder to read zero.
6. Pressure tracings: Permanent records should be captured either on paper or electronically, for subsequent review.
7. Scale: Use an appropriate scale for venous pressure measurements (full range up to 50 mmHg).
8. Venous access: Under local anaesthesia, the right jugular vein is catheterized, a venous introducer is placed, and the catheter is advanced under fluoroscopic control into the inferior vena cava (IVC) and a hepatic vein. Real-time ultrasound facilitates venous access. HVPG can be performed from the left jugular vein or a femoral vein, but these are second choices.
9. FHVP: The FHVP is measured by maintaining the tip of the catheter "free" in the hepatic vein, at 2–4 cm from its opening into the IVC. The FHVP should be close to IVC pressure; if the difference between these pressure values is greater than 2 mmHg, it is likely that the catheter is inadequately placed or that there is a hepatic vein obstruction. In these cases, IVC pressure should be used for calculating HVPG. HVPG should not be calculated with the atrial pressure.
10. WHVP: The WHVP is measured by occluding the hepatic vein, either by "wedging" the catheter into a small branch of a hepatic vein or by inflating a balloon at the tip of the catheter. Adequate occlusion of the hepatic vein is confirmed by slowly injecting 5 ml of contrast dye into the vein with the balloon inflated. No reflux of the dye or washout through communications with other hepatic veins should be observed. Otherwise, WHVP might be underestimating portal pressure. There is no need to obtain measurements in different veins.
11. Balloon versus end-hole occlusion: Occlusion of the hepatic vein by inflating a balloon is preferred, as the volume of the liver circulation transmitting portal pressure is much larger than that attained by wedging the catheter. This reduces the variability of the measurements. If an end-hole catheter is used, measurements should be taken from at least two different sites and averaged. Catheters with side holes should not be used.
12. Duration of measurements: The WHVP should be measured until the value remains stable (usually longer than 40 s). A 15-s stabilization is enough for FHVP.
13. All measurements should be taken at least in duplicate (or triplicate if differences of >1 mmHg are recorded). Final value is calculated as the mean of these measurements.

14. Any event that might cause an artifact, such as coughing, moving, or talking, should be noted.
15. If large pressure oscillations are noted with the respiratory cycle (as may occur in obese patients, in patients with tense ascites, or with encephalopathy), values at end-expiration should be used.

Complications

Measuring the HVPG is a safe procedure. Major complications are infrequent and include local injury at the puncture site (femoral, jugular, or antecubital veins) such as bleeding, hematoma, and—more rarely—arteriovenous fistulae or Horner syndrome (in the case of jugular puncture). Ultrasonographic guidance should always be used when available, as it considerably reduces the risk of complications of the procedure. Passage of the catheter through the right atrium might cause supraventricular arrhythmias (most commonly ectopic beats), but in the authors' experience these are self-limited in over 90% of cases.

Associated Procedures

In addition to pressure measurements, other procedures can also be carried out during hepatic vein catheterization. These include: hepatic blood flow (using indicator dilution techniques), TJLB (discussed below), and retrograde CO_2 portography. Right heart catheterization can be performed through the same venous access and prolongs the procedure by only 5 min, with a minimal incremental risk. Right heart catheterization allows the measurement of pulmonary artery pressure, pulmonary wedge pressure, and cardiac output, which can be very useful in the investigation of cardiopulmonary complications of cirrhosis and for pre-transplant evaluation.

Applications of HVPG Measurement in Cirrhosis

The use of the HVPG for the measurement of portal pressure is "as close as we have come to a validated surrogate outcome measure in hepatology" [11]. This is based on consistent observational data showing that improvements in the HVPG (either medication induced or related to treatment of the underlying cirrhosis etiology, e.g., abstinence from alcohol) are associated with improvements in clinical outcomes.

Risk Prediction in Cirrhosis

The HVPG is a strong and independent predictor of outcomes in both compensated and decompensated cirrhosis. Cross-sectional studies addressing clinical–hemodynamic correlations have shown that an HVPG of ≥10 mmHg is necessary for gastroesophageal varices to form [12, 13]. The importance of this HVPG threshold has been confirmed in a large observational study nested in a randomized trial evaluating patients with compensated cirrhosis [13]. An HVPG of ≥10 mmHg was associated with an increased risk of developing varices, of hepatic decompensation (40% at 4 years) [14], and of hepatocellular carcinoma (HCC) on follow-up [15]. As a result of its prognostic utility, the HVPG threshold of ≥10 mmHg is termed "clinically significant portal hypertension." The HVPG is also relevant in patients with decompensated cirrhosis, where it provides information about the risk of death during follow-up [16–18]. In this setting, 16 mmHg is considered the optimum cutoff value [16, 19, 20]. In the setting of acute variceal hemorrhage, an HVPG of >20 mmHg is an independent predictor of rebleeding and of mortality [21–23]. On the basis of these clinical–hemodynamic links, recent guidelines support that the HVPG should be used to risk stratify patients, particularly in the research setting [24, 25]. For example, trials evaluating therapies for the prevention of varices should ideally focus on patients with a baseline HVPG of ≥10 mmHg. Moreover, it has been

suggested that trials evaluating pharmacological therapy for primary and secondary prophylaxis should ideally include HVPG measurements [26], though this can be logistically challenging. In our view, in trials of secondary prophylaxis, in which the rate of events is high, there is no need to use surrogate endpoints such as HVPG measurements. In trials targeting patients with early chronic liver disease, in which the rate of events is very low, HVPG could be used as a surrogate of efficacy.

HVPG and Hepatocellular Carcinoma

In compensated cirrhotic patients [15], it has been reported that the HVPG, together with assessment of albumin levels and viral etiology, is an independent predictor of the risk of developing HCC. This risk was six times higher in patients with clinically significant portal hypertension (HVPG ≥10 mmHg) than in cirrhotic patients with HVPG values of less than 10 mmHg. The HVPG also plays an important role in the HCC treatment algorithm [27]. In patients with well-compensated cirrhosis and resectable HCC, the presence of clinically significant portal hypertension markedly increases the risk of unresolved hepatic decompensation occurring within 3 months of hepatic resection [28, 29]. Surgical resection for HCC should therefore be restricted to patients without clinically significant portal hypertension [30, 31].

Risk Prediction in Viral Hepatitis

The HVPG has utility in the setting of chronic viral hepatitis. By assessing the liver as a whole, including the potential functional changes in the hepatic microvasculature, it has the potential to provide supplemental information to histology [32]. The correlation of the HVPG with histological fibrosis has been established in both hepatitis B virus-related [33] and hepatitis C virus-related chronic hepatitis [5]. From this data, the majority of patients with significant fibrosis (≥F2; according to the METAVIR scoring system) have an HVPG over 5 mmHg [33]. Antiviral therapy-related changes in the HVPG are a good way to evaluate disease progression and regression in cases of advanced chronic hepatitis C. Several studies have compared HVPG measurements in patients with chronic hepatitis C taken before and after antiviral therapy. These studies have shown a significant HVPG reduction in patients with advanced stage F3 and F4 after treatment for chronic hepatitis C, particularly in the presence of a sustained viral response [34, 35]. In compensated cirrhotic patients without obvious clinically significant portal hypertension (e.g., without esophageal varices), the HVPG is useful to predict the response to antiviral therapy. In one study, a HVPG cutoff of ≥10 mmHg was an independent predictor of response to combination pegylated interferon and ribavirin therapy (sustained virological response of 14 versus 51% in those with HVPG <10 mm Hg). The development of thrombocytopenia was also more pronounced in patients with the higher HVPG [36]. Although very promising as a tool to select patients for antiviral therapy, with the advent of novel Hepatitis C therapies, the predictive power of an HVPG of ≥10 mmHg will require reevaluation [37].

Assessment of the Response to Pharmacological Therapy to Decrease Portal Pressure

Variceal bleeding and ascites occur when HVPG values reach at least 12 mmHg [12, 38]. Longitudinal studies have demonstrated that if the HVPG falls below 12 mmHg, either by drug therapy [39, 40] or spontaneously (owing to an improvement in liver disease), [17] variceal bleeding is prevented and varices decrease in size. However, even if this target is not achieved, a decrease in HVPG of at least 20% [40] from baseline levels offers almost total protection from variceal bleeding in the long term. In patients surviving a bleeding episode, achievement of these targets (reduction below 12 mmHg or more than 20%

from baseline) constitutes the strongest independent predictor of protection from subsequent variceal bleeding, reduces the risk of other portal hypertension-related complications (e.g., ascites, spontaneous bacterial peritonitits), and is associated with an improved survival [41–43]. Interestingly, this survival benefit has not been attributed to an improvement in liver function [44]. These studies are of enormous conceptual importance, as they indicate that the overall prognosis in patients with cirrhosis who survive a variceal bleeding episode can be improved by decreasing portal pressure. The HVPG threshold of 12 mmHg is less precise for predicting bleeding from fundal gastric varices, and occasionally bleeding may occur below this threshold [45].

The clinical application of the prognostic value of changes in HVPG is hampered by the need for repeated measurements of HVPG, and by the fact that a significant number of patients might bleed before a second HVPG measurement is performed [46]. Two studies have shown that evaluation of the acute HVPG response to intravenous propranolol therapy is a useful tool in predicting the efficacy of nonselective beta-blockers in preventing first bleeding or rebleeding [47, 48]. The acute HVPG response to propranolol was independently associated with survival in these patients [49]. It is important to note that the threshold decrease in HVPG that defines a good response (associated with decreased bleeding and mortality) in these studies was a fall of 10–12% from baseline (instead of the 20% decrease that applies when using the chronic response).

A relevant question is whether there is any benefit in monitoring pharmacological therapy for portal hypertension in day-to-day practice. It is important to note that the benefits of beta-blockers in preventing first bleeding and rebleeding were demonstrated in trials in which treatment was not HVPG guided, that is, beta-blockers were given empirically, either without assessing HVPG response or if assessed, not taking into account to guide therapy [50]. To date, an HVPG-guided treatment strategy has not yet been associated with improved clinical outcomes [51, 52], in large part related to the fact that it remains unclear what therapy to offer to nonresponders [46, 51]. Given the invasive nature of the HVPG measurement and the lack of standardization across centers, until further data is available, HVPG-guided therapy is likely to remain limited to the setting of clinical research.

Another important issue is whether the classification of a person as a hemodynamic responder can be maintained over the long term [53]. To evaluate this, 40 hemodynamic responders (in the setting of secondary prophylaxis) were followed with annual HVPG measurements for a mean follow-up period of 48 months. Although all abstinent alcoholic patients retained hemodynamic responsiveness, only 36% of non-abstinent alcoholics and 50% of patients with viral cirrhosis did so. The loss of hemodynamic response was associated with an increased risk of rebleeding, death, and liver transplantation.

Assessment of New Therapeutic Agents

The first step in the assessment of a potential new agent for treating portal hypertension should involve testing its capacity to modify portal pressure (evaluated as HVPG). It should be noted, however, that the demonstration of a portal hypertensive effect for a new drug might not translate into objective clinical benefit. The association between pharmacological reduction in portal pressure and improved outcomes has been consistently demonstrated so far only for beta-blocker-based therapies. Further validation of the accuracy of the HVPG response as a surrogate with new drug classes (other than beta-blockers) is desirable.

Transjugular Liver Biopsy

TJLB is generally performed after HVPG measurements, and only adds 10–15 min to the procedure. TJLB was first described in humans by Weiner (7) and Rosch (8). This technique avoids crossing of the liver capsule by accessing the liver parenchyma via the hepatic vein or IVC, therefore significantly decreasing the risk of bleeding. Table 7.1 shows the main circumstances in which a transjugular approach is preferred

Table 7.1 Clinical circumstances in which transjugular approach is favored over a percutaneous approach

Need for hepatic venous pressure gradient measurement
Coagulopathy: thrombocytopenia, prolongation of prothrombin time or both (cutoffs not well defined and vary across centers)
Ascites
Anatomical conditions in which the liver is not accessible percutaneously (Chilaiditi syndrome, severe liver atrophy, skin infection in the right upper quadrant)
Morbid obesity
Liver congestion (right heart failure or Budd–Chiari syndrome)

Table 7.2 Main contraindications for transjugular liver biopsy

Dilation of the biliary tree (risks of hemobilia or bilhemia). If this is localized, ultrasound (US) guidance might be used to direct the needle
Presence of liver tumors (risk of seeding into the vasculature)
Large liver cysts (risk of cyst complications)
Hydatid cyst (risk of anaphylactic reaction)
Absence of suitable vascular access (thrombosis of both jugular veins)

over a percutaneous approach [54–56]. Main contraindications for the procedure are summarized in Table 7.2.

Needles and Technique

There are two main techniques for obtaining liver samples: aspiration needles or automatic side-cutting needles. The "aspiration-type" biopsy needle (described by Menghini [57]) was the most frequently used for many years. In most centers, this has now been replaced by cutting or Tru-Cut needles. These needles are less likely to cause fragmentation of the sample [58, 59] and therefore, as confirmed in a randomized controlled trial, are superior to aspiration-type needles for obtaining samples adequate for histopathological diagnosis [59]. Two different Tru-Cut sets are currently available for TJLB, the LABS-100 set with its Quick-Core needle (Cook) and the TLAB system with the Flexcore needle (Dextera Surgical). Although a retrospective study suggested that the Flexcore needle was associated with better samples [60], this requires confirmation in a randomized study.

Both types of needles are advanced into the liver through a long sheath with or without a metal cannula inside (Fig. 7.3). Performance of the biopsy from the right hepatic vein is the first choice. The middle hepatic vein is the second choice and usually safe. The left hepatic vein may be used in special cases, but increases the risk of complications and real-time ultrasound guidance is recommended. The routine use of three passes does not increase the risk of complications as compared with fewer passes [61]. Furthermore, a recent study suggests that four passes are equally safe and more effective than three passes in achieving the commonly accepted quality criteria for grading and staging viral hepatitis (a total sample of 20 mm in length including at least 11 portal tracts) [62]. There were no differences between three and four passes in achieving the accepted criteria, the assessment of diffuse liver diseases (15 mm in length and contain six to eight complete portal tracts).

Similar to HVPG measurements, a TJLB can be performed on an outpatient basis. In order to increase comfort during the biopsy, it is a common practice in our center to administer fentanyl (50–100 mcg) after completing the HVPG measurements (which are normally performed under midazolam).

Complications

TJLB is a safe procedure. Major complications occur in around 0.6 % of the cases, with an overall mortality of 0.1 % [63]. Potential complications specific of TJLB (apart from those associated

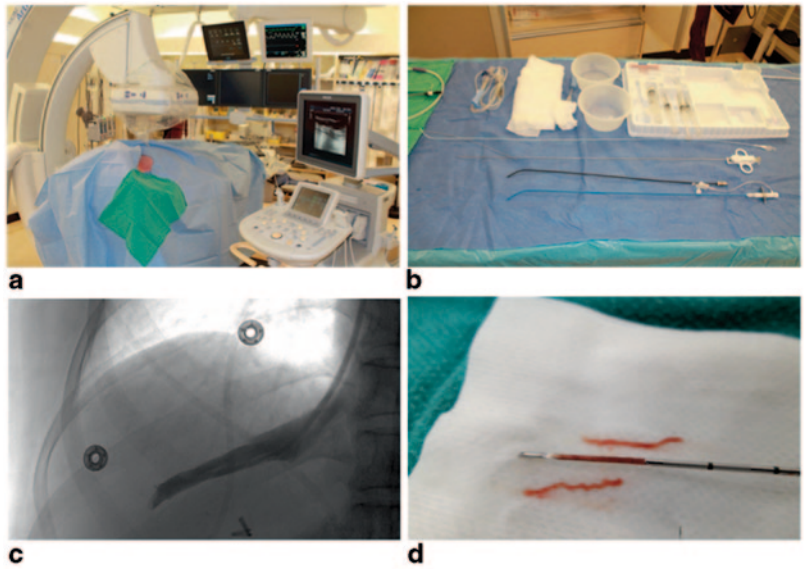

Fig. 7.3 Transjugular liver biopsy. (**a**) Interventional radiology suite with US and multiplanar fluoroscopy units. Patient in supine position with neck slightly turned to the left. Base of the neck exposed for right transjugular access. (**b**) TJLB sets on angiographic table. From *top to bottom*: Multipurpose catheter for hepatic vein access, 18 gauge, 20 mm through Quick-Core biopsy needle, which may be advanced through the nine French angled sheath or metal cannula for the biopsy. Choice of the sheath or cannula will depend on the anatomical situation and user's preference. (**c**) Right hepatic venogram. (**d**) Biopsy samples provided by an 18 gauge, 20 mm throw Quick-Core biopsy needle. The samples have been grossly washed with saline on the figure. All samples occupy the whole length of the biopsy and appear non-fragmented. US ultrasound

with the hepatic venous catheterization) are hepatic hematoma, hemorrhage, hemobilia (due to pucture of intrahepatic bile ducts or gallbladder), and renal puncture (generally asymptomatic and discovered on histological examination).

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Part II

Current Management Strategies for the Complications of Cirrhosis

Reversal of Cirrhosis

8

Gemma Odena, Eva Stein and Ramon Bataller

Cirrhosis is one of the main causes of morbidity and mortality worldwide. At early stages, liver diseases are mostly asymptomatic, so many patients are diagnosed upon the development of liver-related complications (i.e., ascites, variceal bleeding, etc.) [1]. In patients with established cirrhosis, the removal of the causative agent (i.e., response to viral hepatitis therapy, alcohol cessation, etc.) may lead to, at a certain degree, reversibility of the disease. This fact is related to the capability of the liver to dissolve the fibrous bands and restore a nearly normal liver architecture. While there is no doubt that even advanced fibrosis is reversible, it is uncertain if other abnormalities found in advanced cirrhosis (i.e., microthrombosis, avascular nodules, etc.) are reversible.

Liver fibrosis results from chronic damage to the liver with the accumulation of extracellular matrix (ECM) proteins, which is characteristic of most types of chronic liver diseases [2]. The main causes of fibrosis and cirrhosis in industrialized countries include hepatitis C infection (HCV), alcohol abuse, and nonalcoholic steatohepatitis (NASH). The accumulation of ECM proteins distorts the hepatic architecture by forming a fibrous scar and the subsequent development of nodules of regenerating hepatocytes defines cirrhosis. Cirrhosis produces hepatocellular dysfunction and increased intrahepatic resistance to blood flow, resulting in hepatic insufficiency and portal hypertension, respectively [3].

Advanced fibrosis and cirrhosis were historically thought to be passive and irreversible processes, due to the collapse of the hepatic parenchyma and its substitution by a collagen-rich tissue [4]. Currently, fibrosis is considered a model of the wound healing response to chronic liver injury [5]. Liver fibrosis received little attention until the 1980s, when hepatic stellate cells (HSCs) were identified as the main collagen-producing cells in the liver [6]. This cell type undergoes a dramatic phenotypic activation in chronic liver diseases with the acquisition of fibrogenic properties [7]. Besides HSCs, portal myofibroblasts and cells of bone marrow origin have been shown to have fibrogenic potential [8, 9]. At the clinical level, rapid and slower fibrosers were identified, and genetic and environmental factors influencing fibrosis progression have been partially described [10]. The demonstration that even advanced liver fibrosis and cirrhosis are potentially reversible has greatly stimulated researchers to identify targeted therapies [11]. Biotechnology and pharmaceutical companies are increasingly interested in developing antifibrotic programs, and clinical trials are currently under-

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way. However, the most effective therapy to treat advanced fibrosis and cirrhosis is still to remove the causative agent [12]. A number of drugs are able to reduce the accumulation of scar tissue in experimental models of chronic liver injury. Lack of clinical trials is due to the need for long follow-up studies and liver biopsies and should be ameliorated by the current effort to develop noninvasive markers to assess liver fibrosis.

Pathogenesis of Cirrhosis

Early Phase: Liver Fibrogenesis

After an acute liver injury (e.g., viral hepatitis), parenchymal cells regenerate and replace the necrotic or apoptotic cells. This process is associated with an inflammatory response and a limited deposition of ECM. If the hepatic injury persists, this reparative process perpetuates. Eventually, liver regeneration fails and hepatocytes are substituted by abundant ECM including fibrillar collagen. The distribution of this fibrous material depends on the origin of the liver injury.

Liver fibrosis is associated with major alterations in both the quantity and composition of ECM [13]. In advanced stages, the liver contains approximately six times more ECM, including collagens (I, III, and IV), fibronectin, undulin, elastin, laminin, hyaluronan, and proteoglycans. Accumulation of ECM results from both increased synthesis and decreased degradation [14]. Decreased activity of ECM-removing matrix metalloproteinases (MMPs) is mainly due to an overexpression of their specific inhibitors (tissue inhibitors of metalloproteinases (TIMPs)). HSCs are the main ECM-producing cells in the injured liver [15]. In the normal liver, HSCs reside in the space of Disse and are a major storage site of vitamin A. Following chronic injury, HSCs activate or transdifferentiate into myofibroblast-like cells, acquiring contractile, pro-inflammatory, and fibrogenic properties [16]. Activated HSCs migrate and accumulate at the sites of tissue repair, secreting large amounts of ECM and regulating ECM degradation. Other cells like myofibroblasts [17] and cells from bone marrow origin [18]) can be a source of fibrogenic cells in the injured liver. The relative importance of each cell type in liver fibrogenesis may depend on the origin of the liver injury.

A complex interplay among different hepatic cell types takes place during hepatic fibrogenesis [19]. Damaged hepatocytes release reactive oxygen species (ROS) and fibrogenic mediators and induce the infiltration by inflammatory cells. Apoptosis of damaged hepatocytes stimulates the fibrogenic actions of liver myofibroblasts [20]. Inflammatory cells, either lymphocytes or polymorphonuclear cells, activate HSCs to secrete collagen [21]. Activated HSCs secrete inflammatory chemokines, express cell adhesion molecules, and modulate the activation of lymphocytes [22]. Therefore, a vicious circle in which inflammatory and fibrogenic cells stimulate each other is likely to occur [23]. Fibrosis is influenced by different T-helper (Th) subsets, with the Th2 response associated with more active fibrogenesis [24]. Kupffer cells are resident macrophages that play a major role in liver inflammation by releasing ROS and cytokines [25]. Finally, changes in the composition of the ECM can directly stimulate fibrogenesis. Type IV collagen, fibrinogen, and urokinase-type plasminogen activator stimulate resident HSCs by activating latent cytokines such as transforming growth factor beta 1 (TGFβ1) [26]. Fibrillar collagens can bind discoidin domain receptors in HSCs and stimulate collagen synthesis. Moreover, the altered ECM can serve as a reservoir for growth factors and MMPs [27].

Established Cirrhosis

Established cirrhosis results when bridging fibrosis is eventually accompanied by regenerative nodules [28] (Fig. 8.1). In early phases, incomplete septal cirrhosis can be found. It is characterized by the presence of very slender septa radiating from enlarged fields toward the center of the lobule. There are distended efferent vessels around the septum. This type of cirrhosis produces only portal hypertension, and liver failure is not usually observed. The prognosis of these

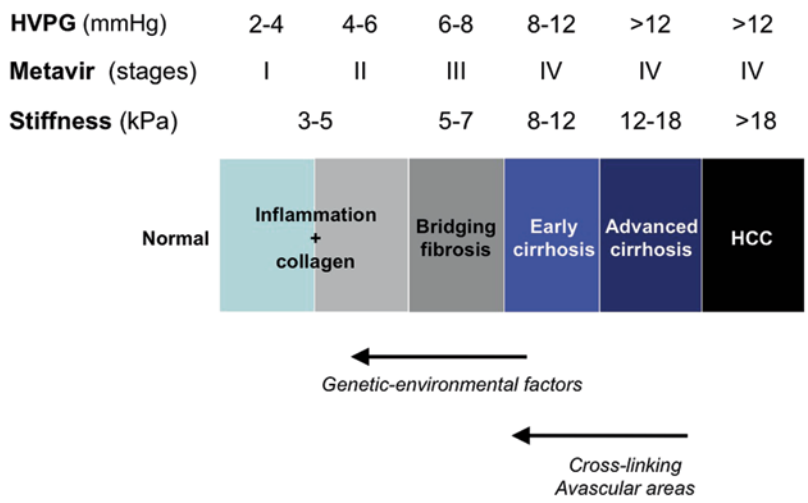

Fig. 8.1 Fibrosis reversibility at different states of chronic liver disease. The capacity of the liver to reverse from fibrosis or cirrhosis to a nearly normal architecture depends on the stage of the liver disease. The genetic and environmental factors regulating fibrosis reversibility are known. While patients with moderate cirrhosis and early cirrhosis can fully reverse upon cessation of the cause of liver injury, the reversibility of patients with advanced cirrhosis can be hampered by cross-linking of collagen and the presence of avascular nodules. The degree of liver fibrosis can be estimated histologically (Metavir stages), by increase in portal pressure (hepatic venous pressure gradient (HVPG)) or by liver stiffness (in kPa)

patients is acceptable if the portal hypertension is controlled. If the cause of liver injury is not removed, the hepatic wound healing response to injury progresses and early cirrhosis develops. In this stage of the liver disease, thin fibrous septa with dissecting nodules are present. As liver damage progresses, wide scars containing clusters of regenerative hepatocytes commonly appear and advanced cirrhosis develops [29, 30]. This stage of the disease is characterized by the accumulation of abundant fibrillar collagen, which is resistant to the collagenolytic actions of MMPs. Moreover, advanced cirrhosis comprises major changes in hepatic microcirculation, endothelial integrity and function, and abnormal hepatocyte organization.

Formation of nodules is the hallmark of advanced cirrhosis. They are divided into dissection and regenerative nodules [31]. Dissection nodules contain remnants of portal tracts and central veins. They contain thin fibrous septa as well as dilated sinusoids especially at their periphery, which appear like multiple central veins produced by the inflow of arterial blood from the surrounding wide scars. Regenerative nodules favored by the rich arterial blood of scar tissue arise in the midst of scars. They are round nodules with a fibrous pseudo capsule with bile ductules due to obstruction of bile flow [32]. Because of their size, they compress the vessels of the capsule, contributing to the perpetuation of the cirrhosis. Importantly, regenerative nodules may undergo dysplastic and malignant changes.

According to the degree of fibrosis and the type of nodules, cirrhosis can be classified into different progressive stages: incomplete septal cirrhosis (incomplete bridging fibrosis, no nodules), early cirrhosis (thin bridging fibrosis with dissecting nodules), moderately advanced cirrhosis (thick bridging fibrosis with dissecting nodules), and advanced cirrhosis (wide septa with regenerative hyperplastic nodules). Histopathologically, advanced cirrhosis can be divided into micro and macronodular [33]. Micronodular cirrhosis is characterized by uniformly small nodules (<3 mm in diameter) and regular bands of connective tissue. Macronodular cirrhosis is characterized by nodules that vary in size (3 mm to 5 cm in diameter) and contain some normal lobular structure (portal tracts, terminal hepatic

venules). Collapse of the normal liver architecture is suggested by the concentration of portal tracts within the fibrous scars. Regeneration in micronodular cirrhosis can result in macronodular or mixed cirrhosis. Conversion from micronodular to macronodular cirrhosis takes more than 2 years.

Vascular changes play a major role in the pathogenesis of advanced cirrhosis [28]. Complete septa may link central veins to central veins, creating anastomoses between draining vessels. Septa linking adjacent portal tracts create vascular anastomoses between afferent vessels of the portal tracts involved. Vascular structures in central–central and portal–portal septa are not the major determinants of a detrimental change in intrahepatic circulation [34]. The key phenomenon in the emergence of a truly cirrhotic state is the development of fibrous vascularized septa linking portal tracts and central veins. Therefore portal–central bridging fibrosis creates direct anastomoses between the afferent (hepatic artery, portal vein) and efferent (centrilobular veins) vessels of the liver, allowing a fraction of the blood to bypass the lobular parenchyma, without functionally contacting a metabolically active parenchyma. In advanced cirrhosis, most of the hepatic blood supply appears to pass through the liver via these channels [35, 36]. Further vascular changes in developing an established liver cirrhosis are due to vascular thrombosis. Thrombosis of medium and large portal veins and hepatic veins is a common occurrence in cirrhosis, and these lesions are important in causing progression of cirrhosis. Investigations on neo-angiogenesis in cirrhosis have focused attention on hypoxia of liver tissue [37]. Hypoxia may result from several mechanisms: impairment in sinusoidal permeability and perfusion, intrahepatic shunts, vasoconstriction, and thrombosis and capillarization of sinusoids. Liver tissue hypoxia aggravates fibrosis progression, so that fibrosis and hypoxia may aggravate each other in the presence of persistent parenchymal injury, leading to a vicious cycle that disrupts the normal tissue repair and thereby promotes the development and progression of cirrhosis [38].

In advanced cirrhosis, there is a local predominance of vasoconstrictors over vasodilators, resulting in a tonic contraction of perisinusoidal HSC cells that increase vascular resistance. Moreover, thrombosis in small vessels occurs and intrahepatic arterial shunts develop [39]. Hepatocytes proliferate in ischemic areas in a disorganized manner, forming regenerative nodules. Pressure in the portal venous system progressively increases, leading to the development of portocollateral veins and esophageal varices [40]. The resulting portal hypertension leads to splanchnic vasodilatation that increases hepatic venous blood flow. Systemic vascular resistance is decreased and eventually there is a marked activation of systemic vasoconstrictor systems that worsen portal hypertension and favor ascites formation. Hepatocellular function is progressively impaired and there is decreased function of the reticuloendothelial system leading to endotoxinemia and increased risk of bacterial infections [41]. Eventually, hepatocellular function fails, leading to severe coagulopathy and hepatic encephalopathy [42]. A profound circulatory dysfunction due to impaired myocardial function and decreased systemic vascular resistance is frequently seen. In very late stages of cirrhosis, renal vasoconstriction develops, leading to the hepatorenal syndrome [43]. In this phase of the disease, most patients die unless a liver transplantation is rapidly performed.

Reversibility of Advanced Fibrosis and Cirrhosis: Clinical Evidence

The reversibility of chronic liver diseases depends on the stage of the disease (Fig. 8.1). Thus, while advanced fibrosis and early cirrhosis may be reversible, reversal of advanced cirrhosis may be hampered by the presence of collagen cross-linking and avascular areas. Therefore, the current paradigm that cirrhosis is reversible should clearly be tempered. It is unclear if the abnormalities of the intrahepatic vasculature regress in human cirrhotic liver. The so-called veno-portal

adhesions may persist even in cases of extensive fibrosis regression, and evident "arterialized" sinusoids appear in the context of intrahepatic arterio-venous shunts [44]. A better staging system of cirrhosis is clearly needed for prognostic purposes and to design prospective studies on cirrhosis reversal.

There are many clinical observations that the removal of the causative agent leads to improvement of liver fibrosis even in patients with F4 (cirrhosis). This observation has been described in patients with alcohol-induced liver injury, chronic hepatitis C, B, and D, secondary biliary cirrhosis, NASH, and autoimmune hepatitis [11, 45–72] (Table 8.1). Obviously, reversal of advanced fibrosis is a slow process that may take months or even years. The time is probably influenced by the underlying cause of the liver disease and its severity. One of the limiting factors is the capacity of the chronically damaged liver to reabsorb scar tissue [73]. In patients with ongoing liver injury, the fibrosis scar is characterized by the presence of thin reticulin fibers and inflammatory cells. This thin fibrotic bands are probably fully reversible. In contrast, long standing fibrosis, which typically contains extensive collagen cross-linking by tissue transglutaminase, presence of elastin, dense acellular/paucicellular ECM, and decreased expression and/or activity of specific metalloproteinases, is largely irreversible [74, 75]. This scenario is probably present in patients with very advanced fibrosis after decades of continuous liver injury. Moreover, there is mounting evidence that long-term fibrogenesis occurring in humans is much less reversible than in rodents, so the current optimism about full reversibility of cirrhosis should be tempered [76].

Mechanisms Involved in Fibrosis Resolution

The mechanisms of resolution of advanced fibrosis have been largely studied in animal models, while data from humans are scarce. For architectural remodeling to occur, the balance between the factors promoting matrix accumulation (synthesis of matrix by fibrogenic factors) and remodeling (matrix breakdown mediated by MMPs) needs to alter, shifting from one that favors matrix accumulation to one of net matrix degradation [77]. Restoration of fibrolytic activity is initiated upon suppression of hepatic TIMPs, following elimination of hepatic myofibroblasts by apoptosis, senescence, or reversion to a quiescent phenotype, suggesting that clearance of activated HSCs is a key step in the onset of fibrosis regression [78]. Recent studies suggest that among these potential outcomes, deactivation of myofibroblastic HSCs into a quiescent phenotype is the prevailing event in fibrosis resolution [79, 80]. Moreover, myeloid cell subsets ("restorative" macrophages and dendritic cells), which constitute a major source of MMP criti-

Table 8.1 Summary of clinical evidence on cirrhosis reversibility

Hepatitis C	Interferon-α + ribavirin	[50, 48, 51]
	New oral antivirals	[49, 52]
Hepatitis B	Lamivudine	[53–55]
	Tenofovir	[56, 57]
	Adefovir	[56, 58, 59]
	Interferon-α/γ	[60–62]
	Entecavir	[63, 64]
Hepatitis D	Interferon	[65, 66]
Alcohol	Abstinence	[45–47]
NASH	Weight loss	[72]
	Bariatric surgery	[69–71]
Biliary obstruction	Surgery	[11, 67, 68]

NASH nonalcoholic steatohepatitis

cal for fibrosis resolution, and endothelial cells, which maintain HSCs in a quiescent phenotype, have also been identified as contributing to the resolution of fibrosis (Fig. 8.2).

Increased Collagenolytic Activity

Fibrillar collagens (I and III) are degraded by interstitial MMPs. During fibrosis resolution, MMP activity increases due to a rapid decrease in the expression of TIMP-1. Partial degradation of fibrillar collagen occurs, and the altered interaction between activated HSCs and ECM favors apoptosis [75]. Removal of activated HSCs by apoptosis precedes fibrosis resolution. Stimulation of death receptors in activated HSCs and a decrease in survival factors, including TIMP-1, can precipitate HSC apoptosis [81]. However, reversibility may only be partial as regenerating nodules and alterations of hepatic microcirculation, both associated with advanced fibrosis, are difficult to revert.

HSC Apoptosis

Follow-up of rats exposed to carbon tetrachloride for 8 weeks has shown that the recovery phase is associated with an early decrease in hepatic TIMP-1 and a parallel decrease in the density of activated HSCs due to apoptosis. Experiments in TIMP-1 transgenic mice and with TIMP-1 scavengers demonstrated the causal relation-

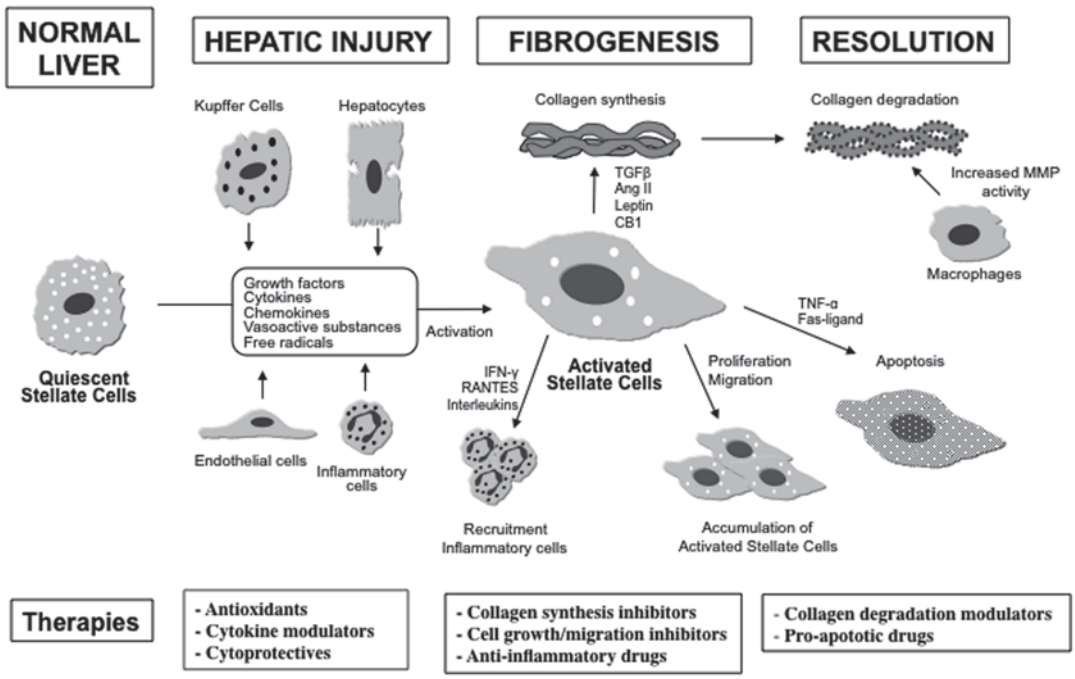

Fig. 8.2 Cellular pathogenesis of fibrosis progression and resolution. In the normal liver, hepatic stellate cells (HSCs) display a quiescent phenotype. Continuous liver injury leads to a wound healing response with the infiltration of inflammatory cells that secrete a number of soluble factors and cytokines that lead to activation of HSCs into collagen-producing cells. In turn, activated HSCs perpetuate liver fibrogenesis and promote inflammation by secreting a number of profibrogenic mediators. If the causal agent is removed, fibrosis resolution initiates by stimulation of collagen degradation and removal of HSCs (either by apoptosis or by regression to quiescence). There are different sites during fibrogenesis and fibrosis resolution that represent potential sites for intervention. Agents capable of reducing HSCs' accumulation or collagen synthesis or those that promote collagen degradation and/or HSCs' apoptosis have been tested in experimental models in rodents. The usefulness and safety of most of these agents to reverse liver fibrosis should be tested in well-designed clinical trials

ship between hepatic TIMP-1 expression, failure of fibrolysis, and increased HSC survival [82]. Further studies identified nuclear factor-kappa B (NF-κB) as an important transcription factor in the upregulation of antiapoptotic genes in activated HSCs and showed that inhibitors of NF-κB signaling induce apoptosis of activated HSCs and reversal of fibrosis [83].

HSC Senescence

Senescent hepatic myofibroblasts may contribute to the regression of fibrosis because they stop proliferating, upregulate the expression of matrix degrading enzymes, and downregulate the expression of ECM proteins. Moreover, senescent hepatic myofibroblasts can be cleared by natural killer cells [84]. Thus, senescence of hepatic myofibroblasts can prevent further proliferation of these ECM-producing cells, promote ECM degradation, and accelerate myofibroblast clearance from the site of injury.

Reversion of HSC Phenotype to an Inactivated State

Recent cell tracking studies have further documented earlier in vitro studies showing that activated HSCs can undergo deactivation to a quiescent phenotype following cessation of liver injury [79, 80]. However, reverted HSCs do not reacquire all of the characteristics of quiescent cells, but rather retain an activated intermediate state with enhanced susceptibility to a fibrogenic stimulus. These data raise the intriguing possibility that reverted HSCs contribute to fibrosis reversal but may promote more rapid and severe fibrosis progression upon recurrence of liver injury.

Scar-Associated Macrophages

Scar tissue contains numerous monocyte-derived macrophages. These monocyte-derived macrophages are a potent source of MMPs, including collagenases such as MMP13, gelatinases (MMPs 2 and 9) and elastases [85]. Besides these collagenases, recent data indicate that vascular endothelial growth factor (VEGF) also plays a role in fibrosis resolution. VEGF promotes sinusoidal permeability, monocyte-endothelial cell adhesion, and the resulting scar-associated macrophages accumulation necessary for fibrosis resolution. VEGF does indeed play a dual role in fibrosis and fibrosis resolution as it has previously been found to play a role in fibrogenesis via a pro-inflammatory effect acting primarily on endothelial cells. Work by a number of groups has demonstrated that macrophages are crucial to the resolution of fibrosis [86, 87]. The removal of the macrophage population at the onset of spontaneous fibrosis resolution in rodent models of liver injury prevents remodeling of fibrosis. Additionally, deletion of the macrophage population is associated with a critical drop in liver levels of key enzymes such as MMP13 and MMP12, identifying the macrophage as a crucial source of these enzymes in fibrosis resolution [88].

Can We Favor Cirrhosis and/or Advanced Fibrosis Resolution?

While the mechanisms and genetic and environmental factors regulating fibrosis progression are well characterized, the modulators of fibrosis reversibility are largely unknown. Clinical and translational studies should identify the main cellular and molecular mechanisms that mediate cirrhosis reversibility. These studies will lead to the identification of potential therapeutic targets to favor disease reversibility. As discussed earlier, regression of advanced fibrosis even at the stage of early cirrhosis can be achieved following treatment of the underlying cause in a variety of chronic liver diseases. However, despite the identification of numerous effective antifibrotic pharmacological targets in experimental models, no clinical translation has yet been achieved. This lack of translation may be due to the fact that fibrosis progression is very slow in humans and therefore long clinical trials (i.e., 3–5 years) are required to demonstrate antifibrotic effects.

Moreover, there is a clear need for noninvasive markers of fibrosis progression/regression, which may allow precise monitoring of the evolution of fibrosis. Altogether, therapeutic trials primarily focused on antifibrotic endpoints remain scarce and have thus far failed to demonstrate any benefit. The pathways and drivers mediating fibrosis resolution are complex and may differ at different stages of cirrhosis. An additional obstacle is that patients with advanced fibrosis and/or cirrhosis are particularly susceptible to develop hepatotoxic effects, as well as liver cancer, which is a concern to develop long-term clinical trials.

Several therapeutic strategies have been tested to reduce liver fibrosis in patients with chronic liver diseases. Corticosteroids exert antifibrogenic actions in autoimmune hepatitis and acute alcoholic hepatitis [89]. Other anti-inflammatory therapies like colchicine or interleukin-10 have been tested but they induced undesirable side effects. A different strategy targets activation and proliferation of HSCs. These strategies include antioxidants (e.g., vitamin E, silimarin, phosphatidylcholine, S-adenosil-metionin) as well as modulators of intracellular pathways of HSCs biological responses [90, 91]. A promising strategy is to inhibit the renin–angiotensin system inhibition, specifically by using angiotensin II receptor type 1 antagonists (AT1) [92]. These strategies have been successful for the treatment of cardiac fibrosis as well as renal fibrosis. Administration of inhibitors of the renin–angiotensin system to treat arterial hypertension in transplanted patients showed a slower progression of hepatic fibrogenesis. Conversely, administration of losartan for 18 months showed that it is well tolerated in chronic hepatitis C patients while diminishing fibrogenic gene expression [93].

The use of different therapeutic strategies may differ according to the etiology of the liver disease. In patients with hepatitis C, therapy with interferon-γ and ribavirin induces antifibrogenic effects regardless of their antiviral action [51]. However, interferon-γ has important side effects [94]. The recent development of highly active oral therapies against HCV opens a new era in the field of fibrosis resolution. These drugs are well tolerated, suggesting that even patients with advanced cirrhosis would clear the viral infection in the coming years. Studies identifying key mediators of cirrhosis reversibility are anticipated in the coming years. Such studies can help in the identification of new targeted therapies that favor fibrosis reversibility. Regarding patients with NASH, therapies increasing insulin sensitivity (e.g., thiazolidinediones and statins) have been shown to decrease the degree of fibrosis [95, 96]. Other therapies that are effective in experimental NASH include profibrogenic cytokines inhibitors (TGFβ1, platelet-derived growth factor(PDGF)) [97–99], chemokine receptors antagonists [88], interleukin-10 [100, 101], and cannabinoid receptor blockers [102]. However, their use in humans is hampered by undesirable side effects.

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Esophageal Varices: Primary and Secondary Prophylaxis

9

Humberto C. Gonzalez and William Sanchez

The existence of gastroesophageal varices in a patient with chronic liver disease implies the presence of significant portal hypertension (hepatic venous pressure gradient [HVPG] 10–12 mmHg), which is usually a progressive complication of cirrhosis [1]. In primary biliary cirrhosis and alcoholic hepatitis, esophageal varices can occur in the absence of cirrhosis as a result of hepatic presinusoidal portal hypertension [2]. In cirrhosis, increased portal pressure is due to increased resistance to flow mainly as a consequence of architectural distortion secondary to fibrosis and regenerative nodules. Intrahepatic vasoconstriction as a result of decreased nitric oxide production also contributes to portal hypertension. Portal hypertension leads to the formation of portosystemic collaterals including gastroesophageal varices [1].

Esophageal varices are present in 50% of patients with cirrhosis. Their presence correlate with increasing severity of liver disease (40% among patients with Child–Pugh class A cirrhosis compared to 85% in class C patients) [3]. Cirrhotic patients without varices develop them at a rate of approximately 8% per year and small varices increase in size at a rate of 8% per year as well [3, 4].

Variceal rupture is the end result of increased intravariceal pressure, increased diameter of the varix, and reduced wall thickness. Wall thickness of a varix can be evaluated visually by the presence of red wale markings (thin areas). Variceal rupture often occurs at the level of the gastroesophageal junction where the varices are very superficial and thus have thinner walls [5]. Variceal hemorrhage occurs at a yearly rate of 5–15% [6]. Despite advances in endoscopic therapy, mortality related to variceal hemorrhage remains high—at least 15–20% at 6 weeks [7, 8, 9].

Clinical Manifestations

Esophageal varices remain asymptomatic until they rupture. Whether a patient has bled from esophageal varices or not the prophylactic measures are divided into primary and secondary. For the evaluation and classification of varices, esophagogastroduodenoscopy (EGD) is currently the gold standard. Varices are best classified according to size as either small (<5 mm) or large (>5 mm) [10] (see Fig. 9.1). When classified into small, medium, and large, medium and large should be paired in one group for treatment purposes [6].

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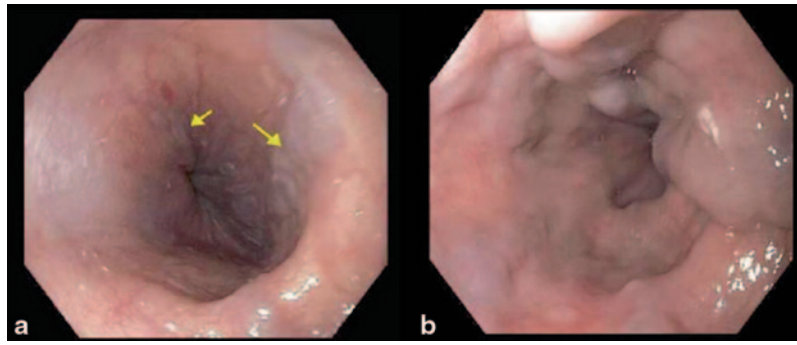

Fig. 9.1 **a** Small esophageal varices (*arrows*). **b** Large esophageal varices

Screening

Screening EGD should be performed at different intervals according cirrhosis status (compensated vs. decompensated) and on previous size of varices (small vs. large) (see Table 9.1 for recommended screening intervals [10–12]). Esophageal varices should be assessed on withdrawal of the endoscope during maximal insufflation while the stomach is decompressed. The presence or absence of high-risk stigmata (i.e., red wale) signs should be noted.

Management

The management of esophageal varices includes prevention of varices formation (preprimary prophylaxis), prevention of the initial hemorrhage (primary prophylaxis), control of acute variceal bleeding (see Chap. 10), and prevention of rebleeding (secondary prophylaxis).

The most commonly used strategies to treat esophageal varices are the use of nonselective β-blockers (NSBBs) and endoscopic band ligation (EVL). Other interventions include nitrates, sclerotherapy, transjugular intrahepatic portosystemic shunt (TIPS), and surgical procedures (shunts and devascularization; see Table 9.2). These last inter-

Table 9.1 Recommendations for varices screening in cirrhosis

Clinical scenario	Interval
At diagnosis	As soon as possible
Compensated without varices	2–3 years
Compensated with small varices	1–2 years
Decompensated cirrhosis	As soon as possible and yearly thereafter

Table 9.2 Prophylaxis of variceal hemorrhage

Type	Preferred	Alternative
Preprimary	None	None
Primary	–	–
Small	None	NSBB
Small with high risk	NSBB	EVL[a]
Large	NSBB	EVL
Large with high risk	EVL or NSBB	NSBB or EVL
Secondary	NSBB + EVL	NSBB + nitrates[b] or TIPS

NSBB nonselective β-blockers, *EVL* endoscopic band ligation, *TIPS* transjugular intrahepatic portosystemic shunt
[a] If technically feasible
[b] Poorly tolerated, not routinely used in clinical practice

ventions are not first-line therapy and should not be used for primary prophylaxis [1].

Preprimary Prophylaxis

The goal of preprimary prophylaxis is to prevent the development of varices in patients with portal hypertension. Treatment of the underlying cause of liver disease is generally advised to prevent progression of portal hypertension and its complications. The only randomized placebo controlled trial investigating the use of NSBBs (timolol) in patients with cirrhosis and portal hypertension for prevention of the development of esophageal varices was found to be infective, and for such reason treatment is generally not recommended [13].

Primary Prophylaxis

Medical Therapy

NSBBs decrease cardiac output (β-1 receptor blockade) and promote vasoconstriction of the mesenteric vasculature (β-2 receptor blockade) resulting in decreased portal venous inflow and consequently portal pressure. The most commonly used NSBBs include propranolol and nadolol [1, 14]. Recently carvedilol, non-cardioselective β-blocker with α-1 blocking properties has been used with promising results [15] (see Table 9.3).

The goal of treatment with NSBBs is to decrease the HVPG to less than 12 mmHg which reduces the risk of hemorrhage and improves survival [16]. A reduction of 10–20% of HVPG baseline decreases the risk of the first variceal hemorrhage [17, 18]. NSBBs are associated with a median reduction of HVPG of 15%, with 37% of patients being responders defined as a reduction of HVPG to < 12 mmHg and/or > 20% from baseline [19]. The reduction of HVPG with NSBBs might have additional benefits beyond the prevention of variceal bleeding, such as decreased frequency of development of ascites, spontaneous bacterial peritonitis, and death [17, 20].

Routine measurement of HVPG to guide β-blockade therapy is not regularly practiced and is limited to specialized referral centers. For this reason, surrogates markers such as a decrease in heart rate of 25% below baseline, heart rate of 55–60 beats per min or maximally tolerated dose are followed as guides for medication adjustment [1, 14]. The risk of bleeding recurs when NSBBs are stopped, so in general, therapy should be continued indefinitely [21].

NSBBs have common side effects that include lightheadedness, fatigue, erectile dysfunction, and shortness of breath. Relative contraindications for the initiation of NSBBs include sinus bradycardia, relative hypotension, and insulin-dependent diabetes. Absolute contraindications are severe obstructive pulmonary disease, heart failure, aortic valve disease, heart block, and peripheral arterial insufficiency [14, 22].

The use of NSBBs for primary prophylaxis reduces the incidence of variceal hemorrhage. Meta-analysis has compared NSBBs versus placebo. These studies have shown that the bleeding rate in the placebo group was 25%, as compared to 15% in the treatment group over a 2-year period [23].

Table 9.3 Medications for primary or secondary prophylaxis of variceal hemorrhage

Drug	Starting dose	Maximal dose	Goals	Follow up/comments
Propranolol	20 mg BID	320 mg BID	HVPG < 12 mmHg HR 50–55/min HR < 25% BL Max. tolerated	PPh: No need to repeat EGD SPh: Confirm EGD Adjust dose every 2–3 days
Nadolol	40 mg QHS	160 mg QHS		
Carvedilol	6.25 mg BID	12.5 mg BID		
Isosorbide-5-mononitrate	10 mg QD	20 mg BID	Max. tolerated SBP > 95 mmHg	Use with stable dose of NSBB Exclusive for SPh Adjust every 2–3 days

mg milligrams, *BID* twice daily, *QHS* once daily at nighttime, *Max* maximum, *HVPG* hepatic venous pressure gradient, *HR* heart rate, *BL* baseline, *SBP* systolic blood pressure, *mmHg* millimeters of mercury, *PPh* primary prophylaxis, *SPh* secondary prophylaxis, *EGD* esophagogastroduodenoscopy

NSBBs for patients with small varices are associated with a nonstatistical reduction in the incidence of the first variceal hemorrhage. The bleeding rate was reduced from 7% in the untreated patients to 2% in those on NSBBs therapy over a 2-year period [23].

A multicenter, single-blinded trial compared the use of nadolol against placebo in the evolution of varices. The treated group showed slower progression to large varices (11 vs. 37%) at 3 years without survival differences. The benefit of β-blockade was an expression of the time patients remained with small sized varices [24].

Special attention should be placed to identify patients with small varices at high risk of bleeding: Child–Pugh class B/C cirrhosis or varices with red wale marks in whom treatment with NSBBs is indicated to prevent the first bleeding episode. In the absence of high-risk features, treatment can be considered for small varices, but its long-term benefit has not been fully established and the benefit may be outweighed by medication side effects. If no treatment is given in this setting, reassessment should be performed in 2 years unless hepatic decompensation occurs (see Table 9.1) [1].

A large meta-analysis that included more than 1100 patients with medium/large varices showed that NSBB therapy reduced the risk of the first variceal bleeding to 14% as compared to 30% in the placebo group. This study also showed benefit in mortality in the pharmacologically treated group. The number needed to treat to prevent one bleeding episode was ten [23, 25].

In general, NSBBs are the first-line therapy which can be switched to EVL if not tolerated, ineffective, or contraindicated. Up to 15% of patients have relative contraindications to the use of NSBBs. Some of the side effects disappear with continued use or dose reduction. Treatment withdrawal occurs in approximately 15% (10% for nadolol and 17% for propranolol) [26]. The selection of treatment modality should consider patient preferences, local resources and contraindication, or adverse effects to therapy [27].

In 2010, a prospective trial reported increased mortality when utilizing NSBB in refractory ascites [28]. Another study described worse outcomes (hemodynamic compromise, hepatorenal syndrome, and reduced transplant free survival) when NSBB were continued after an episode of spontaneous bacterial peritonitis [29]. The concept of a therapeutic window for NSBB for variceal hemorrhage prevention has been hypothesized. The opening point is still debated, but it is believed to be the initiation of gut bacterial translocation in the presence of ascites (beginning of hepatic decompensation). The closing point occurs when the cardiac compensatory reserve is lost (end-stage cirrhosis); hypotension and decrease end organ perfusion (refractory ascites, hepatorenal syndrome, spontaneous bacterial peritonitis) [30]. This concept is still evolving and should be interpreted with caution.

Endoscopic Variceal Ligation

EVL involves suctioning of a varix into the endoscope channel followed by deployment of a rubber band, so that the tissue undergoes necrosis and fibrosis. Bands should be placed in areas that show evidence of recent bleeding (red whale sign or nipple sign) or staring at the gastroesophageal junction and moving proximally every 2 cm in the distal esophagus. If EVL is the treatment chosen, then repeat EGD should be performed every 2–4 weeks until obliteration. The first surveillance EGD should occur in 1–3 months after obliteration and then every 6–12 months to evaluate for recurrence [1, 14].

Although, the literature suggests a slight advantage of EVL in the prevention of the first variceal bleed, well-designed meta-analysis have shown no difference when comparing NSBBs to EVL [31]. No difference in mortality has been shown [32, 33]. Meta-analyses have demonstrated that in high-risk varices (large with or without red wale signs), EVL is associated with a slight but significant decrease risk of the first variceal hemorrhage episode when compared to NSBBs, but without impact on mortality. The rate of adverse events from EVL is lower than NSBB therapy but usually more serious including bleeding from ligation induced esophageal ulcers [34, 35] (see Fig. 9.2).

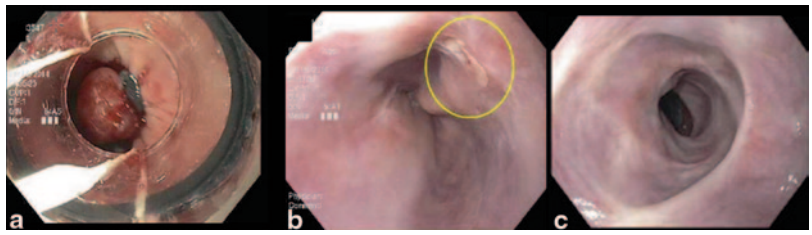

Fig. 9.2 **a** Esophageal varix ligation. **b** Esophageal ulcer (*circle*).**c** Obliterated varices by esophageal band ligation

Other Treatments

Endoscopic sclerotherapy alone or the combined use of NSBBs and nitrates for primary prophylaxis has yielded mixed results. Shunt surgery is effective in preventing the first bleeding but it is associated with higher mortality and hepatic encephalopathy. None of these therapies are recommended for this purpose [1, 36–38].

Secondary Prophylaxis

The importance of aggressive secondary prophylaxis lies in that the absence of therapy is associated with a recurrence rate of 60 % at 1 year and a mortality of 33 % [23, 39]. The use of NSBBs, EVL, or shunt procedures reduces significantly the rebleeding rate. All patients who are potential transplant candidates and that have recovered from variceal bleeding should be referred to a transplant center for evaluation [1].

Medical Therapy

NSBBs alone reduce the rebleeding risk from 63 to 42 % (number needed to treat; NNT 5) when compared to placebo. The mortality in these comparison groups was also reduced from 27 to 20 % (NNT 14) [23]. Besides NSBBs, nitrates have systemic vasodilating effects and reduce portal pressure through splanchnic vasoconstriction as a result of hypotension rather than from intrahepatic vasodilation. Nitrates (isosorbide mononitrate) are not recommended as monotherapy, but when used in combination with NSBBs might have synergistic effects in the reduction of portal pressure [40].

Some randomized clinical trials support a reduction in rebleeding with the combined use of isosorbide–mononitrate and NSBBs, but when pooled data have been assessed in meta-analyses this has not been supported [41–43]. Compared with endoscopic therapy, there may be a survival advantage in using isosorbide mononitrate and NSBBs, but long-term and better designed studies are still needed to validate its routine use [41]. In clinical practice, this form of combination therapy is associated with frequent side effects that mandate discontinuation of therapy [23, 42].

Endoscopic Variceal Ligation

The combination of NSBBs with EVL is the standard of care for secondary prophylaxis. The rebleeding risk is reduced from 38 to 47 % when using EVL alone to 14–23 % for EVL and NSBBs combined [44, 45]. The rebleeding risk is also reduced when combination therapy is compared to medical therapy alone. There is no mortality benefit when EVL and NSBBs are used [46].

Endoscopic Sclerotherapy

Sclerotherapy involves the injection of a sclerosant agent (sodium morrhuate, podidocanol, ethanolamine, alcohol, or sodium tetradecyl sulfate) via EGD into a varix or adjacent to it. While sclerotherapy is an effective treatment to prevent recurrent bleeding from varices, EVL has essentially replaced sclerotherapy for pro-

phylaxis due to superior safety profile. Complications include retrosternal discomfort, ulcers, strictures, esophageal perforation, pleural effusion, acute respiratory distress syndrome (ARDS), pericarditis, fever, bacteremia, distant embolism, and/or abscess [47].

When compared to placebo, sclerotherapy is superior in preventing bleeding and improves survival. The benefit is seen when complete variceal obliteration is accomplished. Sclerotherapy is superior NSBBs in rebleeding prevention, but has more complications without mortality benefit. When comparing sclerotherapy to EVL, benefits favor EVL in reduction of rebleeding, less session to eradicate varices, and fewer complications [47]. At present, sclerotherapy is no longer recommended for secondary prophilaxis [1].

Transjugular Intrahepatic Portosystemic Shunt

TIPS procedure creates a communication between the hepatic vein and an intrahepatic branch of the portal vein using an expandable metallic stent that decompresses the portal system. It involves the puncture of the jugular vein from which a catheter is advanced to the right atrium, through the inferior vena cava and up to the hepatic vein [14]. Polytetrafluoroethylene coated stents provide better outcomes as incidence of pseudointimal proliferation and obstruction is minimal as compared to uncoated stents [48].

With TIPS, the portosystemic pressure gradient should decrease by 50% or below 12 mmHg for it to be effective [48]. TIPS complications include intraperitoneal hemorrhage, sepsis, cardiopulmonary failure, shunt thrombosis or migration, hepatic encephalopathy and progressive hepatic failure [49]. TIPS should be avoided in patients with model for end-stage liver disease (MELD) > 24 [50], the ideal candidate has an MELD score < 14. TIPS is classically indicated as a rescue therapy for acute variceal hemorrhage in those who have failed endoscopic and pharmacological therapy [51]. Compared to other forms of treatment, TIPS does not confer a survival advantage [1].

TIPS effectively reduces portal pressures. Meta-analysis evaluating EVL versus TIPS reveals a rebleeding rate of 47 versus 19%, respectively. Hepatic encephalopathy, the most common complication of TIPS, was more frequently seen in the TIPS treated group; 34 versus 19% in the EVL group, with no impact on mortality [52]. These results suggest that TIPS should not be used as a first-line treatment for secondary prophylaxis and should be considered for failed pharmacological and endoscopic treatment [51]. Special note should be made that the majority of patients in these studies used the non-coated TIPS rather than coated shunts currently in use which are associated with a much lower rate of occlusion and encephalopathy [48].

A multicenter European randomized clinical trial demonstrated a significantly lower rebleeding rate of 3% when early TIPS (coated) for acute variceal bleeding was used, as compared to dual therapy (EVL and NSBBs) of 50%. This study also showed improved survival in the early TIPS group; 86 versus 61% in the combined treatment group [53].

Surgical Therapy

Surgical shunts to address portal hypertension include portocaval shunt and the distal splenorenal shunt. These, spare the portal vein which could be required in case of liver transplantation. Over the last decade the use of surgical shunts has decreased given the availability of TIPS which offers a less invasive and effective option. Surgical shunts are presently reserved for those patients in whom TIPS is contraindicated for technical reasons (such as extensive portal vein thrombosis) or live far from suitable medical care [14]. Surgical expertise with shunts is decreasing and is only available at referral centers.

TIPS and distal splenorenal shunts are similar in rebleeding, encephalopathy, and mortality rates [54]. TIPS is less invasive and often times favored, but local expertise needs to be considered when deciding between these procedures. Another surgical option includes gastroesophageal devascularization (modified Sugiura proce-

dure). This surgery involves devascularization of the upper two thirds of the greater curvature, the upper half of the lesser curvature of the stomach, 5–7 cm of the distal esophagus, splenectomy, bilateral truncal vagotomy with pyloroplasty, and esophageal transection. The procedure is rarely used for recurrent/refractory bleeding to endoscopic and medical therapy but as with surgical shunts, it has largely been replaced by TIPS and expertise is limited to large referral centers [55].

Future Directions

There has been continued interest in noninvasive methods to diagnose esophageal varices. Alone or in combination, physical examination (spider nevi, ascites, and splenomegaly) and laboratory data (alanine transaminase (ALT), albumin, prothrombin time) that reflect liver function have been investigated. Other parameters that reflect portal hypertension have been assessed; platelet count, platelet count/spleen diameter ratio, aspartate aminotransferase (AST)/ALT, nitric oxide, endothelial vascular growth factor within others [56]. None of these is either sensitive or specific enough to replace the current gold standard.

Transient elastography (Fibroscan®) evaluates the liver or spleen stiffness as surrogate marker of hepatic fibrosis or density changes in the spleen. This painless and reproducible technique varies according to gender, etiology of liver disease, body mass index, and necroinflammatory activity. Transient elastography has been used to evaluate for esophageal varices but still lack specificity and appropriate positive predictive values [56].

Multidetector computerized tomography has been found comparable to EGD for the detection of esophageal varices. False positives findings were common, especially for gastric varices, extraluminal pathology, and periesophageal varices. Although noninvasive, cost effective and preferred by patients, there is concern of repeated radiation exposure [56].

Capsule endoscopy specifically designed for the esophagus (photographic capacities in both ends) holds sensitivities and specificities in the 80–85 % range. This diagnostic modality is feasible and preferred by patients as it is less invasive [56]. Limitations of capsule endoscopy include inability to perform in dysphagia, capsule retention, unreliability to evaluate gastric varices, or other stomach pathology and inability to obtain tissue samples if needed [57].

Transient elastography, computerized tomography, and capsule endoscopy are the techniques that hold most promise as noninvasive methods for the diagnosis of esophageal varices in the foreseeable future, but still EGD remains as the gold standard.

Conclusion

Esophageal varices are common in cirrhosis with portal hypertension. New techniques are being developed to diagnose esophageal varices, but EGD remains the gold standard. Primary and secondary prophylaxis reduces the bleeding and mortality risk. Primary prophylaxis mainly encompasses NSBB, unless high-risk varices or intolerance/side effects to NSBB are present when EVL is favored. First-line therapy in secondary prophylaxis is based on the combination of EVL and NSBB. Alternatively, TIPS or NSBB with nitrates can be used. Surgical shunts and sclerotherapy are not recommended in primary prophylaxis and have fallen out of favor in secondary prophylaxis. NSBB should be used with caution in end-stage cirrhosis.

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Acute Variceal Bleeding

10

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Acute variceal bleeding (AVB) is a frequent and severe complication of patients with portal hypertension. In 90 % of cases, patients will have cirrhosis as the underlying etiology of portal hypertension; other etiologies such as thrombosis of the portal vein or idiopathic portal hypertension should be considered as the underlying cause if cirrhosis is not present. Rupture of gastroesophageal varices is the most common cause of upper gastrointestinal bleeding in patients with cirrhosis; other causes include bleeding from portal hypertensive gastropathy, peptic ulcer disease, or gastric antral vascular ectasia. Bleeding esophageal varices are the cause of 70–80 % of all upper gastrointestinal bleeding episodes in patients with portal hypertension. Gastric varices, present in about 20 % of patients with portal hypertension are less prevalent than esophageal varices and represent 5–10 % of all upper digestive bleeding episodes in cirrhosis. Recent improvements in both the general management of critically ill patients with cirrhosis and available hemostatic therapies have led to a marked reduction of AVB-related mortality rates at 6 weeks, from 40 % in the 1980s to the current 16–20 % rates [1]. In this chapter, we focus on the goals of the treatment in AVB, namely the control of the AVB episode and the prevention of bleeding-related complications.

Natural History

Esophageal varices are present in 30–40 % of patients with compensated cirrhosis and in 60–80 % of those with decompensated cirrhosis [2]. Variceal bleeding may occur in the early stages of the disease but more commonly it occurs late in the natural history of portal hypertension. For varices to bleed, portal pressure as measured by the hepatic venous pressure gradient (HVPG), must rise above 12 mmHg [2]. Variceal hemorrhage occurs when the tension exerted on the variceal wall exceeds the elastic limit leading to its rupture. Variceal wall tension is determined by transmural variceal pressure (depending on portal pressure), vascular size, and the thickness of the wall. All these factors are influenced by available therapies. Vasoactive drugs and transjugular intrahepatic portosystemic shunt (TIPS) act primarily by reducing portal and variceal pressure whereas endoscopic sclerotherapy (ES) and endoscopic banding ligation (EBL), esophageal balloon tamponade, and self-expandable metallic esophageal stents act by both interrupting the blood flow in the varix and/or sealing the vascular wall.

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Diagnosis

As mentioned, AVB should be suspected in any cirrhotic patient with upper gastrointestinal bleeding. The initial approach must include general measures directed at restoring hypovolemia and preventing complications (i.e., prophylactic antibiotics), and specific therapy with vasoactive drugs to achieve hemostasis. Once hemodynamic stability has been reached, preferably within the first 6–12 h after admission, upper endoscopy should be performed to confirm the variceal origin of the bleed and treat accordingly. Visibility during endoscopy can be improved by emptying the gastric content via nasogastric tube and/or by inducing it with motilin agonists such as intravenous (i.v.) erythromycin at a dose of 125–250 mg 20–30 min before endoscopy.

AVB should be considered the culprit of the bleeding episode in the following: (1) active bleeding, oozing, or spurting from a varix; (2) signs of recent bleeding (white nipple or clot) over the varix; and (3) the presence of varices with no other explainable sources of bleeding [3, 4].

Treatment

General Measures

The initial *airway, breathing, circulation* (ABC) of resuscitation should be applied with the aim of maintaining aerobic metabolism and restoring an appropriate oxygen transport to tissues. At least two large bore peripheral i.v. catheters (16–18 gauge) should be placed for rapid volume expansion with crystalloids. A central i.v. catheter is also recommended in order to closely monitor volume status. In addition, orotracheal intubation should be performed if there are changes in mental status (i.e., hepatic encephalopathy) or if the patient is actively vomiting copious amounts of blood. Table 10.1 describes key steps in the management of AVB.

Blood Volume Restitution and Transfusion

Overexpansion, which may increase portal pressure, impair clot formation, and increase the risk of further bleeding, should be avoided. In fact, a certain degree of hypovolemia and hypotension promote the activation of the endogenous vasoactive system leading to splanchnic vasoconstriction and, therefore, reducing portal blood flow and pressure [2]. A recent randomized controlled trial showed that a restrictive packed red blood cell transfusion strategy improved survival in patients with cirrhosis and AVB [5]. Patients should be transfused when hemoglobin levels drop below 7 g/d aiming for a target level of hemoglobin of 7–9 g/dL [5]. Exceptions such as massive bleeding and cardiovascular comorbidities (acute coronary syndrome, symptomatic peripheral vasculopathy, stroke, etc.) or conditions precluding an adequate physiological response to acute anemia should be considered.

Coagulopathy

Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made on the basis of current data [6]. Liver failure may be associated with both a procoagulant and an anticoagulant status. Therefore, the isolated measurement of prothrombin time or international normalized ratio (INR) is not a reliable indicator of coagulopathy and the risk of further bleeding. In fact, randomized studies do not support the use of fresh frozen plasma or rFVIIa for AVB despite the ability of the later to normalize prothrombin time [7, 8]. Many centers use a transfusion threshold for platelets (<40,000 platelets/mL) although there is no scientific evidence for its use in AVB.

Prevention of Complications

The main complications of AVB are bacterial infections (mainly aspiration pneumonia and infections from enteric microorganisms), hepatic encephalopathy, and impaired renal function.

Table 10.1 Initial treatment of the AVB episode

Control and patient monitoring	Monitor blood pressure, heart rate and O_2 saturation
	Control of diuresis
	Central or good peripheral vascular accesses
Volume replacement	Conservative transfusion policy to:
	Restore and maintain hemodynamic stability (SBP≥90 mmHg)
	Target hemoglobin: 7–9 g/dL (consider comorbidities, hemodynamics, etc.)
Prevention of complications	Orotracheal intubation in patients with hepatic encephalopathy or vomiting
	Nasogastric tube for aspiration of gastric content +/− motilin agonists (erythromycin)
	Lactulose or lactitol and cleansing enemas if the patient has hepatic encephalopathy
	Institute antibiotic prophylaxis from admission: oral quinolones or intravenous ceftriaxone
Pharmacological treatment	In suspected AVB, start vasoactive drugs as soon as possible (only 1 vasoconstrictor) and continued for up to 5 days:
	Terlipressin: 2 mg/4h (24–48 h) followed by 1 mg/4 h intravenously or
	Somatostatin: 250 mcg intravenous bolus followed by infusion of 250–500 mcg/h
	Octreotide: 50 mcg intravenous bolus followed by infusion of 50 mcg/h
	Vapreotide: 50 mcg intravenous bolus followed by infusion of 50 mcg/h
Endoscopic therapy	Recommended in any patient developing AVB:
	Ligation: Once, at time of diagnostic endoscopy
	Sclerotherapy (only if ligation is not possible): Once, at time of diagnostic endoscopy

SBP systolic blood pressure, *AVB* acute variceal bleeding

Bacterial Infections

Bacterial infections may be both a consequence and a precipitating event as they can significantly increase portal pressure. In fact, 20% of patients with AVB may have an active infection at the time of bleeding [9]. Antibiotics significantly reduce the incidence of bacterial infections and improve survival in patients with AVB [10]. Therefore, antibiotic prophylaxis is considered an integral part of therapy in patients with cirrhosis and AVB. Prophylaxis should be instituted as soon as possible as presence of bacterial infection is an independent predictor of failure to control bleeding and death [11].

Aspiration pneumonia is perhaps the most common infection in AVB. Inhalation of blood or gastric content is common in patients with hepatic encephalopathy, especially during hematemesis, upper endoscopy, and esophageal tamponade. Measures to prevent aspiration include monitoring of the neurological status (in specific units with trained nurses), use of a semi-recumbent position (preferably left lateral), and most importantly, orotracheal intubation in patients with hepatic encephalopathy or coma, vomiting copious amount of blood, and those requiring any sedation, i.e., for placement of a balloon tamponade, and/or hemodynamically unstable patients. If aspiration is clinically suspected, the patient should immediately receive appropriate antibiotic treatment. In addition to aspiration pneumonia, patients may develop spontaneous bacterial peritonitis, urinary tract infections, spontaneous bacteremia and nosocomial or community-acquired pneumonia. Enteric pathogens are the most commonly involved microorganisms.

Oral quinolones (norfloxacin 400 mg b.i.d., orally or by nasogastric tube for at least 7 days) are recommended for most patients. Intravenous ceftriaxone (1–2 g daily for 7 days) should be considered in high-risk patients (i.e., those with ascites, severe malnutrition, encephalopathy or serum bilirubin >3 mg/dL), as well as in hospital settings with high prevalence of quinolone-resistant bacterial infections and in patients on previous quinolone prophylaxis [12].

Hepatic Encephalopathy

Nonabsorbable disaccarides (lactulose or lactitol) orally, by nasogastric tube, or in enemas have failed to show any efficacy in the prevention of the development of hepatic encephalopathy [13]. Nevertheless, they are the recommended therapy once hepatic encephalopathy develops [14]. Rifaximin is an effective add-on therapy to lactulose to maintain remission in patients with hepatic encephalopathy [15].

Ascites and Renal Failure

Renal failure is an independent predictor of mortality in AVB. Thus, it is of utmost importance to preserve renal function by replacement of i.v. fluids (avoiding both hypo and hypervolemia) [16]. Administration of diuretics may worsen hypovolemia and nephrotoxic drugs such as aminoglycosides and non-steroidal anti-inflammatory agents (NSAIDs) should be avoided. Acute renal failure may be transient or severe leading to type I hepatorenal syndrome or acute tubular necrosis. Renal function must be monitored with serial measurements of serum creatinine, urea, sodium, potassium, and quantification of daily diuresis.

Tense ascites should be treated because it can cause dyspnea and vomiting as well as increase portal and variceal pressure [17]. Large-volume paracentesis is associated with a significant reduction in portal and collateral pressure, but can be associated with renal failure in up to 18% of the cases despite albumin infusion. Consequently, small-volume paracentesis (less than 5 L) is recommended during the AVB to reduce portal pressure and preserve renal function [16].

Nutrition

Patients often have some degree of malnutrition which confers a high risk of infection. It is important to start oral feeding as soon as the bleeding episode is controlled (i.e., 24 h after achieving hemostasis).

Specific Hemostatic Therapy

Hemostatic therapy in AVB must achieve the initial control of bleeding and also prevent early rebleeding. First-line therapy for AVB includes vasoactive drugs and endoscopic therapy, preferably EBL, once the diagnosis of AVB is confirmed by upper endoscopy. Early TIPS should be considered in patients at high-risk of treatment failure (Child C patients $\leq$13 points and Child B with active bleeding during endoscopy) after initial pharmacological and endoscopic therapy or at any moment as a rescue therapy [18, 19]. Balloon tamponade, and self-expanding covered esophageal metal stents, should be used in massive bleeding or failure to control bleeding as a temporary "bridge" until definitive therapy can be instituted [6].

Pharmacological Treatment

The use of vasoctive drugs before endoscopy decreases the incidence of active bleeding facilitating endoscopic therapy and further control of bleeding [20, 21]. A randomized controlled trial (RCT) also demonstrated that the early administration of terlipressin, during the transfer to hospital, may improve survival [21]. Experts agree that vasoactive therapy must be maintained for at least 5 days to prevent early rebleeding [22]. However, a recent RCT showed that a 24-h course of terlipressin is as effective as a 72-h course when used as an adjunctive therapy to successful endoscopic band ligation [23]. Vasoactive drugs with proven efficacy and a high safety profile include terlipressin, somatostatin, octreotide, and vapreotide. They should always be used in combination with endoscopic therapy.

Terlipressin, a long-acting synthetic derivative of vasopressin (triglycyl-lysine-vasopressin), has shown to effectively control AVB and decrease transfusion requirements and bleeding-related mortality (18% reduction vs. placebo) [24, 25]. Experts recommend starting terlipressin at a dose of 2 mg every 4 h (1.5 mg when weight is 50–70 kg and 1.0 mg when it is $<$50 kg) with titration to 1 mg/4 h. Terlipressin is a potent

vasoconstrictor and therefore it should not be given to patients with ischemic heart disease. Terlipressin has a high safety profile with minor adverse events including abdominal pain and/or diarrhea, pallor and bradycardia in varying degrees immediately following bolus administration [25]. Moreover, terlipressin may induce an acute but reversible reduction in serum sodium concentration [26].

Somatostatin reduces portal pressure by inducing selective splanchnic vasoconstriction without significant systemic effects. Somatostatin has been shown to be as effective as terlipressin both in the control of AVB and in the prevention of early rebleeding [24, 27]. Somatostatin is usually administered as a continuous infusion of 250 mcg/h after an intravenous bolus (250 mcg), which can be repeated if necessary [27]. In a hemodynamic study, patients without a drop of >10% of their HVPG with an infusion of 250 mcg/h of somatostatin, were then able to achieve a marked reduction (>20%) in portal pressure with a higher dose of 500 mcg/h of somatostatin or the administration of 1 mg of terlipressin [28]. In patients actively bleeding at initial endoscopy an infusion dose 500 mcg/h achieves a higher rate of control of bleeding, lower early rebleeding, reduced mortality (at 1 and 6 weeks) and less transfusion requirements compared with a standard dose of 250 mcg/h [29]. The somatostatin analogues octreotide and vapreotide also improve the results of endoscopic therapy when used in combination with band ligation [30], but have uncertain effects if used alone [24, 31].

Endoscopic Therapy

Endoscopic therapy, either ES or EBL, is highly effective in the control of AVB with an immediate efficacy in 85–90% of cases. RCTs that compared both methods in AVB have clearly shown that treatment with EBL and vasoconstrictors is associated with higher efficacy, safety, and improved mortality than ES and vasoconstrictors. Therefore, EBL is considered the endoscopic therapy of choice in AVB. Current guidelines recommend band ligation for AVB, although ES may be used in the acute setting if ligation is technically difficult [6, 32]. As discussed above, placing a nasogastric tube to lavage and empty the stomach together with the use of prokinetic agents may shorten and facilitate endoscopic therapy.

Combination Therapy: Vasoactive Drugs + Endoscopic Therapy

The rationale for combining vasoactive drugs and endoscopic therapy relies on a different and complementary hemostatic mechanism which is the local effect on the varices and the decrease in portal and variceal pressure caused by vasoactive drugs. In fact, RCTs have shown that such a combination is more effective than the isolated use of any of these therapeutic options [30]. At present, the combination of vasoactive drugs and EBL is considered the first therapeutic option in AVB [6].

Failure of First-Line Therapy

Despite the application of gold standard therapy, up to 10–15% of patients have persistent variceal bleeding or early rebleeding [30, 35].

Management of High-Risk Patients

Patients at high risk of failure of initial therapy have been identified as those having high portal pressure (HVPG>20 mmHg), poor liver function (Child-Pugh class C) and active bleeding at initial endoscopy [6]. TIPS has shown to be very effective in this particular setting. TIPS consists on the placement, via internal jugular vein and under light sedation, of a prosthesis communicating the portal vein and the hepatic veins or the inferior vena cava. Multiple studies have shown that TIPS is highly effective in controlling bleeding (90–100% of success) and preventing rebleeding (<20% at 2 years of follow-up) in AVB. TIPS is usually performed by using polytetrafluoroethylene (PTFE)-coated stents. Covered stents have overcome the main problem of previous non-coated TIPS; that is the high incidence of TIPS dysfunction. In practice, TIPS has replaced portal-systemic derivative surgery because of its lower complexity and morbidity

[36]. A recent RCT explored the efficacy of TIPS in the prevention of treatment failure by performing it "early," within the first 24–72 h, in high-risk patients (i.e., Child-Pugh C or B plus active bleeding at initial endoscopy) [18]. The results of this study demonstrated that the use of early TIPS was associated not only with a decrease in variceal rebleeding and portal hypertension related complications but also a significant increase in 6-month and 1-year survival [18, 19].

Management of Failure

TIPS is also considered the rescue therapy of choice in both esophageal and gastric AVB after failure of initial therapy [6, 37, 38]. Experts recommend performing TIPS as soon as possible after initial failure of therapy, because a delay in its placement may worsen hemodynamic impairment and liver dysfunction, increasing the risk of complications and mortality. TIPS may be not feasible due to either lack of medical resources on a 24-h basis or to patient-related limitations (portal vein thrombosis, hepatocellular carcinoma, right cardiac failure, etc.). In those cases, a second endoscopic therapy may be attempted while vasoactive therapies are optimized by doubling the dose of somatostatin and/or changing to terlipressin [2]. A temporary approach for massive or recurrent bleeding is balloon tamponade. Current guidelines recommend using balloon tamponade only in massive bleeding as a temporary "bridge" until definitive treatment could be instituted and for a maximum of 24 h, preferably in the intensive care unit [6, 37]. This is so because balloon tamponade achieves hemostasis by the direct compression of bleeding varices in up to 80–90% of cases, but it is associated with a more than 50% incidence of rebleeding (after deflation of the balloon) and nearly 30% of patients develop major complications, such as esophageal perforation, aspiration pneumonia, etc. There are two types of balloon: the Linton–Nachlas tube used for gastric fundal varices and the Sengstaken–Blakemore tube for esophageal varices.

Preliminary noncontrolled data suggest that self-expandable esophageal covered metal stents may be an effective and safe alternative to tamponade. A recent RCT compared esophageal metal stents ($n=13$) vs. tamponade (by using the Sengstaken–Blakemore balloon; $n=15$) in patients with esophageal variceal bleeding refractory to medical and endoscopic treatment. Success of therapy defined as survival at day 15 with control of bleeding and without serious adverse events was higher in the stent than in tamponade group (66 vs. 20%; $p=0.025$). Therefore, these findings favor the use of esophageal stents in patients with esophageal variceal bleeding uncontrolled with medical and endoscopic treatment [39].

Summary

AVB is a dreaded complication of patients with portal hypertension. Initial management includes appropriate volume replacement, transfusion of blood to keep hemoglobin levels around 7–9 g/L, antibiotic prophylaxis, and endotracheal intubation in selected cases. Standard of care mandates for early administration of vasoactive drug therapy and then EBL or injection ES (if EBL cannot be performed) within the first 6–12 h of the index bleed. The use of pharmacological agents may be prolonged for up to 5 days. Early placement of TIPS (within 72 h) should be considered in patients with Child C cirrhosis (≤ 13 points) and Child B with active bleeding. Patients that fail endoscopic and pharmacologic therapy may require temporary placement of an esophageal stent or balloon tamponade. However, experience with esophageal stents is limited and use of the balloon is associated with potentially lethal complications such as aspiration and perforation of the esophagus. Therefore, both should be placed in experienced units while definitive therapy is planned. An algorithm for the management of AVB is shown in Fig. 10.1.

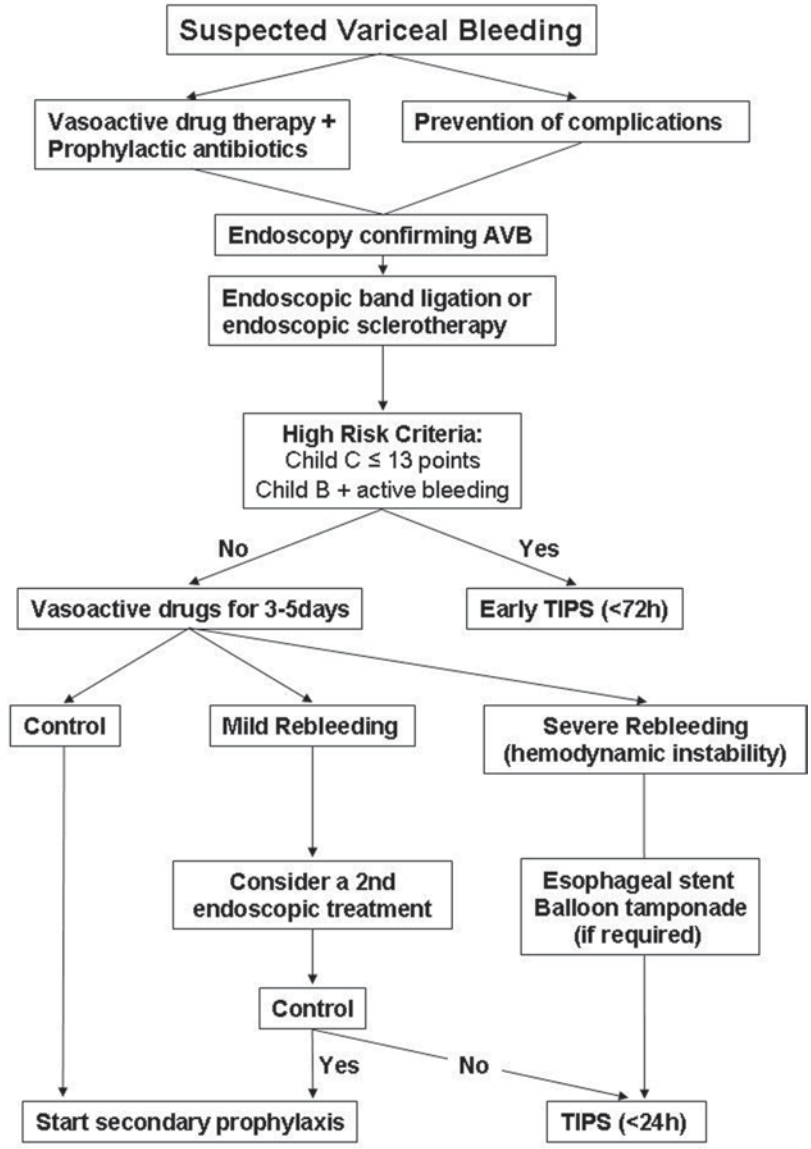

Fig. 10.1 Recommended algorithm for the treatment of an episode of acute variceal bleeding

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Gastric and Ectopic Varices

11

Daniel Schmidt and P Aiden McCormick

The prognosis in patients with variceal bleeding (whether oesophageal, gastric or ectopic) depends critically on the underlying liver function [1]. Patients with extra-hepatic portal hypertension and normal liver function have excellent survival rates. The principles of emergency management of variceal haemorrhage are similar irrespective of the site of bleeding, i.e. resuscitation, antibiotics, vasoconstrictors, avoidance of over transfusion and early specific treatment, e.g. injection sclerotherapy, banding, transjugular intrahepatic portosystemic shunt (TIPS), etc. [2, 3]. The discussion below describes some of the treatment options for gastric and ectopic varices. Because of the paucity of adequately powered randomised controlled trials, it is not possible to give clear treatment recommendations in many cases. The choice of treatment may also be influenced by the available local expertise. In general, surgery would not be considered a first-line therapy for bleeding varices at any site but may be an appropriate option in certain non-cirrhotic patients or if there is a high level of skill with a particular procedure.

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Gastric Varices

Bleeding from gastric varices is less common than from oesophageal varices, but when it occurs, it is typically more severe and has a higher mortality rate. Sarin described the most widely used classification of gastric varices [4] (Fig. 11.1). Gastro-oesophageal varices (GOV) are gastric varices that arise as an extension to oesophageal varices along the lesser curve (GOV1) or fundus or greater curve (GOV2). Isolated gastric varices (IGV) may occur in the fundus (IGV1) or the body or antrum (IGV2). Oesophagogastric varices extending along the lesser curve have similar natural history and response to treatment as oesophageal varices [5]. In contrast, fundal varices or isolated gastric varices (GOV2, IGV1 or IGV2) have higher bleeding risks and worse prognosis. In a large natural history study, Sarin et al. reported bleeding rates of 11.8% for lesser curve varices (GOV1) compared to 55% for gastric fundal varices continuous with oesophageal varices and 78% for isolated gastric fundal varices [4].

Isolated fundal gastric varices, without oesophageal varices, typically occur in patients with splenic vein thrombosis [6]. The condition is termed sinistral or left-sided portal hypertension and can easily be missed by the unwary endoscopist. It usually occurs in patients with pancreatitis or pancreatic carcinoma. It is the one cause of portal hypertension and variceal bleeding which can be completely cured by surgery, i.e. splenectomy. In comparison with oesophageal varices,

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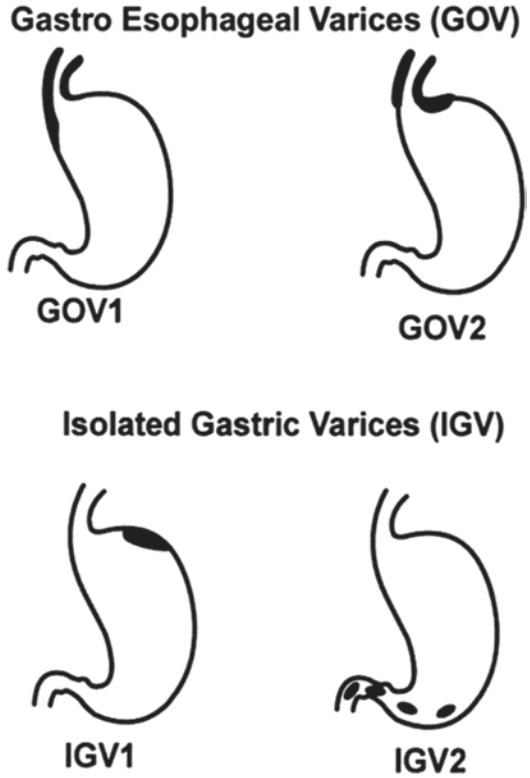

Fig. 11.1 Classification of gastric varices. Gastroesophageal varices: lesser curve GOV1 and fundal GOV2. Isolated gastric varices; fundal IGV1 and other IGV2. Reproduced with permission from John Wiley and Sons from [4]

standard endoscopic techniques such as injection sclerotherapy and/or banding are less effective for gastric varices. More effective treatments include TIPS shunt, glue injection (cyanoacrylate) and balloon-occluded retrograde transvenous occlusion of varices (BRTO). Cyanoacrylate glue injection and TIPS are mainstays of treatment in Western countries, whereas BRTO is widely used in the Far East.

Glue Injection

The advantage of using cyanoacrylate is that it does not require any special equipment and it can be done at the time of the initial diagnostic endoscopy. The main disadvantages are the risks of non-target embolism and glue damage to the endoscope. The risk of embolism is reasonably low. One large Chinese series included 635 patients with gastric varices [7]. Ectopic embolism was reported in five cases (0.8%). These included three splenic infarcts, one small pulmonary infarct and a cerebral embolism causing transient paralysis which resolved after 5 days. Cyanoacrylate may damage the endoscope but this risk can be minimised by careful technique. The technique of cyanoacrylate injection is not standardised [8, 9]. Most centres use a mixture of cyanoacrylate and lipiodol. Typically, the injection needle and catheter are flushed with lipiodol or aterile water beforehand to prevent glue occlusion in the catheter lumen. Cyanoacrylate and lipiodol are mixed before injection. In the literature, various ratios range from 0.5 to 1.5 mls lipiodol per 0.5 ml cyanoacrylate. The volume injected per varix also varies from 1 to 2 mls. Some centres have extensive experience with this technique and use a form of cyanoacrylate which does not require mixing with lipiodol. Good visualisation is important when injecting glue. In active gastric variceal bleeding, the fundus may be obscured by blood or clot. In cases of active bleeding, insertion of a Sengstaken–Blakemore or Linton–Nachlas tube may stabilise the situation, allowing subsequent targeted injection with a clear visual field. To avoid damage to endoscopic equipment, some endoscopists now use recombinant human thrombin instead of cyanoacrylate and report good results [10]. Endoscopic ultrasound guided coil embolization of gastric varices has recently been described. This technique is less likely to result in non-target embolization but requires significant technical expertise [11].

Transjugular Intrahepatic Portosytemic Shunt

TIPS is a well-established treatment option in patients with portal hypertension. It is particularly useful as a salvage therapy for active bleeding not controlled by endoscopic therapy [12]. It is also useful for patients who rebleed despite endoscopic or pharmacological therapy. Portal vein thrombosis is a relative contra-indication. The

major disadvantages are the risks of worsening liver failure in patients with high model for end-stage liver disease (MELD) scores (>24) and the longer term risks of hepatic encephalopathy. Nevertheless, early TIPS has been shown to improve prognosis in patients with oesophageal variceal bleeding and Pugh's scores ≤13 [13]. It should probably be considered early if glue injection fails.

Balloon Occluded Retrograde Transvenous Occlusion of Varices [14] (Fig. 11.2)

BRTO is an alternative to TIPS shunt. The initial descriptions from Japan described injection of ethanolamine oleate via gastrorenal collaterals. Ethanolamine may cause significant haemolysis and Japanese physicians use haptoglobin infusions to deal with this complication. Unfortunately, haptoglobin is not available in the West, which may explain why the technique was not widely adopted in Europe and America. Interventional radiologists in the USA now use a frothy concoction of one part lipiodol, five parts 3% Sotradecol and two parts air/CO_2. The collaterals can be accessed via the spleno–renal route or percutaneously via the portal and splenic veins (as with a TIPS shunt) [15]. The transportal route can be used as an adjunct to TIPS insertion, if required. The main advantage of BRTO is that it can be used in patients with high MELD scores and poor liver function who are not suitable for TIPS. In addition, it can be used in patients with bleeding gastric varices and a history of hepatic encephalopathy, which is a relative contra-indication to TIPS. It can also be used to occlude large portosystemic shunts in patients with disabling hepatic encephalopathy who are unsuitable for liver transplantation. The main disadvantages of the technique are the risk of non-target embolization and an increase in portal venous pressure. This may result in exacerbation of varices elsewhere or precipitate ascites formation. In a large study including 183 patients, technical success was achieved in 97% with procedure related complications in 4.4% [16]. These included five cases of pulmonary thromboembolism, one renal infarction, one ruptured gastro-renal shunt and one case of transient mental changes. In patients without oesophageal varices, new oesophageal varices appeared in 21/36 (58%).

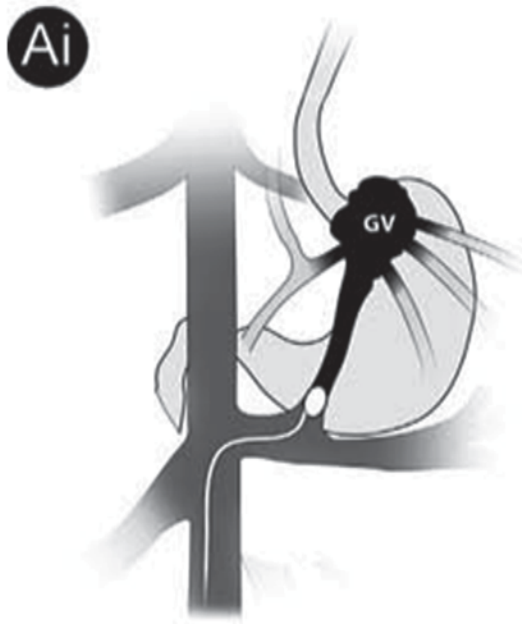

Fig. 11.2 Balloon occluded retrograde transvenous occlusion of varices (*BRTO*). A balloon occlusion catheter is passed from the inferior vena cava and the renal vein into a spleno-renal collateral vessel and sclerosant material injected. GV gastric varices. (Reproduced with permission from Elsevier from [15])

Comparative Studies

Compared to oesophageal varices, there are relatively few randomised controlled trials in patients with gastric varices and the available trials are relatively small. Lo et al. randomised 60 patients with bleeding gastric varices to treatment with either band ligation or cyanoacrylate. The cyanoacrylate group required less blood transfusion (4.2 vs. 2.6 units $p<0.01$) and had fewer rebleeding episodes (54% vs. 31% $p<0.01$) [17]. Mishra et al. randomised 67 patients presenting with gastric variceal bleeding to secondary prophylaxis with either nonselective β-blockade or cyanoacrylate injection [18]. Patients with active

bleeding at the index endoscopy underwent one cyanoacrylate injection prior to randomisation. Patients randomised to cyanoacrylate had endoscopic injection 6 days after the index bleed. All visible gastric varices were injected and successful obliteration confirmed by palpating the varix with the needle hub. Just over half the patients required a repeat session 7 days later to confirm obliteration. Both rebleeding rates (15% vs. 55%) and mortality (3% vs. 25%) were significantly lower in the cyanoacrylate group. Mishra et al. also performed a controlled trial of primary prophylaxis controlled trial comparing cyanoacrylate injection, propranolol and no treatment in 89 patients [19]. Interestingly, the hepatic venous pressure gradient increased in both the injection and no treatment groups but fell in the propranolol group. Over a median follow-up of 24 months, bleeding was significantly less common in the cyanoacrylate group compared to either propranolol or no treatment (13, 28 and 45%, respectively). Survival was significantly higher in the cyanoacrylate group compared to the no treatment group (90% vs. 72%; $p=0.48$).

In terms of preventing rebleeding, TIPS is probably more effective than glue injection but is more invasive and expensive. In patients who had bled from gastric varices, Lo et al. randomised 35 to TIPS and 37 to cyanoacrylate injection [9]. TIPS insertion was successful in all patients. Rebleeding from gastric varices occurred in 4 patients in the TIPS group and 14 patients in the cyanoacrylate group ($p<0.05$). Survival rates were similar. Sabri et al. reported a retrospective analysis on 50 patients treated with either TIPS or BRTO for bleeding gastric varices [20]. Technical success rates were 100% for TIPS and 91% for BRTO with 12-month rebleeding rates of 11 and 0%, respectively.

Ectopic Varices

Prevalence of Ectopic Varices

Ectopic varices are varices which can appear anywhere in the gastrointestinal tract outside of the usual sites, i.e. gastro-oesophageal and anorectal [21]. Bleeding from ectopic varices is relatively uncommon representing 2–5% of upper gastrointestinal haemorrhages [22]. Ectopic varices usually occur at or near sites of anatomical disruption or following venous impairment or thrombosis. Typically, they occur near sites of surgery, around stomas or areas of previous inflammation, e.g. pancreatitis. There is a paucity of data on the true prevalence of ectopic varices. The Japanese Society for Portal Hypertension performed a survey of their members for the years 2001 to 2005 [23]. Thirty-three institutions replied reporting a total of 173 cases. There were 77 rectal, 57 duodenal, 11 small intestinal, 10 anastomotic, 7 colonic and 8 biliary tract varices and 1 diaphragmatic varix. Eighty percent had cirrhosis and 58% had received previous treatment for oesophageal varices. Haemorrhage from ectopic varices occurred in 78/173 (45%) with the most common sites being rectal (30 cases) and duodenal (27 cases).

In terms of treatment, it is important to establish whether portal venous drainage of the site is intact [21]. If drainage is intact TIPS is an option. One study described 24 patients with bleeding from ectopic varices treated with TIPS [24]. Sites of bleeding included stomal [8], ileocolic [6], duodenum [5], anorectal [3], umbilical [1] and peritoneal [1]. Alcoholic cirrhosis was the commonest etiology [13], 12 had Pugh's class B liver disease and 7 Pugh's class C. No embolization was performed at the initial procedure. Cumulative variceal rebleeding rate was 23% with overall survival of 80% at 1 year. BRTO may be an option even in patients with portal vein thrombosis providing it is possible to access the appropriate collateral vessels. Local therapies, e.g. injection or banding are frequently used. Surgery may be appropriate in some cases.

Rectal Varices

Bleeding from rectal varices can be challenging, both diagnostically and therapeutically. Poorly targeted sclerotherapy or banding in the anorectum can cause troublesome ulceration and recurrent bleeding. Endoscopic ultrasound may be

helpful in delineating rectal varices, which are not always easily apparent at endoscopy [25]. Some experts suggest that endoscopic bands should be placed at the highest point of inflow through perforating veins. This is analogous to the situation with oesophageal varices where banding or sclerotherapy are most effective when applied in the distal oesophagus where the perforating veins occur. TIPS shunt is another option although TIPS may be less effective for bleeding remote from the central portal venous system. TIPS combined with transvenous embolization may be useful. In one study of 12 patients with bleeding rectal varices [22], TIPS was successfully inserted in 11/12. One patient had uncontrolled bleeding despite TIPS; another rebled despite a patent TIPS shunt. Successful treatment with endoscopic sclerotherapy (5% ethanolamine), BRTO and endoscopic ultrasound guided cyanoacrylate injection with coiling have all been described [26–28]. Surgery may also have a role. Kaul and Skaife describe a surgical rectal stapling technique used successfully in nine patients [29]. The technique is similar to stapling haemorrhoidectomy although the purse-string suture has to run beneath all the visible varices. After the device is fired, individual bleeding points are identified and sutured. This procedure should probably only be done by surgeons experienced in the technique.

Duodenal Varices (Fig. 11.3)

Bleeding from duodenal varices is uncommon and may be difficult to diagnose. The varix may be collapsed at the time of diagnostic endoscopy and/or be obscured by bleeding. In a Japanese experience of 57 cases, 2 were in the bulb, 47 in the descending part and 8 in the third part [23]. Duodenal varices may occur in the absence of cirrhosis or other oesophago-gastric varices. Treatment options include banding, injection of cyano-acrylate, TIPS, BRTO and surgery. A review of the literature revealed 19 cases treated with banding [30]. Rebleeding occurred in 3/19 after banding. Two patients died of liver failure within 7 days. Two patients required surgery: one for recurrent bleeding and one for a duodenal perforation

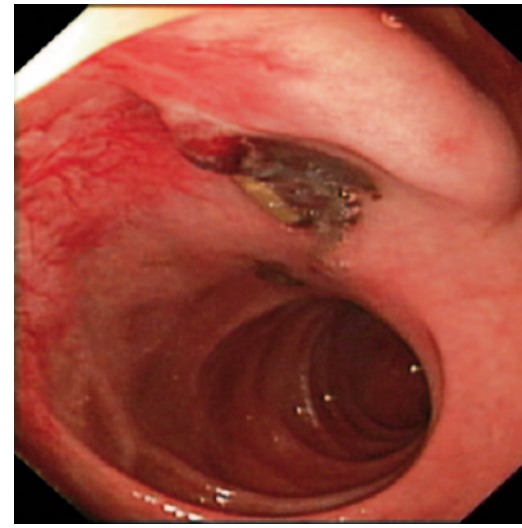

Fig. 11.3 Duodenal varix: recent bleed

secondary to injection sclerotherapy for recurrent bleeding. There is a reported case of occlusion of the ampulla of Vater by banding, underlining the importance of identifying landmarks in this area [31]. Injection of cyanoacrylate can also be effective. Liu et al. described four patients with duodenal varices treated with cyanoacrylate and Mora-Soler described a further five [32, 33]. In the Spanish series, two patients rebled and three died during the initial hospital admission (one from active bleeding and two from liver failure/sepsis). In a Chinese series, there was no rebleeding. Two of the four patients died at 7 and 24 months of liver failure and sepsis, respectively. Cyanoacrylate injection can also cause biliary obstruction [34]. Kochar et al. described four patients treated with TIPS for bleeding duodenal varices [22]. Bleeding was controlled in 3/4. Tanaka et al. reviewed 12 cases of BRTO for bleeding duodenal varices [35]. Bleeding was controlled in all cases. There were two cases of new oesophageal varices but no reports of rebleeding.

Parastomal Varices

Bleeding from stomal varices affects up to 5% of patients with an entero-cutaneous stoma. Most patients have primary sclerosing cholangitis.

Portal systemic collaterals form around the stoma but are not easily visible, even when bleeding. Active bleeding is rarely life threatening and usually responds to local pressure. However, bleeding nearly always recurs and blood loss may be significant. Pennick and Artioukh recently reviewed the literature on the management of stomal variceal bleeding [(36]. While local approaches are frequently used, they are usually ineffective with rebleeding rates of around 80%. TIPS is very effective with rebleeding rates of around 20%. In our experience, TIPS is often combined with transjugular embolization of the collateral vessels to improve efficacy. Some patients have recurrent bleeding despite TIPS and embolization. Surgical revision of the stoma may be required. Liver transplantation is the most effective treatment, if it is indicated for the underlying liver disease.

Colonic Varices

Bleeding from isolated colonic varices is a rare cause of lower gastrointestinal bleeding, with a reported incidence of 0.07%. Case reports have described treatment by surgical resection, BRTO, TIPS and venous coil embolization [37]. The outcome probably depends more on the underlying liver function than on the specific therapy employed.

Retroperitoneal Varices

Spontaneous rupture of intra-abdominal collaterals may occur with resultant haematoperitoneum. This is most common in cirrhotics but may also occur in patients with non-cirrhotic portal hypertension [38]. Spontaneous retroperitoneal haematoma is a rare complication in patients with decompensated liver disease. The presentation is usually with abdominal and/or back pain associated with a drop in haemoglobin level. Discoloration of the flanks due to blood tracking along fascial planes may appear after a day or two (Grey Turner's sign) [39]. Diagnosis may be confirmed by a computerized tomography (CT) scan. Management is conservative as most of these patients have advanced disease and are not fit for decompressive procedures such as TIPS. Mortality is high. A Chinese series reviewed 1276 cirrhotic patients admitted over a 2-year period. Nineteen were found to have haematoperitoneum, in six of who it appeared to be spontaneous. All had advanced liver disease and none were fit for surgery or TIPS. Three died of haemorrhagic shock within 24 h and the other three died of liver failure within 10 days [40].

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Portal Hypertensive Gastropathy and Gastric Antral Vascular Ectasia

12

Mary Drinane and Vijay H. Shah

Portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE) are two common gastric mucosal lesions that occur in patients with portal hypertension. In some patients both conditions may be responsible for acute gastrointestinal bleeding, but more commonly they cause chronic gastrointestinal bleeding. The pathophysiology of PHG is related to portal hypertension, whereas the underlying factors responsible for GAVE are due to local changes in the gastric mucosa. These entities share similar clinical features, but have characteristic endoscopic findings that are different. The management of PHG is aimed at reducing portal hypertension (PHTN) with pharmacological therapy and in some cases transjugular intrahepatic portosystemic shunts (TIPS) and the management of GAVE rely on endoscopic thermal therapies.

Pathophysiology

PHG

The pathogenesis of PHG is closely related to PHTN, which has been found to be necessary for the development of PHG. In patients with PHTN, 70% will develop PHG [1]. The severity of the PHG has been shown to correlate with the degree of PHTN [2] and resolution of PHG has been noted post TIPS [1]. In a study by Kumar et al. of 294 patients with cirrhosis, a mean hepatic venous pressure gradient >12 mmHg had an odds ratio of 2.97 for the development of PHG [3]. Additionally, patients with PHG had higher cardiac output and lower systemic and pulmonary resistance compared to patient with cirrhosis and no PHG [3]. These findings indicate that PHG is one manifestation of the systemic changes that occur in patients with cirrhosis and PHTN. Local factors at the mucosa have also been implicated in the development of PHG including tumor necrosis factor (TNF)-α, endothelin-1 (ET-1), nitric oxide (NO), and prostaglandins [4, 5], although the molecular mechanisms of their involvement have not been well outlined. Key components of the pathophysiological changes of PHG and GAVE are described in Table 12.1.

GAVE

Unlike PHG, the pathogenesis of GAVE is not related to PHTN. Multiple studies have found that GAVE does not respond to TIPS [1, 6]. In the study by Kamath et al., 89% of patients with mild PHG and 71% of patients with severe PHG responded 6 months after TIPS procedure compared to 12.5% of patients with GAVE [1]. In two case reports by Vincent et al., both patients had portal vein thrombosis and underwent liver transplant with end-to-end portocaval anastomosis and both patients had resolution of GAVE

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Table 12.1 Summary of the key components in the pathophysiology of GAVE and PHG

	GAVE	PHG
Portal hypertension (PHTN)	PHTN is not necessary for the development of GAVE [6, 7]	70% of patients with PHTN develop PHG [1], degree of PHTN correlates to degree of PHG [2]
Physiologic changes	Increased antral area halftime [12]	Decreased systemic vascular resistance in patients with cirrhosis and PHG compared with patients with cirrhosis and no PHG [3]
Implicated mediators	Gastrin [8–10], PGE2 [11]	TNF-α, NO, ET-1 [4, 5], prostacyclin [13]

GAVE gastric antral vascular ectasia, *PHG* portal hypertensive gastropathy, *NO* nitric oxide, *ET-1* endothelin-1, *PGE2* prostaglandin E2, *TNF-α* tumor necrosis factor-alpha

despite continued PHTN [7]. Taken together, these findings show a lack of response of GAVE to normalization of portal pressure after TIPS, and a positive response of GAVE to liver transplant despite continued PHTN. Several potential mediators have been implicated in the pathogenesis of GAVE. Early studies by Quintero et al. and Gostout et al. noted hypergasteremia in patients with GAVE [8, 9], but a later study by Payen et al. found reduced gastrin levels when patients with GAVE were compared to patients with severe PHTN and normal controls [10]. Saperas et al. found that prostaglandin E2 (PGE2) levels were significantly higher in the antrum and corpus of cirrhotic patients with GAVE compared to patients with cirrhosis without GAVE [11]. PGE2 is a potent vasodilator and may give a potential mechanism to the development of the ectatic capillaries noted in GAVE. Examination of antral motility revealed a significant increase in the antral area halftime in patients with cirrhosis and GAVE when compared to normal controls and patient with cirrhosis and no GAVE [12]. This has led to the hypothesis that the lesions in GAVE might be due to recurrent trauma, but this is yet to be definitively proven.

Diagnosis

In the majority of cases, the diagnosis can be made by endoscopic appearance. However, severe PHG can appear similar to GAVE at endoscopy. In these patients, histology can lead to diagnosis. Examples of the histology and endoscopic appearance are given in Fig. 12.1. Summary of the key histologic and endoscopic findings are provided in Table 12.2.

PHG

At endoscopy, the lesions from PHG are found in the fundus of the stomach, but similar lesions can be seen throughout the gastrointestinal tract. Mild PHG has the appearance of a snake-skin mosaic pattern with severe PHG appearing flat or as bulging red spots. There are multiple different classification systems based on endoscopic appearance which are outlined in Table 12.3 with the North Italian Endoscopic Club (NIEC) classification being most commonly used. On histology, there is mild-to-moderate dilation of the veins and capillaries of the gastric mucosa and submucosa and no changes in the blood vessel wall [4].

GAVE

GAVE is typically noted in the antrum of the stomach on endoscopy and is limited to the stomach. The lesions of GAVE appear as flat red spots without the background mosaic pattern that is seen in PHG. The red spots can merge causing stripes into the pylorus, which has led to the term "watermelon stomach." The histology is characterized by marked dilation of capillaries and venules in the gastric mucosa, submucosa with areas of intimal thickening, spindle cell proliferation, fibrohyalinosis, and thrombi [4, 10]. The features of the histologic appearance of GAVE

Table 12.2 Summary of the key components in the diagnosis of GAVE and PHG

	GAVE	PHG
Location	Antrum, limited to stomach	Fundus, similar lesions throughout GI tract
Endoscopic appearance	Flat red spots without background mosaic pattern, can blur together causing stripes into the pylorus (watermelon stomach) or be diffuse (honeycomb stomach)	Snake-skin mosaic pattern (mild) with flat or bulging red spots (severe)
Histology	Marked dilation of capillaries and venules in gastric mucosa and submucosa with areas of intimal thickening and thrombi, spindle cell proliferation, fibrohyalinosis [10]	Mild-to-moderate dilation of veins and capillaries of gastric mucosa and submucosa. No changes in vessel walls [4]

PHG portal hypertensive gastropathy, *GAVE* gastric antral vascular ectasia

are used in the GAVE score (Table 12.4) which has an 80% diagnostic accuracy in separating GAVE from PHG with a cutoff of GAVE score ≥3 [10].

Management

The focus of management for both PHG and GAVE is maintaining adequate hemoglobin and reducing the number of blood transfusions required. Therefore, if either PHG or GAVE is noted at endoscopy in patients maintaining a normal hemoglobin, no therapy is required. Summary of the management of PHG and GAVE is given in Table 12.5.

PHG

In patients with chronic bleeding, the first-line therapy is iron replacement. If iron therapy is not sufficient to maintain the hemoglobin, further treatments are necessary with the initial goal of lowering the portal pressure in patients with chronic bleeding. Nonselective beta-blockers have been used for medical therapy with studies finding the most benefit in patients with mild PHG [14] with only modest effects noted in patients with severe PHG [15]. In patients who do not respond to medical therapy, TIPS procedure may be considered. In a study by Kamath et al., 75% of patients with severe PHG showed improvement after TIPS as measured by improvement on endoscopic appearance and a decrease in transfusion requirement [1]. Improvement post TIPS procedure was noted as early as 2 weeks based on stabilization of hemoglobin and decreased transfusion requirements [1].

Acute bleeding can rarely occur from PHG; one large study found an incidence of 2.5% for acute bleeding from PHG compared to 10.8% for chronic bleeding [16]. Acute bleeding from PHG is managed similarly to variceal bleeding,

Table 12.3 Classification of PHG based on endoscopic appearance [4]

Classification	New Italian Endoscopic Club (NIEC) for the study and treatment of esophageal varices	McComack et al.	Tanoue et al.
Mild	"Mosaic-like pattern"—diffusely pink areola (mild), flat red spot in the center of pink areola (moderate), diffusely red areola (severe)	Fine speckling or "scarlatina" type of rash, superficial reddening, "snake-skin" pattern	Mild reddening, congestive mucosa
Moderate	N/A	N/A	Severe redness and fine reticular pattern separating areas of raised mucosa
Severe	"Red marks"—red lesions of variable diameter, flat or slightly protruding. Discrete or confluent	Cherry red spots, confluent or not, diffuse hemorrhage	Grade plus point bleeding

PHG portal hypertensive gastropathy

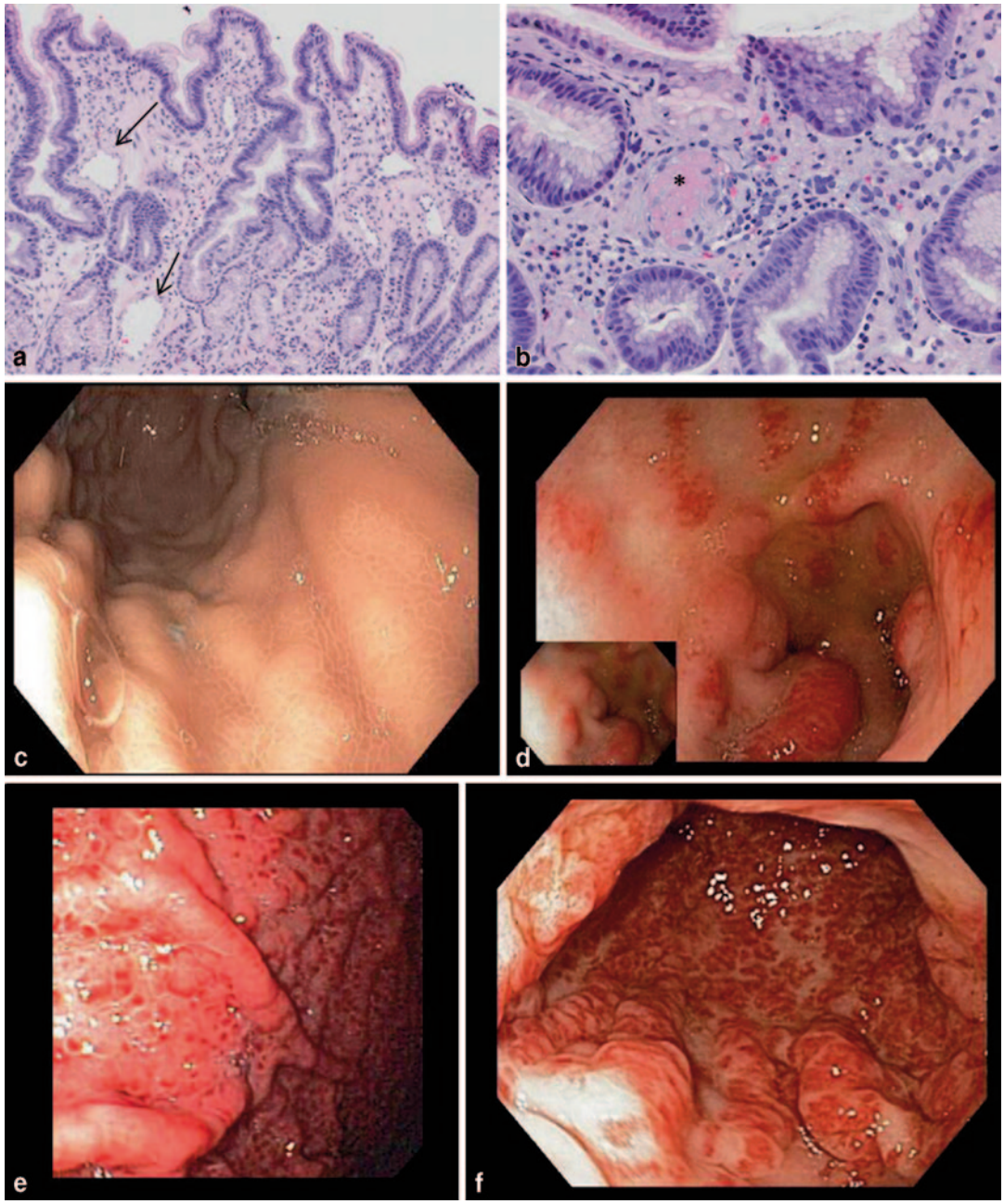

Fig. 12.1 Histology of PHG and GAVE, and endoscopy images. *Histology of PHG and GAVE:* **a** PHG (*arrow*—capillarydilation). **b** GAVE (*star*—fibrin thrombi in ecactic vessel). *Endoscopy images*. **c** Mild PHG. **d** Classic "watermelon" GAVE. **e** Severe PHG. **f** Diffuse GAVE (histology images were kindly provided by Dr. Arief Suriawinata, Department of Pathology, Dartmouth–Hitchock Medical Center, Lebanon, NH. Endoscopic images were kindly provided by Dr. Louis M. Wong Kee Song, Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN). *PHG* portal hypertensive gastropathy, *GAVE* gastric antral vascular ectasia

Table 12.4 GAVE score for histology; 80% diagnostic accuracy for scores ≥3 [10]

Score	Fibrin thrombi and/or vascularectasia	Spindle cell proliferation	Fibrohyalinosis
0	Both absent	Absent	Absent
1	One present	Increased	Present
2	Both present	Marked increase	

GAVE gastric antral vascular ectasia

Table 12.5 Summary of management of GAVE and PHG

	GAVE	PHG
Asymptomatic (normal hemoglobin, not receiving iron or transfusions)	No therapy	No therapy
Chronic bleeding	Iron, transfusions, argon plasma coagulation (APC), cryotherapy [34], EBL [30, 31], RFA [35], antrectomy [36], liver transplant [7]	Iron, transfusion, beta-blockers [15], TIPS, APC for patients unresponsive to beta blockers and not surgical candidates [21]
Acute bleeding	Endoscopic therapy	Vasoactive medication (somatostatin, vasopressin, octreotide, terlipressin) [17–20]
Rescue therapy	Antrectomy	TIPS, portocaval shunt

GAVE gastric antral vascular ectasia, *PHG* portal hypertensive gastropathy, *EBL* endoscopic band ligation, *TIPS* transjugular intrahepatic portosystemic shunts, *RFA* radio-frequency ablation

with initial management consisting of appropriate resuscitation and antibiotic coverage. The main goal of medical therapy in acute bleeding is the reduction of the portal pressure. Agents that have been described in the literature include somatostatin [17], vasopressin [18], octreotide [19], and terlipressin [20]. In severe cases of acute bleeding, TIPS or surgical shunt may be necessary for management. For patients who fail medical therapy and who are not surgical candidates, there is evidence that endoscopic therapy with argon plasma coagulation (APC) could be an alternative therapy [21]. In a prospective trial by Herrera et al., APC therapy was examined in 29 patients admitted for upper gastrointestinal bleeding, with 11 patients having an underlying diagnosis of PHG. Herrera et al. found that APC was a successful therapy in 81% patients with APC with success defined as no further episode of upper gastrointestinal bleeding and an increase of hemoglobin by 30% or an increase in hematocrit of 10%. In this study, the average number of sessions of APC required was 2.2 for patients with PHG and the average follow-up was 23.1 months [21]. One small case series of four patients examined the use of hemospray, a hemostatic agent licensed for endoscopic hemostasis in non-variceal upper gastrointestinal bleeding in Europe and Canada [22]. The rationale for the use of hemospray was that it would allow for the treatment of a large area and in this study hemostasis was achieved in all four patients; However, one patient passed away from a perforated viscous and subsequent sepsis indicating the need for caution [22].

GAVE

Similar to management of mild PHG, the initial therapy for chronic bleeding from GAVE is iron replacement and transfusions. In patients requiring frequent transfusions and who demonstrate unresponsiveness to iron therapy, endoscopic therapies can be used. Multiple different thermocoagulation techniques have been used including neodymium-doped yttrium aluminum garnet (Nd:YAG) laser [23, 24], heater probe, bipolar probe, and APC [21]. A recent meta-analysis comparing the evidence of the various types

of endoscopic therapy found the most number of studies examining either Nd:YAG or APC with eight and ten studies, respectively, included in the meta-analysis [25]. There were similar rates of complications and overall mortality between Nd:YAG and APC with complications occurring in 20 and 21%, respectively, and overall mortality 28 and 25%, respectively [25]. There were no reports of perforation in studies of APC, but there was a 1.6% perforation rate reported with Nd:YAG [25]. In one study that did report a perforation with Nd:YAG in a patient with GAVE, it was noted that this patient was a 72-year-old man with cryptogenic cirrhosis with heavy upper gastrointestinal bleeding. This patient was treated with a large amount of laser energy (14,000 J), which the authors noted in retrospect was likely excessive [23]. Treatment failure occurred in 6% of patients treated with Nd:YAG and 1.6% of patients with APC [25]. For APC therapy 1–4 treatments are required [21, 26–28]. The recurrence rate for GAVE after APC therapy is reported between 25 and 40% [26–28]. Currently, APC therapy is the first-line endoscopy therapy for patients who fail to respond to iron replacement and periodic transfusions.

More recent additions to potential endoscopic therapy include endoscopic band ligation (EBL) and cryotherapy. An observational comparative study with 13 patients in the endoscopic thermal therapy group and nine patients in the EBL group, found an increase in bleeding cessation in the EBL group (23 vs. 67%), fewer treatment sessions for EBL (4.7 vs. 1.9), and a decrease in transfusion requirement in the EBL group (−5.2 vs. −12.7), although four patients in the EBL group had undergone prior endoscopic thermal therapy [29]. A retrospective study that examined EBL versus APC also noted a statistically significant improvement in the endoscopic appearance of GAVE and a trend towards fewer transfusions for patients receiving EBL [30]. This study also has the caveat that 75% of the patients in the EBL group had failed APC therapy with an average of 4.7 sessions of APC prior to EBL [30]. Another study prospectively enrolled patients with GAVE secondary to liver disease to either APC or EBL, which resulted in a lower recurrence rate in the EBL group (68.2 vs. 8.3%) [31]. However, the rate of recurrence noted in the APC group appears to be much higher than previous studies where recurrence rates were noted between 12.5 and 16% [21, 25, 32]. The inconsistences in the recurrence rates may be secondary differences in the definition of recurrence, variation in follow-up times, and that the majority of studies did not separate patients with GAVE based on the underlying pathology (liver disease, autoimmune disease, or renal failure). There is some speculation in the literature that EBL may be favored over APC as no specialized equipment is required; however, further studies are needed before this becomes standard of care [33].

The cryotherapy data are similar to the EBL data, in that many of the patients had failed APC treatment. A study looking at outcome of patients receiving cryotherapy noted that 67% of the patients enrolled had previous failed APC with an average of 6 prior APC treatments [34]. Despite having a large percentage of refractory patients, 50% of the 12 patients in this study had a complete response with the other six patients having a partial response to cryotherapy [34]. The authors noted a mean increase in hemoglobin (Hb) of 1.4 g/dL in the 3 months post-cryotherapy with an associated reduction of number of blood transfusion by 2.9 units [34]. Additionally, it was noted that in 89% of the cryotherapy session it was possible to treat more than 90% of the GAVE lesions that were present [34]. In an open label prospective trial using radio-frequency ablation (RFA) therapy with GAVE which was refractory to APC, 21 patients underwent RFA, with 86% of patients remaining transfusion independent at the 6-month follow-up [35]. Two patients had adverse events, one had minor acute bleeding and the other was superficial ulceration; both events resolved without intervention [35]. Endoscopic images from APC, cryotherapy, and RFA are given in Fig. 12.2.

For patients with acute bleeding secondary to GAVE, which is a rare occurrence, endoscopic therapy is the first-line therapy. In patients in whom endoscopic therapy is not successful in controlling bleeding in the acute setting, or in patients with chronic therapy that remain trans-

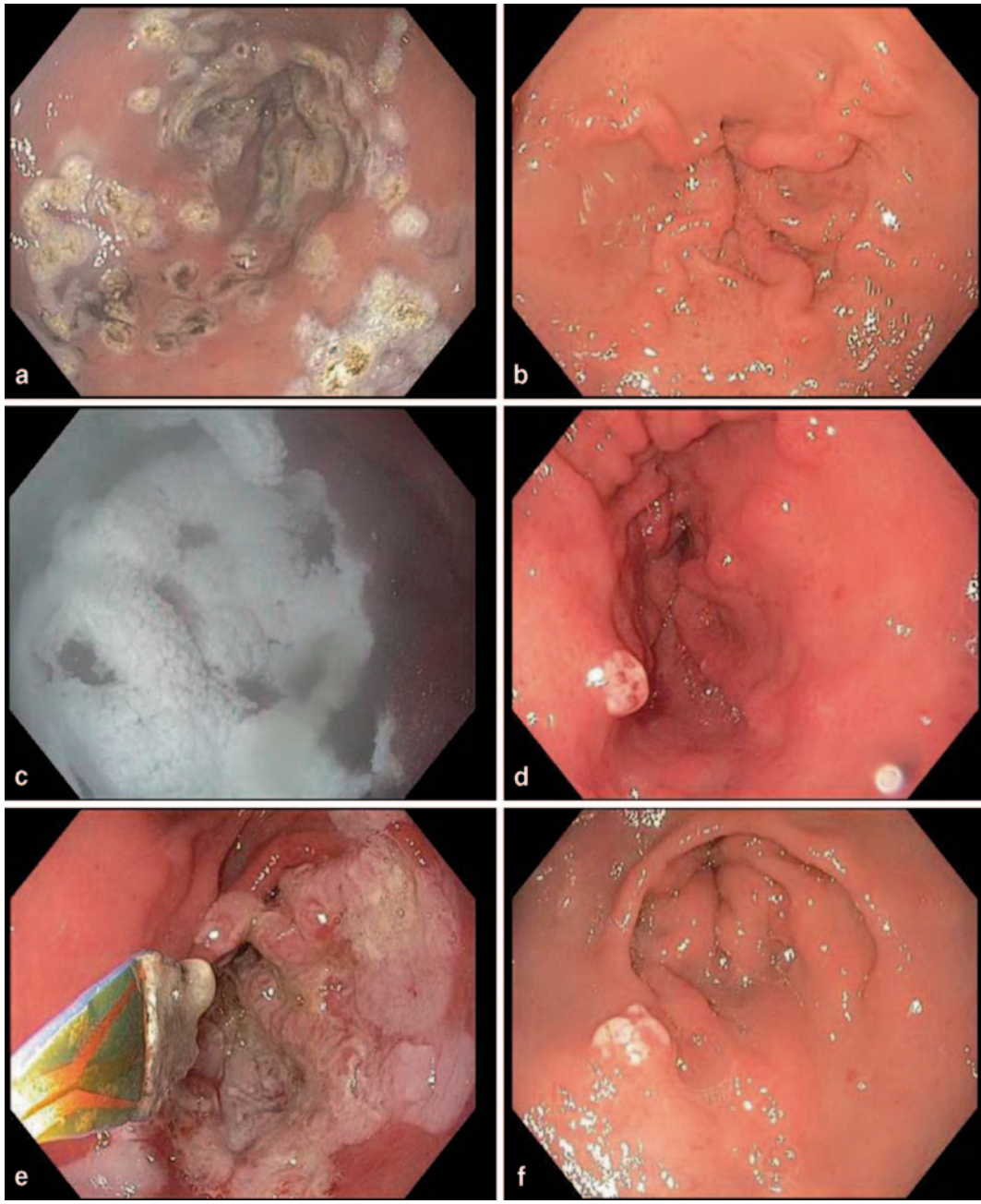

Fig. 12.2 Images from a single patient with GAVE who received APC, cryotherapy, and RFA (in respective order) for treatment of GAVE **a** APC treatment, **b** post-APC therapy, **c** cryotherapy, **d** post-cryotherapy, **e** RFA, **f** post-RFA). *GAVE* gastric antral vascular ectasia, *APC* argon plasma coagulation, *RFA* radio-frequency ablation

fusion dependent despite repeated endoscopic therapy, surgery may be considered. The surgical procedure is most often an antrectomy [36]. In patients that undergo antrectomy there has been no report of recurrence of GAVE, but the procedure is associated with 6.6% 30-day mortality with multiorgan failure being the leading cause of death [36]. Portocaval shunts and TIPS do not

play any role in the management of GAVE. In patients with cirrhosis as the underlying cause of GAVE have been noted to have complete resolution of their GAVE post-liver transplant even if there is persistent portal hypertension [7].

Multiple different medical therapies have been investigated for patients with GAVE. Combination estrogen–progesterone therapy has been studied in small trials, including an open label study in cirrhotic only patients, and been shown to be effective in controlling bleeding [37, 38]. The drawbacks to this therapy is that the lesions persist with bleeding recurring with cessation of therapy, and an increased risk of breast cancer and coronary artery disease with prolonged hormonal therapy [37, 39, 40]. In another study, octreotide was used in patients with various vascular abnormalities of the gastrointestinal tract including three patients with GAVE and cirrhosis [41]. Of the three patients with GAVE, one remained free of iron therapy or transfusions after 6 months of therapy, two required cyclical therapy with octreotide with one of these patients requiring iron therapy and periodic transfusions [41].

Summary

In summary, PHG and GAVE are two distinct entities that lead to upper gastrointestinal bleeding in patients with cirrhosis. While the pathogenesis of PHG is closely linked to portal hypertension, this is not the case in patients with GAVE. In patients with cirrhosis and GAVE, it appears that the underlying liver disease leads to systemic changes that result in the vascular ectasia. The diagnosis can usually be made at endoscopy, but in severe cases the appearance of PHG and GAVE may overlap. In these patients, histology can be used to help distinguish the underlying diagnosis which is necessary given the differences in management. For PHG, the management focuses on lowering portal pressure and TIPS can be used in severe cases. In GAVE, the management is centered on controlling bleeding through endoscopic treatment. Liver transplantation is another potential option for patients with GAVE and cirrhosis if the patient is a transplant candidate.

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Ascites and Refractory Ascites

13

Angelo Paredes and Arun J. Sanyal

Ascites is the most common complication of liver cirrhosis associated with a poor prognosis and prevalence of 10 %. Ascites is the pathologic accumulation of fluid in the peritoneal cavity most often encountered in the setting of cirrhosis. Over a 10-year period, 50 % of patients with previously compensated cirrhosis are expected to develop ascites [1]. Ascites also causes considerable morbidity by producing abdominal distension, respiratory distress, worsening nutritional status, and increased susceptibility to infections. Survival of a cirrhotic patient who develops ascites changes from 80 % at 5 years to 50 % at 5 years without liver transplantation [2, 3].

Pathophysiology

Cirrhosis progressively distorts the hepatic architecture causing an increased resistance to portal blood flow. Ascites results from an intricate response to portal hypertension by the endogenous vasoactive systems and renal function. There is a simultaneous increase in vascular tone due to vasoconstrictors such as angiotensin, endothelin, cysteinyl leukotrienes, and thromboxane. Portal pressures continue to increase triggering a parallel rise in circulating nitric oxide (NO) in response to shear stress stimuli [4]. In addition to shear stress, tumor necrosis factor-α (TNF-α) and endotoxin have been linked with enhanced production of NO. Patients with cirrhosis are susceptible to bacterial infections, which are caused mainly by gram-negative organisms of the enteric system. Intestinal bacterial translocation, described in patients and animal models with cirrhosis is associated with a significant increase of plasma TNF-α levels and thus may augment NO overproduction [5–7]. Additionally, there is an enhanced production of NO through an upregulation of inducible NO synthase in response to lipopolysaccharides, a major cell-wall component of gram-negative bacteria and proinflammatory cytokines. Finally, this collective stimulation of NO production leads to vasodilation most notably in the splanchnic circulatory beds [8].

In early advanced fibrosis, activation of vasodilatory substances is minimal and an increase in cardiac output compensates for the splanchnic arterial vasodilation with only a slight decrease in systemic vascular resistance (SVR). Additionally, there is progressive portosystemic shunt formation in the form of collaterals that diverts blood and vasodilators from the splanchnic bed to the systemic circulation [9]. With continued hepatic dysfunction, the cardiac output is unable to compensate for the continued circulatory vasodilatation leading to a decrease in SVR. There is baroreceptor-mediated stimulation of the renin–angiotensin–aldosterone system, sympathetic nervous system, and the secretion of antidiuretic

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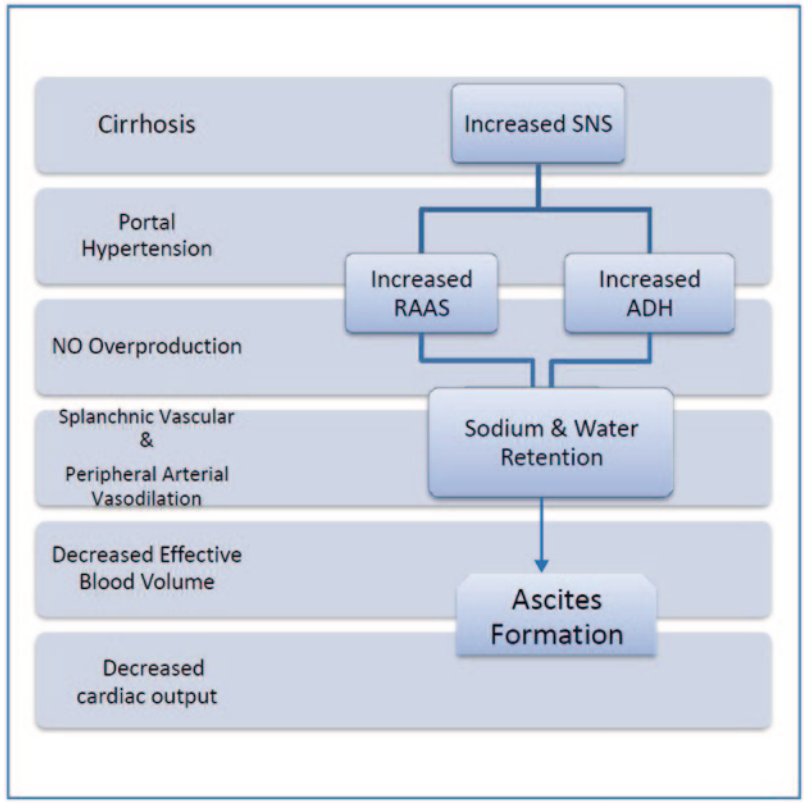

Fig. 13.1 The pathophysiology of ascites. *RAAS* renin–angiotensin–aldosterone system, *ADH* antidiuretic hormone, *NO* nitric oxide

hormone [10]. This leads to a gradual increase in renal sodium and water retention (Fig. 13.1).

In an effort to maintain homeostasis, this new altered hemodynamic state and renal response results in a continuous escape of fluid from the hepatic sinusoids and from the splanchnic capillaries into the interstitial space. Once again, there is an initial compensatory response to absorb the fluid in the peritoneal cavity through the lymphatic system and thoracic duct. However, with concomitant worsening hepatic dysfunction, the lymphatic system becomes overwhelmed resulting in net accumulation of fluid in the peritoneal cavity resulting in ascites [11].

Treatment

An understanding of the mechanisms that lead to ascites formation lends to understanding the treatment strategies and their shortcomings. The fundamental goal of ascites management is to induce a negative sodium balance. This is achieved through a combination of restriction of sodium intake and diuretics. Factors to consider in treatment strategies include grade or severity of ascites and initial presentation (Fig. 13.2).

A key consideration early in management is an analysis of the ascites itself. It is meant to confirm cirrhosis as a cause of the ascites and to exclude complicating conditions such as infections etc. Typically, cirrhosis-related ascites has a low total protein and albumin especially with respect to circulating albumin levels. Thus, the serum to ascites albumin gradient is usually more than 1.1 in those with cirrhosis. Cirrhosis-associated ascites typically has a low white blood cells (WBC) count. When the neutrophil count exceeds 250/mm^3, spontaneous bacterial peritonitis is considered to be present. When in doubt regarding the presence of spontaneous bacterial infection, ascites fluid should be injected into

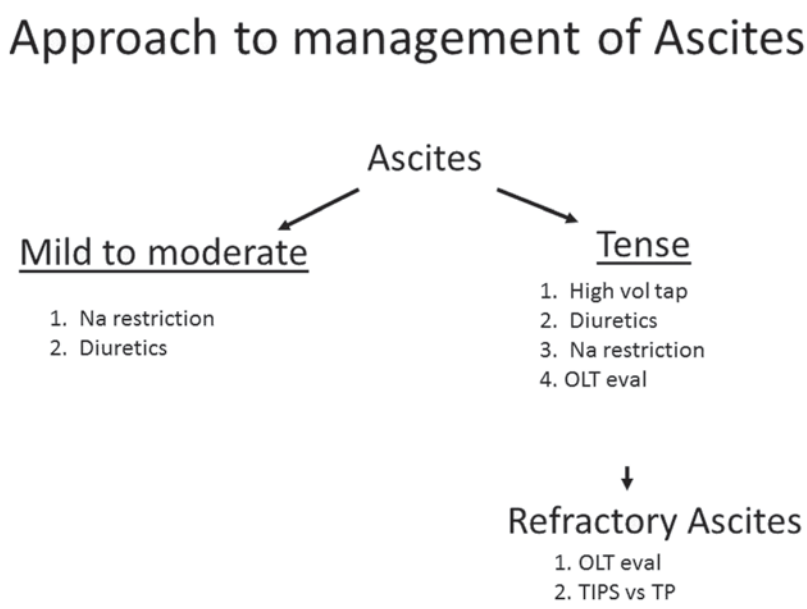

Fig. 13.2 An initial approach to management of ascites. *Vol* volume, *OLT* orthotopic liver transplantation, *TIPS* transjugular intrahepatic protosystemic shunt, *TP* therapeutic paracentesis

Table 13.1 Classification of ascites according to severity and treatment strategy

Severity	Definition
Grade 1 (mild)	Ascites is only diagnosed on ultrasonography Treatment: No treatment is indicated
Grade 2 (moderate)	Clinically evident ascites associated with abdominal distension Treatment: Dietary sodium restriction and diuretics
Grade 3 (large)	Clinically marked ascites or tense ascites of the abdomen Treatment: Large-volume paracentesis followed by dietary sodium restriction and diuretics
Uncomplicated	Not infected or associated with hepatorenal syndrome
Refractory	Cannot be mobilized, early recurrence after LVP, not prevented satisfactorily with medical treatment
Diuretic resistance	Ascites that is unresponsive to sodium restricted diet and high-dose diuretic treatment
Diuretic intractable	Diuretic-induced adverse effects preclude the use of an effective diuretic dosage

blood culture bottles for bacterial culture. Hemorrhagic ascites should raise concern for malignant or tuberculous ascites. When the ascites appears milky, a chylous ascites is usually present and confirmed by a high triglyceride level (level >200 mg/dL). In those who consume a large amount of alcohol, pancreatic ascites can be diagnosed by the presence of a high protein and amylase levels (usually 1000 IU/l) in ascites. Ascites cytology may be useful sometimes in diagnosis of peritoneal carcinomatosis; however, a negative study does not exclude the condition and may require additional imaging and direct visualization of the peritoneum with biopsies to confirm the diagnosis.

The International Ascites Club has proposed a treatment approached based on the quantitative severity (Table 13.1). In patients with grade 1 ascites, those with ascites detectable by ultrasound alone, no treatment is recommended. There are no data available as to the management or natural history with or without intervention. Grade 2 or moderate ascites is more readily encountered and the diagnosis made clinically. These patients

have impairment in renal sodium excretion; sodium excretion is low comparative to sodium intake. Grade 3 ascites is defined as large or gross ascites with marked abdominal distension best addressed with sequential large volume paracentesis (LVP) followed by sodium restriction and diuretics.

Dietary Sodium Restriction

Dietary sodium should be restricted to 2000 mg/day (88 mmol/day). Compliance with such dietary restrictions becomes a barrier to therapeutic efficacy. Salt substitutes containing high potassium content should be used cautiously particularly when used with potassium-sparring diuretics as this can result in hyperkalemia. A negative sodium balanced is successful in 10–20% of cirrhotic patients particularly those presenting with their first episode of ascites [12]. There is no evidence to suggest a benefit in sodium restriction in cirrhotic patients who have never developed ascites.

Diuretics

Diuretics block sodium reabsorption along the nephron leading to natriuresis and passive water excretion. Most commonly used is a combination of spironolactone (an aldosterone antagonist) and furosemide (loop diuretic) at doses of 100 mg and 40 mg/day, respectively. The site of action on the nephron is important in understanding how these diuretics compliment each other. Spironolactone works in the distal tubule by blocking aldosterone resulting in a decrease in sodium reabsorption. Loop diuretics work more proximally to prevent sodium reabsorption. Mechanistically, loop diuretics alone are not therapeutically efficacious, as the sodium not reabsorbed in the loop of Henle would later be reabsorbed distally in the setting of a hyperaldosterone state [13]. The evidence for the use of spironolactone as monotherapy in patients with a first episode of ascites is extrapolated from studies comparing monotherapy with sequential use of furosemide to nonresponders versus dual therapy both with a stepwise increase in doses. Therefore, in patients with new ascites, spironolactone alone can be started at 100 mg/day and increased in a stepwise fashion every 7 days (100 mg steps) to a maximum of 400 mg/day [14, 15]. To prevent electrolyte derangement and acute kidney injury from diuretics, the goals of therapy should be weight loss of 0.5 kg/day in patients without peripheral edema and 1 kg/day in patients with peripheral edema [16]. Furosemide can be added at a dose of 40 mg/day in patients who are not responding to monotherapy and gradually increased to 160 mg/day. In patients with recurrent ascites, combination therapy with spironolactone and furosemide beginning with 100 and 40 mg, respectively, should be the strategy of choice with a stepwise simultaneous increase in doses maintaining the same ratio of dosages.

Side effects of spironolactone include hyperkalemia and decreased libido, impotence, and gynecomastia in men and menstrual irregularity in women, as a result of its antiandrogenic activity. Amiloride is an alternative in patients with tender gynecomastia, but was shown to be more expensive and less efficacious that spironolactone [17]. Tamoxifen has been reported to be effective in managing the symptoms of gynecomastia [18]. Clonidine, a central alpha-2 agonist, has sympatholytic activity in patients with cirrhosis. Simultaneous use of clonidine and spironolactone has been shown in studies to increase natriuresis and body weight loss more efficiently [19].

Refractory Ascites

Ascites becomes refractory to diuretics and salt restriction in 10% of cases. Refractory ascites (RA) has been defined as ascites that cannot be mobilized or the early recurrence of which cannot be prevented by medical therapy (Table 13.1) [20]. The prognosis associated with RA is poor, with about a 50% 1-year survival rate [21]. As a consequence, patients with RA should be considered for liver transplantation. Current avail-

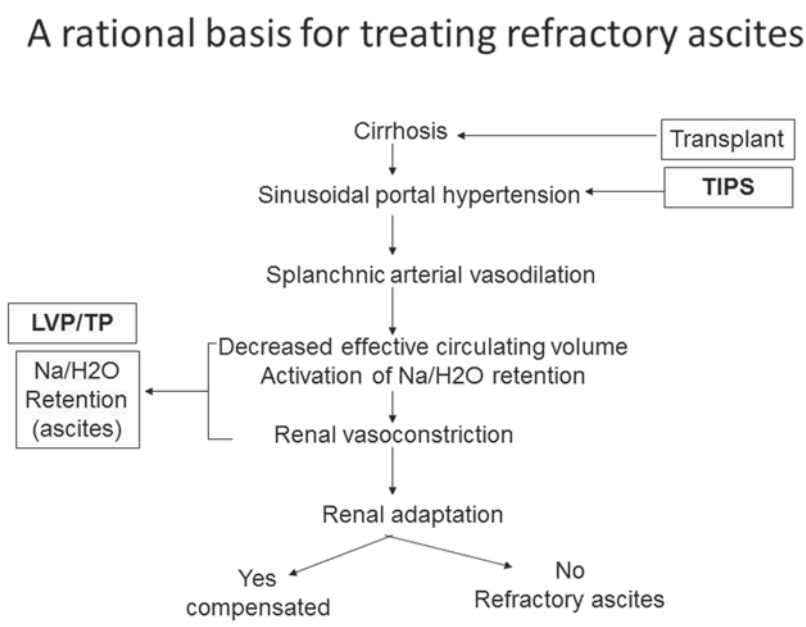

Fig. 13.3 The pathophysiological rationale for the treatment of refractory ascites. *TIPS* transjugular intrahepatic portosystemic shunt, *LVP* large-volume paracentesis, *TP* therapeutic paracentesis

able treatments include LVP with albumin infusions, peritoneal shunts, or liver transplantation (Fig. 13.3).

Large-Volume Paracentesis

Paracentesis is the first-line treatment of RA. It offers the advantage of quickly relieving tense ascites safer than high-dose diuretics and found to shorten duration of hospitalization, though survival is similar to those of diuretic therapy [22]. The frequency and volume of LVP is a reflection of the patient's sodium intake. In general, a patient adherent to sodium restriction of 88 mmol/day will accumulate less than 4 L of ascites per week. Repeated LVP is relatively safe, despite a cirrhotic patient's bleeding diathesis. The incidence of significant peritoneal bleeding complications during paracentesis has been reported 0.5–1%, despite cirrhotic patients having coagulopathies and thrombocytopenia [23, 24]. In patients with renal failure (e.g., hepatorenal syndrome, HRS type 2), the risk of bleeding may be higher due to dysfunctional circulating platelets and may require an extended post paracentesis observation.

The most common complication of LVP is paracentesis-induced circulatory dysfunction (PICD) caused by effective hypovolemia and accompanying marked activation of the renin–angiotensin axis. PICD can result in worsening vasodilation, hyponatremia, and renal impairment in 20% of cases [25]. More importantly, PICD may persist for months and is linked with subsequent adverse clinical events such as an increased rate of recurrent ascites, the development of HRS, and reduce survival [26]. The incidence of PICD correlates with the volume of ascites removed during paracentesis. Incidence of PICD is only 7%, with little clinical consequence with a paracentesis less than 6 L [27]. However, the use of albumin given intravenously at a dose of 6–8 g/L of ascites removed can decrease the incidence of PICD when performing a paracentesis greater than 5 L. The frequency is approximately 75% when LVP is performed without the administration of plasma expanders [17]. Albumin's superiority over synthetic volume expanders (e.g.,

polygeline) was seen a double-blind, randomized pilot study showing a decrease in liver-related complications [28]. Beyond its role as a volume expander, albumin is thought to work on the endothelial dysfunction and circulatory disturbances associated with cirrhosis [26]. A meta-analysis showed that albumin is the most effective agent in the prevention of hemodynamic and clinical effects associated with PICD [29].

Not having addressed the underlying pathophysiology, patients with RA will undergo repeated LVP without any other intervention. The persistent ascites increases their risk for developing spontaneous bacterial peritonitis and HRS. Furthermore, there is an indirect impact on worsening nutrition: Ascites accumulation is associated with decreased caloric intake coupled with protein losses with repeated paracentesis.

Transjugular Intrahepatic Portosystemic Shunt

The transjugular intrahepatic portosystemic shunt (TIPS) is an established procedure that has proven benefit in the treatment of patients with RA. TIPS reduces the portosystemic pressure gradient, one of the pathogenetic mechanisms of ascites formation, by functioning as a side-to-side portocaval shunt. Within 4 weeks after TIPS, urinary sodium excretion and serum creatinine improve significantly and can normalize within 6–12 months. This is associated with an increase in serum sodium concentration, urinary volume, and glomerular filtration rate together with a normalization of plasma renin activity, aldosterone, and noradrenaline concentrations during 4–6 months of follow-up [30, 31]. Patients should follow a sodium-restricted diet immediate post TIPS period and may require the use of diuretics to facilitate ascites clearance. Complete resolution of ascites is seen in two thirds and partial response in the other third within a 6-month follow-up period. At 12 months post TIPS, approximately 80 % of patients will completely clear their ascites [32]. Unrecognized cirrhotic cardiomyopathy is an identified risk factor for lack of ascites clearance after TIPS [33]. Cirrhotic cardiomyopathy is characterized by blunted contractile responsiveness to stress, and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease and in the setting of cirrhosis [34].

Five randomized controlled trials have compared LVP versus TIPS as a treatment for ascites [35–39]. All have showed that TIPS is much more effective than LVP in controlling ascites, though at the expense of more episodes of hepatic encephalopathy (Table 13.2). Two separate meta-analyses showed a survival advantage with TIPS in carefully selected patients when compared to LVP (Table 13.3). Additionally, TIPS has shown to improve renal function, nutritional status, and improvement in quality of life [31, 40, 41]. The advent of polytetrafluoroethylene (PTFE)-covered stents has also improved long-term shunt patency.

Table 13.2 Randomized controlled trials to comparing TIPS and repeated paracentesis in the management of refractory ascites

Author, year	Number of patients		Ascites improved (%)		1-year survival (%)		*P* value
	TIPS	LVP	TIPS	LVP	TIPS	LVP	
Lebrec et al. [35]	13	12	38	0	29	56	< .05[a]
Rössle et al. [36]	29	31	84	43	58	32	NS
Ginès et al. [37]	35	35	51	17	26	30	NS
Sanyal et al. [38]	52	57	58	16	35	33	NS
Salerno et al. [39]	33	33	79	42	59	29	.021

NS not statistically significant, *TIPS* transjugular intrahepatic portosystemic shunt, *LVP* large-volume paracentesis
[a] 2-year survival

Table 13.3 Contraindications to placement of a transjugular intrahepatic portosystemic shunt

Absolute	Relative
Primary prevention of variceal bleeding	Hepatocellular carcinoma
Congestive heart failure	Obstruction of all hepatic veins
Severe tricuspid regurgitation	Portal vein thrombosis
Severe pulmonary hypertension	Moderate pulmonary hypertension
Multiple hepatic cysts	Severe coagulopathy (INR > 5)
Uncontrolled systemic infection or sepsis	Thrombocytopenia of < 20,000 cells/cm^3
Unrelieved biliary obstruction	Hepatic encephalopathy

INR International Normalized Ratio

Other Treatments

In RA, LVP, and TIPS have disadvantages that could result in increased morbidity or contraindications that preclude their application; hence, alternative strategies have been pursued.

Peritoneovenous shunt (e.g., Denver or LeVeen shunt) has been used for the treatment of RA but interest has waned because of the increased risk of complications, such as disseminated intravascular coagulation, infection, and occlusion of the subclavian vein and superior vena cava, which can preclude a liver transplantation [19, 42]. As such, peritoneovenous shunts have been discarded from routine clinical use. Shunting should be reserved for patients who are not candidates for transplantation or TIPS and who are not candidates for multiple LVPs (i.e., multiple scars, long distances from medical facility).

Vasoconstrictors, midodrine and terlipressin, have been used to improve splanchnic blood flow and increase arterial hemodynamics in the setting of HRS. In the setting of RA, improved systemic hemodynamics has preliminary shown benefits with natriuresis but larger studies needed [43].

Vasopressin V2 receptor antagonists, vaptans, are drugs that compete with vasopressin for attachment onto the V2 receptor at the renal collecting duct to inhibit water reabsorption. This results in an increase in solute-free water excretion and serum sodium concentration. This class of drugs has been studied in the management of hypervolemic hyponatremia associated with cirrhosis and ascites, heart failure, and syndrome of inappropriate antidiuretic hormone secretion [44]. Initial phase II studies suggested that the V2 receptor antagonist satavaptan helped decrease ascites volume and need for LVP in cirrhotic patients [45]. Subsequently, three randomized double-blind studies comparing satavaptan with placebo in uncomplicated ascites, with and without concomitant diuretics, were performed and the findings were pooled [46]. There was no clinical long-term benefit found in using satavaptan with or without diuretics in the management of ascites and edema in cirrhosis.

The ALFA pump system (Sequana Medical AG, Zurich, Switzerland) is a battery-powered peritoneo-vesical shunt that pumps excess peritoneal fluid into the bladder where it can be eliminated through normal urination [47]. In a multicenter study of 40 patients with RA, the ALFA pump system was associated with a significant reduction in the number of LVPs [48]. Forty percent of patients did not require any LVP and 70% of patients required less than one paracentesis per month after pump implantation. Most of the complications observed were related to technical placement of the bladder catheter. With the implementation of antibiotic prophylaxis during the trial, the rate of infectious complications (e.g., urinary tract infections, spontaneous bacterial peritonitis) was significantly reduced. A prospective multicenter trial comparing LVPs versus ALFA pump is underway to confirm these preliminary results.

Conclusion

Ascites results from an intricate and dynamic response to portal hypertension, by the endogenous vasoactive systems and renal function. Our improved understanding of the pathophysiology of

ascites has allowed us to be more successful in treating ascites. Despite our appreciation for the disruption in volume, the medical management has not changed significantly. Dietary sodium restriction and diuretics are the mainstay of managing ascites. RA portends overall poor outcomes and warrants a referral for liver transplantation. In RA, LVP remains an effective first-line treatment modality. The concomitant use of albumin with LVP $\geq$5 L has decreased the incidence of paracentesis-induced circulatory dysfunction. Our evolution in TIPS placement and stent quality has added an effective treatment tool for managing RA in carefully selected patients.

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Conflicts of Interest Serves as a consultant to Abbvie, Bristol Myers-Squibb, Genfit, Exhalenz, Salix, Islet Pharmaceuticals, Nimbus, Nitto-Denko and Tobira. His institution receives research funding from Gilead, Galectin, Novartis, Ikaria, La Jolla Pharmaceuticals, Salix, Cumberland and Intercept Pharmaceuticals. He has also served as a nonremunerated consultant to Immuron and Echosens.

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Elliot B. Tapper and Andrés Cárdenas

Decompensated cirrhosis complicated by ascites results in a multifactorial functional renal impairment that can lead to the retention of sodium and solute-free water [1]. Disproportionate retention of water relative to sodium leads to a dilutional state, the so-called hypervolemic or hypoosmolar hyponatremia. In general, hyponatremia is defined as a serum sodium level below 135 mEq/L [2]. The definition is different for patients with cirrhosis who often have a serum sodium concentration above 130 mEq/L and below 135 mEq/L. While these patients may display pathogenic and clinical features similar, if less pronounced, to those with serum sodium below 130 mEq/L, pathologic hyponatremia in cirrhosis has been defined as a serum sodium concentration of less than 130 mE/L in the presence of ascites or edema [3–5].

The development of hyponatremia spells a time of increased morbidity and mortality. Hyponatremia occurs in close association with impaired renal function, the development of ascites, and correlates with poor prognosis. Indeed, patients with cirrhosis who are hospitalized with ascites have a 37% 5-year probability of developing hyponatremia. Thereafter, these patients, largely Child C have a 25% probability of survival at 1 year [6]. Roughly, 22% of patients with decompensated cirrhosis have serum sodium levels <130 mEq/L; however, in patients with refractory ascites or hepatorenal syndrome (HRS), this proportion may increase to more than 50% [7]. Serum sodium therefore functions as a powerful biomarker. In patients with cirrhosis awaiting liver transplantation, serum sodium predicts prognosis and may be associated with an increased morbidity, particularly neurological complications, and reduced survival after transplantation [8–12]. Additionally, many studies have demonstrated that the incorporation of serum sodium can improve the predictive accuracy of the model for end-stage liver disease (MELD) score in patients listed for liver transplantation [12–14].

Types of Hyponatremia

Patients with cirrhosis—like any patient—may develop, hypervolemic, hypovolemic, or euvolemic hyponatremia. Hypervolemic or dilutional hyponatremia, a state of expanded extracellular fluid and plasma volume, is both the most common and important type that occurs in patients with cirrhosis. Such a state results from the development of a marked impairment in the renal capacity to eliminate solute-free water with disproportionate water retention with respect

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to sodium retention. As discussed below, the physiology of patients with cirrhosis results in a chronic cardiac underfilling for which compensatory mechanisms to stabilize cardiac output can eventually lead to hyponatremia especially when exacerbated by stressors to the patient's intravascular volume status (e.g., bacterial infections or hemorrhage). [15]. By contrast, hypovolemic hyponatremia is less common and is due to significant losses of extracellular fluid, particularly from the kidney due to overdiuresis or from gastrointestinal tract due to bleeding or diarrhea. Accordingly, most patients with hypovolemic hyponatremia show an improvement of serum sodium levels after the administration of normal saline or by temporarily increasing dietary sodium content. Herein, we focus on the pathogenesis and treatment of hypervolemic hyponatremia.

Pathogenesis

The pathogenesis of solute-free water retention in patients with cirrhosis is intricate and involves several factors, including high levels of arginine vasopressin (AVP), reduced renal prostaglandins synthesis, and reduced delivery of filtrate to the ascending limb of the loop of Henle [1, 3, 4]. Among these, AVP is the most important factor in the pathogenesis of water retention in patients with cirrhosis and ascites [16]. In cirrhosis, owing to a double-hit from synthetic dysfunction and portal hypertension, vasodilatory substances go unmetabolized (e.g., serotonin and nitric oxide) are allowed to predominate in the splanchnic circulation. Pooling of blood leads to reduced venous return and therefore arterial underfilling. The resulting transient decrement in stroke volume unloads high-pressure baroreceptors that stimulate compensatory catecholamine release and nonosmotic hypersecretion of AVP leading to solute-free water retention and hyponatremia (Fig. 14.1) [16]. The physiological actions of AVP are exerted through three types of receptors present in target cells throughout the body [17]. These receptors are G-protein-coupled receptors known as V1a, V1b, and V2 receptors. V1a and V1b are associated to the phosphoinositol signaling pathway with intracellular calcium as second messenger. V1a is responsible for vascular smooth

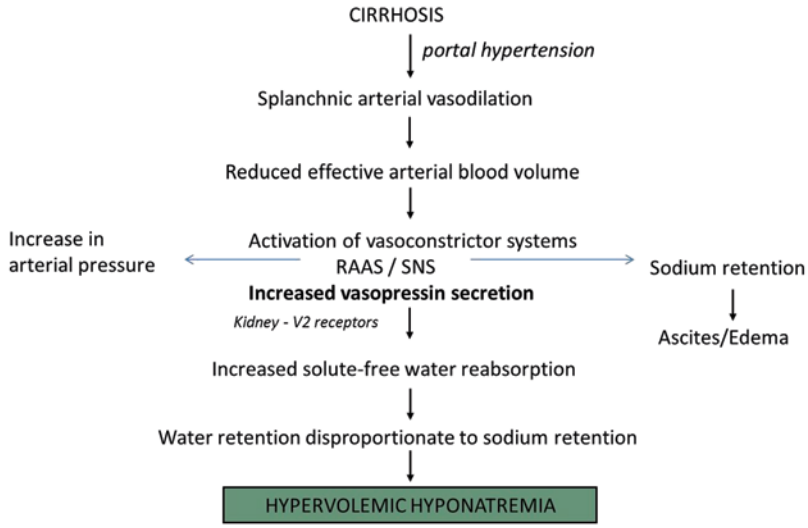

Fig. 14.1 Proposed pathogenesis of hypervolemic hyponatremia in cirrhosis. Portal hypertension causes splanchnic vasodilatation with subsequent activation of the renin–angiotensin–aldosterone system (*RAAS*) and sympathetic nervous system (*SNS*), and a nonosmotic hypersecretion of arginine vasopressin (*AVP*) is due to decreased effective arterial blood volume that activates baroreceptors and stimulates the hypothalamic release of AVP causing renal solute-free water retention through the action of V2 receptors and hypervolemic hyponatremia

muscle cell contraction, platelet aggregation, and hepatic glycogenolysis, and V1b is expressed in the anterior pituitary where it intervenes in adrenocorticotropin release [17].

Located on the basolateral (capillary) membrane of renal collecting duct principal cells, V2 receptors are responsible for the AVP-induced solute-free water reabsorption [3, 16–19]. The binding of AVP to the V2 receptor stimulates adenyl cyclase via a stimulatory G protein. The resulting intracellular cyclic AMP (cAMP) binds to a regulatory subunit of protein kinase A and activates it, which in turn phosphorylates aquaporin 2 (AQP2). AQP2 is then translocated from cytosolic vesicles to the luminal (apical) plasma membrane of the principle cell where it increases water permeability facilitating water reabsorption down a gradient [3]. The water entering the cell by the luminal plasma membrane leaves the cell through the basolateral membrane and enters the capillaries in contact with the tubular cells. Data from patients with cirrhosis and hypervolemic hyponatremia in whom V2 receptor antagonists of AVP (vaptans) were administered indicate that hypersecretion of AVP plays a major role in the development of hyponatremia because these drugs increase the serum sodium concentration in a large proportion (60–70%) of patients [20]. However, there are a number of patients in whom serum sodium levels do not increase with vaptans which suggests that other mechansims involved in solute-free water retetion play an important role in the pathogenesis of hypervolemic hyponatremia in cirrhosis.

Clinical Features

The specific clinical consequences of hypervolemic hyponatremia for patients with cirrhosis are largely obscure. Given that hyponatremia occurs in the setting of advanced liver failure, the symptoms with which patients with hyponatremia may present are often attributable to concomitant cirrhotic complications, including encephalopathy, renal failure, and infection. Furthermore, the lack of effective treatments for hyponatremia does not permit a controlled evaluation of symptoms in the presence and absence of hyponatremia.

Neurological Features

When it develops in the absence of liver disease, hyponatremia is primarily associated with a wide range of neurological manifestations. Owing to compensatory intracellular water shifts, these manifestations are related to the development of brain edema, such as headache, confusion, focal neurological deficits, seizures, and, in some cases, death due to cerebral herniation [2]. The severity of neurological symptoms in patients with hyponatremia without liver disease correlates reliably with serum osmolality and sodium. Given the existence of homeostatic compensatory mechanisms, rather than the absolute reduction in serum sodium levels, the most important determinant of the severity of neurological symptoms is the rate of fall in serum sodium levels [2]. Patients with acute hyponatremia have a much higher incidence of neurological symptoms than those with chronic hyponatremia.

No study has specifically evaluated neurological symptoms in patients with cirrhosis and hyponatremia. Clinical experience, however, suggests that neurological manifestations such as headache, focal deficits, seizures, and cerebral herniation are very uncommon. The relatively low incidence of neurological manifestations in patients with cirrhosis and dilutional hyponatremia is likely related to timescale over which their sodium concentration falls, allowing sufficient time for adaptation. In most patients with cirrhosis, hyponatremia is asymptomatic but may be associated with a higher risk of hepatic encephalopathy (HE) [21–23]. The underlying pathogenesis of HE is partially based on ammonia and other toxins inducing low-grade cerebral edema due to astrocyte swelling. When portosystemic shunting results in elevated ammonia levels, the astrocyte begins metabolizing excess ammonia via intracellular glutamine synthetase. The result is increased intra-astrocyte levels of glutamine that both acts as an osmolyte and alters astrocyte function [24]. Accordingly, the low serum osmolality reflective of hyponatremia likely contributes to HE by exacerbating astrocyte swelling as the brain takes on water to compensate for

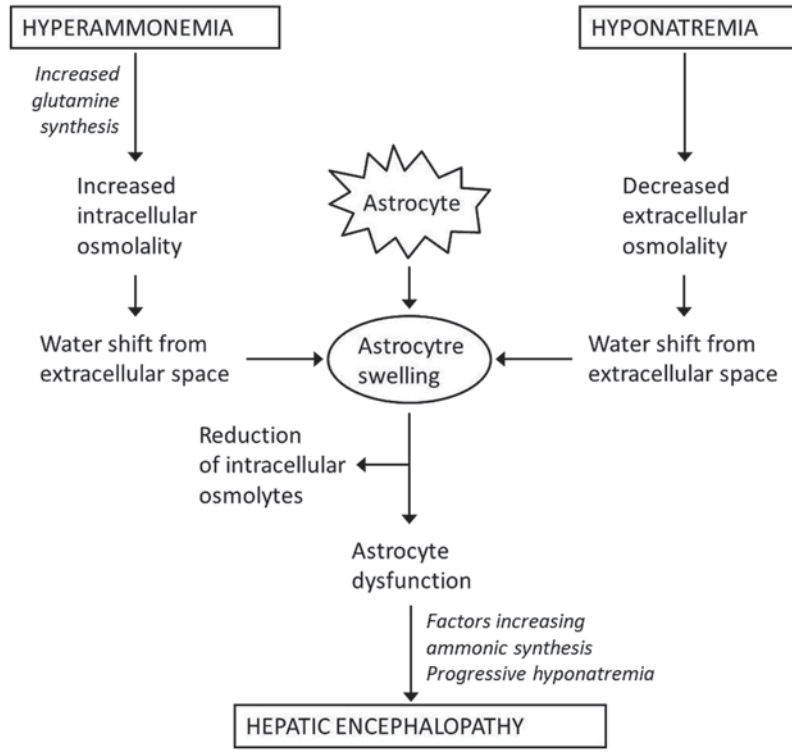

Fig. 14.2 Proposed interaction between hyperammonemia and hyponatremia on brain astrocytes and possible pathogenic relationship with hepatic encephalopathy

serum changes (Fig. 14.2). Consequences that attend astrocyte swelling include alterations in gene expression and oxidative stress that alter glioneuronal communication and disturb neurological function, leading to encephalopathy [24, 25]. Hyponatremia in combination with hyperammonemia lead to astrocyte swelling and may increase the risk of HE.

Complications of Cirrhosis

Beyond HE, hyponatremia is also associated with other complications of cirrhosis. As discussed above, in the majority of patients, hyponatremia is a marker of illness and advanced liver failure, often occurring in close association with renal failure and correlates with poor prognosis [15, 26]. Patients with ascites and hyponatremia constitute a population at a very high risk of developing HRS [27]. On the other hand, low serum sodium levels are a very common finding in patients with HRS. Hyponatremia is also a frequent finding in patients with cirrhosis and bacterial infections. Furthermore, owing both to the illness it reflects, its toxic effects and the results of the fluid intake restrictions imposed to prevent its progression, hyponatremia is an independent predictive factor of the impaired health-related quality of life [28].

Management of Hyponatremia

The first step in the management of hyponatremia in cirrhosis is to determine the patient's volume status. The management of hypovolemic hyponatremia is fundamentally different from that of hypervolemic hyponatremia. Regardless, diuretic treatment—for its effect of intravascular volume and natriuresis, should be stopped in all patients with hyponatremia [4, 5]. Thereafter, hypovolemic hyponatremia treatment consists of the identification and treatment of the cause of sodium loss together with the aim of repleting

extracellular sodium (either intravenous saline or a diet with normal sodium content).

The management of hypervolemic hyponatremia, on the other hand, aims to reduce total body water and requires maneuvers to increase renal solute-free water excretion. The available therapeutic methods for the management of hypervolemic hyponatremia are summarized below.

Fluid and Water Restriction

Fluid restriction (1.5 L/day) is still considered the first step in the management of hypervolemic hyponatremia [5]. There are no studies specifically assessing the effectiveness of fluid restriction in this setting but it is likely necessary to prevent a progressive decrease in serum sodium levels. Fluid restriction rarely increases serum sodium concentration in a significant manner, largely because the volume restriction required to effect significant changes—generally 500 mL—are profoundly less than typically prescribed by physicians or tolerated by patients [29].

Sodium Chloride

The use of intravenous hypertonic sodium chloride is neither advisable nor previously investigated in randomized studies of patients with cirrhosis. There are three reasons. First, the effect of hypertonic sodium is short-lived. Second, it has no effect on renal solute-free water excretion. While cardiac underfilling in patients with cirrhosis trigged significant AVP-mediated free water retention, it also stimulates sodium avidity via the renin–angiotensin system. Accordingly, third, hypertonic saline will invariably increase the patient's ascites and edema.

Albumin

Two short-term studies, one in 1990 and the other only published in abstract form, including a low number of patients suggest that the administration of albumin could improve serum sodium concentration in patients with hypervolemic hyponatremia [30, 31]. By improving circulatory function, albumin likely suppresses the sodium and water-retaining systems, including nonosmotic AVP release. Unfortunately, the effects of albumin infusion were studied over only 1 week. As the half-life of infused albumin is short, the changes it can bring are fundamentally short lived. It is also a costly therapy. Accordingly, further studies should focus on the subset of high risk patients that would benefit from a short-term therapy, namely, those with profound hyponatremia awaiting liver transplantation.

AVP Antagonists: The Vaptans

The pharmacological approach to the treatment of hypervolemic hyponatremia appeared revamped with the introduction of vaptans. These drugs cause a selective blockade of the V2 receptors of AVP in the principal cells of the collecting ducts [32]. Vaptans are aquaretics. In healthy subjects, vaptan treatment induces a marked and dose-dependent increase in urine volume with low urine osmolality due to a marked increase in solute-free water excretion, but without an increase in urinary sodium excretion. Randomized, double-blind, comparative studies indicate that treatment with oral vaptans for a short period of time (up to 1 month), including tolvaptan, lixivaptan, and satavaptan, improves serum sodium concentration in patients with cirrhosis and hypervolemic hyponatremia [33–37]. A small study suggests that intravenous conivaptan, a vaptan that is not only an antagonist of the V2 receptors but also of the V1 receptors of AVP, is also effective in patients with cirrhosis and hyponatremia [38]. The increase in serum sodium concentration occurs within the first 7 days of treatment and normalization of serum sodium concentration has been observed in up to 80 % of patients [33–37]. A specific analysis in patients with cirrhosis and hyponatremia revealed a significant increase in free water clearance associated with weight loss without renal impairment and normalization of serum sodium to > 135 mEq/L in 41 % of patients at day 4 and 33 % at day 30 [37] (Fig. 14.3). A secondary analysis also found a significant improvement in health-related quality of life scores

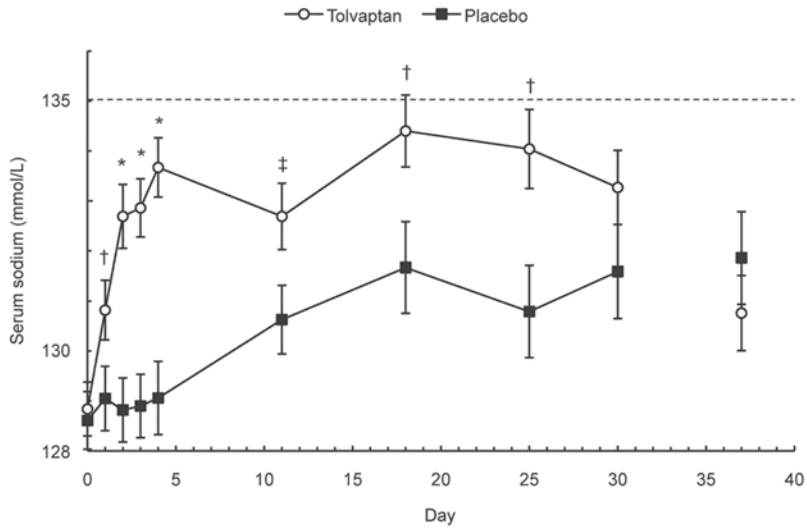

Fig. 14.3 Observed serum sodium concentration in patients with hyponatremia that received tolvaptan or placebo for 30 days and 7 days after stopping (day 37) Error bars are ± SE. *$P < 0.001$, tolvaptan versus placebo; †$P < 0.01$, tolvaptan versus placebo; ‡$P < 0.05$, tolvaptan versus placebo. (From Ref. [37])

in patients treated with tolvaptan [37]. Hyponatremia reliably recurs upon treatment discontinuation. Unfortunately, for some patients, as many as one third in some of the studies above, serum sodium increases more than 5 mEq/L but does not reach values >130 mEq/L. Therefore, vaptans are potentially effective in the short-term treatment of hypervolemic hyponatremia in patients with cirrhosis.

Overall, the vaptans do not seem to improve major outcomes in cirrhosis. A meta-analysis evaluated outcomes in 2266 patients from 12 randomized trials of tolvaptan, satavaptan, and lixivaptan. The primary outcome measure was mortality and secondary outcomes included, but were not limited to complications of cirrhosis and mobilization of ascites [39]. While the vaptans increased serum sodium, reduced mean body weight (mean difference of—1.82 kg) and increased time to first large volume paracentesis (RR = 0.76; 0.60–0.83), there was no mortality benefit (RR = 1.06; 0.90–1.26). There was a significant increase in thirst (RR = 3.97; 1.78–8.83) and excessive urine volume of >5 L/day (RR = 9.96; 1.38–71.68). These adverse effects are important particularly in a patient population that is predisposed to encephalopathy limiting access to water and physical deconditioning limiting mobility.

Therefore, future of this class of medications for patients with cirrhosis is currently in question. First, the effect of vaptans on hyponatremia has only been proven in the short term and they may be associated with severe adverse events in the long term. Unfortunately, phase 3 long-term treatment studies in three different populations of patients with cirrhosis and ascites demonstrated a lack of effect [40]. Moreover, use of satavaptan was associated with increased mortality. Though the reason for this signal could not be determined, it was withdrawn from development. Finally, while, a small study in 18 patients with cirrhosis and ascites without hyponatremia showed that the administration of tolvaptan dose dependently decreased body weight and improved ascites and edema, long-term studies with tolvaptan in other populations were associated with liver injury [41, 42]. Indeed, the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes (TEMPO) 3:4 study evaluated the efficacy and safety of tolvaptan in a population with polycystic kidney

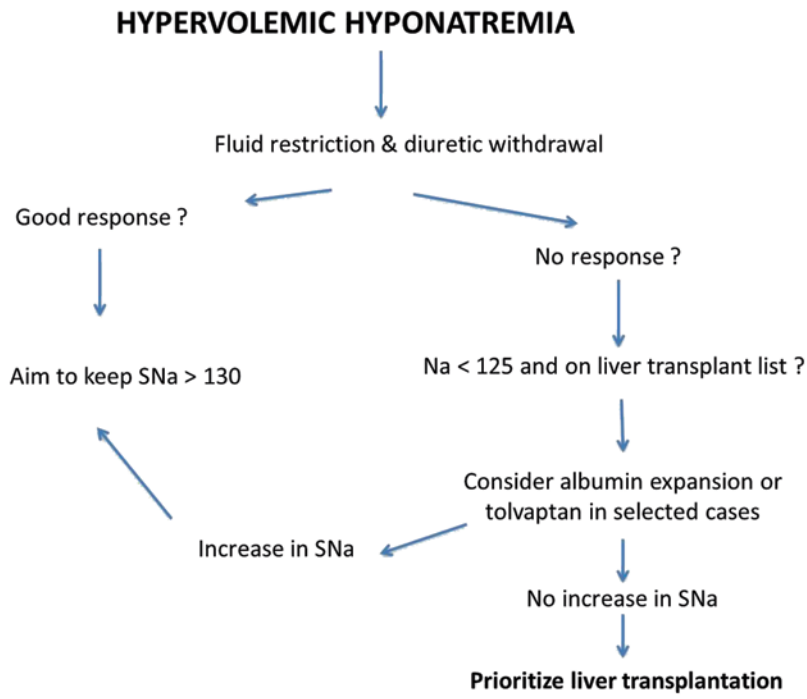

Fig. 14.4 Proposed algorithm for the management of hyponatremia in cirrhosis. Fluid restriction up to 1500 mL/day if hyponatremia persists, despite diuretic withdrawal. In liver transplant candidates with high MELD scores and serum sodium levels <125 mEq/L, tolvaptan (initial dose of 15 mg/day and titrated progressively to 30 and 60 mg/day) is useful in order to reach liver transplantation with a serum sodium <130 mEq/L. Albumin infusion albumin at a dose of 40 g/day for 7–14 days in this scenario may also be useful. *MELD* model for end-stage liver disease

disease and saw a 23 % rate of serious hepatic adverse events [41].

There are a number of difficulties presently associated with vaptan therapy. First, in 2013, the Food and Drug Administration (FDA) placed a black box warning on the drug limiting its use for patients with liver disease [43]. Second, the lived experience of vaptans can be very difficult for patients. The most frequent side effect reported in studies evaluating the vaptans in patients with hyponatremia is thirst which can be profound [33–37]. Third, patients require close observation to avoid a rapid increase in serum sodium that could lead to neurological complications due to osmotic demyelination syndrome. In double-blind studies, an increase greater than 8 mEq/L per day within the first days of therapy has been reported with low and similar frequency in patients treated with vaptans compared to patients treated with placebo, ranging from 4 to 14 % in different studies [33–35]. More importantly, osmotic demyelination syndrome has not been reported. The only vaptan currently approved for clinical use in patients with cirrhosis is conivaptan. As conivaptan is both a V1 and V2 antagonist, it may reduce blood pressure and must be used with extreme caution. Candidate patients to treatment with vaptans are patients with severe hyponatremia (<125 mEq/L) awaiting transplantation. Use of vaptans in patients not candidates to transplantation should be individualized in each case.

Summary

Hyponatremia is a poor prognostic indicator in both the pre- and post-transplant patient population and has been shown to increase the risk of early mortality and complications including infection, renal failure, and encephalopathy. The

treatment options for hyponatremia are limited and are currently based on adequate free water restriction, diuretic cessation, and potentially the use of vaptans in the short term on a patient by patient basis. The vaptans may be of potential benefit in the peri-transplant period; however, the current drugs on the market should not be used for this indication in patients with cirrhosis. Liver transplantation remains the only definitive treatment for end-stage liver disease complicated by hyponatremia. A recommended algorithm for the management of hyponatremia in patients with cirrhosis is depicted in Fig. 14.4.

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Hepatorenal Syndrome

15

Elsa Solà and Pere Ginès

Hepatorenal syndrome (HRS) is a characteristic cause of kidney failure that occurs in patients with advanced cirrhosis. It is characterized by severe functional kidney failure that develops in the absence of significant histological kidney abnormalities and is due to an intense kidney vasoconstriction [1, 2]. The current definition of HRS proposed by the International Ascites Club indicates that: "Hepatorenal syndrome is a potentially reversible syndrome that occurs in patients with cirrhosis, ascites and liver failure that it is characterized by impaired renal function, marked alterations in cardiovascular function and overactivity of the sympathetic nervous system and renin–angiotensin systems. Severe renal vasoconstriction leads to a decrease of glomerular filtration rate. HRS may appear spontaneously, but can also follow a precipitating event." This definition was first proposed in 1999 and was later modified in 2007 [3, 4]. Although in the first definition the existence of an ongoing bacterial infection was an exclusion criterion of the diagnosis of HRS, with the current definition, HRS can be diagnosed in the presence of an infection except if there is septic shock. Diagnostic criteria of HRS are shown in Table 15.1.

Pathophysiology

There is large body of evidence indicating that HRS is of functional origin, such as the absence of significant histological kidney abnormalities, the reversibility of HRS after liver transplant, and the improvement or normalization of kidney function after pharmacological treatment with vasoconstrictors and albumin.

The main cause of functional kidney impairment in cirrhosis is impairment in circulatory function characterized by a reduction in systemic vascular resistance due to splanchnic arterial vasodilation related to portal hypertension [1, 2, 5] (Fig. 15.1). In early stages of the disease, when patients are still asymptomatic, portal hypertension is moderate and there is only slight decrease in systemic vascular resistance. In this stage of cirrhosis, effective arterial blood volume and arterial pressure are maintained within normal levels by an increase in cardiac output. However, in advanced stages of cirrhosis, there is a progressive splanchnic arterial vasodilation leading to a marked reduction in effective arterial blood volume that cannot be balanced by the increase in cardiac output. In this context, in order to maintain arterial pressure within normal levels there

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Table 15.1 Diagnostic criteria of hepatorenal syndrome [4]

Cirrhosis with ascites
Serum creatinine > 133 μmol/L (1.5 mg/dl)
No improvement of serum creatinine (decrease to a level of ≤133 μmol/L) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1g/Kg of body weight up to a maximum of 100 g/day.
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhematuria (> 50 red blood cells per high power field) and/or abnormal renal ultrasonography

is activation of systemic vasoconstrictor systems, including renin–angiotensin system, sympathetic nervous system, and in late stages, non-osmotic hypersecretion of vasopressin. The activation of vasoconstrictor systems have positive effects as they help maintain effective arterial blood volume but they have negative effects in the kidney, particularly sodium and solute-free water retention leading to the development of ascites and edema and hypervolemic hyponatremia. In advanced cirrhosis, the increased activity of vasoconstrictor systems induces an intense renal vasoconstriction leading to the reduction of glomerular filtration rate and the development of HRS. In these stages, there is also a decrease in cardiac output, probably related to cirrhotic cardiomyopathy, which also contributes to extreme arterial underfilling characteristic of HRS [1, 2, 5].

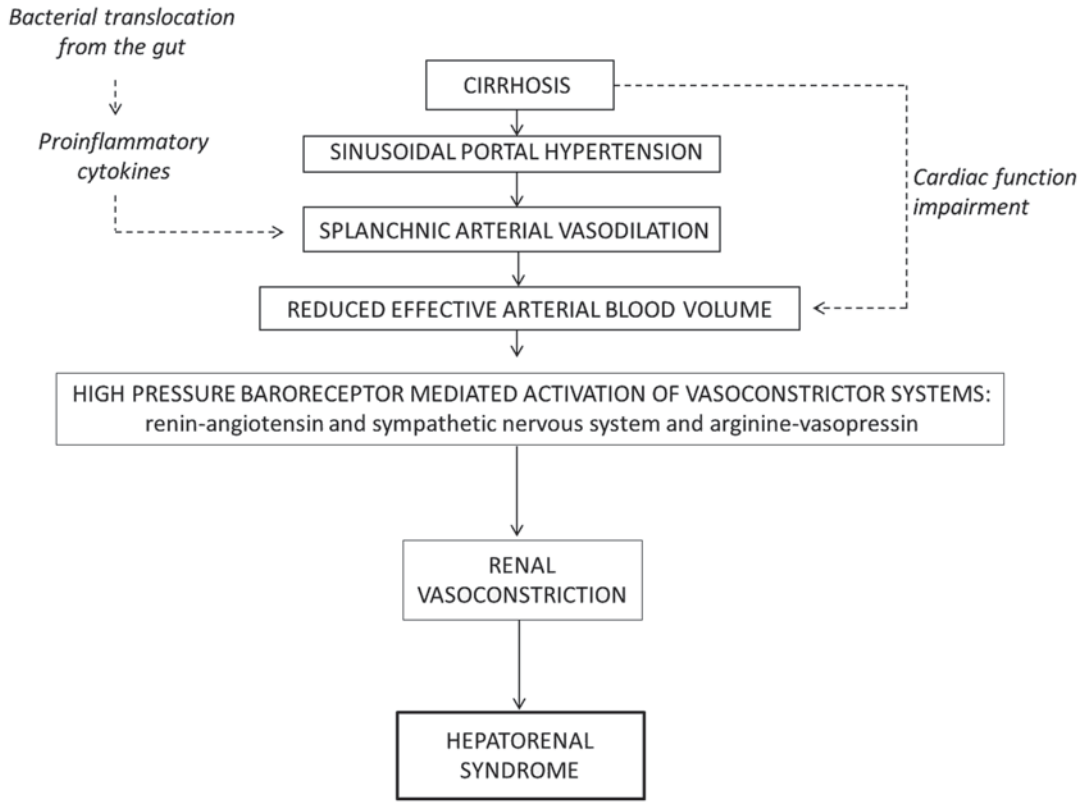

Fig. 15.1 Pathophysiology of circulatory dysfunction in patients with cirrhosis and hepatorenal syndrome

Finally, there is also evidence that inflammation may also play a role in the pathophysiology of HRS. Bacterial translocation (i.e., passage of bacteria from the intestinal lumen to the mesenteric lymph nodes) may play an important role in the impairment of circulatory function leading to the development of HRS. Bacterial translocation induces an inflammatory response, with an increased production of proinflammatory cytokines and vasoactive factors (i.e., nitric oxide) in the splanchnic area leading to a further vasodilation of the splanchnic circulation [6].

Differential Diagnosis of Acute Kidney Failure in Cirrhosis

Besides HRS, patients with cirrhosis may develop kidney failure due to different etiologies such as hypovolemia, bacterial infections, intrinsic acute kidney injury (iAKI), and administration of nephrotoxic agents such as nonsteroidal anti-inflammatory drugs or parenchymal kidney disease [7]. The differential diagnosis of the cause of kidney failure is highly important, as the management and prognosis are completely different. There is no objective variable for the diagnosis of HRS. As described above, the diagnosis of HRS is made after exclusion of other causes of kidney failure.

As described in Chap. 3, in recent years, neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a new biomarker potentially useful for the differential diagnosis of the cause of kidney failure in patients with cirrhosis. Two recent studies showed that urinary levels of NGAL (uNGAL) are significantly higher in patients with iAKI compared to patients with prerenal kidney failure or HRS. Interestingly, patients with HRS have uNGAL levels intermediate between prerenal kidney failure and iAKI [8, 9]. Therefore, if these results are validated in further studies, uNGAL could be incorporated in the daily clinical practice as an objective variable for the differential diagnosis of kidney failure in patients with cirrhosis.

Clinical Classification of HRS

According to the severity and progression of kidney failure, there are two types of HRS. Type 1 HRS is presented as an acute kidney failure with a rapid increase in serum creatinine with a final value above 2.5 mg/dL. It is associated with a dismal prognosis with a median survival of only 2 weeks without treatment. In contrast with type 1 HRS, patients with type 2 HRS develop a moderate kidney failure with serum creatinine levels ranging from 1.5 to 2.5 mg/dL. In patients with type 2 HRS, kidney failure is less progressive and remains stable for some period of time. Type 2 HRS is typically associated with refractory ascites. These patients have a slightly better prognosis with a median survival of 6 months (Fig. 15.2). Finally, during follow-up, patients with type 2 HRS may develop type 1 HRS either spontaneously or associated with a precipitating factor, particularly bacterial infections.

Precipitating Factors

HRS may develop spontaneously without an identifiable precipitating factor. However, in other patients, HRS occurs associated with conditions leading to a further impairment in the circulatory function. The most frequent precipitating events leading to HRS are bacterial infections and, particularly, spontaneous bacterial peritonitis (SBP). Up to one third of patients with SBP develop HRS during or after infection [10, 11]. In approximately one third of these patients, HRS is reversible with the control of infection; however, in the remaining patients, kidney failure is persistent or progressive. Bacterial infections other than SBP may also trigger HRS; however, its frequency and severity is usually low [12, 13].

Gastrointestinal bleeding is another complication of cirrhosis that may also act as a precipitating factor of kidney failure. Nevertheless, kidney failure in the setting of gastrointestinal bleeding is uncommon (approximately 10%) and usually related to hypovolemia and not HRS [14].

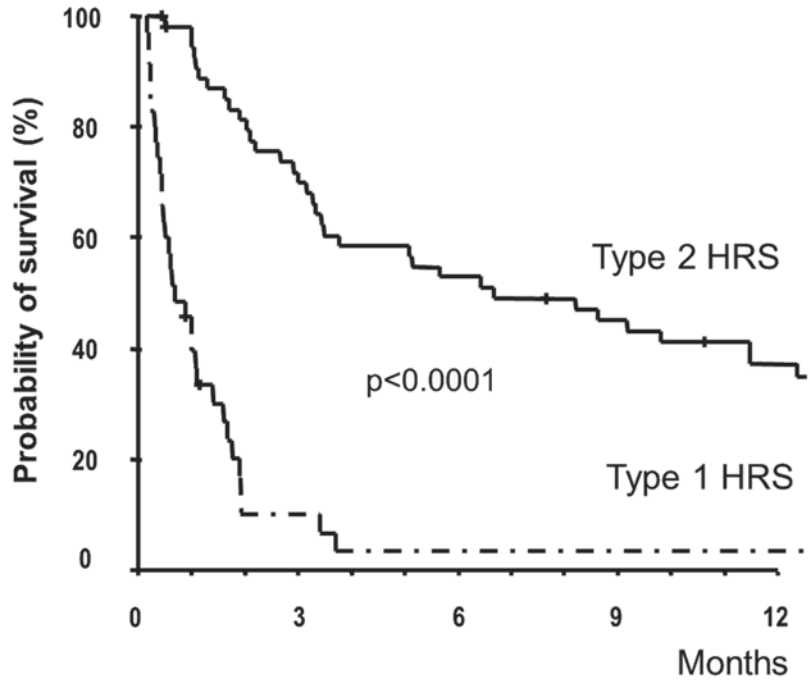

Fig. 15.2 Probability of survival of patients with type 1 and type 2 hepatorenal syndrome

Finally, another condition that may also act as a precipitating event is large-volume paracentesis without intravenous albumin administration. This situation may trigger the development of HRS in approximately 15% of patients and is associated with poor prognosis [15]. One of the main reasons for the administration of intravenous albumin after large-volume paracentesis is the prevention of development of HRS.

Management of HRS

General management of patients with HRS depends on the severity of kidney function. Patients with type 1 HRS on the waiting list for liver transplantation (LT) should be treated in an intensive care unit. Patients should be monitored closely in order to early diagnose associated complications of cirrhosis that may occur, particularly bacterial infections. In contrast with patients with type 1 HRS, patients with type 2 HRS without associated complications should be managed as outpatients. In this chapter, we will focus on the management of patients with type 1 HRS.

Vasoconstrictor Drugs

Treatment with vasoconstrictors associated with intravenous albumin (1 g/kg starting dose, than 20–40 g/day) is considered the first-line therapy for patients with type 1 HRS [16]. The available vasoconstrictor drugs used in HRS include vasopressin analogues, such as terlipressin, and alpha-adrenergic agonists, such as noradrenaline and midodrine. Most of the published data available are related to the treatment with terlipressin.

Randomized controlled trials and a systematic review showed that treatment with terlipressin and albumin was associated with a significant improvement in kidney function in approximately 40–50% of patients [17–19]. Moreover, a systematic review of randomized controlled trials demonstrated that treatment with vasoconstrictors and albumin is associated with improved survival [19]. Although

there are no dose-finding studies, treatment is usually started with 1 mg/4–6 h as i.v. bolus, and the dose is increased up to a maximum of 2 mg/4–6 h after 3 days if there is no response to therapy as defined by a reduction of serum creatinine of less than 25% of pretreatment values. Complete response to treatment is considered when there is a reduction in serum creatinine below 1.5 mg/dL. Recurrence after withdrawal of therapy may occur but is uncommon and re-treatment with terlipressin and albumin is usually effective. A baseline serum bilirubin <10 mg/dL and an increase in mean arterial pressure >5 mmHg at day 3 of therapy are considered predictive factors of response to treatment [20]. Patients should be monitored closely in order to avoid side effects. The most frequent side effects are ischemic or cardiovascular complications, which may occur in approximately 12% of treated patients [16]. Recent studies suggest that the administration of terlipressin as continuous intravenous infusion instead of i.v. bolus may improve its efficacy and decrease adverse events. However, data is still limited and more studies are needed to confirm these results [21].

As described above, the original definition of HRS excluded patients with ongoing sepsis; however, with the new revised definition in 2007, bacterial infections are not considered an exclusion criterion for the diagnosis of HRS except in the presence of septic shock. Therefore, studies assessing the efficacy and safety of terlipressin and albumin for type 1 HRS excluded patients with ongoing bacterial infections. In this context, data on the efficacy and safety of vasoconstrictors and albumin in patients with ongoing infections were not available. A recent prospective, proof-of-concept study, investigated the efficacy and safety of early treatment with terlipressin and albumin in patients with type 1 HRS and ongoing sepsis [22]. The results of this study show that early treatment of type 1 HRS associated with sepsis with terlipressin and albumin is effective and safe, and therefore suggest that this treatment may be recommended in this situation.

Other Vasoconstrictors

Vasoconstrictor drugs other than terlipressin that have been used in the management of type 1 HRS include noradrenaline and midodrine plus octreotide, both in combination with albumin. They represent an alternative therapy to terlipressin because of low cost and wider availability.

Noradrenaline administered as a continuous i.v. infusion with initial dose of 0.5 mg/h seems to be effective for improving kidney function in patients with type 1 HRS, although the number of studies is still limited. Three randomized studies and a recent meta-analysis have compared the efficacy and safety of noradrenaline versus terlipressin in patients with type 1 HRS [23–26]. The results of these studies showed that there were no significant differences regarding HRS reversal and recurrence in patients treated with noradrenaline compared to patients treated with terlipressin. Moreover, the adverse event profile was similar in both groups of patients.

The combination of oral midodrine (7.5 mg orally three times daily, increased to 12.5 mg three times daily if needed) and octreotide (100 μg subcutaneously three times daily, increased to 200 μg three times daily if needed) along with albumin has also been shown to improve kidney function in patients with type 1 HRS. A small study with 14 patients with type 1 HRS analyzed the efficacy of TIPS for patients with type 1 HRS following the improvement of systemic hemodynamics and kidney function with the combination of midodrine, octreotide, and albumin. The treatment improved kidney function in 10 out of the 14 patients, before TIPS [27]. Two studies analyzed the effects of treatment with octreotide plus midodrine on kidney function and 1-month survival in patients with type-1 HRS compared to a control group [28, 29]. Both studies showed that kidney function significantly improved in patients treated with octreotide plus albumin compared to controls. Moreover, 1-month survival was significantly higher in the treatment group compared to the control group. Although the studies described above suggest that treatment with oral midodrine plus octreotide in combination with albumin is effective for patients with HRS, the number of patients treated is still limited and large randomized comparative trials with other vasoconstrictors are lacking.

Transjugular Intrahepatic Portosystemic Shunt

The use of transjugular intrahepatic portosystemic shunt (TIPS) has been suggested as an alternative therapy to vasoconstrictors for HRS, but the applicability of TIPS in patients with type 1 HRS with such advanced liver disease is very limited as many patients have contraindications [16]. Two small studies indicate that TIPS improves kidney function and decreases the activity of endogenous vasoconstrictor systems in approximately 60 % of patients [30, 31]. However, these studies excluded patients with advanced liver disease including previous hepatic encephalopathy, Child-Pugh score ≥ 12, and serum bilirubin > 5 mg/dL. Therefore, the applicability of TIPS in patients with type 1 HRS is very low because TIPS is in most cases contraindicated in patients with severe liver failure, which is very common in the setting.

Renal Replacement Therapy

There are no studies specifically assessing the efficacy of renal replacement therapy (RRT) in patients with HRS. RRT may be used in patients with type 1 HRS who do not respond to treatment with vasoconstrictors and who develop criteria for immediate treatment with RRT (i.e., hypervolemia, hyperkalemia, metabolic acidosis). Although no studies are available, clinical experience indicates that the development of criteria leading to the indication of RRT is uncommon in patients with type 1 HRS.

Other methods such as the use of the molecular readsorbent recirculating system (MARS®), or fractionated plasma separation and adsorption (Prometheus®), are alternative dialysis methods that clear substances from the circulation, including endogenous vasodilators. They appear to be promising but data is still limited and further studies are needed to consider them useful therapeutic alternatives for HRS [32, 33].

Liver Transplantation

All patients with HRS should be considered for LT. LT is a definitive treatment and is the treatment of choice for both type 1 and type 2 HRS [16, 34]. HRS is reversible after LT; therefore, patients should be considered for LT alone. Combined liver–kidney transplantation should be only considered in patients who have been under RRT for 6–8 weeks, as in these patients the probability of reversibility of HRS is low [35].

Patients with type 1 HRS have a high mortality on the waiting list for LT; therefore, these patients should be given high priority while on the waiting list [1, 16, 36]. The use of model for end-stage liver disease (MELD) score for organ allocation, which includes serum creatinine, gives priority to these patients. Although there is no data from prospective studies, it seems that medical treatment before LT in order to improve kidney function may improve outcome after LT. [1, 16, 36].

Summary

HRS is characterized by functional renal failure secondary to renal vasoconstriction in the absence of underlying kidney pathology. The pathogenesis of HRS is complex and is mainly due to the result of an extreme underfilling of the arterial circulation caused by an arterial vasodilation of the splanchnic circulation and a low cardiac output that trigger a compensatory response with activation of vasoconstrictor systems leading to intense renal vasoconstriction. The prognosis of HRS is very poor mainly in those with type 1 HRS and therefore LT should always be considered first because it is the best option in suitable candidates. Pharmacological therapies aimed at improving renal function are based on the use of terlipressin and alpha-adrenergic agonists with plasma expansion with intravenous albumin. Other treatments such as alternative dialysis methods are promising but experience is still limited. A summary of the management of type 1 HRS is shown in Fig. 15.3.

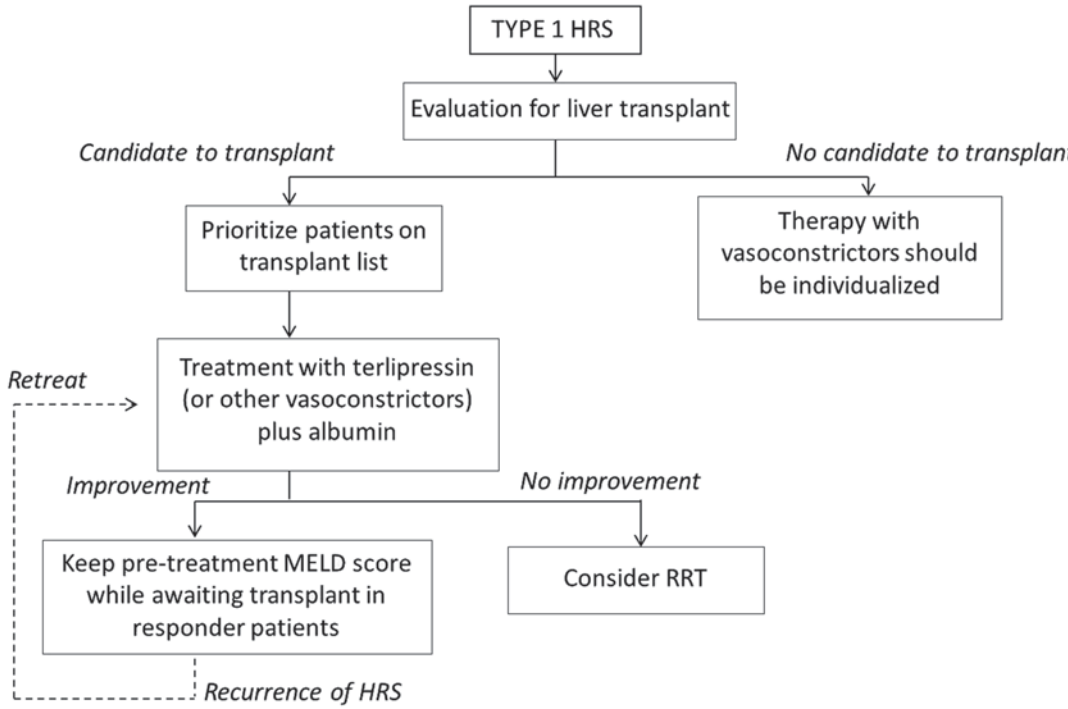

Fig. 15.3 Algorithm for the management of patients with type 1 hepatorenal syndrome. *RRT* renal replacement therapy, *MELD* model for end-stage liver disease. (Modified with permission from Ref. [1])

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Hepatic Encephalopathy

16

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Hepatic encephalopathy (HE) is a spectrum of neuropsychiatric abnormalities seen in patients with liver disease or portosystemic shunting [1]. Based on the 2014 American Associate for the Study of Liver Disease (AASLD)/European Association for the Study of Liver (EASL) clinical practice guidelines, HE is defined as brain dysfunction caused by liver insufficiency and/or portosystemic shunting; it manifests as a wide spectrum of neurological/psychiatric abnormalities ranging from subclinical alterations to coma [2].

HE is divided into two broad categories, covert HE (CHE), which consists of minimal HE (MHE) and grade 1 HE, and overt HE (OHE) [3]. For the purposes of this chapter, MHE and CHE are used synonymously. Diagnostically, HE can be subtle only identified by specialized testing or may represent a constellation of clinical symptoms, CHE being the former and OHE the latter. Cognitive dysfunction or MHE has been reported to occur in 60–80% of those with cirrhosis, whereas OHE has been estimated to be present in up to 45% of cirrhotics [4, 5]. Up to 50% of patients with CHE will develop OHE within 30 months [6]. HE places a significant burden not only on those diagnosed with this condition but also on their families or caretakers, involved physicians, and society as a whole [7]. Thus, it is important for a physician to recognize the signs and symptoms of CHE and OHE so the treatment can be initiated in hopes of preventing progression to an irreversible neuropsychiatric insult.

In 1998, the 11th World Congress of Gastroenterology in Vienna updated the classifications of HE taking into account the type of hepatic abnormality and clinical characteristics, which has been further revised with the AASLD/EASL 2014 guidelines (Table 16.1) [2]. This nomenclature has been broken down into four axes based on: (i) the type of underlying problem, (ii) disease severity, (iii) time course, and (iv) spontaneous onset or precipitating cause (for OHE only). Specifically for the time course, episodic HE is defined as one episode occurring within 6 months, while recurrent HE implies more than one episode in 6 months with normalization of mental status in the intervening time period. In contrast, patients with persistent HE always show signs and symptoms consistent with HE [8]. CHE is only recognized with specialized testing (Fig. 16.1).

The pathogenesis of HE has been studied for more than five decades and has yet to be fully elucidated. CHE and OHE share a common pathogenesis with multifactorial etiologies [9]. These include ammonia, cerebral edema, and inflammatory mediators.

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Table 16.1 Axes to describe hepatic encephalopathy. (AASLD/EASL 2014 Guidelines [2])

Type	Grade		Time course	Spontaneous/precipitated
A (acute liver failure)	MHE	Covert	Episodic (one episode in 6 months)	Spontaneous (no precipitating factor found)
	1			
B (portosystemic bypass)	2	Overt	Recurrent > 1 episodes in 6 months)	
C (cirrhosis)	3		Persistent (never returned to normal)	Precipitated
	4			

MHE minimal hepatic encephalopathy

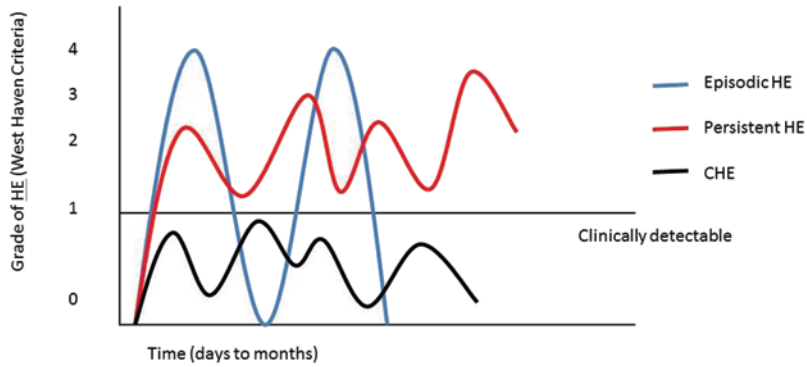

Fig. 16.1 Time course of various forms of hepatic encephalopathy (HE) depending on clinical detectability. Episodic *HE* in the *blue lines* is undetectable clinically between episodes while covert HE (*black lines*) is under the clinically detectable range. Persistent HE is manifest in patients with symptoms of HE (*red line*) that are always detectable clinically. (Adapted from Bajaj JS 2009)

Increased peripheral ammonia crosses the blood–brain barrier (BBB) and represents a key neurotoxin in the pathogenesis of HE. A major source of ammonia is the intestinal flora and urease-producing bacteria that convert glutamine into glutamate and ammonia. Via the splanchnic circulation, ammonia is metabolized by the liver and renally excreted. In a cirrhotic liver, hyperammonemia results from decreased functioning of hepatocytes and shunting of the blood into the systemic circulation [10]. During times of muscle wasting, release of glutamine from muscle cells into circulation leads to excessive ammonia production, worsening HE [11]. In the setting of systemic alkalosis, the kidneys increase ammonia reabsorption to serve as a buffer and this in turn leads to hyperammonemia.

Ammonia toxicity is thought to affect the brain via astrocytes, which are the unique neural cells that metabolize ammonia via glutamine synthetase and help regulate the BBB [12]. In astrocytes, overwhelming levels of ammonia lead to increased production of glutamine which changes the osmotic gradient and causes intracellular swelling and generalized cerebral edema. As astrocytes become impaired, so does the regulation of the BBB, allowing ammonia to accumulate within the brain, worsening cerebral edema [13, 14].

Proinflammatory cytokines work in conjunction with ammonia to worsen cerebral edema in HE. Inflammation may be secondary to infection, hemorrhage, or intestinal bacterial overgrowth, all common in cirrhotics [15]. High circulating levels of inflammatory markers, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF), are thought to play a role as well [16]. TNF has been shown to affect astrocyte function with increased BBB permeability [17]. Other factors implicated in the pathogenesis of HE include

Table 16.2 Clinical impact of hepatic encephalopathy

Covert hepatic encephalopathy	Overt hepatic encephalopathy
Increased risk of developing OHE	Increased hospitalizations
Impaired cognitive function	Predicts worse patient outcomes
Impaired driving skills; higher rate of motor vehicle crashes	Increased mortality
Decreased HRQOL	–
Burden on socioeconomic status of patient and caregivers	

OHE overt hepatic encephalopathy, *HRQOL* health-related quality of life

increased inhibitory gamma-aminobutyric acid (GABA) receptors, alterations of excitatory glutamate and catecholamine receptors [18–20].

The development of HE in cirrhotics portends a poor prognosis. Those with more advanced liver disease are at greater risk of developing HE [21]. Not only do CHE and OHE affect survival but they also impact a patient's health-related quality of life (HRQOL) and daily functioning as members of society [6, 7].

CHE increases the risk of progression to OHE and has significant impact on daily activities (Table 16.2) [22, 23]. Through self-assessed questionnaires such as the Sickness Impact Profile (SIP) and Short Form Healthy Survey (SF-36), studies have shown that CHE has a negative impact on emotional behaviors, social interactions, level of alertness, and recreational activities; the more severe the liver disease, the worse the HRQOL [23, 24]. CHE has a strong association with driving impairment and traffic violations [25–27]. Future studies should be directed at methods to evaluate driving function and identify those at higher risk of driving impairment. Previous studies by Bajaj et al. have shown that not only does HE place a burden on the patient but there are socioeconomic, financial, and personal burdens on caretakers. Specifically, deleterious effects on personal health and sense of entrapment were observed [28]. CHE also negatively impacts work performance, notably those involved in complex, occupational tasks [29]. OHE is associated with increased hospitalization, infection, and mortality rates compared to cirrhotics without OHE [6, 21].

CHE continues to remain a difficult diagnosis to make as it is not clinically evident. Establishing the diagnosis is focused on assessing deficits in attention and processing speed [30]. Testing strategies are divided into three areas: paper and pencil psychometric tests, computerized psychometric tests, and neurophysiological evaluation. In 1998, the hepatic encephalopathy group at the World Congress of Gastroenterology supported a paper–pencil test called the psychometric hepatic encephalopathy score (PHES) as the gold standard for diagnosing CHE. The PHES was specifically designed to detect impairments in attention, processing speed, response inhibition, and visuospatial awareness. The initial seven tests were revised to five tests with better sensitivity. The revised PHES consists of number connection test A (NCT-A) and B (NCT-B), line-tracing test, digit symbol test, and serial dotting test. Each of these five tests is scored from 1 to 3 and a total cutoff score of 4 or lower showed sensitivity and specificity of 96 and 100 %, respectively, for the diagnosis of CHE. The PHES is predominantly used outside of the USA, having been validated in Italy, Germany, and Spain [31, 32]. In the USA, there is no validated test due to copyright issues, and concerns over the cost and resources involved in such tests. Alternatively, the Working Group of Hepatic Encephalopathy has recommended the following four tests: NCT-A, NCT-B, the digits symbol test, or the block design test. Impairment in at least two of these tests, two or more standard deviations beyond matched controls, is indicative of HE [1].

The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) has recommended the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) as a tool to diagnose CHE [33]. The RBANS is an approximately 25-min paper–pencil test, which is less time consuming than PHES. It has been used to diagnose other cognitive disorders such as traumatic brain injury, multiple

sclerosis, and dementia. The test assesses cortical and subcortical domains. The modified RBANS focuses specifically on cognitive deficits associated with OHE and CHE. The modified RBANS is available for use in the USA, but like the PHES, it is not routinely performed because of copyright concerns and its cost, as a psychologist must interpret the results.

Paper–pencil testing requires adept motor function and multiple cognitive abilities to complete the test successfully. Computerized testing relies on reaction time as one only has to push buttons. The inhibitory control test (ICT) evaluates response inhibition and attention span [34]. The test takes place on a computer screen, and target letters, such as X and Y, are presented on the screen every 500 ms. The "lures" are the non-X and Y targets interspersed throughout target letters. For example, a screen will read one letter at a time and a patient should press the button only when the X and Y's are displayed. The percentage of times a patient responds to the targets and lures are recorded. Studies have shown good sensitivities for this test, comparable to the PHES [35]. The ICT test is easily administered, inexpensive, and reproducible, making it an attractive diagnostic tool for CHE. Another such test is the Cognitive Drug Research (CDR) battery that uses five psychometric tests to assess cognition and is presented as a set of yes/no responses [36]. The CDR shows comparable results to the PHES and is validated in populations such as dementia [37]. Although not validated in the USA, the CDR test has reproducible results, is easy to use, and only takes 30 min to complete, also making it a good diagnostic tool for CHE.

The third category for diagnosing CHE is neurophysiological evaluation. The critical flicker frequency (CFF) measures cortical function and correlates with psychometric abnormalities [38]. Patients are shown initial light pulses that gradually reduce in frequency, making it easier to detect when the light appears to flicker. A frequency of 39 Hz and below diagnoses CHE with sensitivity of 80 % and specificity of 65 %, results that correlate with paper and pencil testing [39]. CFF is convenient, has minimal costs, and does not require a psychologist to interpret, making it a potential future screening option.

The Stroop app test is a short, valid, and reliable tool used to screen for CHE. Originally studied by Bajaj et al. in 2013, the Stroop application is available on smartphones and iTunes and tests psychomotor speed and cognitive alertness, with focus on the attention system [40]. Though it needs to be further validated in multiple populations, the Stroop test is easy to use, inexpensive, and accessible which would make it a reasonable screening tool for CHE [41]. Other testing strategies include spectral electroencephalography (EEG), used to predict prognosis and mortality in cirrhotics with HE and evoked potentials, where visual, sensory, and auditory stimuli are applied to the brain and response times are evaluated [42, 43]. EEG's are limited by the large equipment needed, the amount of time it takes, cost, and the requirement of an expert neurologist to interpret the EEG [44].

The 2014 AASLD/EASL guidelines have streamlined the strategies used to diagnose CHE for single-center and multicenter studies. Investigators at single-center sites can employ one modality with which they are familiar that has established norms. Multicenter studies, however, would require at least two types of modalities (paper–pencil (PHES or equivalent), computerized (Scan, Stroop, ICT, CDR, etc.) or neurophysiological tests (CFF, EEG, etc.)) to be impaired in order to increase uniformity of diagnosis between different centers [2].

OHE is diagnosed clinically and there are several systems that have been used to risk-stratify severity of disease. The West Haven criteria (WHC) are one of the most widely used stratification systems that assist with the management of CHE and OHE (Table 16.3) [45]. Though subjective and not clinically obvious, CHE, consisting of stages 0 and 1, is diagnosed with a set of neuropsychological evaluations described above. OHE, consisting of stages 2 through 4, is diagnosed clinically. Other methods used to assess mental status include the Glasgow Coma Scale for those with moderate to severe HE and the HE scoring algorithm (HESA) which uses psychometric and clinical evaluations [46, 47]. In 2012, Salam et al. proposed a simple eight question modified-orientation log (MO-log) for inpatient cirrhotics that rapidly evaluates the depth

Table 16.3 West Haven criteria for hepatic encephalopathy

Stage	Level of consciousness	Symptoms	Examination findings
0	Normal	None	Normal; possible impaired psychomotor testing
1	Mild lack of awareness	Short attention span; abnormal sleep pattern; impaired addition or subtraction	Possible asterixis or tremor
2	Lethargy or apathy	Minimal disorientation to time or place; inappropriate behavior; subtle personality change	Obvious asterixis; slurred speech
3	Somnolent to stupor but arousable to verbal stimuli	Gross disorientation; bizarre behavior	Muscular rigidity; clonus; hyperreflexia
4	Coma (unarousable to noxious or verbal stimuli)	Coma	Decerebrate posturing

Table 16.4 Treatment goals for hepatic encephalopathy

Covert hepatic encephalopathy	Acute overt hepatic encephalopathy episodes	Long-term management of overt hepatic encephalopathy
Prevent progression to OHE	Treat inciting factors	Prevent future episodes of HE
Improve quality of life	Improve mental status	Improve quality of life
Improve cognition	–	–
–	Evaluate for liver transplantation	

OHE overt hepatic encephalopathy, *HE* hepatic encephalopathy

of disorientation in a more standardized manner and is able to predict inhospital mortality. Further studies are needed to validate the MO-log in larger populations [48].

OHE is a diagnosis of exclusion, meaning that other causes of altered mentation and motor dysfunction should first be ruled out, including cerebrovascular attacks (CVA), cerebral hematomas, infection, and other metabolic disorders. The diagnosis of OHE should focus on the neurological examination. Signs that favor HE tends to be more global than focal, such as those in CVA. In WHC stages 2 and 3, patients with OHE exhibit signs of hyperreflexia and asterixis. Asterixis is not pathognomonic for HE, as it is also seen in uremia and other disease processes. Other motor exam findings include bradykinesia, rigidity, and tremors. Slurred speech, fetor hepaticus, and ataxia may also be found.

Laboratory studies are generally not needed but may aid in ruling out other causes of encephalopathy including renal failure, sepsis, and electrolyte derangements. Ammonia levels are not needed to diagnose OHE and may not predict or correlate with actual outcomes [49]. The accuracy of ammonia levels are influenced by multiple factors, including the use of a tourniquet, fist clenching, and immediate placement of the sample on ice. Though not a validated diagnostic tool, brain imaging may help exclude other causes of altered mental status. Computed tomography (CT) and magnetic resonance imaging (MRI) may show cerebral edema in those with HE.

Treatment strategies for HE should be based on the severity and acuity of disease. While most patients with only CHE are managed and treated as outpatients, OHE is treated in both in-hospital and outpatient settings. Therapeutic goals vary based on CHE, acute OHE, or chronic OHE (Table 16.4).

Treatment of CHE improves quality of life and psychometric testing. The administration of lactulose and rifaximin has been shown to improve outcomes but there is no standard of care at this time [2]. A recent open-label study using

probiotics demonstrated a reduction in OHE episodes but this approach needs to be validated using a placebo-controlled trial [50]. Bajaj et al. conducted a randomized control trial using yogurt with probiotic compared to no treatment; none of the subjects in the yogurt group developed OHE [51]. Larger multicentered trials that target clinically relevant outcomes are needed to assess patient comfort and valid therapeutic outcomes in treating CHE.

Management of an acute episode of OHE consists of assessing severity, identifying precipitating factors, and empiric treatment for OHE. Patients with greater than stage 2 HE should be admitted to the hospital for further evaluation of life-threatening cases. In severe OHE, admission to an intensive care setting may be needed to protect the airway and reduce the risk of aspiration via endotracheal intubation [44]. After proper triaging of a patient with acute OHE, the clinician must assess for precipitating factors that affect ammonia levels, the inflammatory state, or mental status (Table 16.5). After inciting events are thoroughly investigated and treated, subsequent management should focus on OHE-specific therapy, directed mostly at the gut [49].

Table 16.5 Precipitating factors for hepatic encephalopathy

Gastrointestinal bleeding
Infection
Cellulitis
Pneumonia
Spontaneous bacterial peritonitis
Dehydration
Diarrhea
Vomiting
Inadequate intake
Constipation or ileus
Hypo/hypernatremia
Hypo/hyperkalemia
Alkalosis
Recent surgeries/interventions (e.g., transjugular intrahepatic portosystemic shunt placement)
Medical noncompliance
Uremia
Central nervous system altering drugs

Lactulose, a nonabsorbable disaccharide, is the mainstay of therapy. Another option is lactitol but this medication is not available in the USA. While its mechanism of action is not fully understood, lactulose is believed to work by decreasing colonic pH, evacuating bacteria through stool, and decreasing glutamine uptake, thereby decreasing the amount of ammonia absorbed. Lactulose is given via oral, nasogastric, or as an enema, which should be used in those with stage 3 or greater HE. The goal should be two to three soft bowel movements daily. Major side effects include bloating, diarrhea, hypernatremia, and severe dehydration [52].

Antibiotics play a role in OHE through alteration of the gut flora. Rifaximin is nonabsorbable and has been shown in European and US studies to produce favorable and quicker outcomes in patients with acute OHE [53, 54]. Generally well tolerated, it was approved by the US Food and Drug Administration in 2010 for use in the treatment of OHE at a dose of 550 mg twice a day orally. Prior to the introduction of rifaximin, neomycin and metronidazole were commonly administered in the acute setting. The use of neomycin was limited by serious side effects including nephrotoxicity and irreversible ototoxicity. Metronidazole fell out of favor due to nausea, vomiting, and a painful peripheral neuropathy associated with its long-term use. Other drugs such as L-ornithine-L-aspartate, which accelerates ammonia elimination, flumazenil, a GABA antagonist, and zinc, a mineral that is commonly deficient in cirrhotics, are under investigation as additional therapeutic options [55].

Appropriate nutritional management for hospitalized patients with OHE includes a diet with sufficient protein to maintain muscle mass and prevent increased ammonia levels [56]. In 2006, the European Society for Parenteral and Enteral Nutrition recommended the intake of 1.2 g/kg of protein daily. An increased intake of branched-chain amino acids (BCAA) has been shown to decrease length of hospital stay, admissions, and increase the chance of recovery from HE [57]. However, BCAAs are expensive and not widely available.

Once discharged from the hospital after an episode of OHE, the goal is to prevent recurrent episodes and maintain HRQOL through the administration of effective long-term medical therapy [44]. In a randomized control trial, lactulose showed a significant reduction in number of recurrent HE episodes after the initial one, compared to placebo [58]. The use of rifaximin plus lactulose was more effective in preventing HE episodes within 6 months after having two or more episodes, when compared to lactulose alone [59]. Another recent study showed that glyceryl phenylbutyrate also improved outcomes in, but only in OHE patients who were not already on rifaximin [60]. Adherence to lactulose remains difficult as compared with rifaximin, due to the former's requirement for daily self-titrating of the dose needed to achieve the goal number of bowel movements and lactulose's predictable gastrointestinal side effects.

In those patients whose mental status does not improve despite aggressive medical therapies, liver transplantation (LT) is the definitive treatment. In the era of the model for end-stage liver disease (MELD) score as the method to severity of complications of cirrhosis and allocate liver allografts, HE is underappreciated. Stewart et al. in 2007 showed that the prognosis of those receiving an LT based on OHE is worse than those receiving one indicated by their MELD score [21]. Once an acute episode of OHE is corrected, referral for LT evaluation is indicated.

Future areas of research in HE include developing easy-to-use, objective, and cost-conscious means to diagnose CHE, evaluate the severity of HE, and determine appropriate treatment strategies. Earlier identification of those with HE is important given its adverse impact on patients' HRQOL and the burden it places on caregivers and the broader community. The identification of individualized cost-effective therapies across the spectrum of HE which maximize adherence and reduce the morbidity of this complication is a priority in managing patients with cirrhosis.

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Cirrhotic Cardiomyopathy: Pathogenic Mechanisms and Management Strategies

17

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Patients with cirrhosis have a hyperdynamic circulation, which includes decreased vascular resistance and increased cardiac output (CO) at rest. The heart in cirrhosis keeps working at a high load and this in the long run impairs its contractile function. Other cardiac contractility inhibitors, such as tumor necrosis factor-alpha (TNF-α) [1], nitric oxide (NO) [2] and carbon monoxide [3], are increased in cirrhosis. Animal models have also shown that myocardial proapoptotic factors play an inhibitory role in cardiac contractility [4]. In patients with cirrhosis, CO does not increase sufficiently to meet the body's requirements when challenged; thus, the latent cardiac dysfunction manifests as overt heart failure.

It took a long time for clinicians to recognize the existence of cirrhotic cardiomyopathy. In 1953, Kowalski and Abelmann described the hyperdynamic circulation seen in patients with cirrhosis [5]. This was characterized by increased CO, decreased peripheral vascular resistance, and arterial hypotension. It was initially assumed that cardiac function must have been normal. However, studies from the late 1960s showed that ventricular contractile responsiveness to various stimuli such as drugs and exercise was blunted, providing the evidence for a latent cardiomyopathy [6–10]. For example, Gould et al. found that in cirrhotic patients, exercise doubled the left ventricular end-diastolic pressure but not the CO, indicating a markedly blunted cardiac response [11]. However, the early studies were performed in patients with alcoholic cirrhosis and the cardiac dysfunction was presumed to reflect latent alcoholic cardiomyopathy. A vast amount of accumulating evidence over the past three decades showed that humans and animal models with nonalcoholic cirrhosis also demonstrate a similar myocardial hyporesponsiveness to stimuli [6–10]. Indeed, both systolic and diastolic ventricular dysfunction are present in nonalcoholic cirrhosis in humans and animal cirrhotic models [6–10]. This chapter describes the pathophysiology, clinical features, diagnosis, and treatment of cirrhotic cardiomyopathy.

Pathophysiology

Cardiac contractility is regulated by several systems including the sympathetic nervous system (SNS). The β-adrenergic receptor (β-AR) is one of the major regulators. β1-AR dominates the adrenergic receptors in the heart and is linked to G_s protein (G-stimulatory). G_s activates adenylate cyclase, resulting in an increase of cyclic adenosine monophosphate (cAMP). One of the downstream effectors of cAMP is cAMP-dependent protein kinase (PKA) which catalyzes phosphorylation of sarcoplasmic reticulum (SR) proteins

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(calcium-releasing receptors, called ryanodine receptors, RyR) that ultimately result in calcium transients. Increased intracellular calcium induces actin–myosin cross-bridging and thus cell contraction [12–14].

In the heart of cirrhotic rats, we previously demonstrated several defects in βAR signaling pathways including decreased βAR density, reduced G_s and G_i protein levels, uncoupling of the βAR–ligand complex from G protein, and reduced generation of cAMP [14–16]. Another aspect affecting βAR function is the plasma membrane microenvironment. In biophysics, the ability of lipid moieties that comprise the membrane lipid bilayer to move freely is termed "fluidity", and unimpaired movement is essential for proper membrane function. Our rat study showed that altered membrane characteristics, including decreased fluidity, impaired cardiomyocyte function [17]. In the cirrhotic cardiomyocyte membrane, the cholesterol-to-phospholipid ratio is increased which decreases the fluidity, and the βAR-stimulated cAMP production is decreased by 37 %. When the membrane physical properties of the cirrhotic rats were restored to normal by an in vitro fluidizing agent, isoproterenol-stimulated cAMP production also increased to levels similar to control animals. Restoration of membrane physical properties had no effect on either beta-adrenoceptor density or binding affinity. These data suggested that the increased rigidity of cardiomyocyte plasma membranes is associated with decreased beta-adrenoceptor function [17]. Moreover, restoring normal physical properties may result in restoration of beta-adrenoceptor-mediated contractile function [17].

Nitric Oxide and Cardiac Contractility

Nitric oxide is important in cardiovascular regulation [18, 19]. There are three isoforms of NO synthases (NOS): neuronal (nNOS or NOS1), inducible (iNOS or NOS2), and endothelial constitutive (eNOS or NOS3) isoforms. NO stimulates soluble guanylate cyclase to produce cyclic guanosine monophosphate (cGMP) which stimulates the protein kinase G (PKG) enzymes to signal at several intracellular domains. NO and its metabolites, nitrite and nitrate, also exert effects by PKG-independent means, chiefly by protein nitration (discussed below). Normal heart tissue contains nNOS and eNOS, and it appears that NO generated by NOS exerts a mild tonic inhibition of βAR-induced stimulation [18, 19]. Significant iNOS expression has been documented in several diverse cardiac disease states, including dilated cardiomyopathy, transplant rejection, and ischemic heart disease [18, 19]. In many of these disease states, it appears that the dominant effect of the NO generated by iNOS is to antagonize the inotropic and chronotropic effects of the βAR. Specifically, NO-stimulated cGMP inhibits βAR-mediated slow inward calcium current and also decreases myofilament affinity for calcium[18]. It is also known that cGMP, the second messenger of NO, is involved in the cardiac muscarinic-mediated inhibition of βAR action, an effect that had previously been thought to be solely mediated by inhibition of adenylate cyclase by Gi protein [20].

We have demonstrated a role for NO in cirrhotic cardiomyopathy [2]. iNOS mRNA and protein content are increased in cirrhotic cardiomyocytes, and the end products of NO activation, nitrites and nitrates, are also increased in the cirrhotic heart and plasma. Moreover, incubation of isolated ventricular papillary muscles with the NOS inhibitor L-NG-nitroarginine methyl ester (L-NAME)-restored contractile responsiveness to the βAR agonist isoproterenol [2]. iNOS is likely stimulated by an inflammatory phenotype in the myocardium of cirrhosis, as we demonstrated increased levels of several pro-inflammatory cytokines such as TNF-α and interleukin (IL)-1β [2].

NO and Redox Disequilibrium

All tissues generate reactive oxygen (ROS) and nitrogen (RNS) species. The heart contains large amounts of oxidases and NOS, and in human and animal models of congestive heart failure, upregulation of ROS-generating enzymes such as nicotinamide adenine dinucleotide phosphate

(NADPH) oxidase and xanthine oxidoreductase (XOR) is well documented. In cirrhosis, footprints of ROS and RNS activation in many tissues such as the liver, kidney, and gut have been extensively documented. However, it remains unsettled whether the effects shown in vitro are actually causative mechanisms in vivo. In the heart, the demonstration of improved or restored contractility by acute antioxidant treatment is not compatible with irreversible oxidative damage. Thus, the concept that ROS/RNS cross talk is a critical regulator of function and dysfunction in the cardiovascular system is gaining wide acceptance. NO induces posttranslational modification of protein function by S-nitrosation of cysteine residues producing reactive S-nitrosothiols (SNO) and also by nitrating tyrosine residues to form nitrotyrosine. The NO/redox equilibrium status in the cirrhotic heart remains virtually unstudied to date. Mani et al. [21] found evidence of protein nitration (increased protein nitrotyrosine levels) in cirrhotic bile duct-ligated (BDL) rat hearts, and blunted isolated atrial chronotropic responses to isoproterenol. Both *N*-acetylcysteine (NAC) and L-NAME treatment given for 1 week restored the chronotropic responsiveness of cirrhotic atria and reduced nitrotyrosine levels, the latter presumably by decreasing NO and the former by unclear mechanisms [21]. In this study, F_2-isoprostane levels, an index of oxidative stress, were elevated in the cirrhotic heart but these were unaffected by NAC and L-NAME, suggesting that while ROS may be activated in the cirrhotic heart, they are not directly causing the blunted chronotropic response. Thus in cirrhosis, NO acting via cGMP-independent RNS mechanisms (formation of *S*-nitrosothiols and nitrotyrosines) on proteins may contribute to the observed cardiodepression. We found that oxidative stress was indeed increased in BDL rats. Erythropoietin treatment significantly decreased TNF-α and oxidative stress and reversed the impaired cardiac function [22].

Two studies suggested molecular mechanisms by which redox dysequilibrium may regulate cardiovascular function. Whelan et al. [23] showed that in murine hearts, the plasmalemmal membrane GRK2 (G-protein-coupled receptor kinase 2) that phosphorylates the βAR and leads to internalization and ultimate proteolysis of the receptor was inhibited by SNO which appears to act by nitrosylating Cys340 of the GRK2. At first glance, this would seem directly contrary to the notion that RNS contribute to cardiodepression. However, NO physiology is rarely a simple "all-or-none" mechanism, and this demonstration that SNO regulates βAR, even in the opposite direction (in this instance), at least provides evidence of the connection between RNS and βAR. Many other factors may influence the nature of the signaling connection; for example, NO may have contrary effects depending on concentration, and iNOS is known to produce much higher levels of NO and RNS products compared to the constitutive NOS isoforms. A second study reported that the PKGIα isoform of PKG in heart and aorta acts as a cysteine redox sensor and is directly activated by H_2O_2-induced oxidation [24]. Oxidation causes disulfide bond formation between two adjacent Cys42 residues in the PKGIα homodimer complex, making the enzyme catalytically active [24]. That study did not examine RNS effects, and in that respect, it is known that peroxynitrite exerts an even stronger effect than H_2O_2 on thiols.

TNF-α Signaling by NFκB

Circulating and local tissue levels of cytokines/chemokines are elevated in both humans and animal models of cirrhosis [25, 26]. This is mainly due to gut bacterial translocation, as shown in cirrhotic animal models [27]. In the cirrhotic rat heart and plasma, we demonstrated increased TNF-α and IL-1β levels [2]. Moreover, pretreatment of papillary muscles with L-NAME blocks the cardiodepressant effect of TNF-α [2], suggesting that the effects are mediated by the NOS—NO pathway. Evidence from a murine model of inflammatory cardiodepression indicates that the NO generated through the TNF-α—NOS pathway exerts its effects by inhibiting βAR signaling [28].

TNF-α effects are amplified by the IκB/nuclear factor-kappa B (NFκB) system. NFκB is

an inducible nuclear transcription factor composed of several subunits such as RelA (also called p65), cRel, RelB, p50, and p52 [29, 30]. The endogenous IκB system serves as its inhibitor; in the cytoplasm, it binds tightly to the p65 or other subunits of NFκB. The cytoplasmic NFκB–IκB complex is inactive and activation only occurs when factors such as TNF-α stimulate IκB kinases (IKK) that phosphorylate the IkB-α subunit. The phosphorylated IkB is then ubiquitinated and degraded in 26S proteosomes. The IKK complex has two catalytic subunits, IKKα and IKKβ, and a noncatalytic regulatory unit, IKKγ (also called NFκB essential modulator, NEMO). The NEMO-binding domain (NBD) links NEMO to the other two IKK subunits and is critical for NFκB activation [31]. Once IκB is cleaved off, free NFκB translocates to the nucleus where it stimulates the gene transcription of numerous regulatory molecules involved in inflammation such as TNF-α, iNOS, cycloxygenase (COX)-2, intercellular adhesion molecule (ICAM)-1, and several ILs. NFκB activation is found in the BDL cirrhotic rat heart and its pharmacological inhibition improves systolic and diastolic contractility [32].

Endocannabinoids

Endogenous cannabinoids such as anandamide are also involved. Batkai et al. [33] reported increased circulating anandamide and expression of CB1 receptors in vascular endothelial cells of cirrhotic rats and patients. We recently showed that blockade of endocannabinoid signaling improved cardiac contractility in cirrhotic rats both in vitro [34] and in vivo [35], through a CB1-mediated pathway dependent on Gi protein. The source of endocannabinoids appears to be local cardiac overproduction, stimulated by a stress such as tachycardia. Thus, cannabinoids may contribute to the blunted responsiveness to cardiovascular stimuli, but do not appear to affect baseline contractility.

Apoptosis

Apoptosis is an important factor in modulating heart function in variety of heart diseases. Low levels of myocyte apoptosis are sufficient to cause a lethal, dilated cardiomyopathy [36]. Inhibition of cardiac myocyte death largely prevents the development of cardiac dilation and contractile dysfunction [36–39]. Dysregulation of hepatocyte apoptosis is a principal contributor in the pathogenesis of various liver diseases [40–42]. Apoptosis is a tightly regulated program controlled by a complex set of factors. One of the pathways is the extrinsic pathway; another is the intrinsic pathway. Our study showed that a myocardial net proapoptotic imbalance induced via the extrinsic pathway plays a significant role in the pathogenesis of cirrhotic cardiomyopathy [4].

Clinical Relevance of Cirrhotic Cardiomyopathy

The cardiac dysfunction is latent at rest. With some type of cardiovascular challenge, the clinical significance of this syndrome manifests itself (Table 17.1). Wong et al. found that patients with cirrhosis had impaired exercise capacity such that, under peak exercise, the responses of heart rate, ejection fraction, and cardiac index were significantly compromised [43]. In clinical practice, cardiovascular challenges such as insertion of a transjugular intrahepatic portosystemic shunt (TIPS) and the widespread use of liver transplantation (LT) have highlighted the limitation of cardiac reserve. Up to 56% of patients, most with no previous history of cardiac disease, develop clinical or radiographic evidence of pulmonary edema in the first month after LT [44]. Patients with left ventricular hypertrophy have lower posttransplant survival compared with those without left ventricular hypertrophy [45]. Approximately 7–15% of all posttransplantation deaths are because of cardiac causes [10, 11].

Other surgical stresses including TIPS insertion and surgical portosystemic shunting procedures have also been reported to precipitate overt heart failure [7, 8, 10, 46]. In a large randomized

Table 17.1 Possible clinical syndromes associated with the heart in cirrhosis

Organ or tissue	Clinical syndrome or problem	Role of cardiac dysfunction or problem	Comments	Reference (first author, year)
Heart, endocardium	Infective endocarditis	Increased prevalence	0.34 vs. 0.1 % of noncirrhotics in large autopsy series	Snyder, 1977 [63]
Liver	TIPS insertion	Aggravate diastolic dysfunction; precipitate overt LVF	Usually transient; related to increased preload. LVF in 12 % post TIPS*	Huonker 1999 [64], Merli 2002 [46], Gines 2002 [47]
Liver	Mortality after TIPS	Aggravate diastolic dysfunction	Diastolic function 4 weeks after TIPS only predictor of 1-year mortality	Cazzaniga 2007 [48]
Liver	Transplantation	Precipitate overt LVF; worsen outcomes	Usually transient, but 12–56 % shows LVF in postoperative phase. 7–15 % deaths post transplantation due to cardiac causes	Sampathkumar 1998 [65], Nasraway 1995 [66], Rayes 1995 [67], Donovan 1996 [44]
Lung	HPS	CCM—involved in pathogenesis?	Inadequate right ventricular contractility may contribute to hypoxia or pulmonary vascular abnormalities	No clear studies to date
Kidney	HRS following SBP	Precipitate HRS	Patients with HRS after SBP have inadequate LV function, lower CO associated with developing HRS	Ruiz del Arbol 2003 [50], Ruiz del Arbol 2005 [51]
Kidney	Salt/water retention	CCM—involved in pathogenesis?	Inadequate pump function decreases effective circulating volume?	No clear studies to date
Whole body, brain	Reduced quality of life; fatigue	CCM—involved in pathogenesis?	Fatigue unrelated to CCM in one study to date	Girgrah, 2003 [68]

CCM cirrhotic cardiomyopathy, *CO* cardiac output, *TIPS* transjugular intrahepatic portosystemic shunt, *LVF* left ventricular failure, *HPS* hepatopulmonary syndrome, *HRS* hepatorenal syndrome, *SBP* spontaneous bacterial peritonitis

trial comparing TIPS to large volume paracentesis, 12 % of the TIPS group developed overt heart failure, whereas this was not observed in any patient undergoing paracentesis [47].

Cazzaniga et al. examined the predictive risk factors for death after TIPS insertion [48]. On multivariate analysis, only the degree of diastolic dysfunction (E/A ratio) at day 28 after the procedure (but not baseline E/A) was a significant predictor of 1-year mortality. Thus, the diastolic response to the increased preload caused by the TIPS is crucial [49]. In that study, it was noteworthy that none of the traditional prognostic markers of liver failure such as model for end-stage liver disease (MELD) score and Child–Pugh score, were able to predict mortality—only the diastolic response of the heart a month after the cardiovascular challenge of the TIPS insertion proved to be a useful predictor [48].

Moreover, another study suggested that an insufficient ventricular contractile reserve contributes to the pathogenesis of hepatorenal syndrome (HRS). Ruiz del Arbol et al. studied 23 cirrhotic patients who were admitted with spontaneous bacterial peritonitis (SBP) [50]. SBP is a known risk factor for the development of type 1 HRS. Despite antibiotic treatment and infection resolution, eight patients developed HRS, whereas 15 had unimpaired renal function. The major difference between these two groups was the cardiac response: The HRS group had a lower baseline CO than the other group. Moreover, CO actually declined after infection resolution in the HRS group, whereas it remained unchanged in

Table 17.2 Diagnostic criteria for cirrhotic cardiomyopathy

1. Abnormal systolic contractile responses to stress
2. Diastolic dysfunction at rest
3. Absence of clinically significant cardiopulmonary disease
Systolic dysfunction (at least one of the following):
1. Blunted increase in CO with exercise, volume challenge or pharmacological stimuli
2. Resting LVEF < 55 %
Diastolic dysfunction (at least one of the following):
1. E/A ratio (age corrected) < 1.0
2. Prolonged deceleration time (> 200 ms)
3. Prolonged isovolumic relaxation time (> 80 ms)
Supportive criteria:
1. Electrophysiological abnormalities including the following:
Abnormal chronotropic response to stress
Electromechanical uncoupling/dyssynchrony
Prolonged QTc interval
2. Heart chamber alterations: enlarged LA, increased LVWT
3. Increased pro-BNP and BNP
4. Increased troponin I

BNP brain natriuretic peptide, *CO* cardiac output, *LVEF* left ventricular ejection fraction, *LA* left atrium, *LVWT* left ventricular wall thickness, *BNP* brain natriuretic peptide

the other group. A separate longitudinal study by these authors found that among a cohort of 66 patients with severe cirrhosis, 27 who went on to develop HRS had lower CO and elevated serum markers of a hyperdynamic circulation [51].

Specific diagnostic criteria for CCM have recently been formulated by an international expert consensus committee.[1] The consensus definition of cirrhotic cardiomyopathy is: "Chronic cardiac dysfunction in patients with cirrhosis, characterized by blunted contractile responsiveness to stress, and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of known cardiac disease." While patients with cirrhosis have baseline increase in CO, when challenged, they demonstrate attenuated systolic and diastolic contractile responses to stress stimuli, electrophysiological repolarization changes, including prolonged QT interval, and enlargement or hypertrophy of cardiac chambers. The diagnostic criteria are listed in Table 17.2 [52].

[1] These are the preliminary Cirrhotic Cardiomyopathy Working Group criteria presented at the Montreal World Congress of Gastroenterology 2005 consensus meeting organized by SS Lee.

Treatment

Peripheral vasodilatation exists universally in patients with cirrhosis and therefore, unless the heart is stressed, overt ventricular failure is usually absent. In effect, the vasodilatation "autotreats" the latent heart failure and may mask its presence. Physicians need to be vigilant when patients with cirrhosis face challenges such as TIPS insertion, infection, or LT. If overt heart failure occurs, general supportive treatment should be applied which includes bed rest, administration of oxygen, salt and water restriction, diuretic therapy, and careful preload reduction by appropriate drugs.

One of the effective treatments for noncirrhotic heart failure is vasodilators. However, due to the peculiar hemodynamic disturbances of cirrhosis that includes marked vasodilatation, afterload reduction with vasodilators may not be useful in cirrhotic cardiomyopathy. Indeed, vasodilators may aggravate the arterial hypotension and further decrease the effective circulating volume. In terms of other, more specific treatments to improve heart failure in cirrhotic cardiomyopathy, there is a major paucity of clinical trials in an area of urgent need for such studies.

The scant evidence of various drug treatments can be summarized as follows.

β-Adrenergic Receptor Blockers (β-Blockers)

Sympathetic nervous activity is significantly increased in cirrhotic patients [53]; thus, β-blockers may protect the heart from damage resulting from the over-activated sympathetic system. It is well documented that β-blockers (propranolol/nadolol) and combined α- and β-blockers (carvedilol) are effective in decreasing portal venous hypertension and for prophylaxis of variceal bleeding in cirrhotic patients [54].

As mentioned previously, cardiovascular events occur in many patients after LT. Chopra et al. [55] demonstrated that during the perioperative period, a significant catecholamine surge occurs, producing elevations in heart rate and blood pressure. Safadi and colleagues tested the protective effects of β-blockers in the perioperative period of LT [56]. They found that these drugs attenuate both the sympathetic and neuroendocrine responses to stress; they balance myocardial oxygen supply/demand mismatch, and reduce inflammatory markers and free radicals. Therefore, β-blockers protected patients undergoing LT from adverse cardiac outcomes during the perioperative period. β-blockers significantly increased the probability of survival in the early postoperative period (30 days) in liver recipients [56].

Prolonged QT interval is associated with severe arrhythmias and sudden death in patients with noncirrhotic heart disease, but whether this applies to cirrhotic patients with prolonged QT interval remains unclear [53]. However, Zambruni and colleagues showed that in 30 patients with cirrhosis, chronic β-blocker dosing over 1–3 months significantly shortened the QTc interval, but only in the subgroup of those who had a baseline prolonged QTc interval [57]. Again, whether normalizing the prolonged QT interval exerts any long-term beneficial effect remains unknown, but most clinicians would agree that this certainly could not do any harm and may very well be beneficial.

There are some controversies over β-blocker usage in some specific subgroups of patients with cirrhosis. Krag and colleagues postulated that in HRS, treatment with β-blockers further decreases heart rate and CO and may therefore have deleterious effects on hemodynamics and renal function and thereby reduce survival [58].

Combination Vasoconstrictors and Albumin

For type 1 HRS, systemic vasoconstrictors combined with plasma expansion are currently the only available form of pharmacologic therapy. The combined administration of intravenous albumin and vasoconstrictors (e.g., terlipressin or alpha-1 agonists) normalizes circulatory function and serum creatinine in a significant number of patients with type 1 HRS. These effects, however, are rarely obtained when vasoconstrictors or intravenous albumin are given alone [51].

Splanchnic vasoconstrictors and albumin coadministration counteract the intense vasodilation in the splanchnic bed, thereby improving effective arterial blood volume. This improvement, in turn, suppresses the endogenous vasoconstrictors (e.g., renin-angiotensin-aldosterone system, RAAS;SNS) that are responsible for renal vasoconstriction. Albumin administration, by expanding the circulating blood volume, on one hand, increases cardiac preload and CO and on the other hand, improves glomerular filtration rate [59].

Aldosterone Antagonists

The RAAS is the most important system controlling blood pressure, cardiovascular, and renal function. Moreover, RAAS activation may be a prime regulator of fibrogenesis in several tissues including the heart. Several clinical trials suggest that RAAS blockade is the single most important cardioprotective strategy for cardiovascular diseases [60]. Since the RAAS is activated in cirrhotic patients [61], it is rational to speculate that RAAS blockade will exert cardioprotective effects on cirrhotic

cardiomyopathy. Ponzi et al. conducted the only RAAS-related study on cirrhotic cardiomyopathy [62]. They administrated the aldosterone antagonist potassium canrenoate to Child class A post-viral preascitic cirrhotic patients. After 6 months of treatment, the authors found some improvement in left ventricular hypertrophy and wall thickness, and a trend towards improved diastolic function indices that did not reach statistical significance; however, they suggested that 6 months was an insufficient duration to see significant normalization of diastolic dysfunction; a longer course of treatment was probably needed. These results suggest that aldosterone antagonists, probably through an anti-fibrogenic effect may improve the morphologic myocardial changes or at least retard or block the contractility deterioration in cirrhotic cardiomyopathy. These results also suggest that drugs blocking the fibrogenic effects of the aldosterone system are beneficial, and that cardiac remodeling might occur in cirrhosis. Much more research is necessary.

In summary, cirrhotic cardiomyopathy manifests as heart failure under challenges such as physical stress and surgery. The mechanisms are not clear—NO, carbon monoxide, endocanabinoinds, and apoptosis may all play a role. There is no specific treatment. β-adrenergic blocker may protect the heart from damage resulting from the over-activated sympathetic system, while long-term aldosterone antagonists administration may be helpful. Albumin may improve cardiac function. LT eventually normalizes heart function.

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Hepatopulmonary Syndrome

18

David S. Goldberg and Michael B. Fallon

Hepatopulmonary syndrome (HPS) is a pulmonary vascular disorder characterized by altered gas exchange due to intrapulmonary vascular dilatations occurring in the setting of hepatic dysfunction, usually with portal hypertension [1, 2]. It is a common complication found in up to 32% of patients [1–4] with portal hypertension and cirrhosis. The shunting of blood through the intrapulmonary vascular dilatations prevents gas exchange in the lungs, resulting in varying degrees of hypoxemia depending on the size and number of vascular dilatations. The hallmark of HPS is hypoxemia and intrapulmonary shunting of blood, with the diagnosis being made based on a constellation of clinical, laboratory, and imaging data [5, 6]. HPS is defined by: (1) the presence of liver disease, usually with cirrhosis and portal hypertension; (2) abnormal arterial oxygenation, with an alveolar–arterial (A–a) gradient ≥15 mmHg (or ≥20 mmHg in patients ≥65 years of age) or an arterial partial pressure of oxygen (PaO_2) less than 80 mmHg while breathing room air; (3) evidence of intrapulmonary shunting; and (4) the absence of cardiopulmonary disease that would otherwise cause hypoxemia (Table 18.1) [5, 6].

Epidemiology of Hepatopulmonary Syndrome

The true prevalence of HPS among all patients with cirrhosis is unknown. Published estimates from case series and multicenter studies are that anywhere from 8 to 35% of patients with cirrhosis have HPS. The upper bound of these estimates derives from a cohort of patients being evaluated for liver transplantation (LT) in the USA [1, 5, 7, 8]. However, an even greater proportion of patients with cirrhosis have evidence of intrapulmonary shunting without hypoxemia, underscoring the need to screen patients for HPS with pulse oximetry [9, 10]. Although HPS is classically described as occurring only among cirrhotics with portal hypertension, it has been described in the setting of acute or chronic hepatitis, or chronic liver disease with advanced fibrosis but not cirrhosis [11–13].

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Table 18.1 Diagnostic criteria for hepatopulmonary syndrome

Physiologic abnormality	Diagnostic criteria
Impaired gas exchange	Arterial blood gas sampling while breathing ambient air with:
	$PaO_2 < 80$ mm Hg or
	Alveolar–arterial oxygen gradient ≥ 15 mmHg if age <65 years, or ≥ 20 mmHg if age ≥ 65 years[a]
Intrapulmonary shunting	Transthoracic echocardiogram with agitated saline demonstrating "late passage" (after >3 cardiac cycles) of bubbles into left atrium
	Radiolabeled macroaggregated albumin scan with a brain shunt fraction of >6%
Liver disease	Cirrhosis and/or portal hypertension[b]
	No specific defined testing required, but other causes of hypoxemia must be ruled out[c]

[a] $AaPO_2 = (FiO_2[P_{atm} - PH_2O] - [PCO_2/0.8]) - PaO_2$, where PaO_2 represents partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen, P_{atm} atmospheric pressure, PH_2O partial pressure of water vapor at body temperature, and $PaCO_2$ partial pressure of arterial carbon dioxide (0.8 corresponds to the standard gas exchange respiratory ratio at rest)

[b] Patients may have acute and/or chronic hepatitis in the absence of cirrhosis and/or portal hypertension, although nearly all patients with HPS have cirrhosis

[c] Testing may include high-resolution pulmonary CT scanning to assess for parenchymal abnormalities, or pulmonary function testing to evaluate for obstructive or restrictive defects

Pathophysiology of Hepatopulmonary Syndrome

Our current understanding of the pathogenesis of HPS draws from experimental studies using animal models (Fig. 18.1). The presence of cirrhosis leads to increased mediators of endothelial injury within the lungs. Animal models of HPS demonstrate that these endothelial cells lead to the production of compounds which result in pre- and post-capillary dilatation of the pulmonary vasculature, and subsequent intrapulmonary shunting of blood that characterizes HPS [14, 15]. Compounding these vascular dilations is decreased capillary tone within the pulmonary vasculature due to mechanistic pathways involving angiogenesis, remodeling, and vasculogenesis [16, 17].

Clinical Manifestations of Hepatopulmonary Syndrome

A symptomatic patient with HPS may present with a constellation of complaints and physical exam findings described below; conversely, the disease can manifest only as asymptomatic hypoxemia. Nearly 50% of cirrhotic patients with HPS being evaluated for LT may complain of dyspnea [7]. However, several other potential etiologies for these symptoms commonly exist in this patient population and must be evaluated in order to diagnose HPS. Patients with large-volume ascites may complain of dyspnea due to decreased thoracic compression by abdominal contents. Other cardiopulmonary conditions, including obstructive sleep apnea, chronic obstructive pulmonary disease, and congestive heart failure are common in this population, and may lead to dyspnea [7].

Dyspnea due to HPS may occur with either exertion or at rest, but patients may also note exacerbation of dyspnea while upright. This symptom which can be seen in other disease states is platypnea. It is manifest as worsening dyspnea, while in the upright position compared with the supine position, as distinct from worsening of shortness of breath in the supine position (orthopnea) that is classically ascribed to congestive heart failure [7]. Platypnea is thought to be caused by preferential shunting of blood to the lower lung fields in the upright position, where there are a greater number of intrapulmonary vascular dilations that cause right-to-left shunting of blood within the pulmonary vasculature.

On physical exam, patients may have stigmata of chronic liver disease that include muscle wast-

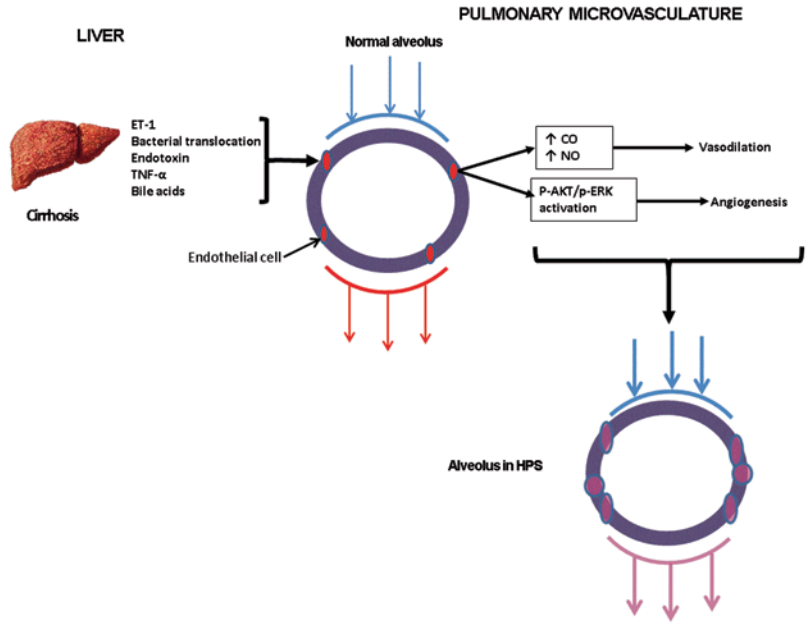

Fig. 18.1 Pathogenesis of hepatopulmonary syndrome. HPS hepatopulmonary syndrome, ET endothelin, TNF tumor necrosis factor, CO carbon monoxide, NO nitric oxide, Pakt phopsho-Akt, p-ERK phosphor-ERK

ing, jaundice, or abdominal distention due to ascites. Spider angiomata, which are dilated blood vessels on the surface of the skin found in a subset of patients with cirrhosis, are more commonly seen in patients with HPS [7]. Distal cyanosis or clubbing may be present; however, either of these findings may also be seen in patients with cirrhosis, irrespective of HPS, and/or in patients with chronic lung disease. The sensitivity of any of these clinical signs for characterizing HPS is low, as they are reported in a limited (10%) subset of HPS patients [7].

By definition, patients with HPS must have some degree of arterial hypoxemia, which will manifest clinically as hypoxia measured using standard pulse oximetry. Although an arterial blood gas is needed for diagnosing HPS, since pulse oximetry may overestimate arterial oxygenation in this patient population, pulse oximetry remains a key tool for identifying HPS in at-risk patients with chronic liver disease. An oxygen saturation on pulse oximetry (SpO_2) of ≤97% has a 96% sensitivity and positive likelihood ratio of 3.9 for detecting arterial hypoxemia, with a cutoff value ≤94% identifying all subjects with a PaO_2 <60 mmHg [9]. The degree of hypoxemia may be exaggerated when a patient with HPS moves from the supine to upright position—this decrease in oxygen saturation being called orthodeoxia, the laboratory correlate to platypnea. Due to preferential shunting of blood to other lung fields in the upright position, there is increased ventilation/perfusion (V/Q) mismatch that causes a decrease in patient's SpO_2 when moving from the supine to upright position [17].

Diagnosis of Hepatopulmonary Syndrome

Figure 18.2 highlights a proposed diagnostic algorithm to evaluate a patient with cirrhosis for HPS. The first step is the measurement of room air oxygen saturation in order to detect HPS at an early stage, or in an asymptomatic patient. A detailed description of the required diagnostic elements for HPS is described below.

a. *Hypoxemia:* The intrapulmonary shunting of blood through the pulmonary vasculature

without being exposed to the high oxygen environment leads to arterial hypoxemia. While pulse oximetry is an accurate screening test for HPS, arterial blood gas sampling is required for the diagnosis. Two definitions of hypoxemia are accepted for the diagnosis of HPS: (1) $PaO_2 < 80$ mmHg or (2) A–a gradient ≥ 15 mmHg in subjects < 65 years of age, or ≥ 20 mmHg in those ≥ 65 years of age [7, 18]. However, the A–a gradient is the optimal measurement and diagnostic test as using a PaO_2 cutoff may lead to the underdiagnosis of HPS. The A–a gradient is a more objective measure of gas exchange, and accounts for the respiratory abnormalities commonly encountered in patients with cirrhosis. Specifically, the calculation of the A–a gradient requires both the PaO_2 and the partial pressure of carbon dioxide ($PaCO_2$). The hyperventilation commonly seen in cirrhotics may result in exhalation of increased levels of CO_2, which leads to a corresponding increase in PaO_2. For example, a patient with a $PaCO_2$ of 25 mmHg (normal 35–45 mmHg) and a PaO_2 of 85 mmHg has significant gas-exchange abnormalities as indicated by an A–a gradient of 33 mmHg, yet would not be diagnosed as HPS based on a cutoff of < 80 mmHg. Accordingly, National Institutes of Health-sponsored clinical trials of treatments for HPS rely on the A–a gradient as the oxygenation level inclusion criterion [19].

b. *Intrapulmonary shunting:* The second diagnostic criterion for HPS requires demonstration of intrapulmonary shunting of blood (right-to-left shunting) via pulmonary vascular dilations. The most commonly used imaging technique for identifying the right-to-left shunting of blood is a transthoracic echocardiogram (TTE) with agitated saline (also known as a "bubble echo"). This modality requires that a patient undergo a standard TTE with an intravenous injection of agitated saline that contains bubbles, while the heart is visualized in a four-chamber view. These microscopic bubbles are trapped in the pulmonary capillaries of normal subjects after passing from the right atrium through the right ventricle into the pulmonary artery. Yet, they may be shunted directly to the left side in the presence of atrial (i.e., atrial septal defect, patent foramen ovale) or ventricular abnormalities (i.e., ventricular septal defect), or intrapulmonary shunts as seen in HPS [20].

In the four-chamber TTE view, bubbles seen in the left atrium may be due to intra-atrial or intrapulmonary shunts. Intra-atrial shunts cause "early" bubbles, visualized in the left atrium in the first three cardiac cycles. By contrast, "late" passage of bubbles is seen in HPS. These microbubbles are visualized in the left atrium after three cardiac cycles following injection of agitated saline as the bubbles bypass the lungs through intrapulmonary vascular dilations [20]. The presence of an intracardiac shunt, and/or patient body habitus precluding high-quality four-chamber views, may make it difficult to visualize intrapulmonary shunting; in such cases, a transesophageal echocardiography or a radiolabeled macroaggregated albumin (MAA) scan are alternative tests. The premise behind an MAA scan is similar to that of the "bubble echo," whereby radiolabeled albumin is injected intravenously, with subsequent imaging quantifying the uptake of radiolabeled albumin in the patient's brain. In the absence of right-to-left shunting, the shunt fraction, or value of albumin in the brain relative to the lung should be $< 6\%$ [21].

c. *Exclusion of other cardiopulmonary conditions:* Although there are no formalized guidelines for testing to exclude other cardiopulmonary conditions, patients may have hypoxemia and intrapulmonary shunting, yet not have HPS. Other causes of hypoxemia, including intrinsic lung disease (i.e., chronic obstructive pulmonary disease) or other pulmonary complications of liver disease (i.e., hepatic hydrothorax), should be excluded. Performance of pulmonary function tests is strongly advised, especially in those with risk factors for intrinsic lung disease (i.e., history of cigarette smoking), as nearly 20% of LT candidates evaluated for HPS may have obstructive or restrictive ventilatory defects precluding the diagnosis of HPS [7].

Clinical Implications of Hepatopulmonary Syndrome

Hepatopulmonary syndrome has important clinical implications in regard to patients' quality of life (QOL), as well as survival. Among patients with end-stage liver disease evaluated for LT, those with HPS have significantly lower functional capacity as measured by the New York Heart Association (NYHA) functional class [7]. Additionally, HPS patients reported significantly worse QOL in several domains of the Short Form-36 (SF-36) questionnaire; specifically the general health, mental component score, role emotional, and mental health scales [7].

Beyond impairments in QOL measures, HPS is associated with significantly increased mortality. This was examined in a prospective cohort study among patients evaluated for LT in seven US transplant centers [7]. Patients with HPS had a 2–2.4 times increased risk of mortality compared to all other patients being evaluated for transplantation. This increased risk persisted even after accounting for several patient factors associated with mortality. In a separate cohort of cirrhotic patients evaluated for LT in Austria over a 2-year period, HPS patients had a significantly increased risk of mortality from the time of evaluation, with a median survival of 10.6 months, compared with 40.6 months in those without HPS [8].

Treatment of Hepatopulmonary Syndrome

There are currently no treatments approved by the Federal Drug Administration for the treatment of HPS. Several medications have been studied, including pentoxifylline [22, 23] and garlic [24, 25]. While promising in animal studies and case series, no durable improvement in pulmonary function was demonstrated with either drug. Thus, the management of HPS is centered on symptom management, including supplemental oxygen as needed, and the prevention of pulmonary infections through vaccination for pneumococcus and influenza [20].

The only widely accepted curative option for HPS remains LT. Resolution of hypoxemia and normalization of pulmonary function has been well documented after transplantation in patients with HPS [2, 7, 10, 26, 27]. In fact, long-term posttransplant patient survival in transplant recipients with HPS is similar to that of recipients with other indications for LT [2, 7, 10, 26–28]. Due to the increased risk of increased wait-list mortality, combined with the risk of posttransplant mortality associated with HPS, current Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) policy allows for increased wait-list prioritization for patients with HPS. Since 2005, wait-listed patients with HPS have been eligible to receive standardized upgrades, entitled model for end-stage liver disease exception points, to increase their wait-list priority.

A long-standing concern has been the potential for inferior posttransplant outcomes in transplant recipients with HPS who have severe gas-exchange abnormalities. Based on data from the early 2000s, the cut point defining higher risk was a PaO_2 <50 mmHg [10]. Subsequent publications challenged this notion, demonstrating similar posttransplant mortality in all transplant recipients with HPS, regardless of the degree of hypoxemia [26, 27]. However, these studies were based on small case series, and a recent analysis of all national transplant data from 2002 to 2012 reported that although post-LT outcomes in transplant recipients with HPS are very good, those with the most severe hypoxemia, specifically a PaO_2 ≤44.0 mmHg, had the lowest posttransplant survival rates, with 3-year posttransplant survival of 68%, compared with 3-year survival rates of 84 and 86% in transplant recipients with PaO_2 levels of 44.1–54.0, and 54.1–61.0 mmHg, respectively (Fig. 18.2).

Given the invasive nature of LT to cure HPS, especially among patients for whom HPS is the only clinical manifestation of their liver disease, several alternative procedures have been tested and reported as case reports or case series. There have been several reports of placement of a transjugular intrahepatic portosystemic shunt (TIPS) for HPS, given its ability to ameliorate portal

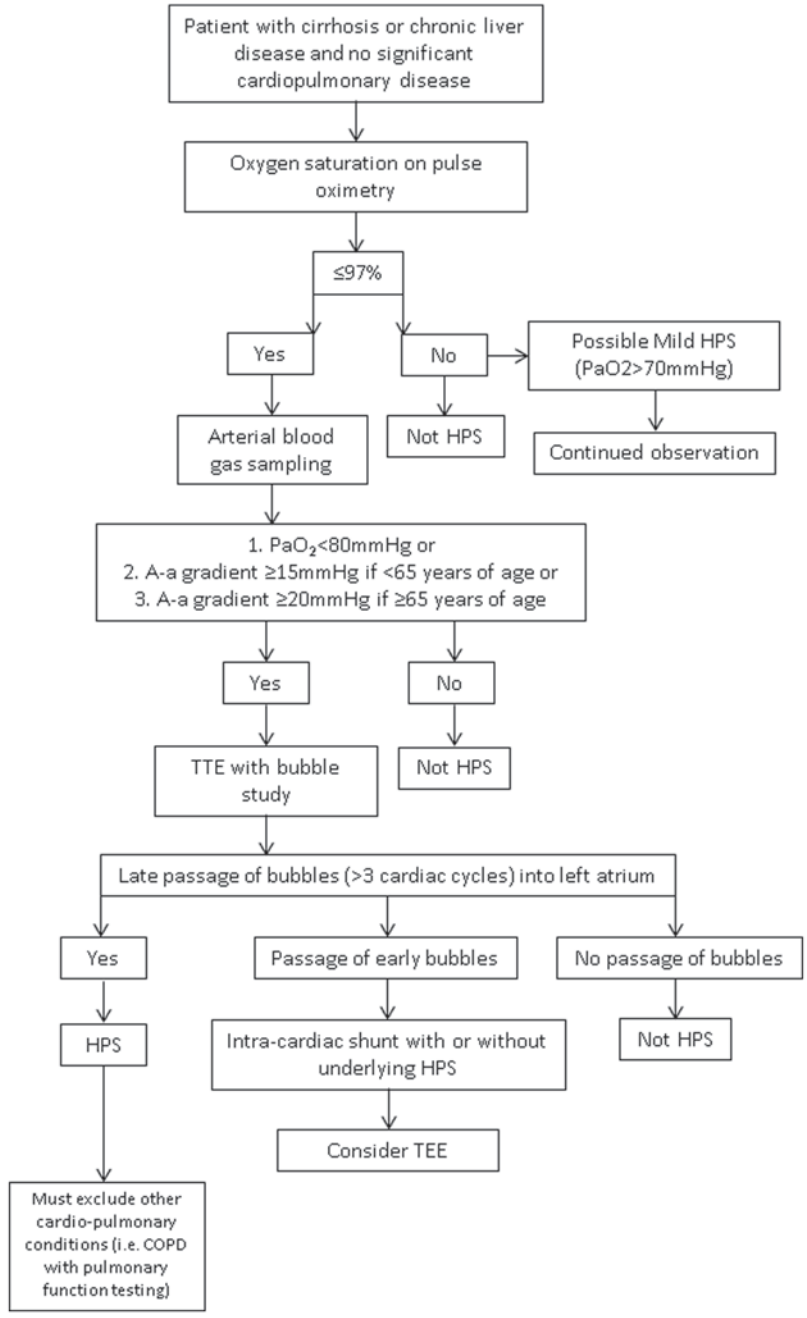

Fig. 18.2 Diagnostic algorithm for hepatopulmonary syndrome. *HPS* hepatopulmonary syndrome, PaO_2 partial pressure of arterial oxygen, *A–a gradient* alveolar–arterial gradient, *TTE* transthoracic echocardiogram, *TEE* transesophageal echocardiogram, *COPD* chronic obstructive pulmonary disease

hypertension, and thus potentially HPS. While improvement in HPS has been described with placement of a TIPS shunt, there are limited data supporting its efficacy [29–31].

Conclusion

In summary, HPS is a common, yet underrecognized disorder in patients with cirrhosis. Key to diagnosing HPS is screening patients at risk with pulse oximetry. The diagnosis is based on the combination of hypoxemia and right-to-left intrapulmonary shunting. While the only current treatment is LT, ongoing clinical trials are testing novel compounds as potential agents to stabilize, or even reverse HPS.

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Portopulmonary Hypertension

19

Rodrigo Cartin-Ceba and Michael J. Krowka

Definition and Epidemiology

Portopulmonary hypertension (POPH) refers to the development of pulmonary arterial hypertension (PAH) as a consequence of portal hypertension [1]. Classified within group I of the 5th World Symposium on Pulmonary Hypertension, it is similar (pathologically and hemodynamically) to other causes of precapillary pulmonary hypertension [1]. In the presence of documented portal hypertension, POPH is defined according to the following hemodynamic data obtained during a right heart catheterization (RHC):

a. Mean pulmonary artery pressure (MPAP) ≥25 mmHg
b. Pulmonary vascular resistance (PVR) ≥240 dynes/s/cm^{-5}
c. Pulmonary artery wedge pressure (PAWP) ≤15 mmHg

Importantly, different pulmonary hemodynamic patterns complicate advanced liver disease [2, 3] as documented by RHC (Table 19.1). Distinguishing these patterns is important to provide correct management [4]. Excess volume due to fluid retention may occur and be reflected by increased PAWP. An increase in *both* PVR and PAWP can confuse the interpretation of pulmonary hemodynamics [3]. In that scenario, which may occur in up to 25% patients with POPH [5], obstruction to pulmonary arterial flow is manifest by an increased transpulmonary gradient (MPAP–PAWP >12 mmHg). These patients should not be excluded from the diagnosis of POPH due to high PAWP alone.

POPH should be distinguished from hepatopulmonary syndrome (HPS) [2, 6]. In HPS, arterial hypoxemia (which may be severe) is caused by intrapulmonary vascular dilatations, as opposed to vascular obstructions of POPH. HPS presents with normal PVR and a high flow state characterized by increased cardiac output (CO). This distinction is important if liver transplant (LT) is being considered due to differences in risk, treatment options, and outcomes [6].

POPH affects predominantly adults and is notably rare in the pediatric age group [5]. Female gender and autoimmune liver disorders are more frequently associated with POPH [7]. No correlation exists between the severity of POPH and the degree of liver dysfunction as characterized by the Child–Turcotte–Pugh (CTP) or model for end-stage liver disease (MELD) scores [5, 8]. Compared to idiopathic PAH (IPAH), POPH is characterized by higher CO and less severity as measured by MPAP and PVR [9, 10].

The term POPH was apparently coined by Yoshida et al. in 1993, as they described the first case of POPH to undergo successful LT [11]. Subsequently, several small series and case re-

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Table 19.1 Pulmonary hemodynamic patterns documented by right heart catheterization in advanced liver disease

	Mean pulmonary artery pressure (normal 9–18 mmHg)	Pulmonary vascular resistance (normal <2 Wood units)	Cardiac output (normal 4.0–8.0 L/min)	Pulmonary artery wedge pressure (normal 6–12 mmHg)
Vasoconstriction with vasoproliferation (POPH)	Elevated	Elevated	Low or normal	Normal
Fluid overload (excess volume)	Elevated	Normal or elevated	Elevated[a]	Elevated
Hyperdynamic circulatory state (high flow)	Elevated	Normal	Elevated	Normal

POPH portopulmonary hypertension
[a] In the absence of underlying heart disease

ports with autopsy results described pulmonary arterial obstruction and pulmonary plexogenic arteriopathy [12–16]. An unselected series of 17,901 autopsies revealed that PAH was five times more likely in cirrhotic patients than those without liver disease [17]. Within the 1981–1987 National Institutes of Health national registry of "primary" pulmonary hypertension from 32 centers reported by Rich [18], additional analyses by Groves concluded that 8.3% likely had POPH (17/204; 187 had primary pulmonary hypertension) [19]. Hadengue reported the largest prospective study of patients with portal hypertension ($n=507$) in which portopulmonary hemodynamic measurements concluded that 2% had POPH [8].

Prospective studies have focused on the frequency of POPH in clinic settings, including national registries and individual transplant center experiences. In the French pulmonary hypertension registry experience over a 12-month period (2002–2003), Humbert reported a 10.4% frequency of POPH (70/674) from 17 university hospitals [20]. In the USA, the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) documented a 5.3% POPH frequency (174/3525), in which there were 68% prevalent and 32% incident cases satisfying the criteria of a MPAP ≥25 mmHg, PVR ≥240 dynes/s/cm−5, and a PAWP ≤15 mmHg [9]. Following slightly different PVR diagnostic criteria as part of outpatient RHC diagnostic assessments, the largest POPH-LT center experiences reported to date are as follows: 8.5% (Baylor Dallas, 102/1205; PVR >120 dynes/s/cm^{-5}), 6.1% (Clichy, France 10/165; PVR >120 dynes/s/cm−5), and 5.3% (Mayo Clinic 66/1235; PVR >240 dynes/s/cm−5) [3, 21, 22].

Pathophysiology

The pulmonary histopathology of POPH individuals is indistinguishable from other PAH phenotypes [4, 12]. Based upon autopsy and lung explant studies, POPH is characterized by a spectrum of obstructive and remodeling changes in the pulmonary arterial bed. Initially, medial hypertrophy with smooth muscle proliferation and a transition to myofibroblasts has been documented. As this proliferative pathologic process advances, plexogenic arteriopathy eventually develops [4, 12].

The pulmonary vascular pathology occurs within the context of a hyperdynamic state caused by extrahepatic (splanchnic) vasodilation [5]. It is unknown if this persistent high flow state initiates (by shear stress) or exacerbates (in combination with circulating mediators) the pulmonary vascular proliferative process. In addition, it is possible that a genetic predisposition may also play a role, since not all patients with portal hypertension due to cirrhosis develop POPH [23]. Pulmonary endothelial cells lack prostacyclin

synthase in patients with POPH (hence a lack of prostacyclin vasodilation) [24]. The pulmonary vascular bed is exposed to increased levels of circulating endothelin 1 in the setting of cirrhosis (a potent vasoconstrictor and facilitator of smooth muscle proliferation) [25, 26] and may be deficient in local nitric oxide effect (for vasodilation) [27]. The role of other circulating and receptor factors that may affect the pulmonary endothelium due to the existence of portal hypertension is speculative. These factors include vasoconstrictive/proliferative mediators such as serotonin, thromboxane, vasoactive intestinal peptide, and vascular endothelial growth factor, as well as the possible imbalance of endothelin receptors (ET_A—mediating vasoconstriction; ET_B—mediating vasodilation) in the pulmonary arterial bed [27]. The mechanistic link between estrogen signaling, serum estradiol levels, circulating endothelial progenitor cells, and the development of POPH is a current research hypothesis of interest [28, 29].

As the pulmonary vasoproliferative process progresses, the increasing resistance to flow restricts the degree of CO flowing through the pulmonary vascular bed. Strain on the right ventricle will be seen with dilation of the right ventricle and reduction in systolic function. Progressive reduction in CO will evolve with right heart failure leading to hepatic venous engorgement and worsening portal hypertension. Death from either right heart failure or portal hypertension complications will inevitably occur without therapeutic intervention [5].

Clinical Manifestations and Screening

The most common and predominant symptom of POPH is dyspnea on exertion. POPH may be unnoticed as patients with advanced liver disease have multiple reasons for dyspnea including ascites, anemia, fluid retention, and muscle wasting. Chest pain and syncope are symptoms suggestive of severe POPH [5]. Physical findings in POPH may be absent or subtle and nonspecific; however, the presence of a hyperdynamic precordium, an accentuated second heart sound (best heard at the apex), and a systolic murmur due to tricuspid valve regurgitation may be noted. With severe POPH, there may be marked distension of the jugular veins, peripheral edema, ascites, and a right ventricular third heart sound (S3). The lung examination is usually normal and it is uncommon to have clubbing or cyanosis (as seen in HPS). Mild hypoxemia is common and often associated with abnormal overnight pulse oximetry. The chest radiograph usually demonstrates cardiomegaly and enlargement of the central pulmonary arteries as the duration and severity of POPH progresses [5]. The electrocardiogram may show rightward electrical axis, right bundle branch block pattern and when POPH is severe, the presence of inverted T-waves in the precordial V1–V4 leads can be seen, which suggests a severe effect on the right ventricle. Although rare, it is important to rule out chronic pulmonary emboli as a cause of PAH even in the context of liver disease, especially in the setting of portal vein and hepatic vein thromboses. Pulmonary function tests are usually not helpful in the diagnosis or management of POPH because reduced single breath diffusing capacity (a common abnormality seen in PAH) is frequently seen in most patients with advanced liver disease.

Screening for POPH via transthoracic echocardiography (TTE) has been the most practical method to detect POPH [30–32]. By assessing the tricuspid regurgitant peak velocity (TR), estimating the right atrial pressure by inferior vena cava changes with inspiration and using the modified Bernoulli equation, an estimate of right ventricle systolic pressure (RVSP) can be determined in approximately 80% of patients with portal hypertension [30]. This quantitative approach allows one to decide which patients should precede to RHC for the definitive characterization of pulmonary hemodynamics. RVSP > 50 mmHg has been the cutoff criteria used in the current Mayo Clinic algorithm to perform RHC [3]; rarely, immeasurable TR with abnormal qualitative right ventricular size or function results in RHC. TTE was noted to have a 97% sensitivity and 77% specificity to detect moderate-to-severe PAH prior to LT [30].

Management and Treatment

Deciding who needs pulmonary artery PAH-specific therapy and determining the risks for potential LT are critical in the management of patients with POPH (Fig. 19.1). POPH patients with MPAP > 35 mmHg are particularly vulnerable to poor outcomes with attempted LT, especially if there is no attempt to treat the POPH with current PAH-specific medications. The immediate goal in the treatment of POPH is to improve pulmonary hemodynamics by reducing the obstruction to pulmonary arterial flow (↓MPAP, ↓PVR, and ↑CO), ultimately improving and/or normalizing RV function. This can be accomplished by medications that result in vasodilation, antiplatelet aggregation and have antiproliferative effects[5]. Drug therapy may augment the lack of pulmonary endothelial prostacyclin synthase deficiency (prostacyclin infusion), block circulating endothelin-1 effects (endothelin receptor antagonists), and enhance local nitric oxide vasodilatation effects (phosphodiesterase inhibitors and soluble guanylate cyclase stimulator) [5, 33].

Aside from one study evaluating the effect of riociguat (a soluble guanylate cyclase stimulator) in PAH [33], controlled randomized studies evaluating PAH-specific therapies have excluded POPH patients. Evidence regarding therapy in POPH has originated from uncontrolled studies, where PAH-specific therapies used for other types of PAH proved to be beneficial for patients with POPH [34–51] (Table 19.2). Improvements in both MPAP and PVR are the ideal goals in treating POPH. However, MPAP may not decrease as much as desired, as increases in CO associated with reduced obstruction to flow (measured by decreased PVR) will result in higher flow (and increased pressure).

Prostanoids: In a summary of 48 patients treated with intravenous epoprostenol from five studies, MPAP decreased by 25% (48–36 mmHg), PVR decreased by 52% (550–262 dynes/s/cm^{-5}), and CO increased by 38% (6.3–8.7 L/min, all $p < 0.01$) [14, 36–39]. Other prostanoids (intravenous treprostinil and inhaled iloprost) have resulted in significant pulmonary hemodynamic improvement in POPH [43, 47, 49].

Endothelin receptor antagonists: Hoeper et al. documented 1- and 3-year survival of 94 and 89%, respectively, in 18 patients with POPH and Child class A severity liver disease using the nonselective endothelin antagonist bosentan [42]. No liver toxicity was noted. Cartin-Ceba et al. re-

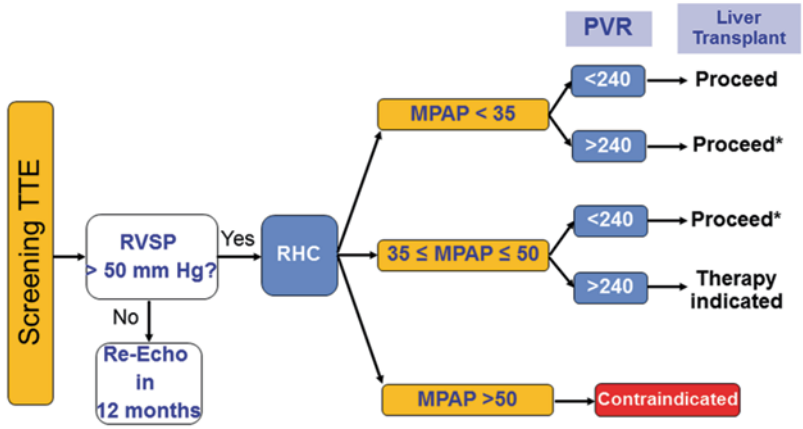

Fig. 19.1 Current portopulmonary hypertension screening evaluation and treatment algorithm used at the Mayo Clinic. TTE transthoracic echocardiography, RVSP right ventricular systolic pressure estimated by transthoracic echocardiography, RHC right heart catheterization, MPAP mean pulmonary artery pressure (normal <25 mmHg), PVR pulmonary vascular resistance (normal <240 dyne/s/cm^{-5} (or 3 Wood units)), Contraindicated: high risk of intraoperative event at graft reperfusion.*Provided right ventricular function size and function are adequate

Table 19.2 PAH-specific therapy use in POPH

PAH-specific therapy group	Drug	Study's first author	Number of subjects included	Study main outcomes
Endothelin receptor antagonist	Bosentan	Hoeper [42]	18	1- and 3-year survivals 94 and 89%, respectively
	Bosentan	Savale [52]	34	Event-free survival estimates were 82, 63 and 47% at 1, 2, and 3 years, respectively
	Ambrisentan	Cartin-Ceba [35]	13	At 1 year, MPAP and PVR improved in 8/8; PVR normalized in five
Phosphodiesterase inhibitors	Sildenafil	Reichenberger [48]	12	Improvement at 3 months; not sustained at 1 year
	Sildenafil	Gough [38]	11	PVR decreased in all at first RHC follow-up
	Sildenafil	Hemnes [40]	10	At 1-year MPAP and PVR decreased in 3/5 patients
Prostanoids	Epoprostenol	Kuo [46]	4	MPAP and PVR improved
	Epoprostenol	Krowka [45]	15	15 MPAP and PVR improved
	Epoprostenol	Ashfaq [34]	16	Successful LT in 11 patients; 5-year survival 67%
	Epoprostenol	Fix [37]	19	PVR improved in 14/14; MPAP improved in 11/14
	Epoprostenol	Sussman [50]	8	MPAP and PVR improved in 7/8
	Trepostinil	Sakai [49]	3	Successful LT in two patients (moderate portopulmonary hypertension)
	Inhaled iloprost	Hoeper [42]	13	1- and 3-year survivals 77 and 46%, respectively
	Inhaled iloprost	Melgosa [47]	21	Acute, but no long-term hemodynamic improvement
	Epoprostenol	Awdish [69]	21	Clearance for transplant in 52% of patients within 1 year
Combination therapy	Sildenafil alone or combined with prostacyclins in nine patients	Hollatz [43]	11	MPAP and PVR improved in all patients, all underwent LT and 7/11 are off PAH-specific therapy
	Sildenafil and Bosentan combined in six patients, one patient only on prostacyclins	Raevens [51]	7	MPAP and PVR improved in the 5/6 patients treated with combination of sildenafil and bosentan, two underwent LT

MPAP mean pulmonary artery pressure, *PVR* pulmonary vascular resistance, *LT* liver transplantation, *IV* intravenous, *RHC* right heart catheterization, *POPH* portopulmonary hypertension, *PAH* pulmonary arterial hypertension

Table 19.3 Model for end-stage liver disease exception criteria for portopulmonary hypertension

1. Moderate-to-severe POPH diagnosis confirmed by right heart catheterization
a. MPAP ≥ 35 mmHg
b. PVR ≥ 240 dynes/sec/cm^{-5}
c. PAWP ≤ 15 mmHg
2. PAH-specific therapy initiated; improvement documented
a. MPAP < 35 mmHg
b. PVR < 400 dynes/s/cm^{-5}[a]
c. Satisfactory right ventricular function by transthoracic echocardiography
3. MELD exception updated every three months
a. Give additional MELD exception if RHC data satisfies criteria # 2

POPH portopulmonary hypertension, *PAH* pulmonary arterial hypertension, *MPAP* mean pulmonary artery pressure, *PVR* pulmonary vascular resistance, *PAWP* pulmonary artery wedge pressure, *RHC* right heart catheterization, *MELD* model for end-stage liver disease

[a] If PVR is normal, higher MPAP may be allowed and reconsidered due to physiology that is now high flow rather than obstruction to flow due to the therapy

ported 13 POPH patients using the ET_A receptor antagonist ambrisentan (10 mg daily) and documented at 1-year improvement in each of eight POPH patients (MPAP fell from 58 to 41 mmHg and PVR went from 445 to 174 dynes/s/cm^{-5}; $p = 0.004$). Of note, five of the eight patients normalized their PVR [35]. In further support of ambrisentan in POPH, Halank et al. described significant improvement in both exercise capacity and symptoms in 14 POPH patients [39]. Importantly, neither of the uncontrolled ambrisentan studies was associated with significant hepatic toxicity. More recently, Savale et al. described 34 cirrhotics (Child class A or B) with POPH treated with bosentan documenting significant hemodynamic improvement (more so in the Child class B subgroup) and event-free survival estimates were 82, 63, and 47% at 1, 2, and 3 years, respectively [52].

Phosphodiesterase-5 inhibitors: The use of phosphodiesterase inhibition (sildenafil) to enhance nitric oxide vasodilating effect, either alone or in combination with other PAH-specific therapies, has successfully improved POPH pulmonary hemodynamics and facilitated successful LT. Most of the published experiences have been in patients with less severe forms of POPH [38, 40, 48].

Other therapies and interventions in POPH: The use of beta-blockers to prevent gastrointestinal bleeding by reducing the degree of portal hypertension, may impair nRV function. In moderate-to-severe POPH ($n = 10$; mean MPAP = 52 mmHg), withdrawal of beta-blockade increased CO by 28%, decreased PVR by 19% with no change in MPAP and increased the 6-min walk by 79 m [53]. TIPS, as a treatment for gastrointestinal bleeding or refractory ascites, can temporarily increase MPAP, CO, and PVR. In a study of 16 cirrhotic patients without pulmonary hypertension, the increase in MPAP was greater than that noted in CO, suggesting an increase in the PVR after TIPS [54, 55].

Liver transplantation: LT is a potentially curative intervention for POPH, at least from a hemodynamic perspective. The outcome of POPH following LT remains unpredictable despite screening, careful patient selection, higher allocation priority, and advances in single and combination PAH-specific therapies [56–65]. Effective PAH therapy has resulted in successful LT and subsequent liberation from pre-LT PAH-specific therapy in some individuals. Current treatment targets for POPH that meet MELD score exception criteria in the USA are shown in Table 19.3. This policy has interrupted the natural history of POPH in US LT programs, reducing wait-list deaths and improving post-LT survival. PAH-specific therapy can be stopped once pulmonary hemodynamics normalize post-LT.

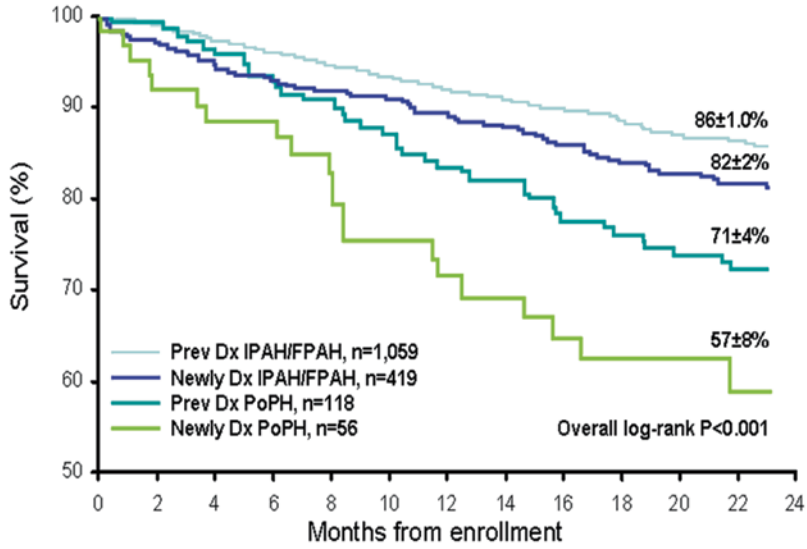

Fig. 19.2 Registry to evaluate early and long-term pulmonary arterial hypertension. Disease management (REVEAL) 2-year survival patterns for POPH and IPAH categorized by previous versus newly diagnosed at the time of entry into the registry. POPH portopulmonary hypertension, IPAH idiopathic pulmonary arterial hypertension, FPAH familial pulmonary arterial hypertension, REVEAL Registry to Evaluate Early and Long-Term PAH Disease Management. Reprinted with permission from CHEST [9]

Prognosis

The overall prognosis of POPH has been confounded by small series from eras in which none of the current PAH-specific medications were available compared with the present, when there is increasing experience in PAH-specific therapies and LT. Robalino and Moodie reported a 5-year survival of 4% ($n=78$) in an era prior to the introduction of continuous intravenous (IV) prostacyclin infusion [66]. Swanson reported a 14% 5-year survival in POPH patients ($n=19$) denied LT and not treated with any of the current PAH-specific therapies [67]. From the French National Center for PAH ($n=154$ over a 20 year span until 2004), Le Pavec described 1, 3, and 5 year survivals of 88, 75, and 68%, respectively, for patients with POPH (mainly Child classification A and alcohol as the etiology of cirrhosis) [68]. Causes of death in all series mentioned herein were equally distributed between right heart failure due to POPH and direct complications of liver disease (bleeding, sepsis, hepatocellular carcinoma). More recently, the REVEAL reported two important POPH observations [9]. First, the use of any PAH-specific therapy for POPH was delayed compared to patients diagnosed with IPAH. Specifically, at the time of entry into the registry only 25% were on PAH-specific therapy; by the end of 12 months follow-up, 74% of those alive were on treatment. Second, although baseline hemodynamics in POPH (MPAP and PVR) were significantly better than those with IPAH, the 1- and 3-year survivals were worse (Fig. 19.2); the 5-year survival for all POPH patients was 40 vs. 64% for IPAH. Liver disease etiologies and causes of death were not determined and survival was not analyzed by the type of PAH-specific therapy.

Conclusions

POPH is an uncommon, serious, yet treatable pulmonary vascular complication of portal hypertension that can lead to right heart failure and death, if untreated. Due to the spectrum of pulmonary hemodynamic variations associated with hepatic dysfunction, screening by TTE and confirmation by RHC are necessary for accurate

diagnosis and therapy. Despite the lack of controlled studies, PAH-specific therapies in POPH can significantly improve pulmonary hemodynamics and RV function. The potential to "cure" POPH, at least hemodynamically, with a combination of PAH-specific therapy and LT appears to be an attainable goal in a cohort of POPH patients yet to be optimally characterized.

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Portal Vein Thrombosis

20

Dominique-Charles Valla

Currently available noninvasive imaging procedures (ultrasound, computed tomography and magnetic resonance) now allow for an accurate diagnosis of portal vein thrombosis (PVT). The routine use of these imaging procedures has resulted in an increased recognition of PVT in patients with cirrhosis. With increasing awareness, several issues, mostly concerning causes, consequences, and therapy of PVT, have arisen, which this chapter discusses.

Definition

PVT is characterized by a thrombus occupying part (partial thrombosis) or whole (occlusive thrombosis) of the lumen of the portal vein. Isolated thrombosis of the left or right portal vein branches is usually included in the entity PVT. However, isolated splenic or superior or inferior mesenteric vein thromboses are considered separate entities. Several classifications have been proposed to grade the cross-sectional occupancy of the lumen, as well as the extent of the thrombus upstream (into the splenic and superior mesenteric veins) and downstream (into the portal vein and its branches; reviewed by Rodriguez-Castro et al. [1]. The widely used classification by Yerdel et al. [2] is presented in Table 20.1. It should be emphasized that this classification has been designed mostly to evaluate the impact on liver transplantation (LT) rather than to make an accurate anatomic or physiologic description of the obstruction. In adults, portal cavernoma (also named cavernous transformation of the portal vein) is usually assumed to be a *sequela* of past PVT.

Epidemiology

Estimates of the prevalence of PVT have fallen into a relatively broad range (about 4–25%), probably due to variations in the characteristics of the patients and the definition used to define PVT [1, 3, 4]. Overall, it appears that in patients with cirrhosis admitted to hospital but otherwise unselected, the prevalence of partial and occlusive PVT is in the order of 7–10% and 2–4%, respectively. The incidence of PVT has been reported 7.8% over a mean follow-up period of 12 months in patients wait-listed for LT [5], 16% over a mean follow-up period of 16 months in patients participating in an endoscopic sclerotherapy program after variceal bleeding [6], and 10.7% by 5 years when assessed prospectively in patients initially with Child A cirrhosis and no hepatocellular carcinoma (HCC) [7].

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Table 20.1 Grading of portal vein thrombosis according to Yerdel et al. [2]

Grade 1. Cross-sectional obstruction of less than 50% of the portal vein lumen
Minimal or absent extension into the superior mesenteric vein
Grade 2. Cross-sectional obstruction of more than 50% of the portal vein lumen
Minimal or absent extension into the superior mesenteric vein
Grade 3. Complete obstruction of the portal vein and proximal superior mesenteric vein
Patent distal superior mesenteric vein
Grade 4. Complete obstruction of the portal vein, proximal, and distal superior mesenteric vein

Causal Factors

The causal factors most commonly implicated in the development of PVT are listed in Table 20.2. Searching for possible causes in patients with cirrhosis has generated many data. However, the cross-sectional design of most studies makes it difficult to infer whether cause or consequence explains the observed associations with PVT. Cross-sectional studies have shown PVT to be associated with smaller liver weight, higher model for end-stage liver disease (MELD), or Child–Pugh scores, ascites, and encephalopathy [4, 5, 8, 9]. A recent prospective study in patients with compensated cirrhosis at baseline found that PVT developed more frequently in patients with features of initially more severe liver disease, but there was no evidence for a direct temporal relationship between progression of liver disease and the occurrence of PVT [7]. Therefore, it remains unclear if progression of liver disease causes the development of PVT.

In patients with cirrhosis, PVT has been associated with decreased levels of coagulation inhibitors [9–11]. The direction of this association is likewise difficult to interpret because advanced liver disease induces a decrease in plasma levels of coagulation inhibitors (particularly protein C, but also protein S and antithrombin). Molecular studies of Factor V Leiden and prothrombin gene mutation have given inconsistent results regarding any association with the development of PVT [10, 11].

Recent studies have shown that contrary to general belief, thrombin generation capacity is preserved in plasma from patients with cirrhosis (provided platelet counts are above 60,000/μL), which contrasts with the decreased levels of most coagulation factors [10]. This apparent paradox is actually explained by a simultaneous decrease in the plasma levels of both coagulation inhibitors and most coagulation factors. Furthermore, a degree of resistance to the activation of the protein C pathway system has been shown, corresponding to a procoagulant state. This pro-

Table 20.2 Features associated with PVT and which could be causal or precipitating factors

Age
Obesity
Diabetes
Underlying thrombophilia (factor V Leiden or prothrombin gene mutation)
Alcohol as a cause for cirrhosis
Liver atrophy
High MELD or Child–Pugh score
Splenectomy
Past surgery for portal hypertension
Endoscopic sclerotherapy
Decreased portal vein blood flow velocity
Large spontaneous portosystemic shunts

MELD model for end-stage liver disease, *PVT* portal vein thrombosis

coagulant state could be related to the marked decrease in plasma protein C levels, together with the marked increase in plasma factor VIII levels. The magnitude of these changes parallels the severity of cirrhosis. The clinical relevance of these laboratory changes is suggested by epidemiological evidence for an increased risk of venous thromboembolism in patients with cirrhosis. However, the data linking procoagulant changes with an increased risk of venous thrombosis in general—and PVT in particular—are still lacking.

A prospective longitudinal study disclosed a strong association of reduced portal vein blood flow velocity at baseline with the subsequent (1-year) development of PVT, independent of baseline MELD score [12]. In another study, however, the decrease in portal blood flow velocity with time was not found to be an independent factor for the later development of PVT [7]. The limitations in assessing portal blood flow velocity by noninvasive means cannot be ignored. This area clearly deserves further study.

Several surveys found PVT to be associated with previous splenectomy, surgical portosystemic shunting, or endoscopic therapy for esophageal varices [3, 9, 13]. However, in the absence of randomized control trials, it is not possible to assess whether surgery directly caused PVT, or whether the need for surgery (i.e., severe portal hypertension) was a marker for a greater risk of developing PVT.

Alcoholic cirrhosis, diabetes, and obesity have been associated with the development of PVT [13, 14]. However, a comprehensive assessment, taking into account all the possible causal factors for cirrhosis and particularly the metabolic syndrome, remains to be performed.

Diagnosis

Routine imaging for HCC screening is the most frequent situation in which PVT is currently recognized, followed by a recent complication of cirrhosis, including gastrointestinal bleeding; and much less commonly, features of intestinal ischemia [4, 9]. It is difficult to determine whether symptoms or complications, if any, are directly related to the development of PVT or whether they led to a fortuitous uncovering of PVT. PVT in patients with cirrhosis does not appear to induce clinical or laboratory features of hepatic ischemia. However, among patients with cirrhosis, and acute ischemic hepatitis related to bleeding, the prevalence of PVT was 29% [15], which is about twice the prevalence expected among unselected patients with cirrhosis and acute bleeding (16%) [16].

An accurate diagnosis can be obtained at Doppler ultrasound of the portal vein and its main branches [17]. Doppler assessment is needed to avoid a false-negative result at ultrasound where a void-appearing portal vein can actually be occupied by a fresh thrombus. Enhanced computerized tomography (CT) or magnetic resonance imaging (MRI) confirms the diagnosis of PVT. It may be easier to assess the degree (partial or occlusive) and the extent (venous segments involved) at CT scan or MRI than at ultrasound.

The main differential diagnosis for PVT in patients with cirrhosis is portal venous invasion by a malignant tumor (usually HCC; Table 20.3). This entity has been mistakenly referred to as "malignant PVT," although the obstruction is not related to thrombosis but to tumor ingrowth. The main differential feature is enhancement of the endoluminal material at the arterial phase of a CT or MRI scan [18, 19]. Additional features favoring a diagnosis of tumor invasion include

Table 20.3 Features of portal venous obstruction which suggest tumor invasion rather than nonmalignant thrombosis

Enhancement of solid endoluminal material at the arterial phase of contrast medium injection (contrast medium-enhanced ultrasound, computed tomography or magnetic resonance imaging)
Washout of solid endoluminal material at the portal or late phase of contrast medium injection
Marked enlargement of portal vein lumen at the level of obstruction (>5 cm)
Vicinity to a nodule of hepatocellular carcinoma

proximity to a typical HCC nodule, a markedly enlarged portal vein, and washout of the endoluminal material at the portal and late phase [18, 19]. It is almost impossible to differentiate pure tumor invasion from tumor invasion with superimposed thrombosis. The clinical relevance of the latter distinction is doubtful, whereas the differentiation of pure thrombosis from malignant invasion is critical. A marked elevation in serum α-fetoprotein level may be seen with malignant vascular invasion.

In some patients, particularly those with large extrahepatic portosystemic shunts, portal flow is reversed (hepatofugal) or stagnant. Rarely, in such patients, the portal vein may not even be visible at all.

Course and Impact

A spontaneous decrease in size or resolution of PVT has been reported in up to 40% of patients at subsequent 3–6-month imaging [7, 20–22]. However, extension has also been reported in up to 72% of patients not given anticoagulation [23]. Data are missing to clarify whether resolution is influenced by the partial or occlusive nature of the thrombus and the length of its extent. Short-term recurrence after disappearance also appears to be common but not constant [24]. Development of a portal cavernoma seems to be extremely unusual in patients with a persistent thrombus [7, 21, 22]. Therefore, venous changes following acute PVT differ considerably when cirrhosis is present from when it is absent [25].

The impact of PVT on outcome remains difficult to ascertain. Table 20.4 lists features associated with the development of PVT. As noted above, the association of PVT with the severity of cirrhosis could be explained by PVT causing liver disease to worsen. Indeed, PVT could exacerbate portal hypertension by superimposing a prehepatic block to the intrahepatic block, precipitating gastrointestinal bleeding and ascites formation, increasing portosystemic shunting and encephalopathy. Furthermore, by decreasing portal perfusion, PVT could induce parenchymal atrophy and worsen hepatic dysfunction. Studies that address this issue are sparse. In a prospective study, the development of PVT at any time during the course of initially compensated cirrhosis was not associated with a subsequent progression of liver disease [7]. Similarly, retrospective but longitudinal surveys disclosed no association between the persistence or the resolution of PVT and the progression of liver disease [21, 22]. In a recent controlled trial, enoxaparin administration for 48 weeks prevented the progression of liver disease, much more so than the development of PVT [26]. Therefore, it is unlikely that the obstruction to portal flow, created by a thrombus, explains the totality of the association between PVT and progression of liver disease. Actually, three *scenarios* could explain the association of PVT with liver disease progression: (i) advanced liver disease could precipitate the development of PVT, (ii) PVT could induce a progression of liver disease, and (iii) a common determinant (e.g., disordered hepatic or intestinal circulation) could independently and simultaneously

Table 20.4 Features associated with portal vein thrombosis (PVT) in patients with cirrhosis, which could be a consequence of PVT

Liver atrophy
Increasing MELD or Child–Pugh scores
Ascites
Encephalopathy
Gastrointestinal bleeding
Failure to control bleeding
Delayed eradication of varices using endoscopic band ligation
Increased sensitivity of the liver to circulatory failure
Impossibility to restore and maintain portal perfusion to grafted liver
Decreased survival after liver transplantation
Decreased benefit from liver transplantation

MELD model for end-stage liver disease

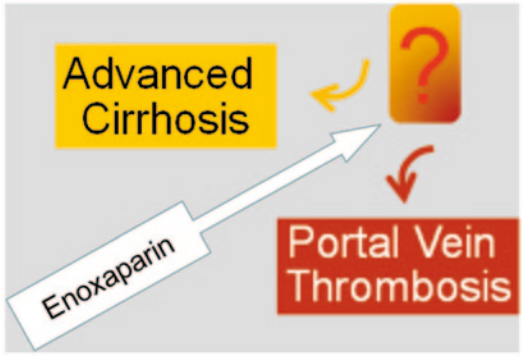

Fig. 20.1 Schematic illustration of the indirect link between portal vein thrombosis (PVT) and progression of liver disease. Enoxaparin could target a common determinant (indicated by a question mark) to the progression of liver disease and the development of PVT. This hypothesis would explain **a** the absence of direct relationship between PVT and progression of liver disease; and **b** a disproportionate benefit from the administration of enoxaparin on the prevention of progression of liver disease over the prevention of PVT

explain the progression of liver disease and the development of PVT, as illustrated in Fig. 20.1. These *scenarios* are not mutually exclusive. Scenario (iii) appears to be most compatible with the data discussed above. Clarifying which of these *scenarios* is correct would tip the balance for or against potential treatments targeting portal vein recanalization.

Interpreting the data on the impact of PVT on LT is likewise not straightforward. Technical failure to restore and maintain portal blood perfusion to the allograft causes its primary nonfunction [1, 5]. A preexisting PVT may prevent adequate portal blood perfusion being established, mostly depending on the degree (partial or occlusive) and the extent of the thrombus in the superior mesenteric vein. Whenever simple thrombectomy or an anastomosis between the recipient mesenteric vein and donor portal vein restores physiological portal blood perfusion to the allograft, the independent impact on overall outcome appears to be limited [27]. This is not the case for nonphysiological operations (e.g., caval hemitransposition or renal- to portal vein anastomosis) where operative and postoperative mortality and morbidity are greatly increased [27].

Independently of its impact on portal blood perfusion to the graft, pretransplant PVT appears to be a factor in decreased posttransplant survival. Intriguingly, however, this negative influence seems to be limited to patients with the lowest MELD scores at the time of transplantation [13, 28]. One of several possible explanations could be that patients with low MELD scores and PVT have an underlying disorder that is responsible for their poor condition (and possibly for PVT), but it is not cured by LT.

Treatment

Treatment of PVT in patients with cirrhosis can be considered from a prophylactic or a curative perspective. Experience, although increasing, is still too limited to provide solid evidence-based therapeutic recommendations.

Prophylactic options have been based on the assumptions that (i) the development of PVT is responsible for progression of liver disease, for worse outcomes after LT, or for both of these consequences, and (ii) preventing the development or the extension of PVT will prevent complications and improve patient outcomes. Actually, one randomized controlled trial in patients with Child–Pugh classification B7-C10 cirrhosis compared 34 patients receiving enoxaparin subcutaneously 4000 IU daily for 48 weeks to 36 patients receiving no such treatment [26]. Evaluation at 96 weeks showed markedly decreased incidences of PVT, decompensation, progression of liver disease, and death in the treated group as compared to the control group. As discussed above, this trial unexpectedly showed a greater benefit in terms of prevention of complications than the development of PVT. Other uncontrolled studies performed in patients with PVT generally showed the absence of progression of PVT in patients receiving anticoagulation (low molecular weight heparin initially, with or without a transition to warfarin) [5, 23, 24, 29]. Therefore, not only does anticoagulation appear to block the development or the extension of the thrombus but this effect may also be accompanied by clinically relevant improvements in patient outcomes.

Curative therapy options have been less well evaluated than prophylactic ones. Transjugular intrahepatic portosystemic shunt (TIPS), thrombolysis, and anticoagulation have all been considered. Available data consist of retrospective observational studies, from which it is difficult to draw conclusions regarding robust end points such as decompensation or death. Indications for TIPS in patients with PVT have mostly comprised refractory bleeding or ascites [23, 30–32]. Findings have been consistent in indicating that (i) TIPS insertion is feasible when intrahepatic portal veins are visible, (ii) the incidence of encephalopathy and TIPS dysfunction are similar in patients with or without PVT, and (iii) resolution of partial thrombosis may occur in the absence of anticoagulation. Thus, PVT is not a contraindication to placing a TIPS. However, it has not been established if TIPS provides a benefit in clinically relevant end points as compared to other options (including no specific therapy) in patients with cirrhosis and PVT.

Anticoagulation therapy has been evaluated in patients with advanced cirrhosis, many of whom were candidates for LT [5, 23, 24, 29]. Anticoagulation protocols consisted generally of low-molecular-weight heparin initially, with or without a secondary shift to warfarin. The duration of anticoagulation ranged from several weeks to months in each series. The findings are relatively consistent in showing (i) complete recanalization of the portal vein in about 45% of patients, and a partial recanalization in about 15%, while extension was extremely unusual, (ii) the absence of bleeding related deaths, and (iii) the absence of obvious increase in the incidence of gastrointestinal bleeding or other spontaneous bleeding. However, the data do not allow for an assessment of the impact of anticoagulation on clinically relevant end points such as decompensation or mortality, before or after transplantation. Furthermore, the proportion of treated patients with a partial PVT was unclear, making it difficult to assess whether this feature is a determinant in recanalization. There are little data to recommend any specific anticoagulant agent, the monitoring tools, and the target coagulation variable to be achieved [33]. Data on the use of thrombolysis whether given systemically or locally are thus far only anecdotal [34].

Based on this information, it is impossible to make strong treatment recommendations. The prophylactic use of enoxaparin is certainly an exciting prospect but confirmatory clinical trials are needed before any definitive recommendation can be made. In patients with refractory bleeding or ascites, TIPS insertion can be attempted, although its impact on survival can be expected to be limited. Placing a TIPS only for prevention of an extension of PVT is questionable. Similarly, at present, the indication for anticoagulation based only on the presence of PVT is not sufficiently grounded in data. While its benefit is unproven, anticoagulation might be considered in patients with PVT who are candidates for LT, with the purpose of preventing extension of thrombosis, and thus facilitating restoration of physiological portal blood perfusion to the allograft. Other situations deserve a case-by-case discussion, particularly in rare patients where a strongly prothrombotic condition has been diagnosed or patients with extensive thrombosis of the superior mesenteric vein in whom there is evidence of past or recent intestinal ischemia.

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Coagulation Disorders in Patients with Cirrhosis

21

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The coagulation cascade, a group of plasma proteins involved in clot formation, was discovered and fully elucidated in the study of congenital clotting disorders, especially hemophilia A. The makeup and function of each factor, I–XII, was elucidated through a classic "reverse engineering" process in the days before modern protein chemistry techniques were available. The clinical presentation of a patient with a congenital clotting disorder was observed and the defect in the coagulation cascade was determined initially by deduction and comparison with other known clotting disorders. While a major step forward for these patients, the intensive study dedicated to this specific part of the hemostasis system led to the widespread teaching of the plasma protein makeup of hemostasis without much regard to other equally important portions of the hemostasis system. A complete description of hemostasis is beyond the scope of this chapter [1]; however, the modern cell-based theory of hemostasis and the perturbations in patients with cirrhosis follows.

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Primary Hemostasis

The initial phase of hemostasis begins with the exposure of tissue factor to the circulating blood due to a rupture in the endothelium and the first line of defense is the activation and recruitment of circulating platelets through receptor interactions with the endothelial adhesive protein von Willebrand factor (vWF), glycoprotein IIb/IIa, and other membrane and subendothelial receptors. This initial platelet binding causes changes in platelet structure and function and eventual degranulation which amplify a positive-feedback mechanism to recruit and activate more platelets. The initial collection of activated platelets at the site of injury functions to temporarily stop blood loss but this "platelet plug" is short lived and unstable due to the transient nature of platelet activation and adhesion. The clinical correlate of primary hemostasis frequently seen by gastroenterologists and hepatologists is the "white clot" or "nipple sign" observed on recently bleeding esophageal varices during endoscopy.

The etiology of thrombocytopenia in cirrhosis is multifactorial and includes splenic sequestration due to portal hypertension [2] and decreased hepatic production of thrombopoietin [3]. However, there are compensatory mechanisms to help the hemostasis system achieve a rebalance in these patients despite the significant thrombocytopenia frequently seen. When tested under laboratory conditions simulating the laminar flow of small vessels [4, 5], platelets from patients with

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cirrhosis when exposed to plasma from cirrhosis patients have similar adhesion properties to controls. The mechanism for this is thought to be a significant elevation in vWF levels in patients with cirrhosis which allows for increased platelet adherence despite some functional and quantitative defects seen in cirrhosis.

Coagulation

The classically taught "coagulation cascade" is the second phase of hemostasis and is responsible for the fibrin mesh that holds the activated platelets in place and assures time for tissue rebuilding, healing of vascular breaches, and formation of the true "clot." It should be emphasized that while the plasma coagulation factors are required for formation of the fibrin mesh (fibrinogen cleaved to fibrin by the serine protease thrombin), much of the reaction takes place on the lipid-rich surface of the activated platelet. Similarly, the presence of activated platelets initiates a positive feedback "thrombin burst" which promotes the further recruitment of platelets and production of more thrombin thereby enhancing clot formation [6]. Patients with hepatic synthetic dysfunction are deficient in coagulation factors II, VII, IX, and X as well as factor V and XI. From patient to patient, there is a significant variation in the functional levels of these proteins but as hepatic dysfunction progresses the activity of these enzymes typically decreases. These factor deficiencies are directly responsible for the elevated prothrombin time (PT) and international normalized ratio (INR) and are a reasonable indicator over time of hepatic protein synthetic deficiency and worsening liver function. Despite this, research has shown that in the setting of adequate numbers of platelets, the ability to generate thrombin is preserved in patients with cirrhosis compared to controls [7]. This is likely due to the low levels of these plasma enzymes actually required to propagate the clotting process. In summary, while coagulation protein levels are decreased, once again compensatory mechanisms are in place to preserve baseline hemostasis in patients with cirrhosis.

Fibrinolysis

The final stage in hemostasis is the breakdown of the previously formed clot once tissue repair is adequate and endothelial function is restored. In order to prevent catastrophic disseminated coagulation, a complex and sensitive clot breakdown mechanism works at the site of the injury to moderate and eventually resorb the products of coagulation. There are various first-level enzymes and proteinases such as plasmin, which directly cleaves the fibrin mesh, as well as activated protein C (aPC), protein S, and antithrombin, which inhibit various points in the coagulation cascade. In turn, there are multiple second-level controller enzymes which inhibit or promote the first-level molecules in a complex control system that modulates the breakdown of clot in the local environment (Fig. 21.1). While most of these enzymes are produced directly by the endothelium, hepatic function is required for efficient degradation and investigators have shown that many patients with progressive cirrhosis have a corresponding decrease in aPC activity that approaches that of patients with the extremely thrombophilic state of congenital aPC deficiency [8]. This relative deficiency of innate anticoagulant proteins effectively counterbalances the procoagulant protein deficiencies described above. Disruption, especially overaction of the fibrinolytic pathway likely due to local persistence and overaction of tissue plasminogen activator [9, 10], can lead to a clinical syndrome of persistent mucosal or wound hemorrhage termed hyperfibrinolysis. This disorder is fairly common in clinical practice although infrequently severe (about 1% of admitted cirrhosis patients) and it responds to therapy with epsilon-aminocaproic acid [11].

While the stable patient with cirrhosis is in a rebalanced state of hemostasis, the balance is tenuous and easily disturbed (Fig. 21.1). Many factors, both extrinsic (infection, surgery, other medical comorbidity or acute illness) and intrinsic (acute and chronic renal disease, mechanical sources of bleeding such as esophageal varices) can cause a loss of balance and result in various clinical disorders such as hemorrhage, portal vein

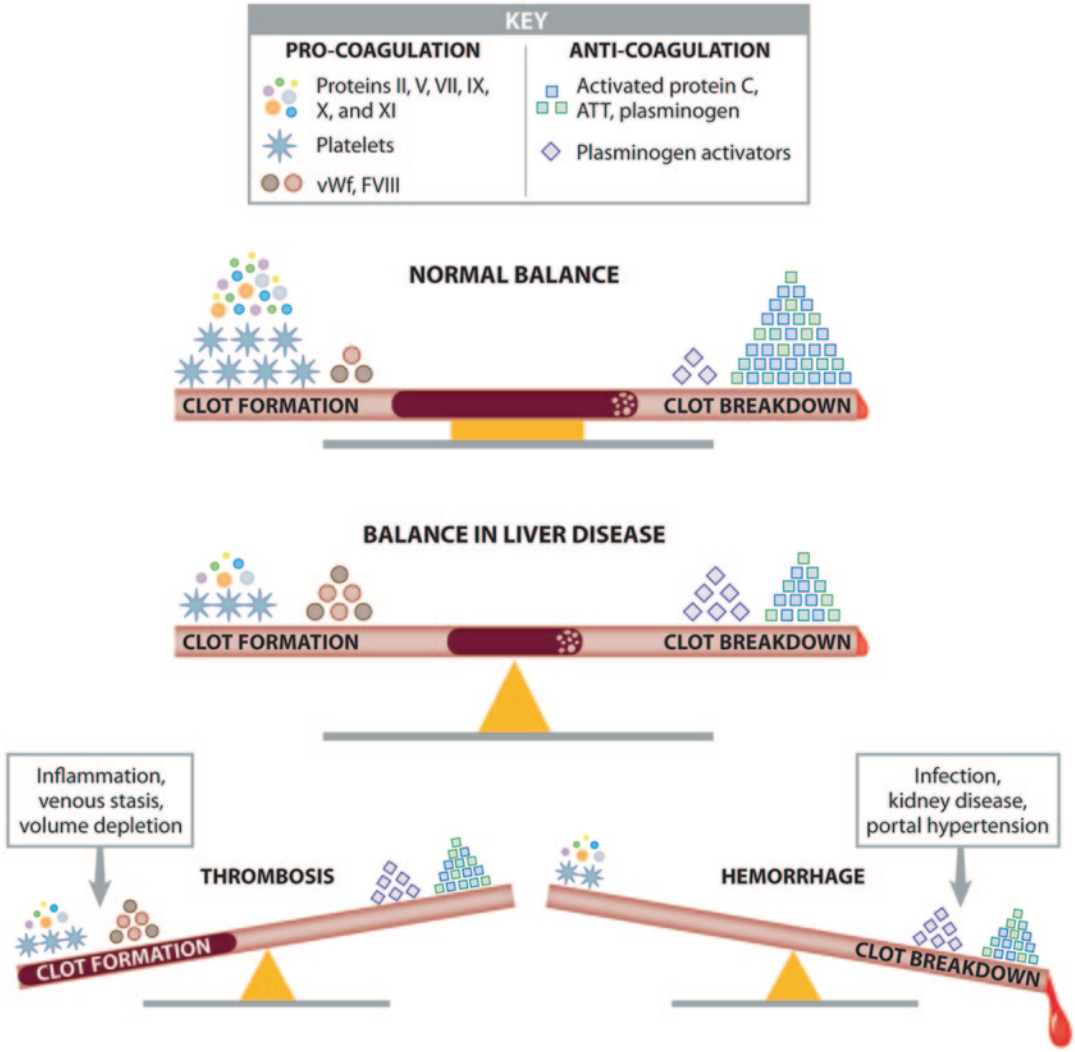

Fig. 21.1 The balance and rebalance of hemostasis in cirrhosis. Patients without liver disease maintain a balance of procoagulant and anticoagulant proteins. Patients with cirrhosis have decreased levels of both and other compensatory mechanisms but at steady state maintain an effective rebalance of hemostasis. Many factors, both extrinsic and intrinsic can lead to imbalance and bleeding or clotting disorders in patients with cirrhosis (Illustration by Anita Impagliazzo)

thrombosis, venous thromboembolism (VTE), or hyperfibrinolysis. Clinically available diagnostic tests are currently inadequate to fully describe the hemostasis system in an individual patient and we will discuss the options currently available to the practicing clinician in the next section.

Evaluation of the Coagulation Status of a Cirrhosis Patient

Plasma-Based Laboratory Studies

Table 21.1 summarizes some commonly available laboratory studies used in clinical practice.

Table 21.1 Diagnostic tests and the special considerations needed in patients with chronic liver disease

Diagnostic test	Special consideration in cirrhosis
International normalized ratio	Inaccurate due to variation with reagents and provides poor predictability for pre-procedure bleeding risk stratification
Platelet count	Thrombocytopenia in portal hypertension is multifactorial in etiology. Levels greater than 55,000/mcL provide adequate primary hemostasis and allow for thrombin generation during coagulation. Levels greater than 100,000/mcL may be needed for acute bleeding
Fibrinogen	Degradation products increase with severe cirrhosis due to persistent plasminogen activators. Normal plasma levels do not rule out a fibrinolysis disorder
Factor VIII/protein C ratio	Mean ratio in cirrhosis found to be 0.8, but higher values indicate hypercoagulability. Can be an early clinical marker of clotting tendency

International Normalized Ratio The INR was developed in the 1980s to normalize variations in the prothrombin time (PT) and correct for the different reagents utilized in the coagulation laboratory [12]. The foundation for INR measurements is based on extrapolation from plasma testing in patients taking vitamin K antagonists, specifically warfarin. This extrapolation has proven to be inadequate for accurate bleeding risk assessment in cirrhosis patients, as many factors affect coagulation profiles in liver disease patients. Multiple studies show that the variation in INR measurements for cirrhosis patients is dependent on reagents used in the coagulation laboratory [13]. These variations can mislead practitioners and have far-reaching clinical implications, as they can affect model of end-stage liver disease (MELD) scores and liver transplant organ allocation [14]. An INR (liver) based on plasma from liver disease patients has proven to be more accurate; however, it lacks clinical validation and widespread availability [15]. While INR will remain a conventional measure of bleeding risk in the general population, caution should be taken when used to evaluate cirrhosis patients.

Platelets It is reported that 76% of chronic liver disease patients suffer from thrombocytopenia (platelet count $<150{,}000/mm^3$) [16]. The cause of thrombocytopenia is likely multifactorial with marrow suppression, portal hypertension, splenic sequestration, and reduction in thrombopoietin production, all contributing. Physiologic compensation in cirrhosis patients can lead to increased levels of vWF and thus increased platelet adhesion [4]. However, in vitro studies show that a minimum number of platelets (approximately 55,000/mcL) are needed to generate adequate thrombin production for clot formation [8, 15]. In the setting of adequate platelet numbers and thrombin availability, platelet function analyzers have shown a correction in hematocrit values that further promote the platelet and endothelium interaction [17].

Fibrinogen Severity of liver disease inversely correlates with fibrinogen levels. Fibrin degradation products increase in the setting of severe cirrhosis [18]. In the setting of normal fibrinogen levels, cirrhosis patients may still experience decreased function due to dysfibrinogenemia. The cell turnover in cirrhosis can lead to production of immature fibrinogen, which contributes to the direct measurement of a fibrinogen level, but does not provide a functional component in hemostasis [19].

Factor VIII/Protein C Ratio Factor VIII, a procoagulant, is often increased in cirrhosis due to its release from injured hepatocytes, as well as a relative deficiency in lipoprotein receptor-related protein, its regulator [20]. Conversely, protein C, an anticoagulant, is a protein that experiences decreased production in the setting of liver disease. This deficiency further potentiates a rise in Factor VIII levels due to the presence of a light chain binding site for protein C to inactivate and regulate Factor VIII levels [21]. Therefore, the measurement of these separate components can provide a ratio that correlates with the severity of liver disease [22]. Values in cirrhosis patients have a mean of 0.8, while con-

trols possess a mean value of 0.66. In this manner, a Factor VIII level can differentiate between the presence of hepatic dysfunction from disseminated intravascular coagulation, which is associated with low levels of coagulation factors.

Global Coagulation Measurements

With the multifactorial nature of coagulation in liver disease, there is increasing evidence for the utility of global functional measurements of clot formation. Conventional measures evaluate each component of the blood involved in hemostasis separately; however, their interaction is essential to properly determine bleeding or clotting risk.

Thromboelastography (TEG) This device measures the shear stress needed to oscillate a cuvette with whole blood around a stationary pin at a steady rate. As the blood coagulates from its liquid form, the force needed to maintain a steady rate slowly increases as the liquid blood solidifies. This incorporates the interaction of all the blood components as the clot is formed. This whole blood measurement in cirrhosis patients seems to provide a more accurate measurement of bleeding/clotting risk [23, 24], but its clinical utility outside of the operating room has not been proven.

Rotational Thromboelastometry (ROTEM®) This technique of whole blood measurement is similar to TEG, but involves a rotating pin with a stationary cuvette. Commercially available devices using this technology include several different "channels" that add various activators and inhibitors to the process in order to isolate or enhance an individual component of the hemostasis system to allow detailed analysis. This technique has been studied in the setting of liver transplantation, and has been used to provide guidance with blood product use and utilization of platelets and fibrinogen [25–27].

Sonorheometry (SR) TEG and ROTEM provide whole blood functional measurements on a macroscopic scale. The shearing effect of these devices could theoretically lead to clot disruption affecting the true measurement of clotting times. Sonorheometry uses pulsed ultrasound waves to measure red blood cell movement and its correlation with clot formation. This technique is still under investigation and currently in development [28] but holds promise as a clinically useful whole blood coagulation monitor.

Management of Specific Coagulation Disorders

Bleeding

The majority of bleeding encountered in cirrhosis patients requires treatment of portal hypertension by both medical and mechanical methods. Transfusion of blood products is usually an essential adjunct for resuscitation, but the consequences of overtransfusion should be considered. A practical approach to optimization during active bleeding includes a target transfusion goal of a hemoglobin of 7–8 g/dL [29]. Clinical in vivo studies are sparse, but maintaining platelet count above 55,000/mcL and fibrinogen levels above 100 mg/dL (with cryoprecipitate) are also recommended to support endogenous coagulation systems in actively bleeding patients [30].

Other therapies have been studied to control bleeding in cirrhosis patients. In patients with variceal bleeding, treatment with recombinant factor VIIa(rFVIIa) was no different than placebo in controlling bleeding [31]. Additional reports in the literature describe the use of rFVIIa for rescue therapy in severe and uncontrolled hemorrhage [32]. Currently, the routine use of rFVIIa is limited to specific clinical situations without proof of efficacy from clinical trials [33]. Evidence for the use of prothrombin complex concentrates (PCC) for rescue bleeding in cirrhosis is limited and mainly observational [34, 35]. Hyperfibrinolysis is characterized by delayed bleeding from prior puncture sites or profuse mucosal bleeding and can cause significant steady blood loss. Medications such as tranexamic acid and epsilon-aminocaproic acid are available to treat bleeding from hyperfibrinolysis. One study showed successful

hemostasis with use of epsilon-aminocaproic acid in cirrhosis patients with subcutaneous and soft tissue hemorrhage [11]. While DDAVP may have a role in prophylaxis, investigators showed worse outcomes when DDAVP with terlipressin was administered to patients with acute variceal bleeding compared to terlipressin alone [36].

Bleeding complications in cirrhosis may occur from a variety of physiologic mechanisms that often coexist. As we begin to understand the coagulopathy of cirrhosis and recognize it as a "rebalanced" state, the practice of routine prophylaxis and transfusion should be reevaluated. Furthermore, caution is paramount when manipulating the coagulation system with transfusion or medications due to the risk of initiating unwanted thrombotic events.

Prophylaxis for Bleeding Events

The lack of literature supporting or refuting bleeding prophylaxis in cirrhosis generates uncertainty, causing clinicians to extrapolate recommended strategies from noncirrhosis patients. Guidelines exist for the prevention of bleeding in portal hypertensive-related complications [29, 37]. Recommendations for pre-procedural prophylaxis for percutaneous liver biopsy are relatively nonspecific, but suggest platelet transfusion in patients with platelet count less than 50,000–60,000/mcL [38]. Ultimately, the authors recommend that pre-procedural prophylaxis strategies to liver biopsy be developed specific to each clinical situation. There are no current standardized guidelines for pre-procedural bleeding prophylaxis for other procedures and variation in practice is common [39, 40].

Common tests, like PT and INR, do not accurately predict bleeding and cannot be used to gauge risk [41]. Even so, the practice of transfusing fresh frozen plasma (FFP) to "correct" the INR pervades. Current evidence suggests that this is generally ineffective and may be harmful [15, 42]. Liver transplantation is the most invasive procedure a cirrhosis patient will likely undergo. While improvements in surgical technique and anesthesia management have reduced intraoperative bleeding, this procedure is sometimes associated with massive hemorrhage. Clinical outcomes are directly related to transfusion requirement during the perioperative period [43]. Conventional tests to predict bleeding prior to transplant are generally ineffective [44]. Moreover, evidence is accumulating that avoidance of plasma transfusion and efforts to reduce portal pressures can decrease transfusion requirement and improve outcomes [45, 46].

Other considerations for bleeding prophylaxis include PCC, rFVIIa, vasopressin analogues (desmopressin), antifibrinolytics, and hemopoietic growth factors. PCC contain purified and concentrated coagulation factors II, VII, IX, X, protein C and S (25-fold higher concentration compared to plasma). Use of PCC for bleeding prophylaxis is attractive due to reduced transfused volume, but data are limited and thrombotic complications have been reported [35, 47]. Prophylactic use of rFVIIa has been studied in a variety of clinical situations including prior to liver biopsy, intracranial monitoring in acute liver failure, and liver transplantation [48–50]. Results are inconsistent and use of this agent is limited by expense and risk of thrombosis. DDAVP has been studied in two randomized controlled trials in cirrhosis with patients undergoing dental extraction and liver resection [51, 52]. In the study evaluating dental extraction with DDAVP alone versus prophylactic transfusion of FFP and platelets, there were no differences in bleeding episodes between treated and control groups. Another study evaluating the use of DDAVP versus placebo prior to hepatic resection showed that DDAVP did not decrease transfusion requirement although traditional coagulation parameters showed improvement. The use of aprotinin (an antifibrinolytic agent) has been shown to reduce blood transfusion requirements in patients undergoing liver transplant, but the agent has been withdrawn from the market in the USA and Europe due to observed thrombotic complications in cardiac surgery patients [53, 54]. Recently, eltrombopag (a thrombopoietin analogue) was shown to effectively increase platelet levels and reduce transfusions, but did not reduce bleeding events and was associated with thrombotic

complications [16]. Furthermore, the necessity of empirically increasing platelet counts above the 75,000/mcL level used in this study is questionable and can result in a tendency toward hypercoagulability [13].

Clotting Events

As discussed above, the rebalancing of the hemostasis system in patients with cirrhosis is frequently disturbed. There is now significant evidence that many patients with cirrhosis have a tendency for thrombophilia [22]. Portal vein thrombosis (PVT) and its complications are highly prevalent in cirrhosis patients and are addressed in a separate chapter of this textbook. There is also strong empiric evidence from observational [55] and large-scale epidemiologic [56] studies that patients with cirrhosis are predisposed to VTE, both pulmonary embolism and non-splanchnic deep venous thrombosis. Unlike the venous thromboembolic events, observational data regarding arterial thrombosis (in the nontransplant setting) are less convincing. In nonalcoholic fatty liver disease (NAFLD) there are mounting data, both mechanistic [57, 58] and observational [59], for an increased risk for arterial events. This elevated risk is usually manifested as typical plaque rupture in cardiovascular or cerebrovascular ischemic events.

Outside of the realm of portal vein thrombosis, data for treatment of acute thrombotic events in cirrhosis patients are extremely limited and few definitive conclusions can be drawn from the literature. It is clear that hepatic synthetic dysfunction and impaired renal function, both of which are common in progressive cirrhosis patients, must be considered in dosing and scheduling of antihemostatic medications. Data are now accumulating on pharmacokinetics for many of these agents in cirrhosis patients including the low molecular weight heparins (LMWH) [60], rivaroxaban [61], dabigatran [62], and apixaban [63]. The use of the vitamin K antagonists is difficult because of the innate elevation in INR in patients with liver disease making the narrow therapeutic window difficult to reliably achieve. There is a definitive lack of data regarding the antiplatelet agents in cirrhosis patients, especially in the acute event management setting, aside from scant case reports and subgroup analyses of larger studies [64]. Safety data for therapeutic use of the anticoagulants are significantly lacking except for enoxaparin and the current lack of specific reversal agents make the direct acting anticoagulants (factor X or factor II inhibitors) less comforting despite their wide therapeutic window and easy dosing [65]. It is clear that none of the currently available laboratory tests are adequate to measure therapeutic efficacy or dosing although some research methods, most significantly thrombin generation assays [66], show promise in eventual clinical development. It should be stressed that as liver disease progresses, functional levels of antithrombin decrease remarkably and this may cause confusion and misinterpretation of traditional anti-Xa activity assays which can be useful in monitoring anticoagulant activity in the non-cirrhosis patient [67]. Use of the anti-Xa assay in advanced liver disease can lead to the overdosage of many anticoagulants and should not be used to assess adequacy of anticoagulation in this population. The direct inhibitors of factor X may be monitored with this method but data on the clinical usefulness of this monitoring method are lacking.

Because of the lack of pharmacokinetic, safety, and efficacy data for most anticoagulants and antiplatelet agents in cirrhosis, specific recommendations are difficult and wrought with speculation. The clinician should consider the seriousness of the thrombotic event and potential harm due to therapies and have an informed consent discussion on a case-by-case basis with the patient. At this point, it would seem reasonable to offer traditionally accepted anticoagulant therapies for major thrombotic or thromboembolic events to patients with cirrhosis in this setting until further definitive data are available.

Prophylaxis for Thrombotic Events

There is a similar paucity of data in the area of thromboprophylaxis for cirrhosis patients with

the exception of portal vein thrombosis. Although discussed in other chapters of this textbook, it is worth emphasizing that in a multicenter randomized trial [68], in high-risk patients, prophylaxis for PVT using enoxaparin was generally tolerated well without major bleeding complications and decreased the incidence of PVT from 27.7% in controls to 8.8% in treated subjects over 2 years of observation. Remarkably, in this study there was also a corresponding decrease in hepatic decompensation over 1 year from 59.4% in controls to 11.7% in treated subjects. While this study remains to be confirmed, it presents encouraging data regarding the efficacy and safety of thromboprophylaxis for PVT in cirrhosis patients.

The data regarding coronary and cerebrovascular event prophylaxis in cirrhosis patients are sparse. A population based retrospective cohort study assessing the safety of low-dose aspirin for secondary cerebrovascular event prevention demonstrated slight decreases in second stroke events (hazard ratio of 0.904) and no increase in bleeding events requiring hospital admission [69]. The beneficial effect appeared to be strongest in those patients with NAFLD. There is much less information regarding safety or efficacy in the prevention of VTE in the cirrhosis population, especially acutely ill inpatients. While VTE prophylaxis in the hospitalized medical or surgical patient is considered standard of care, there are scant data regarding the acutely ill hospitalized cirrhosis patient. A cohort of 235 patients with 355 admissions to the hospital wards (non-intensive care unit) for acute hepatic decompensations were treated with various forms of prophylactic dose anticoagulants, mostly LMWH and unfractionated heparin [70]. In this cohort, there was no increase in bleeding events over historical controls related to the prophylaxis. Once again, excluding PVT, while there are minimal data on safety and even less on efficacy of thromboprophylaxis in the cirrhosis patient, it would seem reasonable to offer prophylaxis to patients on a case-by-case basis if the traditional medical risk factors and indications are present.

Summary

The hemostasis system in cirrhosis patients is a complex collection of procoagulants and anticoagulants that is effectively "rebalanced" to allow a tenuous stability. Due to hepatic synthetic dysfunction, there are counterbalanced decreases in procoagulant proteins along with decreases in the anticoagulant proteins. Because the clinically available laboratory testing assesses only a small portion of this rebalanced system, there are no adequate lab tests that give a good representation of hemostasis or disturbances in the system. The INR and traditional coagulation tests are designed for diseases other than cirrhosis and should not be used in isolation to assess bleeding or clotting risk in the liver disease population. Because of the scant available testing, data on safety and efficacy of hemostasis interventions are lacking and the modern clinician is dependent on empiric and observational data when making patient-level decisions. Clinicians need further research in the laboratory and in the clinics in order to understand the complex rebalancing of the hemostasis system in cirrhosis and how to best manipulate the system to benefit their patients.

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Hepatocellular Carcinoma

22

Bubu A. Banini and Lewis R. Roberts

Over the past decade, the global incidence and mortality of hepatocellular carcinoma (HCC) has continued to rise. From 2008 to 2012, HCC rose from third to second place among cancer-related deaths [1]. HCC now has the highest mortality ratio of all cancers, even higher than lung cancer (Table 22.1). Worldwide, the highest rates of HCC continue to occur in Southeast Asia and sub-Saharan Africa, and rates have risen in Europe and the USA (Fig. 22.1). This emphasizes the importance of screening and surveillance in individuals known to be at risk for HCC.

In the USA, data from the surveillance, epidemiology, and end results (SEER) registry showed that the incidence of HCC increased from 3.1 to 5.1 per 100,000 persons from the early 1990s to the mid-2000s. Analysis of more recent SEER data from 2007 to 2010 by Altekruse et al. noted that while HCC incidence rates did not increase significantly, mortality continued to rise [2]. As seen in previous studies, HCC incidence and mortality varied across race, age, and gender, with the highest mortality occurring among Asians, blacks, Hispanics, and white men aged 50 years and above. Geographical differences in mortality within the USA were apparent. The highest mortality rates occurred in Louisiana, Mississippi, Texas, and Washington, DC, underscoring the increased need for focused state and regional efforts to control HCC.

In most patients, HCC is preceded by the development of liver cirrhosis. It is not surprising, therefore, that cirrhosis and HCC share a number of etiologic risk factors. Of particular importance is chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). Worldwide, the most common etiology for HCC is chronic HBV infection, which accounts for about 70% of HCC cases in Africa and Asia. The regional prevalence of hepatitis B surface antigen positivity (HBsAg) in Africa and Asia is greater than 5%, and HBV infected patients with active viral replication develop cirrhosis at a rate of 7.2% per year [3, 4]. In Europe and North America, HCV is the underlying risk factor for the majority of HCC cases [5, 6].

Other factors implicated in the pathogenesis of HCC include alcohol, nonalcoholic fatty liver disease (NAFLD) and fungal aflatoxins. The growing incidence of obesity and metabolic syndrome, especially in developed countries, has resulted in an increasing prevalence of cirrhosis secondary to NAFLD. NAFLD covers a spectrum of disease including simple steatosis, nonalcoholic steatohepatitis (NASH) and cirrhosis. Cirrhosis was found in 46–60% of patients who had HCC in association with NAFLD [7–9]. Several studies have shown that patients with cirrhosis as a consequence of NASH are at increased risk for developing HCC [10–12]. Wong et al. recently reported that NASH was the most

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Table 22.1 Estimated incidence and mortality of the most common cancers worldwide (Adapted with permission from GLOBOCAN 2012 [1])

Cancer type	Incidence	Mortality	Mortality ratio
Lung	1,825,000	1,590,000	0.87
Breast	1,677,000	522,000	0.31
Colorectum	1,360,000	694,000	0.51
Prostate	1,112,000	307,000	0.27
Stomach	952,000	723,000	0.76
Liver	782,000	746,000	0.95

rapidly growing indication for liver transplantation (LT) in patients with HCC in the US [13].

Pathophysiology

The normal liver lobule contains liver parenchymal cells (hepatocytes), cholangiocytes, which line the biliary tree, and other nonparenchymal cells including hepatic stellate cells, Kupffer cells, and liver sinusoidal endothelial cells. The sinusoidal lumen and perisinusoidal space of Disse contain intrahepatic lymphocytes and liver-specific natural killer cells [14]. Chronic exposure to etiologic factors results in repeated cycles of injury, regeneration, and repair, eventually leading to cellular senescence. Some cells escape senescence by activating the telomerase reverse transcriptase gene or alternate mechanisms of telomere maintenance and become immortalized. In the genotoxic milieu of inflammation with enhanced free oxygen radical concentrations, immortalized cells acquire the critical number of mutations needed to transform first into dysplastic, and then neoplastic cells. This process is aided by changes in the cellular microenvironment, as exhaustion of the regenerative capacity of the liver is associated with proliferation and activation of hepatic stellate cells, leading to fibrosis, abnormal remodeling of liver tissue, and the development of cirrhosis.

There is accumulating evidence that chronic HBV and HCV infection both suppress the intrahepatic immune system and create an environment that is more permissive for carcinogenesis [15, 16]. Furthermore, patients with chronic HBV infection almost all acquire integrations of HBV into the host genome, which can induce carcinogenesis through a number of mechanisms, including activation of the telomerase reverse transcriptase (TERT) gene and other oncogenic molecules, the generation of novel oncogenic viral-host fusion proteins, and the generation of novel oncogenic viral-host long noncoding RNAs [17, 18].

The advent of next generation sequencing and other advanced genetic and genomic technologies has led to an improved understanding of the genetic events and cell signaling pathways that are most important in liver tumorigenesis. Key genes include TP53 (p53), TERT, CTNNBI (β-catenin), AXIN1, ARID1A, ARID2, CDKN2A (p16), DMXL1, NFE2L2, NLRP1, PIK3CA, and RPS6KA3. The signaling pathways corresponding to these genes include the mitogen-activated protein kinase, PI3K/Akt/mTOR, Wnt/β-catenin, TGFβ, integrin, antioxidant, and chromatin re-

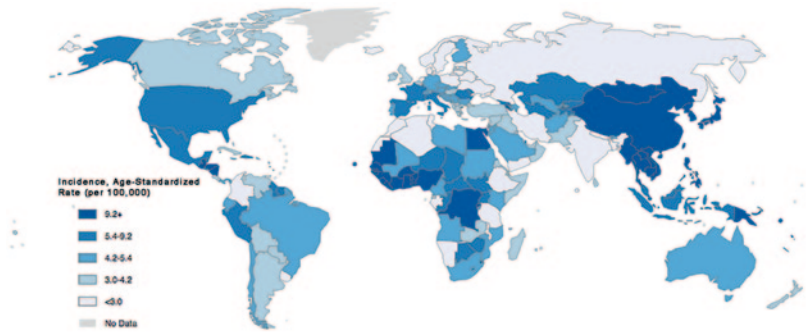

Fig. 22.1 Age-adjusted incidence of liver cancer worldwide, by geographical distribution. (Adapted with permission from GLOBOCAN 2012 [1])

modeling cell signaling pathways. These pathways target both cell proliferation and cell cycle regulation, as well as tumor cell apoptosis, invasion, migration, and the epithelial–mesenchymal transition; they also modulate interactions with microenvironmental factors that affect angiogenesis, inflammation, and antitumor immunity.

Clinical Manifestations

The clinical features of HCC are varied and depend on the degree of hepatic reserve. In cirrhotic patients, HCC may present with hepatic decompensation manifesting as jaundice, ascites, spontaneous bacterial peritonitis, or encephalopathy. In noncirrhotic patients, typical symptoms include anorexia, weight loss, weakness, abdominal pain, or a palpable mass. Although rare, paraneoplastic syndromes including erythrocytosis, hypercalcemia, hypercholesterolemia, thrombocytopenia, and hypoglycemia can occur early in patients with HCC. Such syndromes have been reported in up to 40 % of patients with large tumors and high alpha fetoprotein (AFP) levels. Patients with metastatic disease may present with symptoms related to the location of the metastasis.

Screening and Diagnosis

Early diagnosis of HCC is crucial due to the rapidly progressive nature of the disease as well as the high morbidity and mortality associated with advanced disease. Several organizations provide guidelines for HCC screening. Table 22.2 summarizes screening recommendations from the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver—European Organization for Research and Treatment of Cancer (EASL-EORTC) and the Asia Pacific Association for the Study of the Liver (APASL). Screening of the general population is not recommended. Since there are no experimental data to suggest the degree of risk that warrants surveillance, the decision to screen is based on cost-effectiveness models. In patients requiring surveillance, liver ultrasound and serum AFP every 6 months are the de facto standard for screening, although some experts discourage the use of AFP because of its low sensitivity for early stage disease [19]. In clinical practice, the sensitivity of liver ultrasound alone for detecting early stage HCC in cirrhotic patients was found to be as low as 32 %, although most studies report better performance [20]. The combination of biannual ultrasound and AFP testing increased the sensitivity of early stage HCC detection to 63.4 %. Recent studies suggest that trends or variations in AFP levels are also predictive of HCC development [21, 22]. Other biomarkers including the AFP-L3 % and the des gamma carboxyprothrombin are also

Table 22.2 High-risk groups for whom surveillance for hepatocellular carcinoma is recommended

Surveillance recommended
Cirrhotic patients
Child-Pugh class A and B[a]
Child-Pugh class C awaiting liver transplantation[a]
Stage 4 primary biliary cirrhosis[b]
Patients with cirrhosis and genetic hemochromatosis or alpha 1-antitrypsin deficiency[b]
Other cirrhosis[b]
Chronic HBV/ HCV patients with or without cirrhosis
Cirrhotic hepatitis B carriers[a,b,c]
Noncirrhotic HBV carriers with active hepatitis or family history of HCC[a,b]
African HBV carriers > 20 years[b]
Asian male HBV carriers > 40 years and female HBV carriers > 50 years[b]
Hepatitis C cirrhosis[a,b,c]
Noncirrhotic chronic HCV patients with advanced liver fibrosis F3[a]
Surveillance benefit uncertain
Asian male HBV carriers < 40 years or female HBV carries < 50 years[b]
Hepatitis C with F3 fibrosis[b]
Noncirrhotic NAFLD[b]

HBV hepatitis B virus, *HCV* hepatitis C virus, *HCC* hepatocellular carcinoma, *NAFLD* nonalcoholic fatty liver disease

[a] European Association for the Study of the Liver/ European Organization for Research and Treatment of Cancer *(EASL/EORTC)*

[b] American Association for the Study of Liver Diseases (*AASLD*)

[c] Asia Pacific Association for the Study of the Liver (*APASL*)

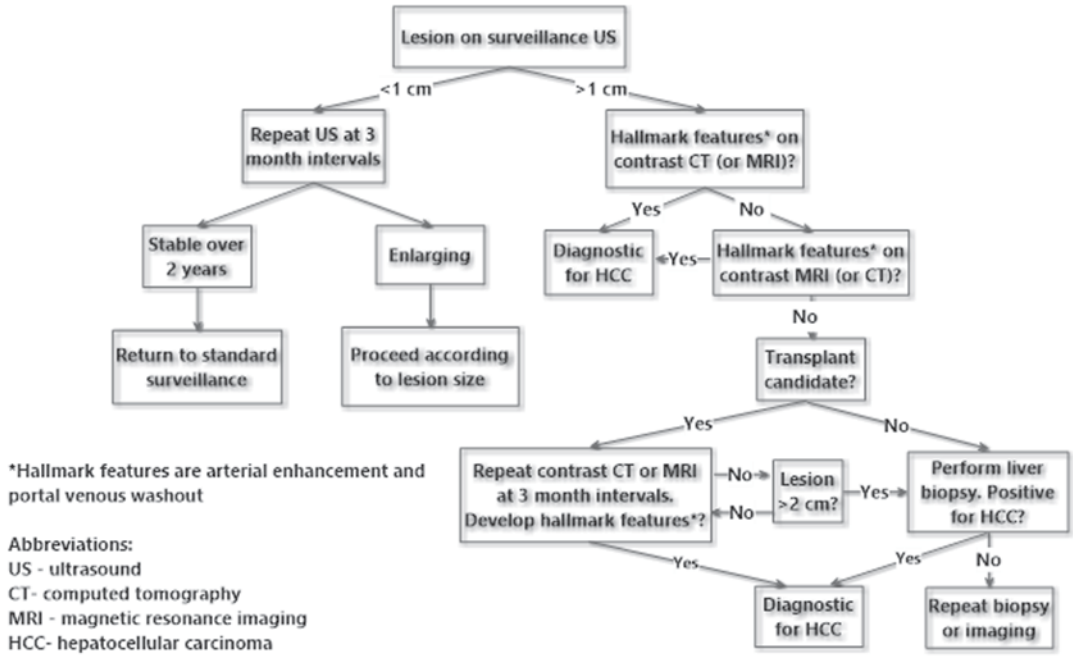

Fig. 22.2 Algorithm for diagnosis of hepatocellular carcinoma

used in some countries for surveillance or risk stratification.

Detection of a liver nodule on ultrasound during surveillance warrants further investigation depending on the size of the nodule (Fig. 22.2). If the nodule is less than 1 cm, repeat ultrasound in 3 months is recommended. For nodules greater than 1 cm on initial ultrasound screening or on follow-up ultrasound examination, imaging with four-phase multidetector computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI) is recommended. In these larger sized lesions, a diagnosis of HCC is made when the hallmark features of arterial hypervascularity and portal venous or delayed phase washout are observed on either imaging modality (Fig. 22.3). Further characterization of HCC can be observed as T2 hyperintensity, intensity on diffusion-weighted imaging, and lack of uptake on delayed hepatobiliary phase sequences with gadoxetate disodium (Eovist) or gadobenate dimeglumine (MultiHance) contrast MRI [23].

When the characteristic features of HCC are not demonstrated on either CT or MRI, the other imaging modality should be utilized. If both CT and MRI fail to show the expected hallmark features in a liver lesion greater than 1 cm, biopsy with pathologic examination is recommended. In practice, the US United Network for Organ Sharing (UNOS) does not assign priority points in the allocation of organs for LT to patients with tumors less than 2 cm in size. Therefore, in transplant eligible patients, most hepatologists will follow these lesions by performing cross-sectional imaging every 3 months until the 2-cm size cutoff is reached. By the time such lesions grow to 2 cm, they will often have acquired typical imaging features of HCC. Consequently, it is reasonable to defer biopsy in this group of patients, so minimizing the small but real risk of needle track seeding, which is a greater concern in patients undergoing LT who will require long-term immunosuppression. Another important consideration when biopsying small lesions is the 10% or greater risk of a false negative result.

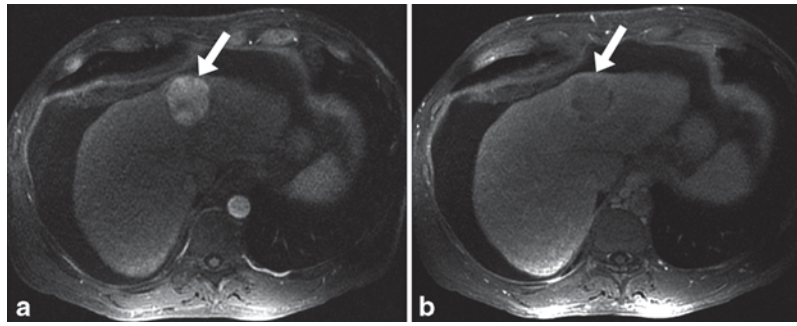

Fig. 22.3 Arterial enhancement (**a**) and portal venous phase washout (**b**) of a hepatocellular carcinoma observed on multiphasic contrast magnetic resonance imaging

Staging

The most widely accepted staging method for HCC is the Barcelona Clinic Liver Cancer (BCLC) staging system, which associates each stage with a treatment recommendation. Based on performance status (PS), tumor characteristics, and liver function as classified by the Child-Pugh (CP) score, BCLC stratifies patients into very early (0), early (A), intermediate (B), advanced (C), and terminal (D) stages (Table 22.3). Patients with very early stage 0 disease have well-preserved liver function (CP A), are asymptomatic (PS 0), with one nodule of less than 2 cm, without satellites or vascular invasion. Patients classified as having early, intermediate, or advanced-stage disease have CP A or B liver function. Those with early stage A disease have PS 0, with a single nodule or up to three nodules less than 3 cm. Patients with intermediate stage B disease have PS 0 and multinodular disease, while those with advanced stage C disease are symptomatic with PS 1-2, and have extensive disease characterized by portal invasion or extrahepatic spread. Patients with terminal stage D disease are symptomatic with PS > 2, CP C or advanced CP B.

Current Therapies

The goal of treatment for patients with very early and early stage HCC is to cure the disease. Intermediate- and advanced-stage HCC should be treated with noncurative (palliative) therapies while symptomatic management is appropriate for patients with terminal stage HCC.

Curative Therapies for Very Early and Early Stage HCC

Surgical Resection

Resection of liver tumors is potentially curative and is the primary approach in patients who present with very early or early stage HCC who do not have clinically significant portal hypertension (defined as the presence of esophageal varices, splenomegaly with a platelet count less than 100,000/μL, or a hepatic venous pressure gradient greater than or equal to 10 mmHg), with a bilirubin < 1 mg/dL, or model for end-stage liver disease (MELD) score up to 8 [24, 25]. Prognostic predictors for surgical resection include tumor size, number of nodules, liver function, and portal pressure [26, 27]. The choice of laparoscopic versus open hepatectomy depends on the expertise of the surgeon and patient preference. Current evidence suggests that there is no difference between laparoscopic versus open hepatectomy in regard to operative complication, recurrence, and survival rates [28, 29]. However, there have been no randomized controlled trials comparing the two methods. Recent publications reporting long-term outcomes of laparoscopic resection as regards tumor recurrence, metastasis, and survival rates suggest that the outcomes are comparable to those from open surgical resection [30].

Table 22.3 The Barcelona clinic liver cancer (*BCLC*) staging for hepatocellular carcinoma, corresponding treatment strategy, and posttreatment overall survival and tumor recurrence. (Adapted from references [49, 59–66])

BCLC stage	Performance status	Child-Pugh	Tumor stage	Treatment approach	Other factors affecting treatment choice	Treatment	Survival after treatment (%)			5-year recurrence (%)
							1-year	2-year	5-year	
0 Very early	0	A	Single, <2 cm	*Curative*	Single nodule, normal portal pressure, normal bilirubin	Resection	>70	>70	40–70	60–70
					Single nodule ≤5 cm, increased portal pressure, no comorbidities	Transplant	>80	>70	>70	15
A Early	0	A–B	Single or up to 3 nodules, each up to 3 cm		2 or 3 nodules, each ≤3 cm, no comorbidities					
					1–3 nodules ≤3 cm, increased portal pressure, with comorbidities	RFA	>80	>70	40–70	>70
B Intermediate	0	A–B	Multinodular	*Noncurative*	–	TACE/TARE	60–80/60–70	10–50/30–60	–	–
C Advanced	1–2	A–B	Vascular invasion or extrahepatic spread		–	Sorafenib/ TARE	40–50/40–50	30/30	15/20	–
D Terminal	3–4	C	Any tumor stage	*Symptomatic*	–	Supportive care	–	–	–	–

RFA radiofrequency ablation, *TACE* transarterial chemoembolization, *TARE* transarterial radioembolization

An adequately sized liver remnant is required for postoperative liver regeneration to restore liver mass and function [31]. Thus, an estimate of the expected future liver remnant (FLR) is obtained by means of multi-detector CT or MRI prior to resection. For a noncirrhotic and cirrhotic liver, the recommended minimal FLR is 25 and 50 %, respectively [32]. In cirrhotic patients in whom the predicted FLR is less than 50 %, preoperative portal vein embolization (PVE), which induces hypertrophy of nonembolized hepatic segments, has been found to decrease the rate of postoperative complications [33].

The 5-year survival rate after surgical resection is 40–70 %, with 5-year tumor recurrence rates estimated around 60–70 %. Early tumor recurrence (within 2 years after resection) is usually the result of intrahepatic spread of HCC prior to resection, while late recurrence results from de novo transformation of precancerous lesions in the remnant liver [26, 34, 35]. In patients with postresection tumor recurrence, potential therapeutic approaches include re-resection, salvage LT, and radiofrequency ablation (RFA).

Liver Transplantation

Transplantation is the treatment of choice for patients not eligible for surgical resection but with tumor that meets transplant criteria. The Milan criteria are the most widely used parameters to determine transplant eligibility [36]. The criteria limit transplant eligibility to patients with a single tumor measuring 5 cm or smaller or two or three tumors, each no larger than 3 cm, without vascular invasion or extrahepatic spread. The 5-year patient survival rates posttransplant improved from 15–40 % in the late 1990s to 70–80 % by the late 2000s with the adoption of the Milan criteria in the selection of patients with HCC for LT [37–40].

In the USA, patients with HCC who are transplant candidates receive a MELD score assignment and an additional 10 % increase every 3 months until they undergo LT or become ineligible for transplantation due to progressive disease. HCC may progress in patients on the transplant waiting list, resulting in a significant drop-out rate. Thus, when the estimated waiting time is longer than 6 months, the current practice is to use TACE or RFA as bridging therapy to reduce the rate of tumor progression [41]. In preliminary studies, the mTOR inhibitor, sirolimus improved tumor-free survival in HCC patients who received an LT. This observation is being further investigated in an ongoing trial [42]. The scarcity of donor livers remains a major obstacle to timely transplantation, and living donor liver transplantation (LDLT), initially developed in Asia, is one approach to increase the pool of liver donors. A recent study found no significant difference in the overall 5-year patient survival or relapse-free survival between LDLT and deceased donor LT recipients [43].

Thermal and Nonthermal Ablative Treatments

In patients with very early and early stage HCC with unresectable disease due to compromised liver function or who are ineligible for LT because of age or comorbidities, ablative treatment using thermal or nonthermal techniques offers an alternative potentially curative strategy. Thermal ablation employs radiofrequency, microwave, laser, or cryoablation, while nonthermal methods use ethanol or acetic acid. Radiofrequency ablation (RFA) appears to be superior to ethanol injection therapy and is the most frequently used technique [44]. RFA causes necrosis in almost 100 % of HCC lesions measuring less than 2 cm, and is considered highly effective for tumors up to 3 cm. In contrast, ethanol injection achieves necrosis in tumors less than 2 cm but is not as effective for larger tumors. RFA should be avoided in HCCs located near the bowel, heart, large bile ducts, or in subscapular areas due to the risk of local injury, or in the vicinity of major blood vessels due to the heat sink effect of the vessels that reduces the effectiveness of this therapy. The 5-year survival of patients with HCC treated with ablative therapy is 40–70 % (Table 22.3).

Treatment for Intermediate Stage HCC

Catheter-Directed Transarterial Therapy

Differences in the blood supply to the liver and HCC provide the rationale for transarterial therapy, which is considered in patients with multifocal disease or large cancers that are not amenable to curative therapies. The hepatic artery supplies 25% of blood to the liver and 95% of blood to HCCs, while the portal vein supplies 75% of blood to the liver and less than 10% of blood to HCCs. Transarterial administration of embolic particles, chemotherapeutic drugs, or radioactive beads or glass microspheres through the hepatic artery results in HCC tumor necrosis without significant adverse effects on the liver [45]. Transarterial chemoembolization (TACE) combines injection of chemotherapeutic drugs with obstruction of the blood supply, effectively trapping the chemotherapy within the tumor. This approach has been shown to improve survival of HCC patients with intermediate stage disease. TACE can also be administered using doxorubicin-impregnated drug-eluting beads [46, 47].

Transarterial radioembolization (TARE) is employed in patients with intermediate or advanced stage HCC due to the low toxicity and excellent antitumor activity of this strategy [48]. TARE has been found to be effective in patients with portal vein tumor thrombosis who are not candidates for TACE. In a retrospective case-control study comparing the outcomes and safety of TARE using β-emitting yttrium-90 glass microspheres versus TACE in patients with unresectable HCC, there was no significant difference in efficacy between TARE and TACE [49]. Studies have shown that patients treated with TARE also report a higher quality of life compared to those treated with TACE [50, 51]. More studies, preferably randomized trials, are needed to further evaluate TARE as an alternative to TACE.

Targeted Therapy for Advanced Stage HCC

Sorafenib

Sorafenib is recommended as the first-line therapy for patients with advanced stage tumors (BCLC stage C) and preserved liver function (CP A or B7), or for patients with disease progression following locoregional therapy. Sorafenib is an oral multiple tyrosine kinase inhibitor that blocks Raf, vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3), platelet-derived growth factor receptor (PDGFR), tyrosine kinases, and c-Kit signaling [52]. There is also increasing evidence that sorafenib acts by downregulation of Mcl-1 and inhibition of protein tyrosine phosphatases [53, 54]. Sorafenib is currently the only systemic therapy to demonstrate a survival advantage for advanced HCC. In the randomized double-blind, placebo-controlled phase III SHARP trial, those patients in the sorafenib group demonstrated a longer time to tumor progression (5.5 months) and greater median survival (10.7 months), compared to patients in the placebo group (2.8 months and 7.9 months, respectively) [55]. In the Asia Pacific trial, in which the majority of patients had hepatitis B infection and more advanced disease than the SHARP trial, the sorafenib group demonstrated a median survival of 6.5 months compared to 4.2 months in the placebo group [56]. In a recent prospective feasibility analysis of advanced HCC patients with CP A versus CP B liver function on sorafenib, the rate of adverse events and drug tolerability was found to be similar between the two groups [57]. The overall survival of CP A versus CP B patients with advanced HCC on sorafenib was 10 versus 3.8 months. A number of trials are currently underway to test combination or sequential treatment strategies with sorafenib, doxorubicin, and other novel targeted therapy agents and also of sorafenib in combination with TACE or TARE.

Assessment of Response to Therapy

The modified response evaluation in solid tumors (mRECIST) or EASL criteria are recommended for assessing HCC response following treatments that inhibit angiogenesis or induce tumor necrosis. Response to treatment is determined based on the combined assessment of target lesions, nontarget lesions, and new lesions by means of imaging. Follow up imaging with multiphasic CT or dynamic contrast-enhanced MRI is usually performed 2–3 months after resection, ablation, locoregional therapy, or initiation of sorafenib. Subsequent repeat cross-sectional imaging should be performed every 3 months for the first year and every 4–6 months thereafter to evaluate for tumor progression or recurrence. A recent study found that the earliest time point to evaluate response to combination therapy was 3 months and that mRECIST and EASL criteria predicted survival [58].

Future Directions in Management

The molecular and clinical heterogeneity of HCC and the rapid progression to advanced or terminal stage disease are some of the challenges faced in developing therapeutic strategies for this complex disease. Several anti-angiogenic tyrosine kinase inhibitors have recently failed in phase III studies, necessitating the development of alternative therapeutic strategies and identification of novel targets. Any discussion of future HCC therapy cannot ignore the effect of newer and more effective therapies that treat or mitigate HCC etiologic factors, preventing liver cirrhosis and ultimately reducing the number of HCC cases. In this context, the use of anti-HBV agents and the development of multiple new oral anti-HCV agents will eventually lead to a reduction in the incidence of HBV- and HCV-mediated HCC.

Some of the molecular pathways and targets currently being investigated for potential HCC therapy include multiple receptor tyrosine kinases, including c-MET, mTOR, glypican 3, histone deacetylases, and the epithelial–mesenchymal transition. Immunotherapeutic approaches to HCC are also being developed, based on the premise that the immune system can be primed or reeducated to mount a successful antitumor response. The heterogeneity of HCC calls for identification of biomarkers that can predict patient response to therapy and guide the clinician in choosing the most appropriate and effective treatment regimen, paving the way for personalized HCC therapy.

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Cholangiocarcinoma

23

William C. Palmer and Denise M. Harnois

Cholangiocarcinoma (CCA) is an uncommon and aggressive adenocarcinoma arising from the biliary tract [1]. The two clinical phenotypes are intrahepatic and extrahepatic cancer. Intrahepatic CCA (IH-CCA) appears to be increasing in incidence, and is associated with a poor prognosis [2]. IH-CCA comprises approximately 25 % of all CCA, and is the second most common primary liver cancer behind hepatocellular carcinoma (HCC). IH-CCA can further be characterized as peripheral mass-forming or central periductal infiltrating tumors. Most patients with IH-CCA do not possess known risk factors, but a strong association with cirrhosis has recently been established [3]. The clinical presentation of IH-CCA can be nonspecific even when the disease is extensive. Management combines surgical resection, systemic chemotherapy, and targeted radiation therapy but is associated with poor long-term survival [4]. Surgically unresectable disease is currently incurable.

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Epidemiology and Risk Factors

CCA is uncommon compared to other biliary tract cancers, such as pancreatic cancer and gallbladder cancer. Data from the Surveillance, Epidemiology, and End Result Program show an increase in age-adjusted annual incidence of IH-CCA in the USA from 0.13 to 0.58 per 100,000 over a 25-year period, with similar trends internationally [5]. A review of international data from 1977 to 2007 defined certain regions with the highest incidence of IH-CCA, including Korea, regions of China, along with northern and central Thailand (Table 23.1) [6]. Autopsy series have reported an overall prevalence of 0.01–0.46 %, [7] with higher prevalence in Asia attributed to endemic parasitic infestations and hepatitis B infection.

Risk factors for IH-CCA have been examined among different demographics and geographic areas [3]. A strong association with cirrhosis has been demonstrated in a large meta-analysis, with a combined odds ratio of 22.92 [3]. Generally, advanced age (>65 years) is considered a risk factor for CCA. Hui, et al. retrospectively reviewed CCA patients with and without cirrhosis, finding that IH-CCA in cirrhosis presented at a relatively younger age, and was associated with formation of portal vein thrombus and a shorter overall survival compared to other CCA patients (Table 23.2) [8]. Other associated IH-CCA risk factors include primary sclerosing cholangitis, biliary cysts, Caroli's disease, hepatitis B and C infections, diabetes mellitus, alcohol use, obesity, thorium dioxide exposure, and certain

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Table 23.1 Regional incidence of intrahepatic compared to extrahepatic cholangiocarcinoma

Countries	IH-CCA cases/100,000	EH-CCA cases/100,000
Thai regions	1.05–51.45	0.15–0.3
Chinese regions	0.2–7.45	0–1.4
Korean regions	3.95–4.55	3.15–4.2
Taiwan	4.1	0.6
Japanese regions	1.25–1.3	1.8–2.1
Singapore	1.1	0.35
Philippines	1.1	0.1
The UK–Scotland	1.05	0.4
Italy	0.88	1.55
Denmark	0.62	0.65
United States of America	0.58	0.88
France	0.2	1.1
Vietnam	0.1	0

IH-CCA intrahepatic cholangiocarcinoma, *EH-CCA* extrahepatic cholangiocarcinoma

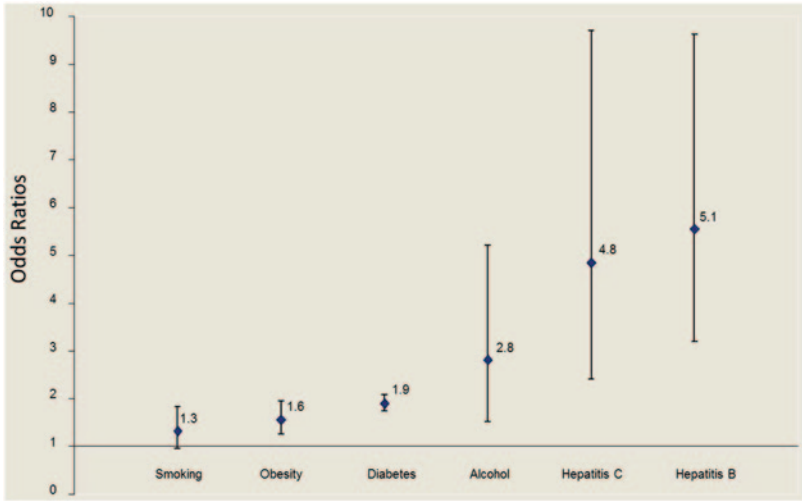

Fig. 23.1 Risk factors for intrahepatic cholangiocarcinoma

chronic parasitic infections (Fig. 23.1) [9]. *Clonorchis sinensis* and *Opisthorchis viverrini* are recognized as group 1 carcinogens for CCA by the International Agency for Research in Cancer of the World Health Organization [10]. Intrahepatic ductal inflammation from hepatolithiasis and hepatic schistosomiasis can also predispose to the development of IH-CCA. Potential risk factors also include smoking and human immunodeficiency virus infection, but further study is needed.

The underlying reason for the steady increase in incidence of IH-CCA is unclear; improved diagnostic testing is contributing, along with the increasing incidence of certain risk factors listed above [11]. Given that few patients with CCA possess established risk factors, host genetic polymorphisms may play a key role in pathogenesis and could be used to identify at-risk individuals. Variations in genes coding for a number of different enzyme systems may place individuals at risk for CCA. The recent consensus guidelines for IH-CCA outlined a set of genes associated with CCA in several case-control studies (Table 23.3) [12]. These studies included a relatively small number of individuals; data from larger numbers

Table 23.2 Cholangiocarcinoma in patients with and without cirrhosis

	Noncirrhotic group	Cirrhotic group	*P*-value
% of overall cohort	73	27	–
% males in group	42	71	0.189
Mean age (years)	73.21 ± 15.92	58.8 ± 14.18	0.001
Portal vein thrombus (% of group)	5	86	0.001
Median survival (months)	16 (range: 6–41)	6 (range: 2–24)	0.036

Table 23.3 Host genetic polymorphisms associated with cholangiocarcinoma

Gene product	Abbreviation	Protein function
Familial Intrahepatic Cholestasis Protein 1	FIC1	Biliary transporter for membrane phosphotidylserine
Glutathione S-transferases	GST01	Detoxification enzymes
Heterozygosity for the alpha1-antitrypsin Z allele	–	Protease inhibitor acting against pro-inflammatory enzymes
Multidrug resistance-associated protein 2	MRP2/ABC2	Biliary transporter for toxin clearing
Natural killer cell receptor in PSC patients	NKG2D	Activates NK cells, key for tumor surveillance in PSC
Prostaglandin-endoperoxide synthase 2/ cyclooxygenase-2	PTGS2, COX-2	Inflammatory mediator
Thymidylate synthase	TS	DNA repair enzyme
X-ray repair cross-complementing group 1	XRCC1	DNA repair protein
5,10-Methylenetetrahydrofolate reductase	MTHFR	Folate metabolism and DNA methylation

PSC primary sclerosing cholangitis

of patients are needed to provide a clearer understanding of the impact of host genetic polymorphisms on disease.

Pathophysiology

CCA can occur along any area of the bile duct, and can be divided anatomically into intrahepatic (IH-CCA), and extrahepatic lesions (EH-CCA), occurring at the hilum, perihilar (p-CCA), and distal bile ducts (d-CCA) [12]. Perihilar cancers involving the left and right hepatic duct junction are referred to commonly as Klatskin tumors [13]. CCA possesses histological and molecular characteristics of adenocarcinoma in 90% of cases. A recent study suggested that pluripotent hepatic stem cells are the progenitor cell line [14]. CCAs are thought to transform in a similar fashion to other adenocarcinomas; from early hyperplasia and metaplasia, to dysplasia and onto carcinoma [15]. Histologically, CCA can range from well differentiated to undifferentiated, with surrounding tissue displaying fibrotic and desmoplastic traits. Chronic inflammation and bile duct obstruction are considered to be major contributors to the development of CCA, making cirrhotic liver tissue an ideal media for oncogenesis [16].

Two pathologically and biologically different IH-CCA have been reported; a peripheral mass-forming lesion, and a central periductal infiltrating tumor [17]. The central periductal IH-CCA tend to present more commonly with portal pedicle and bile duct infiltration, with associated jaundice. Peripheral mass-forming IH-CCA has been linked to chronic hepatitis [18]. The mass-forming lesion typically has less local recurrence (76.1% compared to 92.9%) and a significantly higher median survival (32 months compared to 22 months) than periductal infiltrating tumors [19].

In rare cases, tumors can contain elements of both CCA and HCC. Referred to as mixed tumors, they are diagnosed by positive cytokeratin 19 and cytokeratin 7 immunohistochemistry tissue staining [12]. Liver biopsy is indicated for atypical radiographic findings prior to liver transplantation (LT). One retrospective review

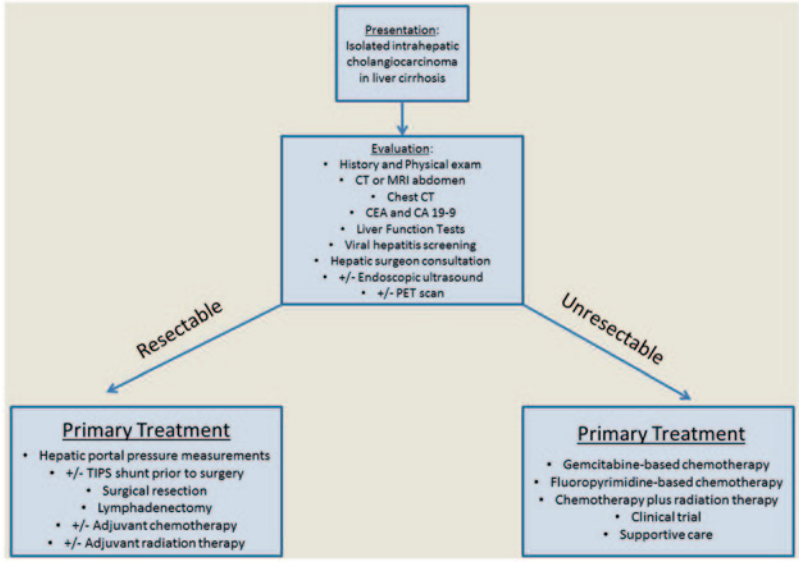

Fig. 23.2 Management of intrahepatic cholangiocarcinoma in the cirrhotic patient. *CT* computer tomography, *MRI* magnetic resonance imaging, *CEA* carcinoembryonic antigen, *CA* 19-9 carbohydrate antigen 19-9; *PET* positron emission tomography; *TIPS* transjugular intrahepatic portosystemic shunt

of patients with mixed tumors following LT failed to identify useful pre-LT serum characteristics for their diagnosis [20]. Retrospective radiographic review of such patients after LT demonstrated progressive contrast enhancement throughout the arterial and portal venous phases without the classic washout seen in pure HCC [21]. Unifocal mixed tumors smaller than 2 cm appear to have similar 1, 3, and 5-year post-LT survival compared to LT for HCC inside accepted criteria [22]. Overall, however, mixed tumors are associated with poorer outcomes following LT than pure HCC, with cumulative 5-year recurrence rates of 65 % [21, 23].

Clinical Presentation, Diagnosis, Staging

Clinical signs and symptoms of CCA at presentation can be difficult to distinguish from decompensated cirrhosis. Abnormal liver function tests, abdominal pain, jaundice, weight loss, and pruritus can occur. IH-CCA more commonly presents with pain than with jaundice, as displaced hepatic parenchyma presses on the liver capsule [24]. Many patients, however, are asymptomatic, and their tumors are only detected incidentally on imaging studies. The diagnosis of IH-CCA requires microscopic tissue examination, as no other serum or imaging test is sufficiently sensitive and specific for disease confirmation (Fig. 23.2). The histological appearance of IH-CCA is similar to metastatic nonhepatic primary tumors and can be difficult to distinguish. Florescence in situ hybridization (FISH) analysis of tissue cells, which uses fluorescently labeled DNA probes to detect chromosomal abnormalities, can increase the specificity of the diagnosis when added to standard cytology [25]. FISH analysis involves scanning for cytologically atypical cells by determining the number of identified peri-centromeric signals on certain chromosomes, along with assessment for nuclear enlargement or irregular nuclear contour. High numbers of specific chromosomal abnormalities detected by FISH can aid in diagnosis. Serum carcinoembryonic antigen (CEA) and CA 19-9 may be elevated in 85 and 40 % of patients, respectively [26], thus facilitating a presumptive diagnosis or assisting in monitoring for recurrence after surgery. However, values must be interpreted with caution, as CA 19-9

elevation can be related to underlying cholangitis or biliary obstruction.

Radiographic differentiation of IH-CCA from HCC can be difficult. Magnetic resonance imaging (MRI) appears to offer an advantage over ultrasound and computer tomography (CT) scans. MRI with intravenous contrast can demonstrate progressive contrast uptake throughout different phases, as opposed to contrast washout in delayed phases as seen with HCC [27]. On MRI, IH-CCA typically appears hypointense on T1-weighted images and hyperintense on T2-weighted images (Fig. 23.3). MRI with cholangiopancreatography (MRI/MRCP) can be helpful in visualizing the ductal system and in determining the anatomic extent of the tumor. A previous study found that CT was limited in detecting the extent of CCA extent, specifically with periductal infiltrating tumors [28]. On CT scan imaging, the typical appearance is of a hypodense mass in the noncontrast phase with generally irregular margins and peripheral rim enhancement in the arterial phase, and then progressive hyperattenuation on venous delayed phase. This is in contrast to HCC, which is characterized by a rapid enhancement during the arterial phase and a washout in the delayed venous phases. This being said, the two lesions can be very difficult to distinguish on imaging. Endoscopic ultrasound (EUS) is useful in assessing and sampling suspicious lymph nodes and can be used for biopsy of the primary lesion. If, however, the lesion is perihilar in nature and LT is being considered, EUS-guided biopsy of the lesion will exclude the patient from LT because of concerns for tumor seeding. Fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning can provide diagnostic utility because of the high glucose uptake of the bile duct epithelium, but is less helpful in smaller or periductal infiltrative tumors [29]. The sensitivity of PET–CT is higher for IH-CCA (90%) than for EH-CCA (60%), with a distant metastatic detection rate reported to be 100% [30]. Despite all attempts at preoperative staging with imaging studies, final determination of resectability occurs at the time of surgery [31]. Tumor size may or may not provide prognostic information for resection. Poor outcomes are associated with positive lymph nodes, positive margins, multiple nodules, and vascular invasion. Lymph node metastases are found in up to 30% of surgically assessed IH-CCAs [32].

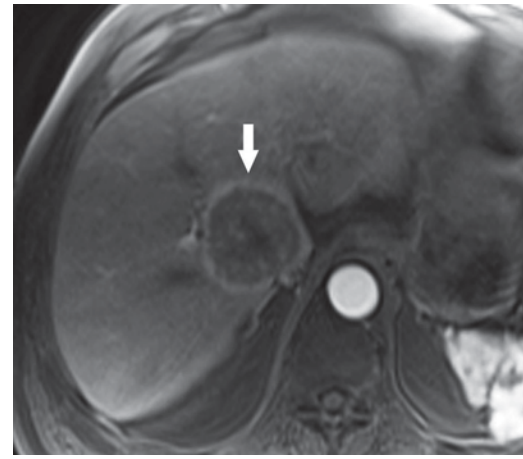

Fig. 23.3 Magnetic resonance imaging of an intrahepatic cholangiocarcinoma. Arterial phase image demonstrating a ring-enhancing mass with central necrosis

Treatment

The natural history of IH-CCA without intervention is ominous. The American Cancer Society reported a 5-year survival of IH-CCA as 15% for localized disease, and only 2% for metastatic CCA. IH-CCA treatment combines surgical resection and lymph node evaluation with systemic chemotherapy and targeted radiation therapy (Figs. 23.2 and 23.4). Guidelines published in the Journal of Hepatology outlined a suggested algorithm of treatment management in patients with IH-CCA [12].

Resectability rates are low and variable (18–70%), with 5-year survival rates after surgery of 20–40% and median survival between 12 and 37.4 months [4]. Surgery should be performed in potentially resectable disease, as complete disease resection is the only chance at cure. Limited data exist for staging laparoscopy at the time

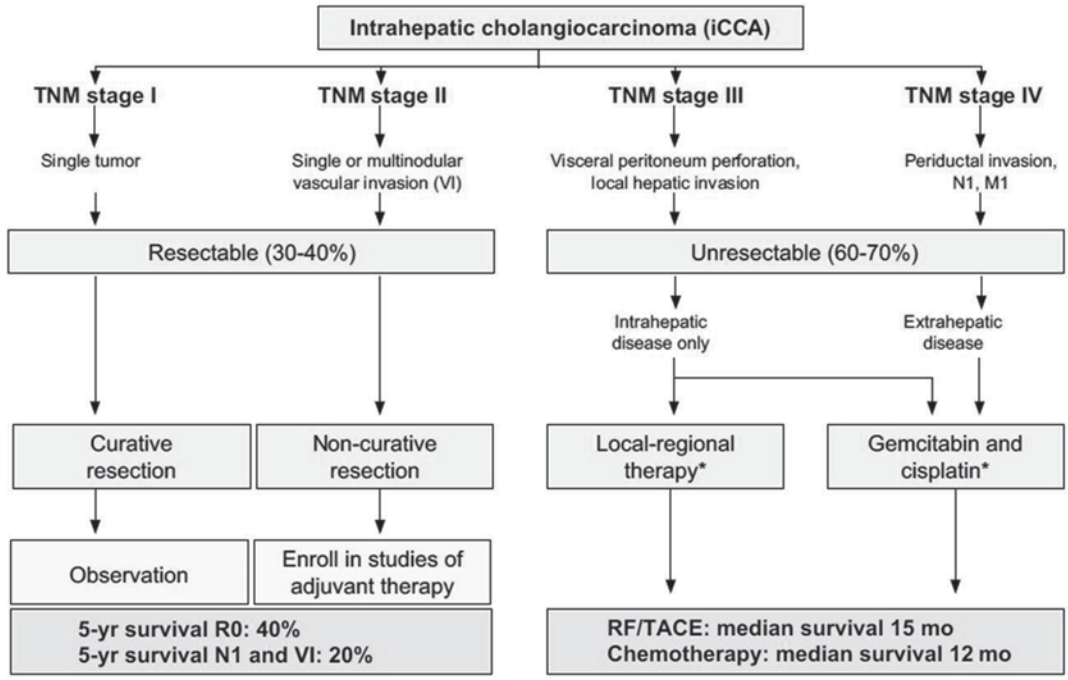

Fig. 23.4 Suggested treatment algorithm for patients with intrahepatic cholangiocarcinoma. *TNM* tumor, necrosis, metastasis, *RF* radiofrequency, *TACE* transcatheter arterial chemoembolization. (Reproduced with permission from Elsevier) [12]

of surgery. Previously undetected metastatic disease was detected in 6 of 22 patients (27%) in a small cohort with IH-CCA who underwent diagnostic laparoscopy [33]. Significant hepatic resection is often required, with a large multicenter series reporting 73% of patients having either hemi-hepatectomy or extensive hepatic resection [32]. Despite conflicting data on routine lymphadenectomy (LAD) at the time of IH-CCA resection, consensus guidelines call for strong consideration of LAD because of the reported 30% rate for diagnosing nodal involvement [34]. Other investigators have argued that patterns of recurrences as well as survival are unaffected by LAD [35]. Adjuvant chemotherapy and targeted radiation therapy should be considered, though there are little data demonstrating any improvement in outcome. A single randomized trial examined adjuvant chemotherapy following surgical resection of hepatobiliary cancers, although it was underpowered for the CCA cohort. Adjuvant therapy with intravenous mitomycin C and Fluorouracil (5-FU) was found to provide no additional benefit in CCA when compared to surgery alone [36]. The liver is the most common site of recurrence, followed by lungs, lymph nodes, and bones [33]. Screening with cross-sectional imaging and tumor markers every 6–12 months is warranted to monitor for recurrence, although second-line therapies have not been proven to be beneficial [12]. In light of the complexities associated with surgical resection of IH-CCA, these procedures are best performed at high-volume experienced hepatobiliary centers [12].

In cirrhotic patients with IH-CCA, special care should be taken to risk stratify those at increased risk for portal hypertensive bleeding perioperatively or acute decompensation postoperatively. Preoperative transhepatic portal pressure measurements and a liver biopsy may be helpful in assessing presurgical risk. As LT is not an option for IH-CCA patients, the risk of hepatic decompensation must be discussed with cirrhotic patients. Perihilar EH-CCA, though not associated with cirrhosis, may be managed with LT at transplant centers experienced in following

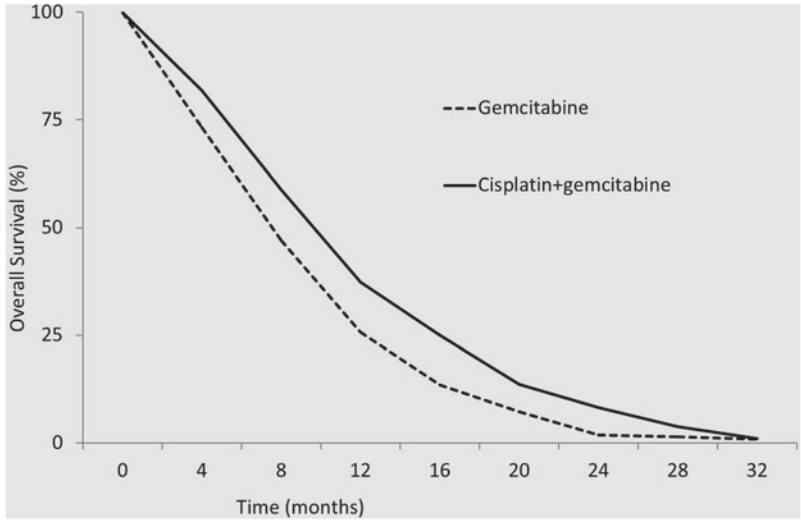

Fig. 23.5 Outcomes of locally advanced and metastatic cholangiocarcinoma in patients receiving chemotherapy

complex and resource-intensive protocols [37]. The perihilar CCA must be less than 3 cm, with no evidence of lymph node involvement or metastatic disease and cannot have been biopsied percutaneously or via EUS guidance [38]. Neoadjuvant chemoradiation therapy is administered prior to listing for LT. The 5-year survival after LT for perihilar CCA is greater than 70%.

Systemic chemotherapy is the primary treatment in unresectable cancer with extrahepatic disease. The uncommon nature of IH-CCA makes large randomized trials difficult to conduct. Several 5-FU-based regimens have been shown to prolong survival times and quality of life as compared to supportive care, including combination with leucovorin and etoposide [39]. Gemcitabine produces relatively good results, with median survival times (MST) ranging from 4.6 to 14 months [40]. The addition of cisplatin can further improve MST and is associated with a minimal increase in side effects (Fig. 23.5) [41]. Several reports of mitomycin D, cisplatin, taxanes, and irinotecan (CPT-11) showed response rates of 10% with MST of 4.5–6.1 months [42]. One trial utilizing oral tegafur/gimeracil/oteracil potassium (S-1) from Japan provided favorable results with response rates of 35% and MST of 9.4 months in 40 patients [43]. A therapeutic trial targeting molecular expression of epithelial growth factor receptors (EGFR) with erlotinib is currently underway, having shown promise in phase II trials [44].

Palliative locoregional therapy can be considered in appropriate candidates with intrahepatic disease only. Transarterial chemoembolization therapy (TACE) has been shown to prolong survival in unresectable disease, with overall 1-year survival of 52% after TACE independent of chemotherapy regimens [45]. Child–Turcotte–Pugh classification A and stability of disease after initial TACE treatment predict improved outcomes. The administration of yttrium-90 (Y90) radioembolization can provide survival length benefit as well, which is most pronounced in unifocal IH-CCA (mean survival of 14.6 months) [46]. Certain patients may even be downstaged to resectable disease after Y90 therapy.

Conclusions

CCA, specifically the intrahepatic type, is associated with liver cirrhosis. Definitive diagnosis requires tissue examination, and aggressive surgical and medical treatments provide only modest survival benefit. Early enrollment in clinical trials and referral to tertiary centers experienced in managing this disease are the best management options, when available. Resection of CCA in cirrhosis warrants diligent preoperative

assessment and management of portal hypertension. Perihilar CCA, if it is within criteria, can be treated successfully with LT. Other therapies include surgical resection, local ablative therapies, and systemic therapies. Small mixed HCC/IH-CCA tumors may be more amenable to LT, but overall survival is decreased compared to LT for HCC inside accepted criteria. There is no role for LT for IH-CCA outside of clinical trials. Future study is needed to evaluate new therapies that will prevent or slow disease progression and improve patient outcomes.

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Bacterial Infections in Patients with Cirrhosis

24

Thierry Gustot and Richard Moreau

In cirrhosis, bacterial infection is defined as a pathologic process caused by invasion of normal sterile tissue, fluid, or cavity by pathogenic or potentially pathogenic microorganisms. Bacterial infection is one of the most common causes of hospital admission in cirrhotic patients. Indeed, infection is present at admission or develops during hospitalization in about 30 % of patients with cirrhosis (incidence that is four- to fivefold higher than in the general population) [1]. Infections may be classified as community acquired (CA) if the diagnosis is made at admission or during the first 48 h after hospitalization and health care associated (HCA) which also occur in the same time period but with a history of previous contact with a health-care environment (i.e., hospitalization or short-term admission for at least 2 days in the previous 90–180 days, residence in a nursing home or a long-term care facility, or chronic hemodialysis) [2]. Infections are considered as nosocomial if the diagnosis is made after 48 h of hospitalization. Approximately, one third of bacterial infections are CA, one third HCA, and one third nosocomial. Spontaneous bacterial peritonitis (SBP) and urinary tract infections (UTI) are the most frequent infections observed, followed by pneumonia, skin and soft tissue infections (SSTI), spontaneous bacteremia and catheter-related infections [3]. Clinical risk factors associated with the appearance of bacterial infections in cirrhosis are high Child-Pugh score, variceal hemorrhage, low ascitic protein levels (< 15 g/L), and a prior episode of SBP [4–7].

Enterobacteriaceae cause the majority of infections in cirrhosis. Therefore, there is a widespread use of beta-lactams and quinolones in this population. Due to this, and increased invasiveness of management, nonclassical pathogen and multiresistant bacteria are increasingly reported.

Infection induces a systemic-host response with three stages of severity; sepsis, severe sepsis (when an acute organ failure occurs), and septic shock (when hypotension does not respond to adequate fluid resuscitation). Patients with cirrhosis have an increased risk of developing bacterial infections, sepsis, sepsis-induced organ failure, and death [8]. Therefore, it is not surprising that mortality rates in this patient population reach 38 % [9]. Cirrhotic patients are two times more likely to die from sepsis than individuals without cirrhosis [10]. In Western countries, bacterial infection is the principal identifiable precipitating event of acute-on-chronic liver failure (ACLF), an increasingly recognized entity characterized

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by rapid deterioration of cirrhosis, frequent requirement of organ support, and high short-term mortality (see Chap. 25) [11].

Pathogenesis

Cirrhotic patients are susceptible to infections due to bacterial translocation (BT). Viable bacteria were frequently isolated from mesenteric lymph nodes and bacterial products, as lipopolysaccharides (LPS) and bacterial DNA, detected in the blood of patients with decompensated cirrhosis [12–14]. BT is allowed by increased intestinal permeability partially due to alterations in tight junction proteins in advanced stages of cirrhosis (Fig. 24.1) [15]. Intestinal bacterial overgrowth and dysbiosis (qualitative changes in microbiome) observed in cirrhosis also contribute to BT [16, 17].

Cirrhotic patients also have altered defense against bacteria due to reduced bacterial clearance. Impairment of macrophage Fcγ-receptor-mediated clearance of antibody-coated bacteria, deficiencies in the complement system, down-regulation of monocyte human leukocyte antigen (HLA-DR) expression, depressed neutrophil phagocytic and intracellular killing contributes to this altered defense [18, 19]. This immune defect facilitates BT [20]. Genetic immune defects could contribute to the high risk of bacterial infections in cirrhosis, particularly SBP. Cirrhotic patients carrying nucleotide-binding oligomerization domain containing 2 (NOD2) variants associated with impairment of recognition of bacterial product, muramyl dipeptide, have a higher risk of SBP and a decreased survival [21]. Mannose-binding lectin deficiency, inducing a defect in opsonophagocytosis of bacteria, also confers a higher risk of bacterial infections in patients with cirrhosis [22].

Besides this immune deficient state, in the early phase of bacterial sepsis, circulating levels of pro-inflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6 are significantly higher in infected patients with cirrhosis compared to those without [23]. This excessive pro-inflammatory response is recapitulated ex vivo with the stimulation of isolated peripheral blood mononuclear cells (PBMCs) or monocytes from patients with cirrhosis by LPS, which are part of the external membrane of Gram-negative bacteria. This hyper-response is in part explained by deficiency of negative feedbacks in toll-like receptor (TLR)-4 pathway [24]. This bacteria-induced "cytokine storm" contributes to sepsis-

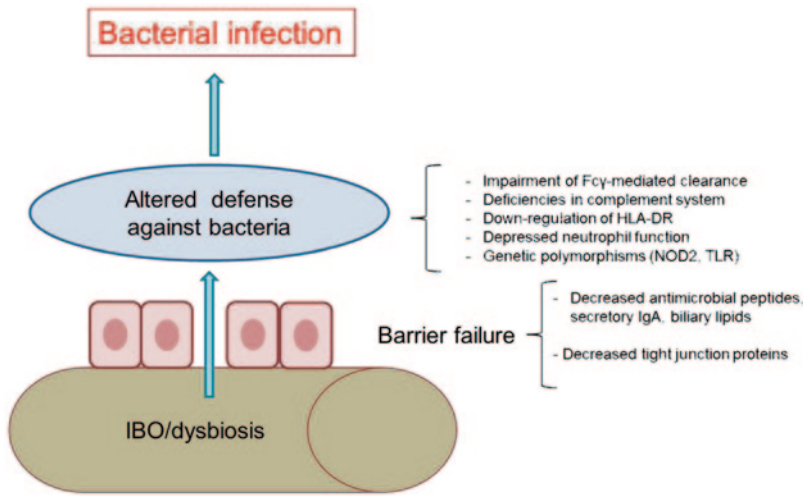

Fig. 24.1 Factors responsible for the susceptibility of cirrhotic patients to bacterial infections. *NOD2* nucleotide-binding oligomerization domain containing 2, *IgA* immunoglobulin A, *IBO* intestinal bacterial overgrowth, *HLA-DR* human leukocyte antigen, *TLR* toll-like receptor

related organ failures. Indeed, there is a relationship between high plasma and ascitic levels of TNF-α and IL-6 and occurrence of renal dysfunction in SBP [25]. Moreover, enhanced neutrophil-induced oxidative stress and elastase production observed in cirrhosis could also participate in sepsis-related organ damages [26].

The Diagnostic Approach

The diagnosis of bacterial infection in cirrhosis is challenging for several reasons.

First, in the early phase of infection, cirrhotic patients may be totally asymptomatic. Second, the classical parameters assessing the inflammatory host response to infection systemic inflammatory response syndrome (SIRS) are not specific for the diagnosis of infection in cirrhosis. SIRS is defined as the presence of at least two of four clinical criteria: body temperature ≥38°C or ≤36°C; heart rate ≥90 beats/min; respiratory rate ≥20 breaths/min; or hyperventilation with a $PaCO_2$ ≤32 mmHg; white blood cell count ≥12,000/mm^3, ≤4000/mm^3, or with >10% immature neutrophils. Decompensated cirrhosis may be associated with some degree of encephalopathy-related tachypnea, tachycardia, or hypersplenism-related leucopenia. SIRS thus has a low sensitivity (57–70%) as a diagnostic tool of infection in patients with decompensated cirrhosis and low specificity (10–30%) in those patients without infection [27, 28]. Common early markers of infection used in the general population such as C-reactive protein (CRP) and procalcitonin are not sufficiently adequate to distinguish infected from noninfected patients. Indeed, CRP >2 mg/dL only has a sensitivity of 78% and specificity of 68% and procalcitonin >3 ng/mL has sensitivity and specificity of 73%.This poor diagnostic accuracy could be explained by a decreased production of acute-phase proteins in the liver, especially CRP. Low CRP values should be interpreted with caution in patients with severe liver insufficiency due to fact that hepatocytes are the main source of CRP. Some randomized-controlled trials have shown good results with the use of procalcitonin algorithms to guide decisions about the initiation and/or discontinuation of antibiotics in patients admitted in the intensive care unit (ICU) but the usefulness in cirrhotic patients has yet to be investigated [29].

Infection should be suspected in any decompensated cirrhotic patient or when a hospitalized patient deteriorates. Therefore, a thorough examination and workup including urinary sediment and culture, diagnostic paracentesis and ascitic fluid culture, blood cultures, and chest X-ray should be promptly performed in order to avoid a delay in the diagnosis and the administration of empiric antibiotics.

Principles for Management of Bacterial Infections in Cirrhosis

The early diagnosis of bacterial infections and the prompt initiation of adequate antibiotic treatment are the cornerstone of management. Each hour of delay in administering antibiotics, or the inappropriate initial choice of antibiotics drastically, worsens the prognosis of patients with septic shock [30]. The choice of initial empirical antibiotics should be based on the type, severity, and origin of infection (CA, nosocomial, or HCA) and on the local epidemiological data of antibiotic resistance. In general, third generation cephalosporins are still considered the gold standard for most infections acquired in the community. In contrast, the empirical treatment of nosocomial or HCA infections should be tailored according to the local epidemiological pattern of multiresistant bacteria.

Spontaneous Bacterial Peritonitis

SBP is defined as a spontaneous ascitic fluid infection without an evident abdominal source. It is the most frequent infection of cirrhotic patients (20–25% of all infections) [3]. In outpatients without symptoms, the prevalence is low (<3%) [31, 32], but it increases to 8–36% in hospitalized patients. The mortality for the first episode ranges from 10 to 25% [33]. However, more important is the fact that 1-year mortality after the

first SBP episode is reported to be at least 30%, suggesting that the deterioration of liver function accelerates [34].

Diagnosis of SBP

Patients with SBP may have one of the following: local symptoms and/or signs of peritonitis (abdominal pain, abdominal tenderness, Blumberg sign, vomiting, diarrhea, ileus). However, it may be asymptomatic in some patients, particularly outpatients. The diagnosis of SBP is based on ascitic neutrophil count $\geq 250/mm^3$ [35]. Ascitic fluid neutrophil count is obtained by centrifugation of the ascitic fluid and then stained with Giemsa and differential cell counts are made with an optical microscope. Reagent strips have been assessed as method of rapid diagnosis, but given the high rate of false-negative results (around 50%) their use has been abandoned [36]. Ascitic fluid lactoferrin levels have been suggested as an alternative method for the diagnosis of SBP. In one study, a cutoff value of 242 ng/mL had a sensitivity and specificity in the diagnosis of SBP of 95 and 97%, respectively [37]. However, there are scarce data, and thus these results must be validated in other centers in order to consider the use of lactoferrin for the diagnosis of SBP in clinical practice. Pleural ascites could also be a site of infection. This infection is called spontaneous bacterial empyema (SBE), and the diagnostic criteria are the same than those for SBP.

Microbiology

Ascitic fluid cultures (10 mL injected into aerobic and anaerobic blood cultures), direct ascitic microscopic exam (to look for a potential polymicrobial infection in the case of secondary peritonitis), and blood cultures (50% of SBP are associated with bacteremia) should also be obtained when SBP is suspected. The ascitic fluid culture is positive in approximately 40% of cases. The most common pathogens are Gram-negative bacteria (GNB; mainly *Escherichia coli, Klebsiella pneumonia, Enterobacter* spp.) and Gram-positive cocci (GPC; mainly *Streptococcus* spp. *and Enterococci*). In Spain, 20% of GNB are resistant to quinolones, and 70% of these are also resistant to trimethoprim–sulfamethoxazole [1]. The long-term norfloxacin administration (see Prevention section) increases the rate of quinolone resistance to 60% and the proportion of GPC. The rate of cephalosporin-resistant GNB is low in community-acquired SBP regardless of long-term norfloxacin prophylaxis. On the other hand, (at least in Spain), extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae are isolated in 30% of nosocomial SBP and methicillin-resistant *Staphylococcus aureus* (MRSA) in 10% of HCA SBP [3].

Some patients have bacterascites, a condition in which cultures are positive but there is an ascitic neutrophil count $<250/mm^3$. When this bacterascites is caused by only one microbe, it usually represents the colonization phase of ascitic fluid infection. It may progress to SBP or in the majority of cases (62–86%) resolve spontaneously [38, 39]. Bacterascites with microorganisms similar to those of the skin flora are probably due to contaminants. If symptoms are present, a second paracentesis is recommended.

Antibiotics

For community-acquired SBP, third-generation cephalosporins (cefotaxime, ceftriaxone) are the gold standard for the empirical antibiotic treatment (see Tables 24.1 and 24.2) [40]. Amoxicillin–clavulanic acid and ciprofloxacin show similar results [41, 42]. However, quinolones are not yet recommended in patients receiving long-term norfloxacin prophylaxis and in geographical areas with high prevalence of quinolone-resistant bacteria. For nosocomial and HCA SBP, there is no clear recommendation at this time and the choice of empirical antibiotics depends on the local epidemiological patterns of resistance. If ESBL-producing Enterobacteriaceae are frequent, carbapenems or tigecycline could be a good choice for the treatment of nosocomial SBP. Another strategy is a step-by-step protocol consisting in a first-line antibiotic treatment, i.e.,

Table 24.1 Recommended empirical antibiotics for infected cirrhotic patients

Type of infection	Recommended empirical antibiotics	
	Community-acquired infections	Nosocomial infections[a]
SBP, SBE and spontaneous bacteremia	Cefotaxime or ceftriaxone or amoxicillin/clavulanic acid	Piperacillin/tazobactam[b] or Meropenem[c] ± glycopeptide[d]
Urinary infections	*Uncomplicated*: ciprofloxacin or cotrimoxazole *If sepsis*: cefotaxime or ceftriaxone or amoxicillin/clavulanic acid	*Uncomplicated:* nitrofurantoin or fosfomycin *If sepsis*: piperacillin/tazobactam[b] or meropenem[c] ± glycopeptide[d]
Pneumonia[e]	Amoxicillin/clavulanic acid or ceftriaxone + macrolide or levofloxacinor moxifloxacin	Piperacillin/tazobactam[b] or meropenem/ceftazidime + ciprofloxacin ± glycopeptide[d] should be added in patients with risk factors for MRSA[g]
Cellulitis	Amoxicillin/clavulanic acid or ceftriaxone + oxacillin	Meropenem/ceftazidime[f] + oxacillin or glycopeptides[d]

[a] Recommended empirical treatment also for HCA urinary infections and pneumonia. Empirical antibiotic treatment of HCA spontaneous infections and cellulitis will be decided on the bases of the severity of infection (patients with severe sepsis should receive the schedule proposed for nosocomial infections) and on the local prevalence of multiresistant bacteria in HCA infections

[b] In areas with a low prevalence of multiresistant bacteria

[c] To cover extended-spectrum β-lactamase (*ESBL*)-producing Enterobacteriaceae

[d] IV vancomycin or teicoplanin in areas with a high prevalence MRSA and vancomycin-susceptible *enterococci* (*VSE*). Glycopeptides must be replaced by IV linezolid in areas with a high prevalence of vancomycin-resistant enterococci (*VRE*)

[e] Liver disease is considered as severe comorbidity for community-acquired pneumonia in guidelines

[f] Antibiotics active against *Pseudomonas auruginosa*

[g] Ventilator-associated pneumonia, previous antibiotic therapy, nasal MRSA carriage

SBP spontaneous bacterial peritonitis, *SBE* spontaneous bacterial empyema, *MRSA* methicillin-resistant *Staphylococcus aureus, HCA* health-care-associated, *IV* intravenous. Dosages of antibiotics have not been formally investigated or defined in cirrhotic population, and we must follow classical recommended dosage

Table 24.2 Recommendations for the management of spontaneous bacterial peritonitis

Therapy
After diagnosis of peritonitis has been made (>250 neutrophils/mm^3 in ascitic fluid), start with third-generation cephalosporins (i.e., cefotaxime 2 g/8–12 h IV or ceftriaxone 1 g/24 h IV) unless risk factors for multirresistant bacteria are present[a]
Infuse albumin (1.5 g/kg at diagnosis of the infection and 1 g/kg 48 h later)
Maintain antibiotic therapy for at least 5 days or until disappearance of signs of infection. Patients should be evaluated daily to assess signs of infection. A follow-up paracentesis helps evaluate response to therapy
After resolution of infection, start long-term oral norfloxacin 400 mg/day
Prevention
Patients with gastrointestinal hemorrhage:
Norfloxacin 400 mg/12 h orally or per gastric tube for 7 days in patients with preserved liver function and not actively bleeding.
Intravenous ceftriaxone 1g/day for 7 days in patients with advanced liver failure and/or actively bleeding.
Patients with ascites with a previous episode of SBP
Norfloxacin 400 mg/day indefinitely
Evaluation for liver transplantation
Patients with ascites and advanced liver diseaseb without a previous episode of SBP and low ascitic fluid protein concentration (< 15 g/liter):
Norfloxacin 400 mg/day indefinitely

[a] Nosocomial acquisition of infection, long-term norfloxacin prophylaxis, β-lactams within the past 3 months

[b] Serum bilirubin >3 mg/dL, Child-Pugh score >10, dilutional hyponatremia (serum sodium <130 mEq/L) and/or renal impairment

SBP spontaneous bacterial peritonitis

piperacillin–tazobactam, followed by an assessment of response (defined by a reduction of ascitic neutrophil count > 25 % at day 2 of antibiotics) and in case of nonresponse, by a shift to a broader antibiotic, i.e., carbapenems.

Special Case: Secondary Peritonitis

Secondary peritonitis is infrequent (5–10 % of all peritonitis) but is associated with a very high mortality rate (66 %) [43]. Secondary peritonitis is suggested when at least two of the following parameters are present in ascites: glucose levels < 50 mg/dL, protein concentration > 10 g/dL, or LDH concentration > normal serum levels but these criteria only have a sensitivity of 67 %. In the case of gut perforation, ascitic amylase or bilirubin levels could be high. In the case of secondary peritonitis, the ascitic culture is frequently positive and polymicrobial. Abdominal computerized tomography (CT) without contrast to avoid renal impairment is diagnostic in 90 %. Prompt treatment with broad-spectrum antibiotics with anti-anaerobic activity (amoxicillin/clavulanic acid, piperacillin/tazobactam, or ceftazidime/metronidazole), and early decision for surgery are essential for the management of secondary peritonitis.

Other Infections

Pneumonia

Deterioration of consciousness secondary to hepatic encephalopathy and basal atelectasis due to tense ascites contributes to the high frequency of lung infections in cirrhosis. In cirrhotic patients with severe sepsis, lung infections are the more frequent infectious foci, suggesting that pneumonia is a severe infection in cirrhosis [44]. Indeed, community-acquired pneumonia (CAP) of cirrhotic patients is more frequently associated with septic shock and higher 1-month-mortality rates than those in the noncirrhotic population (14 vs. 7 %) [45]. The mortality of cirrhotic patients with community-acquired pneumococcal pneumonia requiring hospitalization increases to 34 % (sixfold higher than in the general population) despite adequate antibiotics [46]. The more severe form of lung infection is the acute respiratory distress syndrome (ARDS) defined by severe hypoxemia, bilateral lung infiltration, and the absence of left heart failure. The mortality of ARDS in general population is 65 %, and cirrhosis is independently associated with mortality with a very high odds ratio of 27 [47].

Diagnosis

In the case of pneumonia, patients may have cough, pleuritic chest pain, dyspnea, or sputum production but may be asymptomatic. A chest radiograph may show lobar consolidation, interstitial infiltrates, and/or cavitation. If there is a high-clinical suspicion of pneumonia with a negative chest radiograph, CT scan should be performed. Pneumococcal and legionella urinary antigen tests should also be performed.

Microbiology

Only 28 % of CAP are culture positive with 75 % of GPC and 25 % of GNB [1]. The proportion of GNB and polymicrobial cultures (GNB + GPC) increases in nosocomial infections. Isolated microorganisms are *Streptococcus pneumonia, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Escherichia coli* in order of frequency. *P. aeruginosa* and ESBL-producing Enterobacteriaceae are isolated in nosocomial and HCA pneumonia [3]. Cirrhosis seems also to be a predisposing condition of atypical infections such *Legionella* spp. [48].

Antibiotics

The recommendations for the empiric treatment for CAP do not differ from those of the general population (Table 24.1). As detailed previously, cirrhosis is considered as a major comorbidity, and thus some experts suggest the combination of antibiotics against typical and atypical bacteria [49]. The possibilities are a quinolone (moxifloxacin, levofloxacin) or the combination of a β-lactam (amoxicillin–clavulanate or third-generation cephalosporin) plus a macrolide. For nos-

ocomial and HCA pneumonia, the use of empiric antibiotics should follow local recommendations.

Urinary Tract Infection

UTIs are frequent in cirrhotic patients and, as in the general population, more frequent in women and those with urinary catheters. UTIs are frequently asymptomatic in cirrhotic patients. The hospital mortality rate of UTIs is around 10% and increases to 18% in the case of multiresistant bacteria [3].

Diagnosis of UTI

UTI may be asymptomatic in cirrhotic patients or associated with dysuria, frequency, urgency, and suprapubic pain. In the case of pyelonephritis, patients frequently describe flank pain. If UTI is suspected, urinalysis and urine culture must be performed. The diagnosis is based on ≥10 urinary leukocytes/mm^3 or positive urinary leukocyte esterase. If cirrhotic patients have persistent symptoms of uncomplicated UTI after 48 h of appropriate antibiotic therapy or symptoms of pyelonephritis, renal ultrasound or abdominal CT should be performed to detect a stone, papillary necrosis, obstruction, and/or abscess.

Microbiology

Eighty percent of UTIs in cirrhotic patients are culture positive with a large majority of GNB (76%) in community-acquired UTIs. The proportion of GPC increases in nosocomial infections. *E. coli* is the most frequently isolated microorganism followed by *Enterococcus faecalis, Klebsiella pneumonia,* and *Enterococcus faecium*.

Antibiotics

Third-generation cephalosporins, amoxicillin–clavulanic acid, quinolones, or trimethoprim–sulfamethoxazole are the first choice for community-acquired UTIs (Table 24.1). For uncomplicated UTIs, oral antibiotics are recommended. Quinolones and trimethoprim–sulfamethoxazole are not recommended in patients receiving long-term norfloxacin prophylaxis and in geographical areas with high prevalence of quinolone-resistant bacteria. In nosocomial infections, nitrofurantoin is a good option in uncomplicated UTI. In some regions with a high prevalence of ESBL-producing bacteria, carbapenems should be used. In the case of severe sepsis or septic shock secondary to UTI, a glycopeptide must be added to anti-GNB antibiotic to cover *E. faecium*.

Skin and Soft Tissue Infection

SSTIs, in particular those of lower limb or abdominal wall, are not rare in cirrhotic patients with peripheral edema and/or ascites. SSTIs are observed in 2–11% of cirrhotic patients [50, 51]. In a Spanish cohort, the mortality rate of SSTI was 4% [52]. The mortality could increase to >50% in the case of GNB-related SSTIs [53].

Diagnosis of SSTI

The most common symptom of cellulitis is pain, tenderness, swelling, and redness in a distinct area of skin. For SSTI, ultrasound of the region is a useful tool for excluding occult abscess and to guide microbiological sampling and/or surgical drainage and for making the differential diagnosis with deep venous thrombosis. CT scan should be performed if necrotizing fascitis is suspected.

Microbiology

Skin cultures are positive in nearly 50% of cases. GPC are isolated more frequently than GNB, but up to one third of cultures yielded GNB. Classically, the most commonly isolated GPC are *S. aureus, Streptococcus pyogenes,* and *E. faecalis*. GNB are represented by *E. coli, P. aeruginosa,* and *Enterobacter cloacae*.

Antibiotics

Amoxicillin–clavulanic acid or ceftriaxone and oxacillin, which cover *Staphylococcus,* are the first choice for community-acquired cellulitis (Table 24.1). These antibiotics are ineffective on *Pseudomonas* spp. In these cases, ceftazidime and oxacillin or piperacillin–tazobactam could be a better choice in those with a high risk of *Pseudomonas* spp.

Prevention of Organ Failure: The Use of Albumin

Spontaneous Bacterial Peritonititis

In patients with cirrhosis, an open-label unblinded randomized clinical trial (RCT) in patients with SBP (without shock) treated with cefotaxime showed that the intravenous (IV) administration of a 20% albumin solution reduced the incidence of renal failure and decreased mortality rates from 29 to 10% [54]. In this trial, albumin was given at an arbitrary dose of 1.5 g/kg body weight at the time of diagnosis, followed by 1 g/kg body weight on day 3 (Table 24.2). This effect was not observed in patients with low risk of mortality (total bilirubin <4 mg/dL and creatinine <1 mg/dL) [55]. A recent small unblinded RCT suggested that a 20% albumin solution improved systemic hemodynamics better than a 6% hydroxyethyl starch solution in SBP [56].

Infections Other than SBP

Only a small RCT showed no survival difference between patients treated with and without IV albumin at the classical dose but suggested a survival benefit in the multivariate per-protocol analysis [57]. Albumin seemed to improve renal function but larger studies are needed to recommend the use of albumin in non-SBP infections in cirrhotic patients.

Management of Organ Failures, Severe Sepsis, and Septic Shock

Hemodynamic Therapy

Early Hemodynamic Therapy In the general population, during the first 6 h of severe sepsis and septic shock, mean arterial pressure should be maintained at ≥65 mmHg, central venous pressure between 8 and 12 mmHg, central venous oxygen saturation ≥70% and urinary output ≥5 mL kg^{-1} h^{-1} [58]. These goals are achieved using fluids, vasopressors, inotropes, and blood transfusion. Patients with cirrhosis and septic shock have a lower baseline arterial pressure, are more hyperdynamic, have higher central venous oxygen saturation [59], and lower hematocrit than noncirrhotic patients with severe sepsis. Therefore, specific goals for early hemodynamic therapy should be established in patients with severe sepsis and septic shock. Even if goals are undefined, we recommend prompt (within the first 6 h) resuscitation of sepsis-induced hypoperfusion with the predefined targets described for the general population.

Fluid Therapy and Vasopressors At this time, we have no evidence-based data for the choice of optimal fluid resuscitation and type of vasopressors in the management of severe sepsis and septic shock in the specific population of cirrhotic patients. Strict monitoring of patients' responsiveness to fluid replacement (i.e., pulse pressure variation and stroke volume variation in sedated patients) is necessary to avoid fluid overload, peripheral edema, and abdominal compartment syndrome. Norepinephrine and dopamine remain first-line vasopressors for hypotension in septic shock [60]. Dopamine seems to induce more cardiac arrhythmias than norepinephrine in the general population [61].

Stress-Dose Steroids

Current guidelines only recommend stress-dose steroids in patients with vasopressor-unrespon-

sive septic shock in the general population [62]. Patients with cirrhosis and septic shock frequently have relative adrenal insufficiency (51–68%) which may be related to a reduction in adrenal blood flow and high cytokine expression [63]. A small uncontrolled study assessed in cirrhotic patients (mean Child-Pugh scores of 11) with septic shock who were nonresponders to corticotrophin suggested that hydrocortisone (50 mg IV every 6 h) could shorten the duration of shock resolution and improve survival compared with a historical matched cirrhotic cohort [64]. A large double-blind RCT is needed to evaluate hydrocortisone therapy in cirrhotic patients with septic shock.

Other Therapeutic Modalities

Data about the type of renal replacement therapy, liver extracorporeal support, glucose control, protective ventilation strategy, selective digestive tract decontamination in cirrhotic patients with severe sepsis, and septic shock are lacking. We need studies in this specific population of patients to make clear recommendations.

Prevention of Bacterial Infection in Cirrhosis

Bacterial infections are common and severe in patients with cirrhosis. Thus, it is important to prevent infections in patients who are at risk. Since infection is frequently due to translocation of GNB of intestinal origin, prevention is based on selective intestinal decontamination with a fluoroquinolone (e.g., norfloxacin). The restriction of antibiotic prophylaxis to high-risk patients is essential to prevent the development of antibiotic resistance (Table 24.2).

Patients with Acute Gastrointestinal Hemorrhage In this context, bacterial infections are frequent. A meta-analysis of trials in patients with variceal hemorrhage showed that antibiotic prophylaxis reduced the incidence of severe infection (SBP and/or septicemia) and decreased mortality [4]. There has been a decrease in mortality from variceal hemorrhage from 43 to 15% over a 20-year period, and antibiotic prophylaxis is independently associated with improved survival [65]. A beneficial effect of antibiotic prophylaxis on control of bleeding and prevention of rebleeding has also been observed [66]. Oral norfloxacin (800 mg/day for 7 days) is commonly used [67]. However, an RCT has shown that intravenous ceftriaxone (1 g/day for 7 days) was more effective than oral norfloxacin to prevent severe infections in patients with advanced cirrhosis (at least two of the following: ascites, severe malnutrition, encephalopathy, or bilirubin >3 mg/dL) and variceal bleeding [68]. Baveno V consensus recommends to start antibiotics at admission, ideally before or immediately after endoscopy and to continue this treatment for 7 days [69].

Patients with Low Protein Ascitic Levels and No Prior SBP Primary prophylaxis: Oral norfloxacin administration (400 mg/day) in patients with low protein ascitic levels (<1.5 g/dL) and advanced cirrhosis (Child-Pugh score ≥9 points with serum bilirubin level ≥3 mg/dL) or impaired renal function (serum creatinine level ≥1.2 mg/dL, blood urea nitrogen level ≥25 mg/dL, or serum sodium level ≤130 mEq/L) without a prior SBP episode reduces the probability of SBP and HRS and improves 3-month survival [70]. Similarly, oral ciprofloxacin (500 mg/day, another) reduces the 1-year mortality rate in patients with ascitic protein levels <1.5 g/dL and without prior SBP episode [71]. This primary prophylaxis is indicated until liver transplantation or improvement of liver function occurs.

Patients with Prior SBP: Secondary Prophylaxis After an episode of SBP, the cumulative recurrence rate at 1 year is 70% [72]. Oral norfloxacin decreases the recurrence of SBP from ~70 to 20% [73].

Issues with Long-Term Antibiotic Therapy There is no consensus on the duration of long-term use of oral antibiotic therapy to prevent first SBP

or its recurrence. However, antibiotic therapy is associated with the emergence of resistant organisms.

Nonantibiotic Strategy to Prevent Bacterial Infections in Cirrhotic Patients

Restriction of the Use of Proton Pump Inhibitors Several studies suggest an association between proton pump inhibitor (PPI) use and the occurrence of SBP [74, 75]. Thus, we suggest stopping PPIs if there is no clear indication especially in patients with ascites.

Pentoxifylline A large double-blind RCT showed that oral pentoxifylline administration (1200 mg/day) decreased modestly but significantly the risk of bacterial infection in patients with advanced cirrhosis (Child-Pugh C) [76].

Prophylactic Use of Enoxaparin An unblinded RCT designed to evaluate the efficacy of enoxaparin (4000 IU/day subcutaneously) in preventing portal vein thrombosis in cirrhotic outpatients (Child-Pugh classes between B7 and C10) showed that this prophylaxis significantly reduced the occurrence of SBP and bacteremia (9 vs. 33 % at 1 year) [77]. The mechanisms of this prevention are incompletely understood as there could be a reduction of BT under enoxaparin treatment.

Catheter-Related Infections These infections are common in critically ill cirrhotic patients. These patients may benefit from the following: appropriate hand hygiene, use of chlorhexidine for skin preparation, use of full-barrier precautions during the insertion of central venous catheters, use of the subclavian vein as the preferred site for insertion of the catheter, and the removal of unnecessary central venous catheters [78].

Conclusions

Bacterial infections are a major cause of death in patients with cirrhosis. The outcome remains poor despite important progress in understanding the pathogenesis of sepsis in cirrhosis. The diagnosis of infection remains a challenge for the physicians. Bacterial infection should be suspected, and a systematic screen should be performed in every admission of a cirrhotic patient. Prompt and adequate antibiotic treatment improves the outcome of this severe complication. We urgently need large multicenter RCT that could assess interventions that could potentially improve the prognosis of this severe condition.

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Acute-on-Chronic Liver Failure

25

Vicente Arroyo and Javier Fernandez

Approximately, 10% of patients admitted to hospital for acute decompensation (AD) of cirrhosis (ascites, encephalopathy, bacterial infections, or gastrointestinal hemorrhage) die during hospitalization in relation to a deterioration of liver function and/or other problems (mainly renal failure). The term acute-on-chronic liver failure (ACLF) is frequently used to define this condition. However, until recently definitions have been based on expert opinion or consensus statements [1–3]. For example, in Asia, the following definition is used based on a consensus of experts: *acute hepatic insult manifested as jaundice (serum bilirubin equal or greater than 5 mg/dl) and coagulopathy (INR equal or greater than 1.5) complicated by ascites and/or hepatic encephalopathy within a period of 4 weeks in a patients with previously diagnosed or undiagnosed chronic liver disease (not necessarily cirrhosis)* [2]. A second meeting by European and American experts proposed to define ACLF as *an acute deterioration of liver function in patients with cirrhosis which is usually associated to a precipitating event and results in the failure of one or more organs and high short-term mortality* [1]. Two completely different syndromes therefore arose when the concept and diagnostic criteria of ACLF was only based on expert opinions. The International Society of Gastroenterology after gathering together experts from Asia, Europe, and America took the "Salomonic" decision of including under the term of ACLF the different subtypes of patients previously defined [4].

Due to the distinct concepts of ACLF among the specialists from different geographical regions probably related to differences in the prevalence of the different etiologies of chronic liver diseases, the European Association for the Study of the Liver (EASL)-Chronic Liver Failure (CLF) Consortium decided to perform a prospective observational study CLIF Acute-on-chronic liver failure in cirrhosis (CANONIC study) in a large series of patients with cirrhosis (1343 cases) consecutively admitted to 21 European hospitals with AD. The aim of this study was to assess the concept, prevalence, diagnostic criteria, natural course, and prognosis of ACLF in Europe based on data and not on opinions [5]. The current chapter is largely based on this investigation.

Methodology Used by the CANONIC Study for the Diagnostic Criteria of Organ Failure, ACLF and Grades of Severity of ACLF

Due to the lack of data, some important features had to be prespecified by the group of investigators of the CANONIC study. The first was a

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delineation of the major characteristics of the syndrome. In this respect, there was unanimous agreement on three points: (1) ACLF can be observed either at hospital admission or during hospitalization but always in patients with AD of cirrhosis as defined by the development of ascites, hemorrhage, encephalopathy and/or bacterial infections; (2) the development of one or more organ failures is the most relevant specific characteristic; (3) ACLF should differentiate patients with AD in two groups with different prognosis: the group with ACLF should have relatively high short-term mortality rate; in contrast, patients without ACLF should have a better prognosis.

Since the concept of AD of cirrhosis was clear, only two additional issues had also to be prespecified. The first were the types of organ failure to be included for the diagnosis of ACLF and their diagnostic criteria. The second was the meaning of high short-term mortality.

The sequential organ failure assessment (SOFA) scale was the model selected for the first issue because it is widely used for the assessment of organ failure in patients requiring intensive care and it has a high short-term prognostic accuracy in patients with and without cirrhosis [6]. In patients with cirrhosis admitted to ICU, this scale is significantly more accurate for short-term prognosis than the Child-Pugh score and model for end-stage liver disease (MELD) score [7–9]. Since components of the SOFA score do not take into account some pathophysiological and clinical features of cirrhosis, investigators decided to modify the SOFA and established a new scale called the chronic liver failure SOFA (CLIF-SOFA) score adapted for liver patients (Table 25.1).

The issue "relatively high short-term mortality rate" was defined as a mortality rate equal or greater than 15% within a period of 28 days. This figure represents approximately 50% of the short-term mortality rate associated with severe sepsis or septic shock in the general population [10]. Although debatable, the inclusion of a short-term mortality-rate threshold in the definition of ACLF was unanimously supported because it has important therapeutic implications, i.e., indication of early invasive therapeutic procedures and/or liver transplantation.

Table 25.2 shows the short-term mortality in patients included in the CANONIC study. Mortality rate was clearly related to the presence and number of organ failures as defined by the CLIF-SOFA score. Also, renal dysfunction (as defined by a serum creatinine of 1.5–1.9 mg/dl) and/or moderate (grade 1–2) hepatic encephalopathy, when associated to organ failure were also found to predict prognosis. Based on the presence of organ failure and of short-term mortality rate equal or greater than 15% after enrolment, the following groups of patients were excluded and included from the diagnosis of ACLF:

Table 25.1 Criteria to define organ failure in cirrhosis according to the CANONIC study

Organ/system	0	1	2	3	4
Liver (bilirubin, mg/dL)	<1.2	≥1.2 to ≤1.9	≥2 to ≤5.9	≥6 to <12	≥12
Kidney (creatinine, mg/dL)	<1.2	≥1.2 to ≤1.9	≥2 to <3.5	≥3.5 to <5	≥5
Or use of renal replacement therapy					
Cerebral (HE grade)	No HE	1	2	3	4
Coagulation (INR)	<1.1	≥1.1 to <1.25	≥1.25 to <1.5	≥1.5 to <2.5	≥2.5 or Platelets ≤20×10^9/L
Circulation (MAP, mmHg)	≥70	<70	Dopamine ≤5 or dobutamine or terlipressin	Dopamine >5 or E ≤0.1 or NE ≤0.1	Dopamine >15 or E >0.1 or NE >0.1
Lungs PaO/FiO_2 or SpO_2/FiO_2	>400 or >512	>300 to ≤400 or >357 to ≤512	>200 to ≤300 or >214 to ≤357	>100 to ≤200 or >89 to ≤214	≤100 or ≤89

CANONIC CLIF acute-on-chronic liver failure in cirrhosis, *INR* international normalized ratio, *MAP* mean arterial pressure

Table 25.2 Diagnostic criteria of ACLF and inclusion criteria in the APACHE study

Number and types of organ failures	No kidney dysfunction and no mild-to-moderate hepatic encephalopathy	Kidney dysfunction and/or mild/moderate hepatic encephalopathy
No organ failure	20/577 (3.5)	19/329 (5.8)
Single liver failure	4/75 (5.3)	11/36 (30.6)
Single cerebral failure	2/26 (7.7)	1/5 (20.0)
Single coagulation failure	1/22 (4.6)	2/11 (18.2)
Single circulation/lung failure	1/18 (5.6)	2/8 (25.0)
Single kidney failure	9/58 (15.5)	7/30 (23.3)
Two organ failures	19/75 (25.3)	12/32 (37.5)
Three to four organ failures	19/25 (76.0)	6/12 (50.0)
Five to six organ failures	6/8 (75.0)	2/2 (100.0)

APACHE acute physiology and chronic health evaluation, *ACLF* acute-on-chronic liver failure

1. Excluded: (a) No organ failure; (b) Single nonrenal organ failure with serum creatinine <1.5 mg/dl and no hepatic encephalopathy.
2. Included: (a) Single renal failure; (b) Single nonrenal organ failure plus renal dysfunction and/or grade 1–2 hepatic encephalopathy; (c) two or more organ failures.

Table 25.3 shows the classification of patients with ACLF according to grades of severity. The prevalence of ACLF among patients admitted to hospital with decompensated cirrhosis was 30% (20% at admission and 10% during hospitalization) and the overall 28-day mortality rate was 33%. According to the number of organ/system failures, ACLF is stratified into three grades with different prognosis: grade-1 (one organ failure, 28-day mortality rate 22%), grade 2 (two organ failures, 28-day mortality rate 32%), and grade 3 (three or more organ failures, 28-day mortality rate 73%).

Table 25.3 Grades of ACLF

Grades of ACLF	
No ACLF	No organ failure One organ failure (liver failure, coagulation, circulatory or respiratory failure) with creatinine 1.5 mg/dL and no hepatic encephalopathy Single cerebral failure and creatinine 1.5 mg/dL
ACLF grade 1	Single kidney failure Single "nonkidney" organ failure with serum creatinine ranging from 1.5 to 2.0 mg/dL) and/or mild-to-moderate hepatic encephalopathy
ACLF grade 2	Presence of two organ failures
ACLF grade 3	Presence ≥3 organ failures

ACLF acute-on-chronic liver failure

Precipitating Events

As indicated, experts from Western countries suggested including precipitating events in the definition of ACLF. In patients included in the CANONIC study, the most common precipitating events were bacterial infections, particularly spontaneous bacterial peritonitis and pneumonia, occurring in 33% of patients with ACLF versus 22% in patients without ACLF. The second precipitating event in frequency was active alcoholism during the last 3 months prior to enrolment. It was present in approximately 25% of patients with ACLF versus 15% in patients without ACLF. In the subgroup of patients with active drinking, there were analytical data supporting acute liver injury. Interestingly, in patients with ACLF the prevalence of alcoholic cirrhosis (60%) was higher than the prevalence of active alcoholism, indicating that alcoholic hepatitis accounts for only part of cases of ACLF in patients with alcoholic cirrhosis. There was a small proportion of other precipitating events (8%). As a trigger, gastrointestinal hemorrhage was less frequent in patients with ACLF (13%) than in patients without ACLF, suggesting that hemorrhage, if not associated to other complications (i.e., active drinking and/or bacterial infections) is not clearly related to the development of ACLF. Finally, and most interestingly, in a

significant proportion of patients (45%) ACLF developed in the absence of any identifiable trigger.

Mortality was similar in the presence or absence of precipitating events, indicating that although triggers are important in the development of ACLF, once it develops mortality depends of other factors such as the clinical course (see below) and number of organ failures.

ACLF is Not a Terminal Event of a Long-Standing Cirrhosis

A traditional concept is that renal failure and, therefore, ACLF is the final event in a long-standing history of decompensated cirrhosis. This concept is not supported by the results of the CANONIC study since it revealed that almost half of patients with ACLF did not have a prior history of decompensation or had developed first AD within 3 months prior ACLF. An interesting feature was that patients with no history of decompensated cirrhosis developed a more severe form of ACLF than patients with previous episodes of decompensation.

Clinical Course of ACLF

The clinical course of 388 CANONIC patients with ACLF at enrolment or that developed ACLF during hospitalization was assessed during the first 28 days to understand the natural history of the syndrome. Four major findings were observed (*Thierry Gustot, unpublished observations*). The first was that ACLF is an extraordinarily dynamic syndrome. In only one third of patients, ACLF did not change between diagnosis and final follow-up but even in these cases the profile was fluctuating in 35%. In most cases, ACLF either improved (50%) or worsened (20%). The second was the demonstration of the reversibility of the syndrome. Resolution of ACLF was observed in 40% of patients. The frequency of resolution was high (55%) in patients with ACLF-1 at diagnosis, intermediate (35%) in patients with ACLF-2, and low (15%) in patients with ACLF-3. The third important finding is that despite the correlation of ACLF grade at diagnosis with prognosis, it is the clinical course of the syndrome which determines short-term mortality. Finally, changes in ACLF grade following diagnosis occur very rapidly (1–2 days) or rapidly (3–7 days) following diagnosis in more than 65% of the patients. The early course of ACLF, therefore, is a major determinant of prognosis.

ACLF is Associated with Systemic Inflammation

The CANONIC study has also provided important data to understand the mechanisms of ACLF. The finding of higher white blood cell count (WBC) and serum C reactive protein (CRP) levels in patients with ACLF than in those without it suggests that systemic inflammation plays a role in the development of the syndrome [4]. This is also supported by the finding that, as WBC and CRP levels increase across ACLF grades, the intensity of systemic inflammation is higher and there are more number of organs that fail [4]. Systemic oxidative stress is increased in patients with ACLF in comparison to patients without ACLF and also correlates with the number of organ failures, which further supports systemic inflammation as a mechanism of ACLF [11].

As indicated by the CANIONIC study, in approximately 30% of patients with ACLF, systemic inflammation was chronologically related to bacterial infections. In these patients, therefore, systemic inflammation is probably due to activation of the innate immune system cells (mainly polymorphonuclear leukocytes monocyte-macrophages and endothelial cells) by products released by bacteria (pathogen-associated molecular patterns, PAMPs; i.e., lipopolysaccharide, lypoteichoic acid, peptidoglycan) [12]. In another 25%, ACLF is related to excessive alcohol consumption. Although some of these patients may be infected, many of them do not fulfill criteria of a bacterial infection. In these cases, the systemic inflammatory response is probably unrelated to an infection. This condition is known as “sterile inflammation” and is

typically found in diseases characterized by profound tissue damage [13]. Therefore, in patients with alcoholic hepatitis, both infection-associated and sterile systemic inflammation is a major determinant of ACLF and early mortality. The pathogenesis of sterile inflammation in alcoholic hepatitis is probably related to the release of intracellular molecules (damage-associated molecular patterns, DAMPs) from dying hepatocytes that activate the innate immune systems acting as true "internal pathogens." However, as indicated previously, in approximately 40% of cases with ACLF no clear precipitating event can be identified. Although the cause of systemic inflammation in these patients is unknown, it is possibly related to the release of DAMPs by the damaged liver and/or to the translocation of bacterial products (PAMPs) from the intestinal lumen into the systemic circulation. Translocation of PAMPs in the absence of infection is a well recognized feature in patients with advanced cirrhosis related to intestinal hypomotility and bacterial overgrowth, increased mucosal permeability and impaired intestinal immune system function [14].

PAMPs and DAMPs activate the innate immune system cells by two main mechanisms. They interact with specific receptors (patterns recognition receptors, PRR) which include cell membrane receptors (e.g., toll-like receptors, TLR) or cytosolic receptors (NOD-like receptors, NLR) [15]. These receptors activate specific intracellular signaling cascades (mainly kinases) which converge into the release of inflammatory mediators and other substances, including cytokines, chemokines, vasodilators, procoagulants, reactive oxygen species (ROS) and reactive nitrogen species (RNS) responsible for the clinical features associated with inflammation (recruitment of polymorphonuclear leukocytes and monocytes, vasodilation, increased vascular permeability, intravascular coagulation, bacterial killing, and tissue cell dysfunction, necrosis or apoptosis). A second mechanism of activation of the innate immune cells by DAMPS consists of the assembly of inflammasomes in monocytes and macrophages. Inflammasomes are multiprotein complexes that process the release of IL-1β, which is the cytokine responsible for initiating the "cytokine storm" [16].

Traditionally, impairment in organ function associated to systemic inflammation (e.g., in severe sepsis) is considered to be related to two principal mechanisms: (1) Organ hypoperfusion due to cardiovascular dysfunction (impairment in left ventricular function, arterial vasodilation, and impaired vascular response to endogenous vasoconstrictor systems). This mechanism is related to the overproduction of vasorelaxant substances within the heart and the arteriolar walls including nitric oxide, prostaglandins, and bradykinin [17]; (2) extension of the inflammatory process to other organs. Inflammatory mediators and ROS released within organ tissue impair cell metabolism and may cause cell necrosis or apoptosis [18]. The first of these mechanisms has also been demonstrated to be important in the pathogenesis of type-1 hepatorenal syndrome (HRS) in cirrhosis, a special form of ACLF. Moreover, tissue inflammation has been found in the intestines, heart, and kidneys in experimental models of cirrhosis. The mechanisms of organ failure in ACLF and of sepsis may be therefore closely related.

Cirrhosis is associated with a procoagulant state, i.e., an increase in thrombin generation [19]. This has been shown in patients with decompensated but stable cirrhosis. It is possible that the procoagulant state could be enhanced in patients with ACLF since inflammation is known to be associated with increased tissue factor synthesis in innate immune cells and endothelial cells [20–23]. Increased tissue factor synthesis activates the coagulation cascade and subsequent thrombin formation. This may result in microthrombosis in the microcirculation of vital organs including the liver, favoring tissue hypoperfusion and leading to organ failure. Moreover, the coagulation cascade has intrinsic proinflammatory characteristics thus leading to a vicious circle by which activation of inflammatory cells leads to endothelial dysfunction, increase in thrombin generation, and more inflammation [24]. Microthrombosis in the microcirculation is also considered as a potential mechanism of organ failure in other life-threatening clinical conditions such

as septic shock, severe trauma, or severe acute organ injury (pancreatitis, fulminant hepatitis).

An increased circulating concentration of microparticles (MPs) is an additional potential mechanism in the development of complications associated with systemic inflammation in cirrhosis and in ACLF. MPs are membrane vesicles of cell origin with a diameter ranging from 0.1 to 1 μm that are released to the extracellular space following immune cell activation or apoptosis. Previously, they were considered to be inert cellular debris. However, MPs are currently recognized as structures with powerful biological effects due to the presence at their surface of most of the cell membrane associated molecules.

Circulating MPs (mainly derived from leukoendothelial and hepatic cells) are increased in patients with AD of cirrhosis and correlate directly with the severity of cirrhosis and systemic inflammation. There is evidence that circulating MPs may play a role as a mechanism of ACLF-associated circulatory alterations [25, 26]. MPs are also pro-coagulants because they expose phosphatidylserine, an anionic phospholipid that activates coagulation. Therefore, MPs may be also a mechanism involved in cirrhotic coagulopathy, tissue inflammation, and organ failure.

The mechanism of organ failure in ACLF may be therefore a multifactorial process related to systemic inflammation. This concept could be of interest in the investigation of potential treatments of ACLF other than artificial organ support of liver transplantation.

Albumin Function and ACLF

Impairment in albumin function could be a relevant mechanism of decompensated cirrhosis and ACLF [27, 28]. Albumin is a stable and very flexible molecule with a heart shape, 585 residues and three domains of similar size, each one containing two sub-domains. Many of the physiological functions of human serum albumin (HSA) rely on its ability to bind an extremely wide range of endogenous and exogenous ligands, to increase their solubility in plasma, to transport them to specific tissues and organs, or to dispose of them when they are toxic. The chemical structure of HSA can be altered by some specific processes (oxidation, glication) leading to rapid clearance and catabolism. An outstanding feature of HSA is its capacity to bind lypopolysaccharide and other bacterial products (lypoteitoic acid and peptidoglican), ROS, nitric oxide, and other RNS and prostaglandins. Binding to nitric oxide and prostaglandins are reversible, so they can be transferred to other molecules at different sites from their synthesis. Through these functions, HSA modulates the inflammatory reaction.

In patients with cirrhosis, there is a marked impairment in albumin function. First, the concentration of serum albumin is markedly reduced in patients with cirrhosis. Traditionally, this has been considered a consequence of and impaired hepatic synthesis due to liver failure. However, there is evidence that increased catabolism due oxidation and glication of the molecule related to diabetes and systemic inflammation and oxidative stress could be the predominant mechanism. Second, the binding sites of the albumin molecule are saturated by endogenous and exogenous substances that accumulate secondarily to liver failure. As a consequence, many endogenous and exogenous compounds circulate freely in plasma and easily interact with specific cell sites leading to adverse effects. For example, the concentration of free PGE2, an important inhibitor of the innate immune system, is markedly increased in cirrhosis and contributes to the high risk of these patients developing bacterial infections. Finally, the ability of albumin to bind proinflammatory substances such as PAMPs, ROS, and RNS and endogenous vasodilators such as NO and PGs, which probably play a major role in the pathogenesis of ACLF, is markedly reduced in advanced cirrhosis.

Type-1 HRS is a representative form of ACLF. It is characterized by a rapidly progressive renal failure that develops in closed temporal relationship to a precipitating event (i.e., infection, alcoholic hepatitis) and is associated with other organ failures and high probability of short-term mortality. The intravenous administration of HSA is highly effective in the prevention of type-1 HRS that develops in the context of bacterial infec-

tions [29]. HSA alone or in combination to i.v. vasoconstrictors (terlipressin or noradrenaline) is also effective for the treatment of type-1 HRS. In both circumstances, the administration of HSA is associated with the improvement in survival [30].

The mechanisms of action of HSA in type-1 HRS are not well established. Traditionally, it has been suggested that HSA acts through plasma volume expansion. However, recent studies in human and experimental cirrhosis suggest that HSA may improve ACLF by acting as an immunomodulatory "drug." By trapping PAMPs and DAMPs, ROS, RNS, inflammatory lipid mediators, and cytokines [28, 31–35], HSA may reduce the intensity of systemic inflammation and oxidative stress and improve organ/system function in ACLF. Moreover, HSA may affect MP levels. It is well demonstrated that endothelial MP levels increase in the case of decreased shear stress and normalize when high normal shear stress is restored [35, 36]. The increase in serum albumin concentration increases blood viscosity and shear stress and may decrease the release of MP by endothelial cells and improve systemic hemodynamics and coagulopathy. The potential role of albumin in systemic inflammation and ACLF not associated to type-1 HRS is a relevant topic that should be addressed by specific investigations.

Summary

ACLF is a recently described entity in patients with cirrhosis and an AD which is based on the presence of organ failure(s) and high mortality rates. The prevalence of ACLF among patients with decompensated cirrhosis is nearly 30%. Patients with ACLF have a high prevalence of specific triggers such as bacterial infections or active alcoholism. ACLF occurs in the setting of a severe systemic inflammatory process mainly due to bacterial infections, and acute liver injury. There is no specific treatment for ACLF. However, most patients should be managed with volume replacement with intravenous albumin, vasoconstrictors plus albumin (in patients with HRS), artificial organ support, or liver transplantation.

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Liver Support Systems

26

Mansoor Bangash, Banwari Agarwal and Rajiv Jalan

Liver disease is common, debilitating, and often fatal. In the UK, the incidence of liver disease, particularly liver disease associated with alcohol, has increased by 500% in the past 30 years. Currently, chronic liver diseases are estimated to affect 10% of the world's population, and cirrhosis-related deaths are projected to become the ninth most common cause of death in the developed world by 2015. Acute liver failure (ALF) has an incidence of 2500 cases per year in the USA, with a greater incidence worldwide, and a mortality of around 50% [1]. The only treatment shown to prolong life expectancy for these patients is liver transplantation, but not all patients are suitable candidates for transplantation. Moreover, there is a shortfall of organs, with UK statistics showing that 15–20% of patients listed for liver transplant die waiting for a suitable organ to become available [2]. In those patients who survive transplantation, postoperative complications and long-term immunosuppression present the potential for additional morbidity and mortality. Therefore, this large group of patients with poor quality of life, high risk of death, and limited treatment options presents an unmet clinical need to design effective liver support systems.

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Indications for Use

In ALF, a previously healthy liver rapidly loses function resulting in coagulopathy and hepatic encephalopathy (HE), and variable degree of extrahepatic organ dysfunction. Acute-on-chronic liver failure (ACLF) on the other hand represents acute decompensation of a chronically damaged liver and other organ failure, consequent upon a precipitating event (superimposed new liver injury such as acute alcoholic hepatitis, or non-liver insult-like infections. In end-stage liver disease (ESLD), a chronically damaged liver has no capacity to regenerate and is in a position of static or progressive failure. In all of these conditions, the mortality rate is high and the purpose of a liver support system is to assume functions of the failed liver, thus preventing the manifestations of disease and preventing the slide into multi-organ failure. In the case of ALF, there are the additional important purposes of reducing the need for transplantation by encouraging normal liver function to recover; and in those where normal function does not return, it is to serve as a bridge to transplant. This latter function is

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important in ALF as fulminant hepatic failure is often cataclysmic in progression, and death may occur rapidly within 96 h without transplantation [3]. In ACLF, the aim is to encourage liver function to recover to the pre-decompensated state. In ESLD, liver support systems could be used to manage/prevent the complications of their liver disease (e.g. intractable pruritus) and prolong life (possibly until transplantation) in a similar manner to how haemodialysis is used in patients with chronic renal failure. There are also other situations in which a liver support device could potentially find use, such as following primary graft failure post liver transplantation, small-for-size liver after large resections or live-related liver transplantation (for both the donor and the recipient), and liver failure occurring as a consequence of other conditions such as the multi-organ failure seen in sepsis.

Historical Context and Theoretical Basis for Liver Support

The ideal liver support device would be effective and reliable at performing all vital liver functions, be free of complications for the patient, and is easy and inexpensive to use at the bedside. Despite over 50 years of research in this area, no device currently fits these criteria. As with most forms of organ support, the principle of such a device was that short-term provision of liver function artificially would allow time for recovery of native organ function while any primary pathology was treated (akin to extra corporeal membrane oxygenation and lung rest in severe acute respiratory distress syndrome, ARDS; or continuous veno-venous haemofiltration, CVVH, providing functional cover in acute kidney injury). The liver performs many functions and holds an important role in the crosstalk of integrative regulation between organ systems. In the context of liver failure, the most important functions are synthesis, biotransformation, detoxification, and excretion. When the liver fails, plasma proteins (including albumin, several clotting factors, and acute phase proteins) are no longer produced at the normal rate, drug pharmacokinetics and systemic metabolic cycles (e.g. lactate, glucose, and ammonia regulation) are profoundly altered, the neutralisation and elimination of toxins is hindered, and other functions of the liver such as immune regulation are also deleteriously affected. The accumulation of toxins directly impedes liver repair, and as disease severity worsens the inflammatory response is exacerbated leading to severe regional microcirculatory and systemic haemodynamic derangements.

Given that the range of functions of the liver are greater than that of the kidney or lung, initial attempts at providing liver support involved cell-based therapies. Exchange transfusion, cross-circulation/dialysis with human and primate/canine species, and a bio-artificial liver (BAL) using rabbit hepatocytes were amongst the earliest attempts at liver support [4–8]. Many synthetic functions of the liver can be substituted to some degree by administering glucose, albumin, and clotting factors to the patient, and furthermore, many accumulated toxins in liver failure impair liver regeneration. Therefore, during the development of liver support systems, two pathways emerged—one of which continued along the lines of cell-based therapy and more complete replacement of liver functions, and another which looked toward completely artificial and cell-free therapies, focussing predominantly on the detoxification and excretion that is impaired in liver failure (the earliest artificial systems used charcoal haemoperfusion, where the charcoal provided a large surface area for toxin adsorption). Liver support devices can therefore be divided into artificial systems, which perform only detoxification and excretion, and biological systems which additionally provide some synthetic and biotransformative function.

The Role of Albumin

Albumin is the most abundant plasma protein in the body, constituting 60 % of all plasma protein. It is produced exclusively in the liver with a molecular weight of 65–70 kDa, and provides significant contribution to plasma oncotic pressure. It carries antioxidant properties and importantly,

Table 26.1 Summary of currently available bio-artificial liver devices

Device	Bioreactor detail			Additional treatments
	Cell type	Cell-matrix attachment	Configuration	
HepatAssist BAL	Porcine hepatocytes	Microcarrier attached	Hollow fibre cartridge/chamber	Plasmapheresis and adsorption
AMC–BAL (Academic medical centre–bio artificial liver)	Porcine hepatocytes	Polyester fabric	Perfused matrix/ monolayer cultures	Plasmapheresis
BLSS (Bio-artificial liver support system)	Porcine hepatocytes	Nil	Perfused matrix/ monolayer cultures	Haemofiltration
ELAD (Extracorporeal liver assist device)	C3A human hepatocytes	Nil	Hollow fibre cartridge/chamber	Haemofiltration and adsorption
MELS (Modular extracorporeal liver support device)	Porcine/human hepatocytes	Nil	Hollow fibre cartridge/chamber	Plasmapheresis, haemodialysis, albumin dialysis, and adsorption

serves as a carrier molecule for many hormones (e.g. corticosteroids and T3 and T4), endogenous chemicals (e.g. unconjugated bilirubin, fatty acids, and calcium), drugs, and toxins. In liver failure, both a quantitative and qualitative deterioration in albumin occurs due to impaired synthesis, increased breakdown, and alteration of the binding properties of the molecule, leading to a reduced functional capacity [9].

Human albumin solution is used medically as a colloidal fluid to provide volume expansion. Although albumin supplementation in critically ill patients in general has failed to show any benefit or harm [10, 11], it has been shown that administering albumin in addition to standard treatment in cirrhotic patients results in lower incidence of renal complications in spontaneous bacterial peritonitis and better transplant-free survival in type 1 hepatorenal syndrome. This suggests that in the specific setting of liver diseases, albumin has a pathophysiological role of prognostic significance [9]. Therefore, key features of the different liver support systems in existence are to either:

1. Decouple albumin from toxins that cannot normally be excreted (and therefore accumulate) in liver failure.
2. Regenerate or replace albumin while performing detoxification.

Bio-Artifical Liver Support Systems

The cost and complexity of biological liver support systems are significantly greater than that of artificial systems. A suspension of hepatocytes housed in a chamber (the bioreactor), in series or parallel, with artificial modalities constitutes a typical BAL (Table 26.1). The critical mass of hepatic tissue required for a bioreactor is estimated to be approximately 150–450 g, or 10^{10} hepatocytes [12]. Creating a suspension of primary human hepatocytes is technically challenging as this cell line is not easily available, has less regenerative ability in vitro and due to the loss of gap junctions between cells has diminished functional capacity. To counter this, cell–cell interaction is promoted through the use of a matrix that provides a parenchymal framework to which hepatocytes are attached. Cellular alternatives to primary human hepatocytes include immortalised lines of C3A human hepatoma cells (unlimited expansion in vitro, high albumin production) and primary porcine hepatocytes (abundant supply, maintain a greater degree of metabolic functionality than C3A human hepatoma cells). [13]. However, with the former, there are concerns regarding oncogene transmission and incomplete metabolic functionality, e.g., ammo-

nia detoxification, whereas in the latter concerns about xenozoonoses remain.

Hepatocytes in bioreactors may have been cultured such that they are gel encapsulated, captured within a 3-D matrix, cultured within/around hollow fibres, or immobilised on collagen-coated plates. Irrespective of the details of the architecture and cell line chosen, the cells must be kept in a milieu that prevents cell death. Furthermore, sufficient compartmentalisation is required in order to prevent immune reactions while permitting the passage of toxins, metabolites, and synthesised proteins [3]. Table 26.1 lists the currently available bio-artificial devices and their properties.

Other than the ability to perform biotransformation, the synthetic functions of the bioreactor may be also of relevance, e.g. hepatic growth factors which may stimulate native hepatocyte regeneration and albumin.

Artificial Liver Support Systems

In artificial liver support systems, the primary aim is detoxification and excretion of various compounds that the body is otherwise unable to handle during liver failure. The difficulty in relying on haemofiltration or haemodiafiltration for this is that they only effectively remove small molecular weight and water-soluble molecules, leaving a substantial number of higher molecular weight and/or lipophilic toxins in the bloodstream. Furthermore, the majority of toxins in liver failure are albumin bound, the importance of which has been stressed previously. In order to more completely detoxify blood, modern artificial systems combine haemofiltration with independent units that use albumin solutions and/or semi-permeable membranes with variable cutoffs in molecular weight to selectively target larger molecular weight toxins without the loss of certain large molecules (e.g. immunoglobulins).The loss of larger molecules was a feature of older charcoal haemoperfusion devices. Finally, plasmapheresis is another artificial modality that can be used for detoxification in liver failure.

MARS and SPAD

In extracorporeal albumin dialysis (e.g. MARS—molecular adsorbent recirculatory system; Gambro, Sweden), the patient's blood is drawn off and passed through a cartridge containing a semi-permeable, albumin impregnated polysulfone membrane. The dialysate (20% albumin) is also passing through this cartridge, on the opposite side of the membrane. The transfer of albumin-bound molecules (molecular weight <50 kDa) therefore occurs across this membrane from the high-concentration compartment (patient's blood, saturated binding sites on albumin molecules) to the low concentration compartment (dialysate, empty binding sites on albumin molecules) via the intermediate process of binding to membrane-bound albumin. This is possible due to a greater affinity of membrane-bound albumin for toxins. Fresh dialysate continually replaces that in the cartridge to maintain the concentration gradient, while the toxin-laden dialysate moves on to a standard haemofiltration cartridge where the removal of water-soluble substances occurs in standard fashion (Fig. 26.1). Importantly, prior to returning to the first filter, the post-haemofiltration fluid must pass through adsorption columns containing activated charcoal and ion exchange resins. These remove albumin-bound, non-water-soluble toxins and allow the post-haemofiltration fluid to return to the first filter as fresh albumin dialysate.

A simpler, non-commercial version of this which dispenses with recirculation of the dialysate is single-pass albumin dialysis (SPAD). In this case, 2–5% albumin is used as dialysate and the exchange of protein-bound toxins occurs across a high-flux semi-permeable membrane (albumin does not cross the membrane). The dialysate is discarded after a single pass. Haemofiltration may also be added to enhance clearance of water-soluble material.

Prometheus and SEPET

Alternative systems use fractionated plasma separation and adsorption (FPSA). For this, a

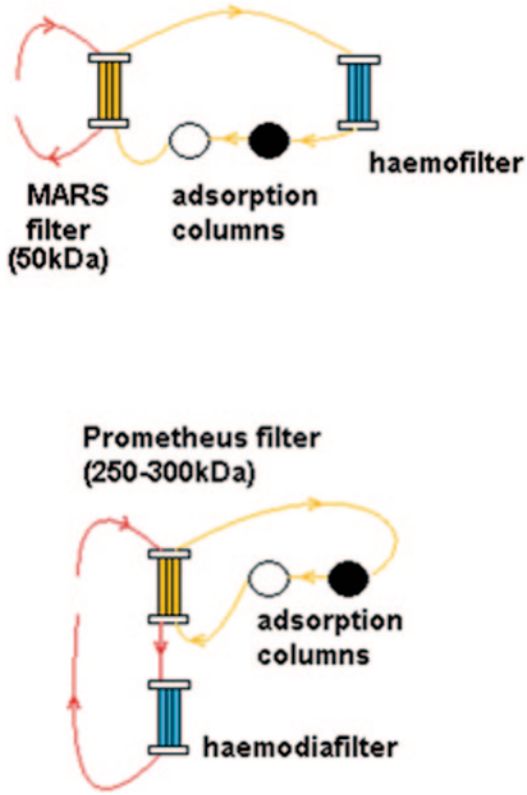

Fig. 26.1 Schematic of MARS (*above*) and Prometheus (*below*) artificial liver support devices. *Red* lines represent draw off and return to patient, *orange* lines represent plasma flow. Filtrate from haemo(dia)filtration is omitted for clarity. *MARS* molecular adsorbent recirculatory system

membrane with a larger cutoff of 250–300 kDa is used, allowing albumin and its bound toxins to pass across into a separate circuit. The fluid in this second circuit is passed through adsorption columns (neutral resin adsorber and anion exchanger), purging the patient's albumin of toxins, and in a sense regenerating it before returning it to the blood from whence it came. In the Prometheus system (Fresenius Medical Care AG, Bad Homburg, Germany), this is combined with high-flux haemodialysis of the patient's blood (Fig. 26.1).

In selective plasma filtration technology (SEPET, Arbios Systems Inc., Los Angeles, CA), a large-pore blood/plasma filter selectively filters and then discards the plasma fraction containing molecules of molecular weight < 100 kDa (therefore including albumin). The lost fluid is replaced with an electrolytic solution, 5% albumin and fresh-frozen plasma. The retained components of fluid include clotting factors, immunoglobulins, complement proteins, and stimulators of hepatic regeneration [14].

Plasmapheresis

In plasmapheresis, a well-established modality used for the treatment of many autoimmune disorders, the patient's blood is treated so that plasma is separated out from cellular components. This plasma is discarded and replaced by donor fresh-frozen plasma and/or albumin. Clearly, this will not only result in the loss of the patient's albumin and any toxins in the plasma but also clears other components in the plasma fraction, such as pro-inflammatory cytokines and circulating antibodies.

Clinical Outcomes Data

Bio-Artificial Systems

Data on bio-artificial systems are sparse. To date, only one multi-centre randomised controlled trial in ALF has been conducted using HepatAssist–BAL [15]). The treatment was well tolerated with few side effects but for thrombocytopenia, and found reduced levels of bilirubin (but not other metabolic factors) in the BAL group. However, the trial was stopped prematurely due to the low likelihood of a significant treatment effect on 30-day mortality (Table 26.2). Subgroup analysis suggested a possible beneficial effect in patients with fulminant/subfulminant hepatic failure. Extracorporeal liver assist device (ELAD) has also been trialed in ALF in much smaller numbers (phase I and II trials only) and has demonstrated safety but did not demonstrate any significant outcome benefits (Table 26.2) [16]. The ELAD device has been modified since this trial to include a greater mass of hepatocytes, a bigger membrane pore size, and a greater cartridge flow rate.

Table 26.2 Major clinical trials of currently available liver support devices

Bio-artificial systems					
Device/setting [ref.]	Type of trial	*N*	Primary outcome	Results	Notes
HepatAssist BAL vs. standard ICU treatment in fulminant/ subfulminant liver failure or primary nonfunction post-transplant [15]	Multi-centre RCT	171	survival—phase II trial for safety and efficacy. Follow-up over 12 months	No significant difference between groups in d30mortality	Terminated early. When accounting for confounders, relative risk of survival (d30) = 0.56 vs. control ($P < 0.05$) in fulminant/subfulminant groups
ELAD vs. standard medical therapy in ALF [16]	Single-centre pilot-RCT	24	Not stated—Pilot study	No significant mortality difference between groups	ELAD device modified after this study
Artificial Systems					
Prometheus vs. standard medical therapy in ACLF [19]	Multi-centre RCT	145	d28 and d90 survival probability	No significant difference between groups	Pre-defined subgroup of MELD > 30 ($n = 48$): 57 vs. 42% (d28) and 48 vs. 9% (d90), $P < 0.02$
MARS vs. standard medical therapy in ACLF [17]	Multi-centre RCT	189	Liver transplant-free survival at d28	No significant difference between groups	Significantly greater decrease in creatinine and bilirubin at d4. No significant change in grade of encephalopathy at d4
MARS vs. conventional therapy in ALF [18]	Multi-centre RCT	102	6-month survival	No significant difference between groups	64.7% of all patients transplanted by a median time of 16.2 h post randomisation
MARS vs. standard medical therapy in ALF or ACLF [21]	Meta-analysis of nine RCT and non-RCT	–	n/a	Significant decreases in bilirubin and grade of hepatic encephalopathy with MARS	No significant difference in mortality. Significant study heterogeneity, small samples, and variable definitions used

BAL bio-artificial liver, *ICU* intensive care unit, *RCT* randomised control trial, *ALF* acute liver failure, *ACLF* acute-on-chronic liver failure, *MELD* model for end-stage renal disease, *MARS* molecular adsorbent recirculatory system

Artificial Systems

MARS, being the older of the artificial systems, has the largest body of evidence regarding treatment efficacy. Although most studies have been small, significant reductions in serum bilirubin, bile acids, ammonia, urea, lactate, and creatinine have been found consistently following MARS treatment, and in keeping with this an improvement in the grade of HE (Table 26.2) [3]. Importantly though, in a large multi-centre randomised controlled trial in the setting of ACLF, MARS did not result in any significant differences in 28-day survival when compared to standard medical therapy, and, though a significant decline in serum creatinine and bilirubin were observed at day 4, a significant improvement in grade of HE was not found compared to control [17]. As in previous trials, the safety profile of MARS was confirmed in this trial (Table 26.2). A multi-centre randomised controlled trial investigating the impact of MARS in ALF on 6-month mortality has also been conducted [18]. No significant benefit was found with MARS treatment, though trends to improved survival at 6 months were found. Almost 70% of patients underwent transplant by a

median time of 16 h from randomisation rendering interpretation of these findings difficult.

Prometheus has also been studied in comparison to standard medical treatment in a multicentre randomised controlled trial in the setting of ACLF (Table 26.2) [19]. This trial found that there were no increased rates of adverse events with Prometheus, that serum bilirubin decreased significantly, but nevertheless there was no significant survival benefit at day 28 or day 90 either. The failure of Prometheus to improve outcomes does not appear to be due to an inability to clear conjugated bilirubin, bile acids, ammonia, creatinine, or urea [3]. Indeed, there is evidence that Prometheus is able to clear many compounds more effectively than MARS (Table 26.2) [14]. Other than clearing toxins, these artificial devices have additional beneficial effects on systemic and regional haemodynamics though the mechanism through which this occurs is not fully understood [14].

High-volume plasmapheresis has also been found to improve HE in ALF and has a role in reducing levels of copper in Wilson's disease, but evidence for significant effects on outcome are lacking (Table 26.2) [20].

Conclusion

With the rising incidence of liver disease, the high mortality associated with liver failure, and the shortfall of organs for transplantation, there is a pressing need for an effective liver support system to support patients with liver failure to spontaneous recovery and/or bridge them to transplantation. An ideal device should supplement/replace native liver function, is able to perform detoxification and modulation of the inflammatory response resulting from the insult/injury to the liver (precipitating event) in acute, and acute-on-chronic, liver failure, and to encourage regeneration of damaged hepatocytes. The temporary nature of the support that the current generations of devices are able to offer makes them ineffective for the treatment of ESLD, except for their application in the periodic control of debilitating symptoms such as pruritis, HE, and fatigue. Bio-artificial systems are designed to replace all functions of the liver, while artificial systems can only provide detoxification. The largest evidence base available thus far is for the artificial systems, but all the studies using these systems thus far have failed to demonstrate a mortality benefit in the acute setting except high-volume plasmapheresis in ALF. The latter observation, however, needs to be confirmed in large well-designed trials. Bio-artificial systems hold much promise, and a number of pivotal studies in the setting of ALF and alcohol-related ACLF (including acute alcoholic hepatitis) are currently under way or nearing completion.

Liver support systems still have not reached a point of clinical validity for ALF and ACLF despite decades of research. Although both artificial and bio-artificial devices have been shown to effectively reduce plasma levels of toxins and have beneficial effects on other aspects of the deranged physiology of liver disease [14], a significant positive effect on outcomes has not been demonstrated, possibly reflecting the complexity of the disease. Bio-artificial devices may offer the greatest potential for eventually replacing liver function, acting as mini livers. Advances are likely to be forthcoming, as the incorporation of other technologies such as endotoxin filters are already in development, allowing another level of detoxification.

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Liver Transplantation

27

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Liver transplantation (LT) was first introduced as a therapeutic option for patients with end-stage liver disease (ESLD) by Thomas Starzl at the University of Colorado in 1963 [1]. Although the longest survival among the first 16 recipients was only 34 days, the early shortcomings of LT were subsequently overcome by advancements in surgical technique, allograft preservation, and immunosuppression; the number of successful operations has since grown exponentially [2]. Approximately 6000 LTs are performed annually in both Europe and the USA [3, 4]. Marked improvements in posttransplant outcomes have paralleled a concomitant rise in the prevalence of chronic liver disease. As a result, we are now faced with the challenge of meeting a high demand for LT with a very limited organ supply. In the USA, only 5600 deceased donor LTs were performed, despite over 15,000 patients being listed for transplant in 2012 [3].

Organ Allocation

Priority for LT was previously based primarily on the Child-Turcotte-Pugh score and waiting time [5]. In 2002, US transplant centers adopted the model for end-stage liver disease (MELD) score as the basis for determining priority for transplantation [5]. The MELD score is an accurate predictor of 3-month and 1-year mortality [6], and its use has had a positive impact on liver allocation and transplantation. The implementation of the MELD score for organ allocation resulted in a reduction in new LT waiting list registrations, an increase in transplantation rates, and a reduction in wait-list mortality, while maintaining excellent patient and graft survival rates [7]. A MELD-based liver allocation system has been adopted by most transplant centers in Europe, and the UK utilizes a similar scoring system (UK model for end-stage liver disease, UKELD) [8].

Indications for Liver Transplantation

LT should be considered for any patient with ESLD or liver cancer. It is also indicated in some cases of acute liver failure (ALF), as well as a variety of chronic liver diseases (Table 27.1) [4, 9]. Some centers are investigating the controversial practice of LT in selected patients with acute alcoholic liver disease [10]. The presence of cirrhosis alone does not necessarily require LT. Indeed, the patients who benefit most are those who have experienced hepatic decompen-

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Table 27.1 Indications for liver transplantation

Indications for liver transplantation
Acute liver failure due to
Acetaminophen overdose
Idiosyncratic drug-induced liver injury
Acute fatty liver of pregnancy
Toxin exposure—*Amanita phalloides* (mushroom poisoning)
Acute viral hepatitis—hepatitis A–E, herpes simplex virus, Epstein–Barr virus, cytomegalovirus
Decompensated liver disease due to
Chronic viral hepatitis—hepatitis B, C
Alcoholic liver disease
Nonalcoholic fatty liver disease
Autoimmune hepatitis
Cholestatic liver disease—primary sclerosing cholangitis, primary biliary cirrhosis
Cryptogenic cirrhosis
Metabolic and genetic disorders
Wilson's disease
Hemochromatosis
α_1-Antitrypsin deficiency
Glycogen storage disease
Primary oxaluria
Familial amyloidosis
Urea cycle enzyme deficiencies
Tyrosinemia
Cystic fibrosis
Complications of chronic liver disease
Hepatocellular carcinoma
Cholangiocarcinoma
Hepatopulmonary syndrome
Portopulmonary hypertension
Vascular disorders
Budd–Chiari syndrome
Sinusoidal obstruction syndrome

sation, including variceal hemorrhage, ascites, or hepatic encephalopathy (HE), as this confers an increased mortality risk relative to expected post-transplant survival [11].

The leading indication for LT in the USA is chronic hepatitis C virus (HCV) infection, now accounting for approximately 40% of all recipients [12, 13]. In Europe, 36% of graft recipients have alcoholic cirrhosis, slightly surpassing HCV as the primary indication for transplantation [4]. Rates of LT for HCV cirrhosis are expected to increase in the coming years as the HCV population ages [14]. It is estimated that as many as 30% of adults in Western countries have nonalcoholic fatty liver disease (NAFLD), of which up to 12% have nonalcoholic steatohepatitis (NASH), and this number is expected to increase in concert with rising rates of associated factors such as obesity and the metabolic syndrome [15, 16]. Accordingly, NASH-related cirrhosis is already the fourth most common indication for LT in the USA and is anticipated to become the leading indication for transplantation in the next 10–20 years [17, 18]. Patients with ALF receive priority listing for LT and account for approximately 10% of the USA and European transplants [19].

Hepatocellular Carcinoma and Other Priorities in Organ Allocation

An increasing proportion of liver transplants are performed for patients with nonresectable hepatocellular carcinoma (HCC) [20]. Drawing on LT experiences in France, Spain, Germany, and Italy, excellent 5-year survival rates were shown for patients with a solitary HCC lesion ≤5 cm or with up to three nodules each ≤3 cm in size, which became known as the Milan criteria [21]. To mitigate the risk for tumor progression beyond Milan criteria, patients with HCC within Milan criteria may receive priority in organ allocation beyond their actual MELD score. Expansion of tumor burden limits beyond the Milan criteria has been proposed and implemented by several transplant centers without adversely impacting patient survival, but this practice has not been universally adopted [22]. Locoregional therapies such as chemoembolization and radiofrequency ablation are often used to downstage patients to within Milan criteria in order to facilitate listing for LT, but this practice is also controversial [23].

In addition to HCC, other etiologies may receive priority when the risk of death or drop-off from the waitlist is not accurately represented by the MELD score (e.g., hepatopulmonary syndrome (HPS)) [24]. Priority is also assigned for certain metabolic diseases with extrahepatic manifestations even when liver function is not compromised (e.g., primary hyperoxaluria, familial amyloidotic polyneuropathy) [24]. These livers can sometimes be used to replace the diseased liver of another patient in a sequential or so-called domino transplant [25]. At many transplant centers, there is a mechanism to petition for priority on a case-by-case basis.

Liver Transplant Evaluation

Formal evaluation for LT involves a multidisciplinary team approach to rigorously examine the need for transplantation and exclude medical, psychiatric, social, or financial factors that would limit successful recovery and survival (Table 27.2). Not all patients with compensated cirrhosis will require LT. Indeed, it has been shown that the survival benefit associated with LT is greatest among those with the highest risk of pre-transplant death [26]. Accordingly, patients should be referred for formal transplant evaluation once there is evidence of hepatic decompensation resulting in an MELD score ≥15 or the development of an index complication, such as ascites, HE, or variceal hemorrhage [11].

Renal Dysfunction

Acute and chronic kidney injury in patients with cirrhosis is associated with a poor prognosis. Outcomes vary by etiology, and patients with hepatorenal syndrome, particularly type I, have the worst survival [27, 28]. The majority of patients with good baseline renal function will remain without renal dysfunction following transplantation [29]. MELD-based allocation has resulted in an increase in simultaneous liver–kidney transplantation (SLK) [30]. Guidelines for SLK continue to evolve in response to the growing number of LT candidates with renal dysfunction and the ongoing organ shortage (Table 27.3) [31].

Coronary Artery Disease

Coronary artery disease (CAD) rates among LT candidates are comparable to those of the general population [32], and graft recipients with CAD may have a postoperative mortality rate as high as 50% at 1 year [33]. All transplant candidates should undergo cardiac evaluation, including electrocardiogram and transthoracic echocardiography. Noninvasive cardiac stress testing, including pharmacological stress echocardiography or nuclear medicine imaging, should be considered for all LT candidates on the basis of CAD risk factors, followed by cardiac catheterization if indicated [34]. Noninvasive cardiac testing to screen for CAD has limited sensitivity in cirrhotics and coronary angiography should be performed in candidates

Table 27.2 Evaluation for liver transplantation

Evaluation for liver transplantation
Medical evaluation
Determine/confirm etiology of liver disease
Explore medical management options
Evaluate medication adherence history
Assess functional status and exercise tolerance
Laboratory evaluation
Assess hepatic and renal function
Exclude alternative or concomitant causes of liver disease
Perform infectious disease workup: testing for viral hepatitis, cytomegalovirus, human immunodeficiency virus, syphilis, tuberculosis
Radiographic evaluation
Doppler ultrasonography to document hepatic vascular anatomy and portal venous system patency
Consider contrast-enhanced computed tomography or magnetic resonance imaging to assess for and characterize any hepatocellular carcinoma or cholangiocarcinoma
Cardiopulmonary evaluation
Plain chest film
Noninvasive evaluation with electrocardiogram and 2D echocardiography
Pharmacological stress testing, consider coronary angiography for patients with cardiac risk factors
Consider pulmonary function testing for patients with signs, symptoms, or a known history of chronic lung disease
Age-appropriate cancer screening
Colonoscopy for patients with age ≥50 years or a history of primary sclerosing cholangitis
Pap smear for females sexually active >3 years or age ≥21 years
Mammogram for females with age ≥50 years
Prostate-specific antigen level measurement for males with age ≥40 years
Surgical consultation
Identify factors that may complicate transplantation, such as morbid obesity, prior abdominal surgery, extensive portal venous thrombosis, or generalized deconditioning
Social work evaluation
Ensure adequate social support and identify any potential social or financial barriers to transplantation
Additional case-specific assessments
Psychiatric consultation to assess for substance abuse disorders or untreated psychiatric comorbid illnesses
Dental assessment for patients with poor dentition
Anesthesia evaluation for patients with high perioperative risk
Nutritional assessment if nutritional needs or problems identified

Table 27.3 Criteria for simultaneous liver–kidney transplantation

Criteria for SLK transplantation
1. Persistent AKI for ≥4 weeks, with one of the following:
(a) stage 3 AKI as defined by modified RIFLE (threefold increase in serum Cr from baseline, serum Cr ≥4 mg/dL with an acute increase ≥0.5 mg/dL or on renal replacement therapy)
(b) estimated GFR ≤35 mL/min or GFR ≤25 mL/min by iothalamate clearance, and
2. CKD for 3 months, with one of the following:
(a) estimated GFR ≤40 mL/min or GFR ≤30 mL/min (iothalamate clearance)
(b) proteinuria ≥2 g daily
(c) kidney biopsy showing >30% global glomerulosclerosis or >30% interstitial fibrosis
(d) metabolic disease

AKI acute kidney injury, *RIFLE* acronym for classification criteria including risk, injury, failure, loss, and end-stage renal disease, *Cr* creatinine, *GFR* glomerular filtration rate, *CKD* chronic kidney disease, SLK, simultaneous liver-kidney

with significant cardiac risk factors [35]. Coronary revascularization should be considered in patients with significant coronary artery stenosis [11].

Age

The average age of graft recipients has increased steadily during the past decade [3, 4]. Overall, data do not support exclusion from LT on the basis of age alone, as favorable outcomes have been observed among recipients aged 70 years or older [36]. This may be in large part due to better selection of patients and exclusion of patients with significant comorbid illnesses or poor functional status.

Obesity

In parallel with the increasing prevalence of obesity in the general population, the proportion of transplant recipients with obesity continues to increase [3]. Obesity is associated with increased perioperative morbidity and mortality after major surgical procedures [37]. Among LT recipients, obesity is associated with significantly increased cardiovascular mortality with a higher prevalence of graft nonfunction and poorer 5-year survival rates [37]. In many centers, a BMI $\geq$40 kg/m^2 is a relative contraindication to LT and should only be pursued in carefully selected cases. All obese patients require diet and counseling regarding weight loss. Concomitant bariatric surgery with LT has been performed successfully in a small number of obese patients with decompensated cirrhosis, but this approach requires careful planning and considerable surgical expertise [38].

Hepatopulmonary Syndrome

LT improves survival in patients with HPS, with 5-year survival rates nearly three times greater among liver allograft recipients compared to patients who are not transplanted [39]. Moreover, LT reverses HPS in nearly all patients who survive more than 6 months, and for these reasons, patients with HPS are often granted priority in LT allocation [40]. All potential transplant recipients should be screened for HPS using pulse oximetry, with further evaluation using arterial blood gases and agitated saline contrast echocardiography in those with hypoxemia [41].

Portopulmonary Hypertension

All patients evaluated for LT must be screened for portopulmonary hypertension (POPH) by echocardiography given the increased perioperative mortality associated with moderate-to-severe POPH [42]. Patients with elevated Doppler-estimated pulmonary artery systolic pressure should undergo right heart catheterization. Posttransplant mortality increases dramatically with increasing mean pulmonary artery pressure (MPAP), approaching 100% in patients with severe POPH (MPAP $\geq$45 mmHg) [43]. As such, severe POPH is an absolute contraindication to LT, and patients with moderate POPH (MPAP 35–44 mmHg) should be considered for pulmonary vasodilator therapy. POPH does not necessarily resolve following LT and many patients may require chronic pulmonary vasodilator therapy posttransplant [44, 45].

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) infection was once considered a contraindication to LT; however, more recently, LT in HIV-infected individuals has resulted in acceptable graft and patient survival rates [46]. An increased rate of HIV-related complications or rapid HIV disease progression has not been observed, but antiretroviral and immunosuppressant medication adjustments are frequently needed to manage complex drug interactions and side effects [47]. Poor outcomes have

been observed among HIV patients coinfected with HCV, particularly among patients with low BMI and the need for SLK transplantation [46]. LT in HIV recipients is primarily pursued at centers with expertise in the care of HIV patients.

Patient Outcomes and Postoperative Complications

Donor Selection

Ideal deceased liver donors are young, previously healthy persons who meet criteria for brain death. Generally speaking, there are few absolute medical contraindications to organ donation apart from malignancy and the presence of transmissible infections that can adversely affect the recipient. Donor factors associated with adverse posttransplant outcomes include advanced age, female sex, donor–recipient gender mismatch, moderate-to-severe hepatic steatosis, hypernatremia, and prolonged circulatory shock. Technical factors, such as cold ischemia time and donor–recipient ABO mismatch, also impact graft viability. In response to the significant organ shortage, several important boundaries to graft utilization have been successfully overcome, including the use of HCV-positive donors in HCV-positive recipients, HIV-positive donors in HIV-positive recipients, and the use of non-heart-beating (donation after cardiac death) donors [48]. The donor risk index, developed using data derived from over 20,000 transplants, can aid physicians in selecting appropriate donors [49].

Posttransplant Survival

There have been dramatic improvements in postoperative outcomes following LT, likely the result of greater surgical expertise, better recipient selection, and improved postoperative management of complications and immunosuppressive therapy [3, 4]. Overall 1-, 5-, and 10-year patient survival rates in Europe are 82, 71, and 61%, respectively, and these rates are dramatically higher among patients surviving beyond the critical first 6 months posttransplantation, when many of the observed cases of graft failure and death occur. Similar survival rates have been observed in the USA, with poorer outcomes observed among older patients, patients with the highest MELD scores at the time of LT, and patients with HCV [3]. Although limited data are available, the rapid emergence of effective direct-acting antiviral agents for HCV is anticipated to result in improved posttransplant outcomes in the HCV population [50]. Intraoperative deaths and deaths due to early primary graft nonfunction are uncommon. Infection is the most common cause of death in the first year following transplantation, while deaths in the late transplant period are caused by recurrent primary liver disease, hepatic failure, malignancy, cardiovascular, and renal disease [51]. Death is rarely attributable to acute or chronic allograft rejection in LT recipients [52].

Postoperative Complications

Close monitoring of liver tests is required following transplantation to allow for timely detection and management of postoperative complications. Abnormal liver tests in the immediate postoperative period can be due to primary allograft nonfunction, vascular occlusion (e.g., hepatic artery thrombosis), biliary tract stricture(s), acute rejection, or preservation injury. Chronic allograft rejection and recurrent primary liver disease such as HCV generally manifest later in the postoperative period. Doppler ultrasonography is warranted to assess for vascular compromise and biliary dilation, and if negative, liver biopsy may be indicated. Initial management of hepatic artery or portal vein stenosis and thrombosis can include catheterization for thrombectomy and stenting, although surgical intervention may be needed in the early postoperative period. Similarly, biliary anastomotic strictures can often be addressed by endoscopic retrograde cholangiopancreatography with dilation and stent placement before biliary reconstructive surgery is pursued. Less than 10% of patients may require re-transplantation

and this rate has been decreasing over time [51]. The need for early re-transplantation is most often due to vascular complications and primary graft nonfunction, while late re-transplantation is most often due to chronic rejection, biliary complications, or recurrence of primary disease [53].

Posttransplant Immunosuppression

To prevent allograft rejection, potent immunosuppression is initiated intraoperatively and continued postoperatively. Immunosuppression usually consists of a multidrug regimen, with the use of two to three agents simultaneously, including a glucocorticoid such as prednisone, calcineurin inhibitors such as tacrolimus or cyclosporine, and antiproliferative medications such as mycophenolate mofetil, azathioprine, or sirolimus (Table 27.4). The majority of graft recipients will require lifelong immunosuppression. Due to the adverse effects associated with the prolonged use of glucocorticoids, they are usually tapered as soon as possible following LT, typically over 3–6 months. Some centers transition patients to monotherapy after the first 6 months, most commonly with a calcineurin inhibitor, while others continue low-dose prednisone and/or mycophenalate mofetil in addition to a calcineurin inhibitor long term.

Posttransplant Infectious Diseases

Due to immunosuppression, LT recipients are at risk for both common and unusual infections. The first 6 months following transplantation represents a high-risk period for opportunistic infec-

Table 27.4 Common immunosuppressive drugs following liver transplantation

Drug	Mechanism of action	Clinical use	Adverse effects
Glucocorticoids	Inhibit multiple inflammatory cytokines	Integral part of immediate posttransplant regimen First line of therapy for acute allograft rejection Typically tapered over first 3–6 months posttransplant	Accelerated bone loss, steroid-induced diabetes, dyslipidemia, poor wound healing, emotional lability, Cushingoid state
CNI Cyclosporine Tacrolimus	Inhibit calcineurin and IL-2 synthesis	Resulted in improved posttransplant outcomes Mainstay of maintenance therapy Tacrolimus superior to cyclosporine with respect to survival, graft loss, and acute rejection	Nephrotoxicity, neurotoxicity, hypertension, gastrointestinal disturbances, electrolyte abnormalities
Anti-proliferatives Mycophenolate mofetil Mycophenolic acid Azathioprine	Antimetabolites that inhibit B- and T-lymphocyte proliferation	Adjunctive agents commonly used with CNI and steroids Useful as CNI-sparing agents Mycophenolate derivatives preferred, safer and more effective than azathioprine	Bone marrow suppression, gastrointestinal disturbances
mTOR Inhibitors Sirolimus Everolimus	Inhibit mTOR pathway, reducing IL-2 mediated B- and T-lymphocyte activation	Adjunctive agents that can also serve as CNI-sparing agents Antineoplastic effects make them attractive for use in patients with hepatocellular carcinoma Side effects limit their role as first-line agents Sirolimus use is associated with hepatic artery thrombosis (black box warning); similar effect not observed with everolimus	Thrombocytopenia, hypercholesterolemia, dyslipidemia, poor wound healing, hepatic artery thrombosis, acute rejection

CNI calcineurin inhibitor, *mTOR* mammalian target of rapamycin

tions, including herpes viruses (cytomegalovirus, herpes zoster and simplex, and Epstein–Barr virus), fungi (*Aspergillus* and *Cryptococcus*), and unusual bacterial infections (*Nocardia*, *Listeria,* and mycobacteria) [52]. As such, antimicrobial prophylaxis is mostly directed to that period of time. Corresponding to a decrease in immunosuppression, the risk of infection is lower following the first 6 months, and the most common infections are intra-abdominal or lower respiratory tract infections by community-acquired pathogens such as enteric gram-negative bacteria, *Streptococcus pneumoniae,* and respiratory viruses.

Long-Term Management of the Posttransplant Patient

Medical management following LT involves awareness of the common long-term complications (Table 27.5) and close communication with the transplant center. Generally, adjustment of immunosuppression is managed by the transplant center, while most other care is transitioned to the patient's primary care provider. Many LT recipients develop complications of nontransplant patients, but at greater frequency and at an earlier age. Most complications can be attributed to the long-term effects of immunosuppression, such as cardiovascular and renal disease as well as malignancies [54]. Providers need to be aware of the potential for recurrent diseases such as HCV, HCC, and drug and alcohol recidivism [55].

Living Donor Liver Transplantation

Living donor liver transplantation (LDLT) developed out of the growing discrepancy between the supply of deceased donor organs and the need for organ transplantation. Waiting times for recipients of LDLT are shorter than for recipients of deceased donors, and the timing of transplantation can be controlled. Organs used for LDLT are of high quality and preservation time is minimized. The disadvantages of LDLT include donor morbidity (bleeding, bile leaks, infections) and donor mortality, estimated to be between 0.1 % for left lobe donors and 0.4–0.5 % for right lobe donors [56]. Recipient complications include bleeding, bile leaks, and small-for-size syndrome [56]. Due to the complex surgical and ethical implications of LDLT, donors and recipients must be selected carefully by separate multidisciplinary teams who can assure that donors are fully informed and there is no element of coercion. Generally, patient and graft survival following LDLT compares favorably with that of deceased donor recipients. LDLT is an important approach to address the organ shortage, particularly for recipients who are disadvantaged by the deceased donor organ allocation system.

Future Challenges

LT has evolved from a largely experimental surgery to the optimal treatment option for many patients with decompensated liver disease and hepatic malignancy. Despite a growing number of potential recipients, the number of annual LT procedures in the USA and Europe has plateaued

Table 27.5 Long-term complications following liver transplantation

Cardiovascular disease (including hypertension)
Hyperlipidemia
Obesity
Glucose intolerance/diabetes
Renal disease
Osteopenia/osteoporosis
Malignancy (particularly nonmelanoma skin cancers and lymphoma)
Recurrent disease (including HCV, fatty liver disease, autoimmune liver disease, HCC and drug/alcohol recidivism)

HCV hepatitis C virus, *HCC* hepatocellular carcinoma

in recent years, and this is largely a function of the limited supply of usable donor organs [3, 4]. LDLT alone cannot overcome this gap in supply and demand, and greater efforts towards expanding the donor pool by means such as the use of extended criteria donors, donation after cardiac death, in situ splitting of livers, and blood-type incompatible LT are required [57]. In addition, while MELD-based allocation systems have improved organ access to the most severely ill patients, ongoing optimization of organ distribution is needed. In particular, attention must be given to addressing geographic inequities in organ availability [5], as well as improving patient selection by understanding factors that increase patient morbidity and mortality without necessarily increasing the MELD score [57].

Much of the success of LT can be attributed to enhanced immunosuppression regimens. However, as posttransplant patients are living longer, we are now faced with addressing the adverse effects of long-term immunosuppression, including cardiovascular disease, renal insufficiency, metabolic syndrome, and malignancy among others [54]. Withdrawal of immunosuppression has been shown to lead to improvements in renal function, hypercholesterolemia, hypertension, and diabetes, and this has heightened interest in developing immunosuppressive regimens that offer an improved adverse effect profile [58]. Proposed methods that warrant further investigation include the use of more targeted immunosuppresants including monoclonal antibodies, the development of immune monitoring assays that allow for more individualized immunosuppressive regimens, and the use of proteogenomics to identify patients who have developed clinical tolerance and are candidates for minimization of immunosuppression [57, 59].

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Assessment and Management of the Patient with Cirrhosis Undergoing Surgery

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It is estimated that up to 10% of patients with cirrhosis will require surgery at some time. The morbidity and mortality associated with surgery can be significant [1]. The mortality of high-risk surgery can exceed 50% and the risk is sevenfold higher for emergency as compared to elective surgery [2]. Abdominal and cardiac operations carry a substantially higher risk than peripheral surgery, such as orthopedic and breast procedures [2–7]. Complications include the following: bleeding, infection, liver decompensation, acute kidney injury (AKI), hepatic encephalopathy (HE), cardiovascular instability as well as issues with fluid management, nutrition, and wound healing. Unfortunately, the assessment and estimation of risk remains an inexact science, with limited data to guide decision making in the individual patient.

Preoperative Evaluation

The preoperative assessment of a patient with liver cirrhosis must include a detailed physical examination and review of prior clinical data. Previous episodes of hepatic decompensation, variceal bleeding, HE, kidney failure, and ascites may all predict an increased risk of similar complications postoperatively. Each of these areas should be addressed to ensure that the patient's condition is optimized. Evaluating a patient for evidence of portal hypertension is important since portal hypertension is an important predictor of perioperative risk. Patients with acute-on-chronic decompensation should not undergo elective surgery until the underlying issues have resolved. Similarly, ongoing or recent alcohol use should be considered a strong contraindication to elective surgery. A thorough review of all medications, including over the counter and herbal remedies is required, with adjustments being made as needed. The clinical exam should include an evaluation for evidence of portopulmonary hypertension and hepatopulmonary syndrome, which will entail appropriate assessment and treatment.

Preoperative Risk Assessment

The Child–Turcotte–Pugh (CTP) score was developed to assess operative risk and remains an important clinical tool (Table 28.1). More recently, the model for end-stage liver disease (MELD) score, has been validated as an effective predictor of perioperative risk; a modified form provides estimates of both short- and longer-term morbidity and mortality. The CTP and MELD scores should be considered complimentary and used

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Table 28.1 Child–Turcotte–Pugh score

Clinical feature	One point	Two points	Three points
Total bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.3	>2.3
Ascites	None	Mild	Moderate to severe
Encephalopathy	None	Grade 1–2	Grade 3–4

Child class A: 5-7 points; Child class B: 7–9 point; Child class C: 10–15 points
INR international normalized ratio

concurrently when assessing operative risk. Neither of these scoring systems captures important comorbidities such as a measurement of portal pressure or past clinical events. The prognostic importance of portal hypertension was demonstrated by a study evaluating the impact of perioperative mortality in patients undergoing cholecystectomy. In this study, mortality was 3.4-fold greater in cirrhotic as compared to noncirrhotic patients, but rose to 12.3-fold in those with portal hypertension [8]. Measurement of liver stiffness by elastography may also have a role in the assessment of surgical risk. While liver stiffness has been shown to correlate with some measures of portal hypertension and with nonoperative mortality, its measurement predicted liver decompensation following liver resection [9–12].

The risk of morbidity and mortality in patients with cirrhosis is influenced by the type of surgery in question as well as the severity of the patients' underlying liver disease (Table 28.2). The risk of mortality from major gastrointestinal surgery is approximately 10% in Child class A patients, 30–31% in Child class B and 76–82% in Child class C. Increasing MELD score is clearly associated with increasing postoperative mortality. For example, Northup et al. reported that mortality increased 1% for every unit of increase in MELD score between 6 and 20 and by 2% above a MELD score of 20 [13]. Some studies have suggested that the risk of abdominal and cardiac surgery becomes unacceptable in those with an MELD score greater than 15. The operative risk for elective surgery is acceptable in patients with Child class A disease, and those with an MELD score <8. Patients with Child class B disease and those with MELD scores between 9 and 15 should have their condition optimized and the need and type of surgery reviewed. Patients with Child class C cirrhosis and/or an MELD score >15 should avoid major surgery if possible.

Cholecystectomy The prevalence of gallstones is increased in patients with cirrhosis and is reported to be between 25 and 30% [14]. There is general agreement that cirrhotic patients with asymptomatic gallstones should not undergo cholecystectomy. For symptomatic disease, patients with Child class A and B disease, cholecystectomy carries an acceptable morbidity (13–33%) and mortality (<5%). Laparoscopic surgery appears to be safer and better tolerated than the open approach,

Table 28.2 Morbidity and mortality of specific types of surgery in patients with cirrhosis

Surgery	Morbidity (%)	Mortality (%)	Comment
Cholecystectomy	8–35	0–8	Risk lower in laparoscopic surgery
Colectomy	43	14	–
Appendectomy	42	9	Laparoscopic approach associated with reduced complication rate
Hernia repair	7–20	0–5	–
Elective cardiac surgery	41–58	2–17	–
Trauma surgery	10–45	11–45	Laparotomy associated with high mortality
Elective knee and hip replacement	10–35	0–4.8	High mortality in small series of those with Child class C disease

but cirrhotic patients carry an increased risk of conversion to open surgery. Patients with Child class C disease should be managed medically or have a cholecystostomy tube inserted in the setting of gallstone-related complications. Common bile duct stones should be managed endoscopically, where possible. Some authors have recommended balloon sphincteroplasty rather than sphincterotomy in those with advanced cirrhosis and coagulopathy [15].

Appendectomy Appendectomy can be performed safely in Child class A and B patients. The laparoscopic approach is preferred since it is associated with lower morbidity and shorter hospital stay [16].

Major Abdominal Surgery The morbidity and mortality of a major abdominal resection (colectomy, pancreatectomy, and gastrectomy) are substantial, particularly in Child class C patients. Overall mortality rates of 0–23%, and morbidity rates of approximately 50% have been reported [17, 18]. Patients undergoing emergency surgery carry the highest risk. A single series of patients undergoing pancreatectomy suggested that the risk was only acceptable in those with Child class A disease [19]. Placement of a transjugular intrahepatic portosystemic shut (TIPS) prior to abdominal surgery has been advocated to decrease portal pressure and reduce operative risk [20, 21]. While the data are largely uncontrolled and no definitive benefit has been demonstrated, it is not unreasonable to insert a TIPS 2–4 weeks prior to surgery in those with severe portal hypertension, as manifest by large varices and/or ascites [1].

Abdominal Wall Hernias Inguinal and umbilical hernias are common, affecting up to 20% of patients with cirrhosis and are associated with a substantial decrease in quality of life. Early management with elective surgery appears to be safer than adopting a conservative approach, as the risk of complications including incarceration and rupture of an umbilical hernia is substantial and is associated with a high operative mortality. In more recent case series, there was no reported mortality from the elective repair of umbilical and inguinal hernias [22, 23]. Use of mesh is associated with about a 50% lower incidence of recurrent umbilical hernia, but may be associated with a higher risk of infection. Some authors have reported that inguinal hernia repair was safe, even in those with Child class C cirrhosis, carrying a low risk of recurrence even with associated ascites [24].

Bariatric Surgery Bariatric surgery may have a special role in the management of obese patients with metabolic syndrome, some of whom have advanced liver disease [25]. Furthermore, weight loss surgery may help prevent disease progression [26]. There are limited data on the safety of bariatric surgery in cirrhosis. A single case–control study did not demonstrate any increased morbidity or mortality in cirrhotic patients with Child class A disease as compared to noncirrhotic controls [27]. In a second study of 23 Child class A patients, eight developed postoperative complications, none of which were life threatening and there was no liver decompensation or early mortality [28].

Cardiac Surgery Cardiac surgery is particularly problematic in the cirrhotic patient, especially when cardiopulmonary bypass is required. Elective surgery carries an acceptable risk in Child class A patients, but mortality rises to between 50 and 100% in Child class B and C class patients and may be higher following repeat surgery [29–34]. In one series, the mortality rate of cirrhotic, predominantly Child class A patients undergoing coronary artery bypass grafting was 17%, compared to 3% in noncirrhotic patients. In a separate study, no increased mortality was observed in cirrhotic patients undergoing off pump bypass, or percutaneous interventions. Given the high mortality associated with cardiac surgery, medical management and percutaneous treatments should be used where possible.

Perioperative Management

Perioperative management is targeted to the optimization of the patient prior to surgery and prevention of liver-related complications. The optimal approach to the management of the coagulopathy associated with liver disease is complex, but can be summarized by saying "less is more" [35]. Routinely used tests of coagulation such as the platelet count, international normalized ratio (INR) and activated partial thromboplastin time (aPTT) do not reflect true hemostatic function in liver disease or risk of bleeding complications [36, 37]. More sophisticated tests of blood coagulation, such as the modified thrombin generation test and whole blood thromboelastography, demonstrate that coagulation function is largely preserved, referred to as hemostatic rebalancing. Unfortunately, these tests are not widely available and have not yet been clinically validated. The preoperative use of blood products to correct platelet count, INR, and aPTT has not been shown to be clinically beneficial and aggressive volume expansion may increase the risk of portal hypertensive bleeding, often the most significant cause of bleeding in this population. Hence, a restrictive approach to the use of red blood cells, platelets, and plasma products is preferred. Furthermore, the use of the thrombopoietin agonist eltrombopag, has been shown to be associated with an increased risk of thrombotic complications [38]. The best approach is therefore to avoid platelet and plasma transfusion prior to procedures and to intervene only where there is clinical evidence of hemostatic failure, often indicated by bleeding from multiple sites. Low fibrinogen levels (< 1 g/L) can be replaced with cryoprecipitate or fibrinogen concentrates to minimize volume expansion. The use of antifibrinolytics and prothrombin complex concentrates is currently being studied in clinical trials. It has been proposed that volume contraction and maintenance of a low intraoperative central venous pressure help reduce the need for blood transfusion during liver transplantation (LT) and liver resection [39–41]. This must be balanced against the risk of reduced perfusion of the kidneys and liver [35, 42]. Prevention of kidney injury, acidosis, hypothermia and hypocalcemia, as well as the early identification and treatment of infection, including the prophylactic use of antibiotics, will all help to improve surgical outcomes and reduce the risk of hemostatic failure.

Cirrhotic patients are also at increased risk of thrombosis, including portal and deep vein thrombosis. The use of anticoagulants in cirrhotic patients is a complex issue and the decision to use anticoagulants should be made on a case-by-case basis. Low molecular weight heparin appears to be safe in patients with Child class A and B disease undergoing surgery and is probably the treatment or choice in this setting [43].

Ascites is managed with salt restriction and diuretics. When paracentesis is required, ascitic fluid should be sent for culture and cell count. Postoperatively, care should be taken to minimize the accumulation of fluid through oral and intravenous salt restriction and judicious use of diuretics. Colloids and blood products can be used for intravascular volume replacement where needed. A key focus in postoperative management is the prevention of renal injury, through adequate volume replacement and avoidance of nephrotoxic agents including antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) and intravenous contrast. Nutritional support should be commenced as soon as possible after surgery, preferably via the enteral route [44].

Pain Management in Patients with Cirrhosis

Pain management in patients with cirrhosis or end-stage liver disease is a clinically challenging issue with many misconceptions that generate much apprehension amongst health-care providers. Adverse events from analgesics are frequently observed and may lead to various complications ranging from the mild to life threatening. These include fluid and sodium retention, HE, hepatorenal syndrome (HRS), and gastrointestinal bleeding.

The metabolism and excretion of most analgesic drugs are dependent on liver and/or kidney function and is summarized in Table 28.3. The ability of the liver to clear drugs is dependent on

Table 28.3 Mechanism of metabolism and route of excretion of commonly used analgesic agents

Medication	Metabolism	Route of excretion
Acetaminophen	Liver: glucuronidation Sulfation	Bile: 2.6% Renal: 5% unchanged, 90% metabolites
NSAIDs		
aspirin	Liver: hydrolysis Conjugation	Renal: 10% unchanged, 90% metabolites
celecoxib	Liver: CYP2C9	Renal: 3% unchanged, 27% metabolites Fecal: 3% unchanged, 57% metabolites
diclofenac	Liver: CYP2C9	Bile: 35% Renal: 65% (almost entirely metabolites)
ibuprofen	Liver: CYP2C9	Renal: 1% unchanged, 45–79% metabolites
indomethacin	Liver: O-demethylation N-deacylation	Fecal: 1.5% unchanged, 33% metabolites Renal: 26% unchanged, 34% metabolites
ketoprofen	Liver: glucuronidation	Renal: 10% unchanged, 70% metabolites Bile: possibly up to 40% due to enterohepatic recirculation
ketorolac	Liver: hydroxylation Glucuronidation	Fecal: 6% Renal: 55% unchanged, 37% metabolites
meloxicam	Liver: CYP2C9 Oxydative metabolism	Fecal: 1.6% unchanged Renal: 0.2% unchanged
naproxen	Liver: glucuronidation Demethylation	Renal: 5–6% unchanged, 90% metabolites
sulindac	Liver: conjugation	Renal: 50% Fecal: 25%
Codeine	Liver: CYP2D6, CYP3A4 Glucuronidation	Renal: 10% unchanged, 80% metabolites
Fentanyl	Liver and Intestinal mucosa: CYP3A4	Renal: 7–10% unchanged, 75% metabolites Fecal: 1% unchanged, 9% metabolites
Hydrocodone	Liver: CYP3A4, CYP2D6 Demethylation 6-keto reduction	Renal: primary route
Hydromorphone	Liver: glucuronidation	Renal: 7% unchanged, 68% metabolites Fecal: 1% unchanged
Meperidine	Liver: hydrolysis Conjugation	Renal: 0.5–5.2% unchanged, 0.6–21% active metabolites, ~30% other metabolites Saliva: if administered by intramuscular injection
Methadone	Liver: CYP3A4, CYP2B6, CYP2C19, CYP2C9, CYP2D6 *N*-demethylation	Renal: 21% unchanged, 13% metabolites Bile: detectable Fecal: 20–40% metabolites
Morphine	Liver: glucuronidation Demethylation	Renal: 2–12% unchanged, 80% metabolites Fecal: 7–10% Bile: small amount of glucuronide conjugates
Oxycodone	Liver: CYP3A4, partially CYP2D6	Renal: primary route, up to 19% unchanged, the remaining in various metabolite forms
Propoxyphene	Liver: 95%	Renal: 20–25%
Tramadol	Liver: CYP2D6, CYP3A4	Renal: 30% unchanged, 60% metabolites

NSAIDs nonsteroidal anti-inflammatory agents, *CYP* cytochrome P450

portal blood flow, hepatic enzyme activity, and plasma protein binding capacity, all of which can be significantly impaired in cirrhosis. Changes in any of these factors may substantially alter the bioavailability of the parent compound or its metabolites, increasing the risk of drug toxicity or adverse events. Increased plasma levels of drugs with a high first pass metabolism are observed in patients with cirrhosis. Highly protein bound drugs are also affected by cirrhosis. Hypoalbuminemia leads to increased levels of free drug, which may cause toxicity. Drugs that are primar-

ily excreted by the kidneys are less often affected by liver disease, but these drugs may still be dependent on hepatic metabolism prior to renal excretion. However, renal dysfunction associated with advanced liver disease can lead to decreased renal metabolism and excretion. In these cases, it is recommended that the dose be adjusted according to the estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault or modification of diet in renal disease (MDRD) equations [45]. These equations often overestimate the GFR in cirrhotic patients, so close monitoring for evidence of toxicity is still recommended, even after the "appropriate" dose modification. It should also be noted that end-organ sensitivity may be increased or decreased in the setting of cirrhosis. For example, cirrhotic patients are often more sensitive to agents with sedative effects and to drugs with adverse effects on the kidney.

Acetaminophen

Acetaminophen is the most commonly prescribed analgesic worldwide. It is also one of the most common identifiable causes of fulminant liver failure, leading to the misunderstanding that it should be strictly prohibited in patients with liver disease [46]. The risk of clinically significant hepatotoxicity from acetaminophen at doses of less than 3–4 g/day is extremely rare [47]. In patients with cirrhosis, cytochrome P450 activity is not increased and glutathione stores are not depleted to critical levels if recommended doses of acetaminophen are taken. Based on limited data, it is reasonable to recommend a dose limit of 2 g/day for long-term acetaminophen use in cirrhotic patients without active alcohol consumption and 3–4 g/day for short term or single use.

Acetaminophen is an active ingredient in hundreds of over-the-counter (OTC) and prescription medicines and about 50% of cases of acetaminophen-induced acute hepatic failure are related to unintentional overdosing. Cirrhotic patients should be counseled about this risk and the prescription of combination drugs containing acetaminophen should be avoided. Acetaminophen can be used separately following the above guidelines. In January 2011, the US Food and Drug Administration (FDA) requested drug manufacturers to limit the strength of acetaminophen in prescription drug products to 325 mg per dosage unit. In January 2014, the FDA recommended health-care providers discontinue prescribing and dispensing prescription combination drug products containing more than 325 mg of acetaminophen. In the near future, the FDA intends to withdraw approval of prescription combination drug products containing more than 325 mg of acetaminophen per dosage unit [48].

Nonsteroidal Anti-Inflammatory Drugs

In contrast to acetaminophen, NSAIDs should be avoided in patients with cirrhosis. Because of decreased metabolism and increased bioavailability, greater exposure to active drug levels is expected and can result in increased toxicity. Besides well-described idiosyncratic hepatotoxicity, nephrotoxicity is frequently observed and is of greater concern. NSAIDs-induced inhibition of cyclooxygenase lowers renal prostaglandin levels which may lead to decreased renal perfusion and a reduction in the GFR. This in turn can result in marked sodium and water retention, increasing the risk of precipitating HRS [49]. Furthermore, NSAID use can cause gastrointestinal ulceration and is associated with a higher risk of gastrointestinal bleeding in cirrhotic patients [50]. Cyclooxygenase type 2 inhibitors (COX-2 inhibitors) are safer from a gastrointestinal perspective, but would not be expected to have decreased nephrotoxicity as compared to nonselective inhibitors. No studies have formally evaluated the safety of selective COX-2 inhibitors in patients with cirrhosis. However, COX-2 is highly expressed in the kidney, is regulated in response to alterations in intravascular volume, and COX-2 metabolites are implicated in the mediation of renin release, regulation of sodium excretion, and the maintenance of renal perfusion [51]. Additionally, the use of selective COX-2 inhibitors is expected to be limited by reports of increased cardiovascular adverse events.

Opioids

Opioids are frequently prescribed when other analgesic agents are not available and/or provide suboptimal pain control. Worsening HE is the most concerning and well-recognized adverse effect of opioids in cirrhotic patients. Many pharmacokinetic studies have demonstrated increased bioavailability and prolonged half-life of most opioids in the cirrhotic state. This is due to altered hepatic metabolic pathways, both decreased oxidation via cytochrome P system and glucuronidation, and decreased plasma protein binding capacity [52, 53]. Thus, dose reduction and close observation are required especially in those with portal hypertension and HE. Of conventional opioids, hydromorphone (at reduced dose) and fentanyl are considered the better choices for those with renal insufficiency because they are least affected by renal dysfunction and their metabolism does not yield toxic metabolites [54]. Tramadol is an alternative option to conventional opioids, as it is thought to result in less sedation and respiratory depression, and lower risk of HE. Because it may lower the seizure threshold, tramadol should be avoided in any patient with a history of epilepsy. Methadone maintenance therapy can be continued safely in cirrhotic patients to achieve abstinence from heroin, but it should be avoided in patients with active alcohol consumption because alcohol inhibits the metabolism of methadone, resulting in elevated plasma concentrations and risk of toxicity. Comprehensive evaluation by a psychiatrist and/or psychologist specialized in substance abuse and addiction is essential to minimize the risk of opioid dependency, especially in the setting of LT.

Other Agents

Besides conventional analgesics, tricyclic antidepressants (TCAs), i.e., amitriptyline and imipramine, and some anticonvulsants which modify or modulate pain perception, i.e., gabapentin and pregabalin, can be considered as analgesics of choice for some cirrhotic patients who are suffering from neuropathic pain. Due to significantly decreased first-pass hepatic metabolism, TCAs should be started at a low dose to avoid potential toxicity and gradually increased under close monitoring. While gabapentin and pregabalin are not metabolized by the liver or bound to plasma proteins, other potential side effects, especially dizziness and sedation, may limit the use of these drugs in patients with cirrhosis [55].

Summary

The morbidity and mortality associated with surgery in patients with cirrhosis can be significant, depending upon the extent of underlying liver disease, presence of portal hypertension, type of surgery and whether the procedure is elective or an emergency operation. Measures to minimize AKI and HE include appropriate fluid resuscitation, avoidance of medications that cause nephrotoxicity, prevention of infections and judicious use of analgesic agents, taking into account the side-effect profile and pharmacokinetics of individual agents.

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29 Promoting a Healthy Lifestyle, Managing Hyperlipidemia, Diabetes Mellitus, Hypertension, and Immunizations in Patients with Cirrhosis

David P. Nunes and Surakit Pungpapong

Malnutrition with loss of lean body mass is a well-recognized complication of end-stage liver disease and is associated with a poor prognosis and an increased risk of developing hepatic encephalopathy (HE), ascites, and complications following liver transplantation (LT). This topic is reviewed elsewhere in this textbook [1]. At the other end of the spectrum, obesity and calorie excess is a significant problem in a substantial proportion of cirrhotic patients, especially in the era of nonalcoholic fatty liver disease (NAFLD), either as the primary cause of liver disease or as a comorbid condition [2, 3]. Cirrhotic patients with features of the metabolic syndrome or diabetes mellitus (DM) should follow diabetic dietary guidelines (e.g., those outlined by the American Diabetic Association) and increase their physical activity [4]. Nonmalnourished, overweight patients should aim to lose 5–10 % of body weight, in line with recommendations for patients with NAFLD [2]. For weight loss, calorie restriction with either a low-fat or low-carbohydrate diet is recommended. The consumption of whole grains, fruit, and vegetables is preferred over the intake of simple carbohydrates and processed highly refined foods. Foods sweetened with high fructose corn syrup should be avoided because of the association with NAFLD [5, 6]. Fruit and other foods with naturally contained fructose can be consumed without restriction [4]. Saturated fats should be replaced by the consumption of mono- and polyunsaturated fats. Omega-3 fatty acids may be beneficial, but we await confirmatory clinical evidence for their use in cirrhotic patients [2].

Coffee

The beneficial effects of coffee have been well documented in recent years. Large epidemiological studies have shown that regular coffee drinkers have a reduced incidence of type 2 DM, stroke, ischemic heart disease, gallstones, Parkinson's disease, and decreased all-cause mortality [7, 8]. Coffee consumption has been shown to reduce levels of gamma glutamyl transferase as well as liver transaminases in those with a variety of liver diseases including viral, alcoholic, and NAFLD [9]. At least one study in a hepatitis C virus (HCV) positive cohort also showed improved liver enzymes in association with consumption of chocolate [10]. Several large cohort and case control studies have shown that coffee consumption, but not other sources of caffeine,

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was associated with a reduced prevalence of chronic liver disease including decreased liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC) and mortality [7, 8, 11–22]. In several studies, a clear dose-dependent effect was observed [12, 21]. For example, in a group of patients with HCV infection and advanced fibrosis, consumption of coffee was associated with a dose-dependent reduction in disease progression, reaching a twofold reduction with consumption of greater than three cups of coffee a day [12]. An approximate 50% reduction in the risk of HCC was observed after correcting for other risk factors [7, 11, 16]. The breadth of these findings would support the recommendation that cirrhotic patients consume two to three cups of filtered coffee daily.

Exercise

Advanced liver disease is associated with loss of muscle and decreased exercise capacity, some of which may be related to unrecognized or subclinical cardiopulmonary disease [23, 24]. Patients with ascites appear to be most affected and decreased exercise tolerance worsens with progressive cirrhosis. Loss of lean body mass and decreased exercise capacity have both been associated with worsened outcomes including mortality and morbidity, as well as postoperative complications following LT [25]. Cirrhotic patients have been shown to respond to exercise with improvement in muscle strength and cardiovascular performance, but it remains unproven that this intervention improves outcomes. However, the other benefits of exercise, including improvement in the metabolic syndrome and reduction in cardiovascular risk, remain compelling reasons to recommend exercise [26].

The optimal form of exercise in patients with cirrhosis has not been defined and there are few clinical data to guide recommendations. Furthermore, any such recommendation should be tailored to the condition of the patient, taking into account the type and severity of liver disease, presence of comorbidities, including his or her cardiac and pulmonary status. Recommendations in patients with chronic diseases suggest 30–40 min of moderate exercise most days of the week (150 min/week) and two further sessions of resistance and flexibility training would be appropriate [23, 27, 28]. Studies suggest that endurance training, such as walking or climbing stairs, can be performed either in a single period or intermittently during the day. Vigorous exercise, including resistance training and high-intensity interval training appear to carry additional benefits, especially in terms of promoting reversal of metabolic syndrome and increased muscle strength [26, 29]. Of some concern is the finding that moderate exercise increases portal pressure and perhaps the risk of variceal bleeding [30, 31]. However, in a limited number of studies, no such complications have been reported. In summary, cirrhotic patients should be encouraged to exercise, the exact type and form of exercise being tailored to their lifestyle and clinical condition.

Management of Hyperlipidemia

The liver plays a central role in fat metabolism, through synthesis of triglycerides, cholesterol, and apolipoproteins as well as clearance of serum lipids. Hyperlipidemia, both hypertriglyceridemia and hypercholesterolemia, has long been recognized in association with a variety of liver diseases, including alcoholic, NAFLD, HCV, and cholestatic liver diseases. Lipid levels fall with the development of cirrhosis and in parallel with the severity of liver dysfunction. While it had previously been thought that cirrhosis was associated with a reduced risk of cardiovascular disease, it is now recognized that patients with hyperlipidemia, particularly when associated with NAFLD, alcoholic liver disease, and HCV, are at increased risk of adverse cardiovascular outcomes [32]. Cirrhosis is also associated with an increased risk of DM, which in turn confers an increased cardiovascular risk. In contrast, chronic hepatitis B is not associated with fatty liver, any significant alteration in lipid profile, or increased cardiovascular risk. Cholestatic liver diseases

are associated with increased cholesterol levels and an abnormal form of low-density lipoprotein (LDL), lipoprotein X. A well-defined increased risk of cardiovascular disease has not been demonstrated in patients with primary biliary cirrhosis [32]. These data clearly show that cardiovascular risk is associated not only with the lipoprotein profile but also with the underlying etiology of liver disease; furthermore, it has been shown that the cardiovascular risk persists following LT in high-risk groups.

Hyperlipidemia should be treated in patients who have other cardiovascular risk factors including those with metabolic syndrome, hypertension, a family history of cardiovascular disease, DM, and in those in whom LT may be an option. Management should include lifestyle changes (exercise and diet) and the use of statins or ezetimibe where appropriate. Statins appear to be safe even in patients with advanced liver disease and some data suggest that statins reduce the risk of HCC [33]. There is currently no information to guide the thresholds for the commencement of statins in cirrhosis. As a result, statins should be used in accordance with current cardiovascular guidelines [34]. Whether all statins are equally safe is unclear; one large study demonstrated a higher incidence of increased liver blood tests with the use of fluvastatin as compared to other agents and a large Taiwanese study found evidence of increased hospitalizations for liver injury in patients receiving high-dose atorvastatin [35, 36]. Ezetimibe does not appear to be associated with significant hepatotoxicity. While increased liver blood tests have been observed, usually in association with the use of a statin, only insignificant increases in liver blood tests have been observed with ezetimibe monotherapy. A few cases of drug induced hepatitis have been reported but this appears to be rare. Ezetimibe is metabolized in the liver, and increased drug levels are observed in patients with reduced hepatic function. As a result, ezetimibe is recommended only in patients with normal liver function, or mild dysfunction [37].

Diabetes Mellitus

DM is a common complication of liver disease affecting between 21 and 40 % of cirrhotic patients and up to 95 % of those with cirrhosis have evidence of insulin resistance [38–40]. Cirrhosis is associated with both hepatic and peripheral insulin resistance, but the risk of DM is also clearly related to the cause of liver disease. NAFLD, HCV infection, alcohol abuse, hemochromatosis, and autoimmune disease are all independently associated with DM or induce insulin resistance [40]. Patients with preexisting DM should be distinguished from cirrhotic patients who develop DM, sometimes referred to as hepatogenous diabetes [40]. Hepatogenous diabetes is associated with a lower risk of macro- and microvascular complications than classical type 2 DM, but both are associated with an increased risk of liver complications including higher rates of liver decompensation and HCC [38, 41–43]. Good glycemic control (a glycosylated hemoglobin less than 7.0 %) has been associated with improved liver outcomes. Unfortunately, the management of DM is complicated by cirrhosis, which impairs glucose regulation and affects treatment selection.

Management

Good glycemic control and correction of insulin resistance are important components of the management of cirrhotic patients with DM. Insulin resistant and diabetic patients should follow the dietary and exercise recommendations as outlined above. Regular physical activity, avoidance of simple carbohydrates, and weight loss in overweight patients remain the cornerstones of management. Treatment of the underlying liver disease, especially alcohol abstinence and eradication of HCV may help reverse insulin resistance and improve blood sugar control. In the majority of diabetic patients, lifestyle modification will not lead to adequate blood sugar control and drug therapy will be required.

Drug Treatment and Insulin

Alterations in drug metabolism and concerns about safety in end-stage liver disease, limit the treatment options for diabetic patients with cirrhosis. Unfortunately, there are few data to help guide therapeutic decisions in cirrhotic patients, but data drawn from the management of patients with NAFLD and comorbid diabetes provide useful insights.

Sulfonylureas Sulfonylureas work predominantly through increasing beta cell insulin secretion, but may also act to decrease hepatic glucose production and increase insulin sensitivity. These agents are primarily metabolized by the liver, such that there is an increased risk of prolonged hypoglycemia in patients with advanced liver disease. Therefore, sulfonylureas should be used with caution and at reduced doses in those with cirrhosis. Also of some concern is the reported association between this class of drugs and an increased risk of HCC [44, 45].

Metformin Metformin reduces gluconeogenesis and increases insulin sensitivity. Current labeling recommends against the use of metformin in advanced liver disease, because metformin may precipitate lactic acidosis. Despite this, there are now several studies showing that treatment with metformin is associated with a reduced risk of HCC, death, or need for LT [45–48]. For instance, the continuation of metformin following a diagnosis of cirrhosis was found to be associated with a marked improvement in overall survival [49]. Furthermore, in a recent case-controlled study, metformin use was associated with a lower incidence of intrahepatic cholangiocarcinoma [50]. Based on these studies, it seems appropriate to recommend the use of metformin in cirrhotic patients with DM. Further studies are needed to assess the role of metformin for the chemoprophylaxis of liver tumors.

Thiazolidinediones: (Rosiglitazone and Pioglitazone) Thiazolidinediones increase hepatic and peripheral insulin sensitivity. Treatment with pioglitazone was shown to reduce hepatic fibrosis in one study of NAFLD patients [51], but was not confirmed in other studies using either rosiglitazone or pioglitazone [52, 53]. However, these agents have been associated with weight gain and increased cardiovascular risk. They are relatively contraindicated in end-stage liver disease and their long-term benefits continue to be questioned.

Glucagon-like peptide mimetics The glucagon-like peptide mimetics, exenatide and liraglutide increase insulin sensitivity and are associated with weight loss but are seldom used as a single agent in the management of DM. They are largely renally excreted and have not been shown to have significant hepatotoxicity. They have been used for the treatment of NAFLD and appear to be safe, but the data are limited, and hence no broad recommendation for their use can be made at the present time [54–57].

Dipeptidyl-peptidase IV inhibitors (gliptins) Gliptins are often used in obese and overweight individuals in combination with insulin or a sulfonylurea. Sitagliptin and saxagliptin are hepatically metabolized via cytochrome P450 3A4 and 3A5 (Cyp 3a) while others are primarily excreted in bile (linaglitpin) or renally excreted (e.g., alogliptin). A number of small-scale studies have demonstrated the apparent effectiveness and safety of these agents in patients with NAFLD and type 2 DM [58, 59]. Liver injury appears to be very rare despite a couple of case reports [60]. In summary, these agents appear to be safe even in the setting of liver disease, but the experience remains small and further data are needed before their use can be broadly recommended [61].

Insulin Insulin is required in a substantial proportion of diabetic patients. Since insulin is metabolized in the liver, dose reductions may be required with advancing liver disease. Interestingly, some data have shown that patients with type 2 DM treated with insulin had worse outcomes, including an increased incidence of HCC, as compared to those who did not require insulin [44]. Whether this is related to the severity of

Table 29.1 Recommendations for immunization of solid organ transplant candidates and recipients

Vaccine	Before transplantation	After transplantation
Influenza **Inactivated** **Live attenuated**	Recommended (yearly) If inactivated not available (2 weeks before transplantation)	Recommended (yearly) Not recommended
Hepatitis B	Recommended if seronegative (3–4 high-dose series)	Recommended if seronegative (3–4 high-dose series)
Hepatitis A	Recommended if seronegative	Recommended if seronegative
Tetanus (Td)	Recommended (every 10 years)	Recommended (every 5 years)
Pertussis (Tdap)	Recommended (substituted for Td once)	Recommended (if not previously received)
Inactivated Polio	Recommended	Recommended
***S. pneumoniae* (PCV13)**	Recommended	Recommended
***N. meningitidis* (MCV4)**	Recommended	Recommended
Human papilloma virus (HPV)	Recommended	Recommended
MMR **Live attenuated**	Recommended if seronegative (4 weeks before transplantation)	Not recommended
Varicella **Live attenuated (Varivax)** **Live attenuated (Zostavax)**	Recommended if seronegative (4 weeks before transplantation) Recommended (4 weeks before transplantation)	Not recommended Not recommended

MMR measles, mumps, and rubella

DM or an adverse effect of insulin is currently unclear, but additional exogenous insulin may be harmful.

Hypertension

Systemic hypertension is uncommon in patients with cirrhosis as a result of abnormal splanchnic and systemic vasodilation. However, hypertension is frequently observed in association with alcohol abuse, NAFLD, and comorbid kidney disease; a minority of patients may have an underlying cause for secondary hypertension. Some patients may have been treated for essential hypertension prior to the diagnosis of cirrhosis and continue to receive antihypertensive agents. In these cases, the need for continued treatment should be reviewed. In those with persistent hypertension and advanced cirrhosis, a secondary cause of hypertension should be considered.

Arterial blood pressure is a good indicator of circulatory dysfunction in cirrhosis. Low systemic pressures are associated with an increased risk of renal and portal hypertensive complications and arterial hypotension is an independent predictor of mortality [62–65]. It is on this background that the use of antihypertensive agents, particularly vasodilators (angiotensin-converting enzyme (ACE) inhibitors, alpha blockers, calcium channel blockers), should be used with caution and discontinued where possible. Current guidelines recommend against the use of ACE inhibitors and angiotensin receptor blockers in patients with ascites [66, 67].

More recently, it has been recognized that nonselective beta blockers have adverse effects in patients with advanced cirrhosis, particularly those with diuretic resistant ascites and those with associated kidney dysfunction [64]. In this setting, beta blockers exacerbate the hemodynamic abnormalities caused by cirrhosis and have been associated with decreased survival. In the majority of cases, these agents were commenced for the treatment of portal hypertensive complications but should be discontinued in those with refractory ascites, evidence of hepatorenal syndrome, or systemic infection [64].

Immunizations in the Cirrhotic Patients

Prevention of infectious complications is an essential element in the management of patients with cirrhosis who eventually become LT candi-

dates/recipients. These patients are at increased risk of infections, with a higher associated morbidity and mortality [68]. Unfortunately, patients with advanced liver disease may fail to mount a protective immune response to appropriate vaccinations. As a result, it is important to administer vaccination early in the course of chronic liver disease, where possible [68, 69]. Furthermore, immunization with live virus vaccines is generally avoided after LT. In some special circumstances, prevention of infection may require multiple modalities, including active and/or passive immunization as well as adjunctive antimicrobial prophylaxis.

Several societies and practice committees have published their guidelines and recommendations for the immunization of solid organ transplant candidates and recipients [70, 71]. Only minor differences can be identified when comparing these guidelines. Table 29.1 summarizes the guidelines recommended by the American Society of Transplantation published in 2013 [70].

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Malnutrition in Patients with Cirrhosis

30

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Malnutrition, defined by any nutritional imbalance, is a frequent and significant complication in patients with chronic liver disease. Studies estimate that malnutrition is present in 50–90 % of patients with cirrhosis, with a higher incidence occurring in patients with alcoholic liver disease [1, 2]. The liver is crucial for numerous metabolic processes; therefore, complications of cirrhosis—ascites, hepatic encephalopathy (HE), and gastrointestinal (GI) bleeding can lead to multiple nutritional deficiencies. Carbohydrates, proteins, and fats are metabolized in the liver. The liver produces and stores glycogen, the primary storage form of glucose in the body. Hepatocytes comprise over 80 % of the total liver mass and aid in metabolism of ammonia and amino acids, as well as in detoxification of drugs and vitamins [3]. A cirrhotic liver has decreased ability to metabolize and store nutrients increasing the likelihood of developing malnutrition.

Malnutrition is associated with a poor prognosis, increased risk for morbidity and mortality, decrease in muscle mass, and impaired immune function [1–5]. The degree of malnutrition in cirrhosis often correlates with the severity of liver disease and the development of complications [3, 5], rather than the etiology of liver disease. A nationwide analysis of complications in hospitalized patients with cirrhosis and protein–calorie malnutrition found a greater prevalence of ascites (65 versus 47.8 % without malnutrition) and hepatorenal syndrome (5.1 versus 2.8 % without malnutrition). In addition, patients with protein–calorie malnutrition had a twofold increase of in-hospital mortality [6]. In a prospective study analyzing nutritional status of patients awaiting liver transplantation (LT), Figueiredo et al. found that all patients had some degree of malnutrition [7].

Causes of Malnutrition

Malnutrition develops as a consequence of multiple abnormalities including decreased oral intake, increased nutrient losses or malabsorption, and adverse metabolic changes.

1. Decreased oral intake

   Poor appetite, nausea, changes in taste and early satiety are almost universal in patients with decompensated liver disease. Patients may develop postprandial fullness secondary to gastroparesis and ascites, often leading to diminished energy and protein intake. Dysgeusia (altered taste sensation) is caused by zinc deficiency or medications [4, 8]. Animal proteins may be avoided due to a perceived

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metallic taste, with patients favoring sweeter, less nutrient-dense foods. Restrictive diets, including those that are low in sodium or protein, may further compound decreased intake by limiting palatable food choices. Patients undergoing inpatient and outpatient testing are often required to fast for hours at a time, decreasing daily intake. HE can impair a person's ability to prepare food and consume an adequate diet [9].

2. Increased nutrient losses or malabsorption
   Fat malabsorption from intraluminal bile acid deficiency may occur with severe cholestasis [2]. Chronic cholestasis may result in lipid-soluble vitamin and calcium malabsorption due to a decrease in dietary calcium absorption and an increase in oxalate absorption [3]. Because of calcium malabsorption, patients with chronic cholestasis should be evaluated for osteoporosis. Exocrine pancreatic insufficiency in patients with alcohol-related cirrhosis from chronic pancreatitis can cause malabsorption.
   Gastrointestinal symptoms of abdominal pain, indigestion, diarrhea, and constipation increase in magnitude in patients with cirrhosis. These symptoms are correlated with the severity of the cirrhosis and recent weight loss [10]. Impaired digestive enzyme production, bacterial overgrowth, and small intestine disease such as celiac disease impede absorption of nutrients. Alcohol's toxic and metabolic effects are a common cause of gastrointestinal nutrient losses [9]. Bacterial translocation and endotoxemia secondary to breakdown of the integrity of the intestinal epithelial barrier complicate alcoholic cirrhosis and contribute to malabsorption [11].
3. Metabolic abnormalities
   Resting energy expenditure (REE) is the amount of energy required to perform vital organ functions in a 24-h period of time. Factors affecting REE include mass of metabolizing tissues, height, age, gender, genetics, and lifestyle. Over 100 equations are utilized to predict and calculate REE. Commonly used equations in hospital and outpatient setting are the Mifflin St. Jeor and Harris Benedict equations, which consider height, weight, age, and gender to determine calorie requirements. Stress factors may be added to the REE to account for disease severity, stressors, and infection. Peng et al. found that 15% of patient with cirrhosis were hypermetabolic and 51% of patients had significant protein depletion [12]. In a cross-sectional study of 473 patients with biopsy-proven cirrhosis, Müller et al. found hypermetabolism in 34% of patients and an REE of more than 30% above the predicted value in 41% of the hypermetabolic patients. Patients with reduced body weight of 64.1 ± 12.2 kg were hypermetabolic; however, hypermetabolism was not associated with clinical or biochemical data of liver function [13].

   Glucose metabolism is altered in cirrhosis, with increased levels of gluconeogenesis and protein catabolism. Hepatocytes have decreased ability to process, store, and break down glycogen leading to a breakdown of lean muscle mass [1, 2]. After 10–12 h fasting, patients with alcoholic cirrhosis enter a starvation state, oxidizing fuels similar to healthy individuals during a 2–3-day fast [14]. As they begin catabolism shortly after fasting, such patients should avoid lengthy periods without nutrition.

Nutrition Assessment

Nutrition assessment in patients with cirrhosis can be challenging due to metabolic abnormalities and fluctuations in weight due to edema and ascites. This assessment should include: (1) diet and weight history, (2) physical examination, and (3) biochemical measurements.

1. Diet and weight history
   A registered dietitian should thoroughly review the patient's typical oral intake to assess energy, protein, fluid, and vitamin consumption. Diet history should review dietary restrictions, food allergies and intolerances, socioeconomic status, ethnic preferences, and

supplements, including the use of vitamin and herbal preparations. The registered dietitian should inquire about common complications that impair nutrition including: anorexia, early satiety, taste changes, nausea, and vomiting. Usual food intake may be assessed using a 24-h recall, food frequency questionnaire, or food diary. Electronic nutrition tracking and analysis programs are readily available and a convenient method to record calorie, protein, and micronutrient intake. Weight history should take account of the patient's usual body weight prior to illness, highest and lowest adult weight, and dry body weight. Caution is required when assessing weight changes in cirrhotics due to fluctuations arising from fluid retention and its treatment. Muscle wasting and subcutaneous fat loss may be masked by edema and ascites.

2. Physical examination
   Since patients with cirrhosis are at increased risk for malnutrition, physical examination should evaluate body composition and assess for subcutaneous fat loss and muscle wasting. Subjective global assessment (SGA) is an objective tool to determine malnutrition through evaluation of weight change in the previous 6 months, dietary changes, gastrointestinal symptoms, functional impairment, and evidence of loss of subcutaneous fat, muscle wasting, and edema [15]. Muscle wasting may be most apparent in the temporal, clavicle, and interosseal regions. SGA score stratifies patients into three categories—well-nourished, mild to moderately malnourished or severely malnourished. In a retrospective study of 109 patients, Stephenson et al. used SGA scoring to predict outcomes after LT. They concluded that all patients had some degree of malnutrition: 35, 32, and 32 patients had mild, moderate, and severe malnutrition, respectively. Patients in the severe malnutrition group required more blood products during surgery. Severely malnourished patients had longer postoperative length of stay (16.9 ± 9 days) when compared to mildly (9 ± 8 days) or moderately malnourished patients (10 ± 5 days) [15].
   Monitoring weight in patients with cirrhosis is often misleading due to changes in fluid status. Bioeletrical impedence analysis (BIA) measures body composition in terms of fat mass and fat-free mass. Once a baseline is established, serial BIA measurements can assess loss of muscle mass and changes in body composition. Another approach using measurements of skinfold and mid-arm muscle circumference requires training for proper use [1]. Further examination of mouth, hair, and nails may reveal vitamin and/or mineral deficiencies.
3. Biochemical measurements
   Albumin, prealbumin, and transferrin are visceral proteins that are dependent upon the liver for their synthesis. However, serum protein levels are not indicators of nutritional status in patients with cirrhosis due to the dilutional effects of increased total-body water and decreased hepatic synthesis [9]. Levels of these protein correlate with severity of illness and can be viewed as indicators of inflammation, rather than nutritional status [16].
   Micronutrient deficiencies are common in patients with cirrhosis due to malabsorption and decreased oral intake. Serum vitamin levels should be routinely assessed and supplemented accordingly. Deficiencies in the fat soluble vitamins A, D, E, K may occur because of decreased hepatic synthesis of carrier and transfer proteins [1, 17]. The reduced concentrations of intraluminal bile in chronic cholestasis increases the risk for fat-soluble vitamin deficiency [2]. In a cross-sectional study of patients awaiting LT, Abbott-Johnson et al. found deficiencies of retinol in 75%, 25-hydroxycholecalciferol in 66%, and vitamin E in 3% of patients, respectively. Fat-soluble vitamin deficiencies were negatively related with Child–Turcotte–Pugh and the model for end-stage liver disease scores, showing a relationship to disease severity [17].
   Patients with alcoholic cirrhosis, continued alcohol use, or poor nutrition should be evaluated for thiamine (B1) deficiency. Chronic alcoholism decreases thiamine absorption from the gastrointestinal tract and diminishes its

storage. Severe thiamine deficiency can cause Wernicke encephalopathy (WE), which may be reversible with early diagnosis and proper supplementation. Korsakoff syndrome (KS), a severe neurological disorder, is a result of untreated WE [18].

Nutrition Management

Energy and Protein

The goal of nutrition management in malnourished cirrhotics is to provide adequate energy, protein, vitamins, and minerals to meet metabolic demands and enhance anabolism. Indirect calorimetry is the gold standard to measure REE. In the absence of indirect calorimetry, predictive equations may be used to estimate daily energy requirements. The American Society for Parenteral and Enteral Nutrition recommends the formula REE × 1.2 − 1.4 to determine energy needs [3]. Additional calories may be provided for weight gain or stressors such as infection and dialysis. Commonly used predictive equations are shown in Table 30.1.

Protein requirements of 1.0–1.5 g/kg/day are advised to maintain lean muscle mass, promote anabolism, and to decrease catabolism due to glucoenogenesis [3]. Because of fluid fluctuations, dry body weight (when available) should be used in predictive equations and calculations. Early research suggested that protein restriction was indicated to decrease ammonia levels and HE; however, recent studies reported that protein restriction worsened malnutrition and muscle wasting. In a randomized study of hospitalized patients with cirrhosis, researchers found no difference in rates of HE with a low-protein diet (0 g progressing to 1.2 g/kg/day) or normal-protein diet (1.2 g protein/kg/day). Patients consuming a low-protein diet showed higher protein breakdown [19].

Table 30.1 Commonly used predictive equations to estimate daily energy requirements

Mifflin St. Jeor:
Men: RMR = (9.99 × weight) + (6.25 × height) − (4.92 × age) + 5
Women: RMR = (9.99 × weight) + (6.25 × height) − (4.92 × age) − 161
(Equations use weight in kilograms and height in centimeters)
Harris–Benedict Equation:
Men: RMR = 66.47 + 13.75(W) + 5(H) − 6.76(A)
Women: RMR = 655.1 + 9.56 (W) + 1.7(H) − 4.7(A)
(Equation uses weight (W) in kilograms (kg), height (H) in centimeters (cm), and age (A) in years)

RMR resting metabolic rate

After the completion of a nutrition assessment and determination of energy and protein needs, an individualized meal plan should be created. As discussed earlier, patients with cirrhosis often experience decreased oral intake. Small, frequent meals can help patients maximize energy and protein intake before early satiety ensues and prevent periods of fasting. Consumption of a nutrient-dense bedtime snack reduces fasting time and can result in accretion of total body protein when taken consistently [1, 20]. Nutrition supplement drinks assist in meeting daily energy and protein requirements [9]. Patients should be encouraged to monitor and document daily intake to ensure goals are being met. A registered dietitian can assist with nutrient analysis and provide suggestions to overcome obstacles. A low-sodium diet of ≤2000 mg/day is indicated for patients with ascites and volume overload [1].

Regular follow-up assessments are strongly encouraged to monitor oral intake and assess changes in body composition, ideally in a dedicated outpatient nutrition clinic that includes a physician and registered dietitian. Serial objective measures can be obtained which provide an ongoing evaluation of malnutrition risk. This setting affords the opportunity to advise patients on specific dietary interventions that address their particular needs.

Nutrition Support

Nutrition support is indicated in patients with cirrhosis who are unable to consume adequate nutrition to maintain lean muscle mass. Early and aggressive nutrition support has been shown to improve morbidity and mortality when oral in-

take is insufficient [1, 21–23]. Malnutrition may progress rapidly; therefore, timely assessment of nutritional intake is essential. Enteral nutrition is the preferred route for patients with a functioning GI tract [3, 9, 21, 24]. A small-bore nasoenteric tube provides continuous or cyclic tube feeding while patients still consume an oral diet [21]. Nocturnal feeding is preferred as this allows patients to be active during the day and also prevents nocturnal starvation. Nocturnal tube feeding ensures that patients can meet their caloric and protein needs. Placement of a gastrostomy tube is often contraindicated due to the presence of ascites and intra-abdominal varices [24]. Parenteral nutrition should only be used in patients with a nonfunctioning GI tract or in those who have failed trials of enteral nutrition.

A concentrated, nutrient dense enteral formula (≥1.5 kcal/mL) is recommended in patients with volume overload or hyponatremia [1]. Concentrated formulas also lend to lower infusion rates and less enteral volume required on a daily basis. Renal enteral formulas are suggested for patients with impaired kidney function with hyperkalemia or hyperphosphatemia. Controversy remains regarding the use and benefit of branched-chain amino acids (BCAA) formulas in patients with refractory HE. Historically, researchers suggested a high concentration of aromatic amino acids (AAA) [methionine, tyrosine, and phenylalanine], and low concentration of branched-chain amino acid (BCAA; isoleucine, leucine, and valine) caused HE through synthesis of false neurotransmitters [21]. In a recent review, Kawaguchi et al. noted four randomized controlled trials showing no benefits of oral BCAA supplementation of HE, while three other larger studies showed benefits of increased BCAA-to-AAA ratio, decreased HE grade, and improvement in mental status [25]. Further research is needed to determine the benefits of BCAA supplementation.

Summary

Malnutrition in patients with cirrhosis is a rapidly progressing complication and is associated with poor prognosis, increased risk for morbidity and mortality, decrease in muscle mass, and impaired immune function. In addition to metabolic alterations, patients often experience decreased oral intake and increased nutrition losses. Thorough nutrition assessment and follow up is essential to determine the degree of malnutrition and assist patients in maximizing oral intake. When unable to consume adequate energy and protein orally, early aggressive enteral nutrition support is warranted.

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Bone Disease in Patients with Cirrhosis

31

Albert Parés and Núria Guañabens

"Hepatic osteodystrophy" has been used for years to describe the bone disease of patients with liver damage, including osteoporosis, which is characterized by the loss of bone mass and quality that leads to fragility fractures, and osteomalacia as the consequence of poor bone mineralization. Osteoporosis is the most prevalent bone disease observed in patients with liver conditions, particularly in those with advanced cirrhosis and with prolonged and severe cholestasis [1]. Osteomalacia is, however, very uncommon and only present when associated with persistent vitamin D deficiency in subjects with deep cholestasis and intestinal malabsorption, in particular from geographical areas with limited sunlight exposure [2].

Development of imaging methods such as bone densitometry has implied an essential progress for the diagnosis of osteoporosis, which previously was based on bone X-rays and histomorphometry. At present, the gold standard for the diagnosis of osteoporosis consists of assessing bone mineral density (BMD) and the recognition of fractures (Fig. 31.1). Hence, the diagnosis of osteoporosis mainly lies on a BMD with a T-score below −2.5. Osteopenia is diagnosed when the T-score is between −1 and −2.5. Severe or "established" osteoporosis refers to individuals who meet densitometric criteria and have one or more fragility fractures [3].

This chapter summarizes the prevalence of osteoporosis and fractures, and focuses on the current understanding of its pathogenesis, as well as in the management of this complication in patients with cirrhosis and chronic cholestasis.

Prevalence of Osteoporosis and Fractures in Liver Diseases

The prevalence of osteoporosis in patients with chronic liver disease is variable and depends on patient selection and diagnostic criteria [4–26] (Table 31.1). Nevertheless, around 30% of patients have osteoporosis, with a higher prevalence in patients with primary biliary cirrhosis [4–12]. The prevalence of osteoporosis in patients with cirrhosis related to chronic alcohol intake or resulting from chronic hepatitis C virus infection ranges from 12 to 39% of cases [14–23]. In a recent study assessing bone disease in patients awaiting liver transplantation, the prevalence of osteoporosis was still very high (30%) [23]. Additionally, around 30% of patients with hemochromatosis may have osteoporosis [24–26].

The prevalence of fractures in liver patients ranges between 7 and 35% [4, 8, 10–13, 15–18, 20, 22, 23). Fractures are more prevalent in

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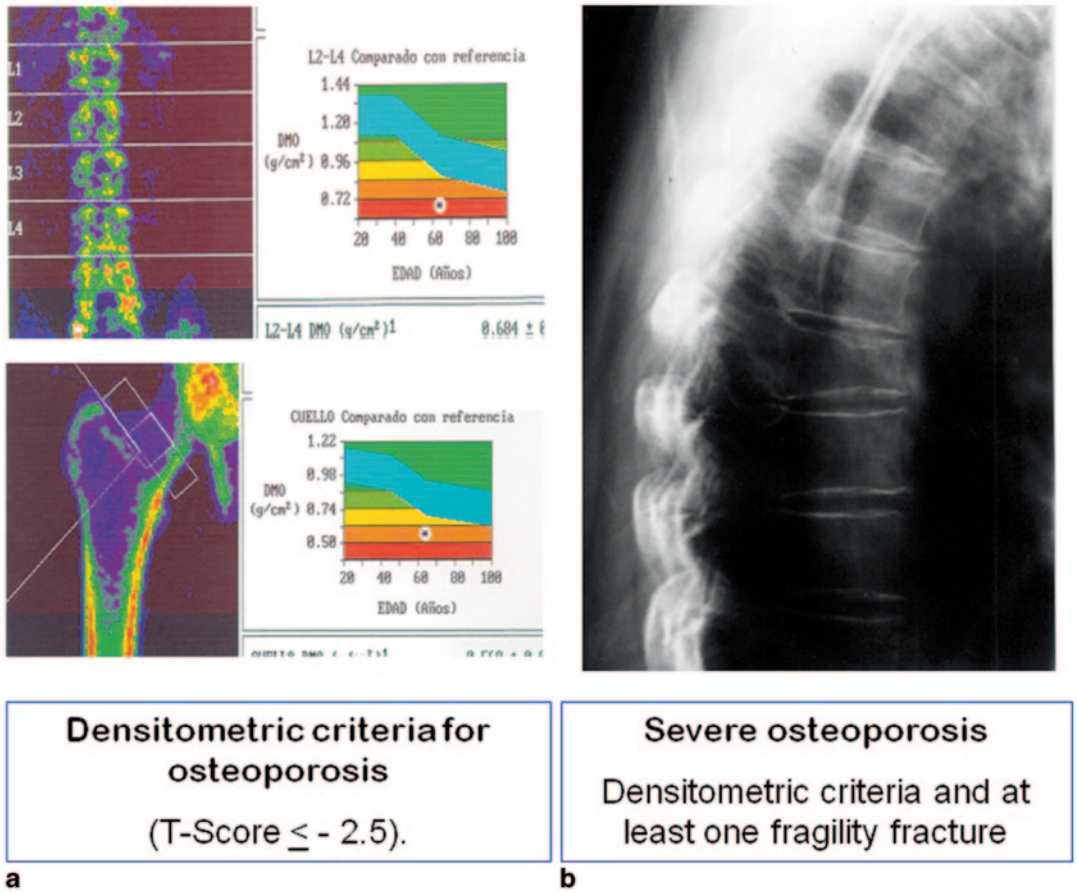

Fig. 31.1 The diagnosis of osteoporosis is based on densitometric criteria (**a**). Severe osteoporosis is diagnosed when besides the densitometric criteria there are one or more fragility fractures (**b**)

postmenopausal women than in males and young women [15], and in patients with autoimmune hepatitis treated with glucocorticoids [27]. In women with primary biliary cirrhosis, vertebral fractures are associated with osteoporosis and osteopenia with a T-score lower than −1.5, whereas osteoporosis and osteopenia are associated with the severity of liver damage [12]. The clear-cut correlation between vertebral fracture and a T-score < −1.5, observed in these patients may indicate that this densitometric measurement is a useful guide for considering therapy.

Osteoporosis with high risk for fracture represents an additional concern in patients who are candidates for liver transplantation. Thus, most liver transplant patients have a rapid bone loss within the first 6 months after transplantation [28]. This is associated with an incidence of fractures between 25 and 35% within the first year of transplantation, being more frequent in women, the elderly, cholestatic [29] and alcoholic patients, and particularly in those with osteoporosis and fragility fractures before transplantation [30]. However, these numbers may have become lower in recent years because of the advances in the management of patients following transplantation [31].

Pathogenesis of Osteoporosis

The mechanisms resulting in osteoporosis in liver disease have not been completely clarified, in part because the amount of bone mass depends on the balance between two opposite processes: bone resorption modulated by osteoclasts, and bone

Table 31.1 Prevalence of osteoporosis and fractures according to the etiology and severity of liver disease

	Author	Year	*N* cases	Etiology	Percent	Advanced disease or cirrhosis (%)	Osteoporosis (%)	Fractures (%)	Females (%)	Postmenopausal (%)
Cholestasis	Guañabens	1994	**38**	PBC	100	94	*45*	*13*	100	63
	Springer	2000	**72**	PBC	100	11	*24*	–	100	68
	Menon	2001	**176**	PBC	100	59	*20*	–	83	45
	Newton	2001	**272**	PBC	100	54	*31*	–	94	63
	Parés	2001	**61**	PBC	100	26	*21*	*13*	100	79
	Solerio	2003	**133**	PBC	100	39	*35*	–	100	70
	Guañabens	2005	**142**	PBC	100	26	*31*	*14*	100	69
	Guichelaar	2006	**156**	PBC	100	100	*44*	*22*	86	76
	Guañabens	2010	**185**	PBC	100	23	*32*	*21*	100	82
	Angulo	2011	**237**	PSC	100	54	*15*	6	42	40
Average	–	–	***147***	–	–	*49*	***30***	***15***	*91*	*66*
Mixed etiology	Bonkovsky	1990	**133**	A and VH	50	86	*26*	–	47	–
	Diamond	1990	**115**	A and VH	57	52	*16*	*28*	37	30*
	Chen	1996	**74**	A and VH	85	100	*20*	*7*	0	–
	Monegal	1997	**56**	A and VH	89	100	*26*	*22*	32	74
	Ninkovic	2000	**37**	A and VH	38	100	*39*	*35*	46	77
	Ninkovic	2001	**243**	A and VH	49	100	*37*	–	47	73
	Carey	2003	**207**	A and VH	100	100	*20*	*24*	37	48
	Sokhi	2004	**104**	A and VH	81	100	*12*	–	48	70
	González-Calvin	2009	**84**	VH	100	100	*43*	–	100	100
	Monegal	2012	**60**	A and VH	77	100	*30*	*33*	32	74
Average	–	–	***111***	–	–	*94*	***27***	***25***	*43*	*63*
Hemochromatosis	Sinigaglia	1997	**32**	HC	100	53	*28*	–	12	–
	Guggenbuhl	2005	**38**	HC	100	NR	*34*	–	0	–
	Valenti	2009	**87**	HC	100	NR	*25*	–	20	47
Average	–	–	***52***	–	–	–	***29***	–	*11*	–

PBC primary biliary cirrhosis, *PSC* primary sclerosing cholangitis, *A* alcoholic liver disease, *VH* viral hepatitis, *HC* hemochromatosis, *NR* not reported
* Hypogonadism

formation induced by osteoblasts (Fig. 31.2) [1]. Up to now, most studies point towards a decreased bone formation, whereas few studies have reported an increased resorption. Impaired osteoblast function resulting in lower mean wall thickness and a defect in matrix synthesis [32], as well as a low bone formation rate have been reported in some studies [32, 33]. These data are consistent with the decreased serum levels of osteocalcin [34], a biochemical marker of bone formation. Furthermore, the noxious effects of bilirubin and retained bile acids as a consequence of cholestasis may also play a role, since deleterious consequences on osteoblast viability, differentiation, and mineralization and increased apoptosis have been reported in different experiments [35–37]. Osteoblast dysfunction may result from reduced trophic factors such as insulin growth factor-1 (IGF-1). Thus, serum IGF-1 levels are decreased in patients with cirrhosis [38] and low doses of IGF-1 increase bone mass in cirrhotic rats [39]. A role for proinflammatory cytokines has been suggested in the pathogenesis of osteoporosis in liver diseases [40]. Thus, serum concentrations of soluble tumor necrosis factor receptor p55 are significantly higher in cirrhotic patients with osteoporosis and are inversely correlated with BMD [41].

Despite the previous data on osteoblasts and subsequent effects on bone formation, past histomorphometric reports have revealed increased bone resorption and turnover even in the absence of osteoporosis as an early feature of bone disease in patients with primary biliary cirrhosis [42]. Reduced trabecular wall thickness and increased bone turnover have been found to be proportional to the severity of hepatic dysfunction and cholestasis [43]. Overt or slight calcium and vitamin D deficiencies leading to secondary hyperparathyroidism have been proposed as the cause of increased bone turnover found in some patients with cholestasis [44]. Moreover, in human osteoblasts, serum from jaundiced patients significantly upregulates the RANKL/OPG (receptor activator of nuclear factor-κB ligand/osteoprotegerin) gene expression ratio, which activates the differentiation of osteoclasts and maintains their function [36]. These effects may partially explain the increased bone resorption described in some patients, particularly in those with chronic cholestasis.

Other conditions including low vitamin D levels, hypogonadism, and poor nutrition may be contributing factors to the full picture of bone disease in liver patients. Thus, hypogonadism, which is frequent in hemochromatosis [25],

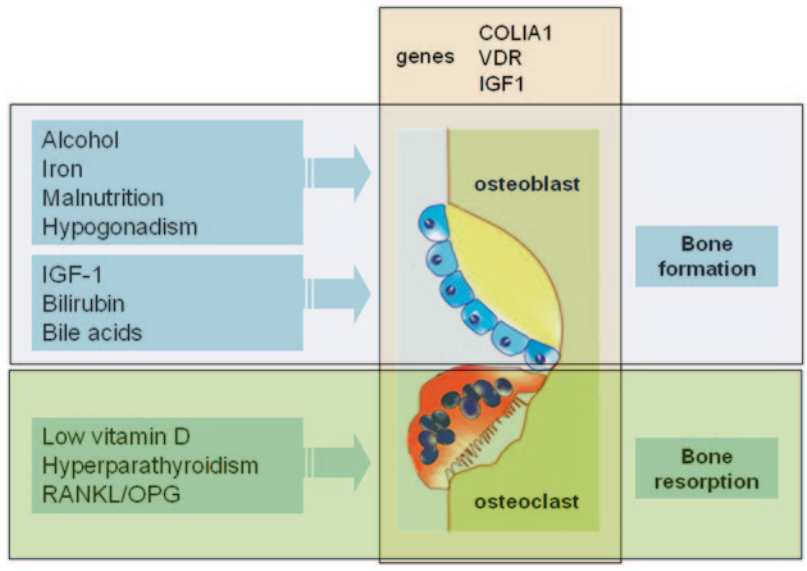

Fig. 31.2 The total amount of bone depends on the balance between bone formation mediated by osteoblasts and bone resorption caused by osteoclasts. The figure summarizes the pathogenic mechanism for bone loss

cirrhosis, and alcoholic liver disease [45], may result in increased bone remodeling and bone loss. Likewise, a reduction in bone formation has been observed in alcoholic patients, with low serum levels of osteocalcin during alcohol intake, which normalizes with abstinence [46]. Deposits of iron may be responsible for low bone formation, due to the direct lesion-producing effects of iron on osteoblast activity in hemochromatosis [47]. Vitamin K deficiency has also been considered as another ancillary factor in the pathogenesis of osteoporosis in liver disease, since vitamin K mediates the carboxylation of glutamyl residues in bone protein such as osteocalcin [1].

Genetic susceptibility for osteoporosis in liver diseases has been assessed with uncertain results. Taken together, gene polymorphisms either do not influence or have a very small effect on the development of osteoporosis in these patients [48].

Assessment of Bone Disease in Cirrhosis

Because of the high prevalence of osteoporosis and thus, increased risk for fractures in patients with chronic cholestasis and end-stage cirrhosis of different etiologies, it seems reasonable to establish guidelines for the diagnosis of bone disease that results in very high morbidity. This is even more important given that patients with advanced cirrhosis may be eligible for liver transplantation. However, there is scarce information about the steps to follow in terms of diagnosis and treatment, as bone disease in patients with cirrhosis has received little attention, except for conditions associated with chronic cholestasis and after liver transplantation [49]. It seems realistic to establish the same recommendations as in patients with other processes that are associated with osteoporosis.

The first step is to identify the risk factors for bone loss, including those recognized for osteoporosis and fractures in the general population and postmenopausal women. The most relevant are chronic alcohol intake, smoking, body mass index lower than 19 kg/m^2, male hypogonadism, early menopause, secondary amenorrhea of more than 6 months, family history of osteoporotic fracture and treatment with glucocorticoids (5 mg/day or more of prednisone for 3 months or longer) as well as advanced age [49]. Then bone densitometry, from lumbar spine and hip should be performed to identify low bone mass and the diagnosis of osteoporosis or osteopenia according to the WHO criteria. Lateral X-rays of dorsal and lumbar spine should also be carried out to disclose vertebral fractures [1, 49], and laboratory assessment is also appropriate to identify abnormal calcium and vitamin D metabolism. Biochemical markers of bone turnover can be assessed, but they are mainly useful to monitor the individual response to low bone mass therapy. Undecalcified transilial bone biopsy is suitable only in the rare cases with suspected osteomalacia.

Bone densitometry should be evaluated in patients with previous fragility fractures, patients treated with glucocorticoids, and before liver transplantation [1, 49, 50]. BMD should be assessed as well in patients with cholestatic diseases or if any of the described risk factors are found, and in cirrhotics (Table 31.2). Densitometry should be repeated after 2–3 years for those patients within the normal range to assess bone loss. However, the screening should be performed in a shorter interval of approximately 1 year in the

Table 31.2 Recommendations for bone mineral density assessment

Previous fragility fractures
Glucocorticosteroid therapy (>3 months; >5 mg/day prednisone)
Cholestasis liver disease at diagnosis
Major risk factors for osteoporosis, particularly in chronic cholestasis and cirrhosis[a]
Alcohol abuse
Hemochromatosis
Before and after liver transplantation

[a] Postmenopausal women, low body mass index, male hypogonadism, early menopause, secondary amenorrea

clinical conditions associated with a rapid bone loss such as in cholestatic patients with more than one risk factor for osteoporosis, and in those recently initiating high dose of corticosteroids. This schedule is also recommended for patients with advanced cirrhosis, particularly in those eligible for transplantation.

Inaccuracies in BMD and bone marker measurements in patients with cirrhosis or chronic cholestasis should be taken into account. Thus, collagen-related markers of bone turnover do not accurately reflect bone remodeling in these patients, since they are influenced by liver collagen metabolism [34]. In addition, BMD in patients with ascites may be falsely reduced, since lumbar and total hip BMD values increase after large-volume paracentesis [51].

Prevention and Treatment of Osteoporosis

Changes in Risk Factors and Supportive Measures for Bone Health

Factors contributing to bone loss must be reduced to a minimum. Thus, discontinuation of alcohol and tobacco use, and adjusting glucocorticoids to the minimum dose needed are mandatory. Physical activity should be recommended, in particular with exercises designed to improve the mechanics of the spine. Additionally, a balanced diet should be prescribed, since patients with cirrhosis often are malnourished. Supplements of calcium (1000–1500 mg/day) and 25-hydroxyvitamin D (400–800 IU/day or 260 μg every 2 weeks) or the dose required to maintain normal levels should be provided [49]. However, there is no definite data confirming the efficacy of these supplements in preventing bone loss in patients with liver disease.

Specific Treatments

Different drugs for osteoporosis have been proposed in patients with liver disease, but most studies have included small numbers of patients, and therefore it is difficult to reach any definite conclusions. Accordingly, the indication for the treatment of osteoporosis in patients with liver disease is based on trials of patients with postmenopausal osteoporosis. Furthermore, no clear anti-fracture effect could be demonstrated, and

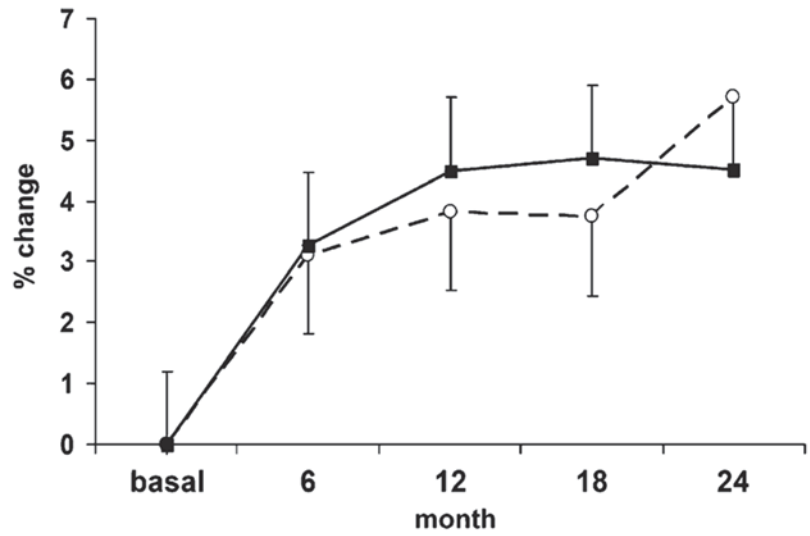

Fig. 31.3 Percent changes in lumbar bone mineral density (*BMD*) with respect to baseline values for patients with primary biliary cirrhosis treated with ibandronate (*broken line*) or alendronate (*solid line*). No significant differences in BMD changes were observed between treatments for each time period, but the increase in BMD was significant in each arm from 6 months. (From reference [60])

except for osteoporosis in primary biliary cirrhosis and after liver transplantation, no consistent studies have been carried out.

There is no agreement concerning the appropriate time to start treatment, but patients with established osteoporosis, and therefore with fragility fractures, should be treated to reduce the risk of further fractures. Taking into account that patients with primary biliary cirrhosis with a lumbar or a proximal femur T-score lower than <-1.5 have a high risk for vertebral fracture, it seems rational to consider specific therapy in these patients [12], mainly if they have additional risk factors for osteoporosis. Likewise, it seems reasonable to treat all patients with osteoporosis before transplantation.

Bisphosphonates

Bisphosphonates are anti-catabolic drugs which increase bone mass and reduce the incidence of fractures in postmenopausal osteoporosis. Their effects in liver disease are not entirely defined, mostly because of the scarce number of studies and the few number of patients treated [52–60]. Nonetheless, both etidronate and alendronate increase bone mass in patients with primary biliary cirrhosis, comparable to what occurs in osteoporosis due to other causes [55, 60]. Our results comparing alendronate 70 mg weekly versus ibandronate 150 mg monthly in primary biliary cirrhosis patients with osteoporosis or low bone mass and fragility fractures, showed that both drugs have similar effects on BMD without adverse effects on liver tests [60] (Fig. 31.3). Serious adverse events have not been observed and potential harmful effects of bisphosphonates such as esophagitis were not detected. Moreover, bisphosphonates in cirrhosis appear to be well tolerated, although it would be reasonable to exercise caution in using the drug in patients with recent esophageal banding/sclerotherapy. Importantly, stringent dosing procedures must be followed by the patient [61].

Parenteral bisphosphonates may have a role in cirrhotic patients, although most trials have been performed in liver transplant recipients. In this setting, pamidronate has been assessed in patients prior to and after liver transplantation [62–64]. The results regarding the efficacy of this agent on preventing bone loss and reducing the fracture rate are weak, although the most recently published placebo-controlled trial indicated that 90 mg of pamidronate given within the first 2 weeks and at 3 months after transplantation preserves lumbar BMD during the first year without significant side effects [59]. Favorable effects have been reported using alendronate and zoledronic acid as well. Thus, weekly alendronate prevents bone loss associated with liver transplantation [59] and zoledronic acid increases BMD [65], reduces bone turnover, and results in lower fracture rate [66].

Hormone Replacement

There is little information on hormonal treatment in patients with advanced liver disease, as for many years this approach was considered harmful in these patients. However, transdermal estrogens prevent bone loss or even increase BMD in patients with primary biliary cirrhosis or autoimmune cirrhosis with no adverse effects on liver disease [67–69]. Treatment with estradiol in postmenopausal women after liver transplantation was associated as well with an increase in lumbar and femoral neck BMD, together with a decrease in the serum levels of a marker of bone formation [70]. Despite these results, hormone therapy is not considered to be the most suitable treatment, as there are other efficacious nonhormonal agents with lesser side effects.

In males with hemochromatosis and hypogonadism, treatment with testosterone and venesection is also effective [71]. One concern about restoring testosterone levels in cirrhotic patients is that this might increase the risk of hepatocellular carcinoma. Therefore, the potential risk/benefit must be discussed with each patient before starting replacement therapy.

Other Treatments

To the best of our knowledge, there are no studies assessing the effects of anabolic drugs in patients

with osteoporosis and liver diseases. Only one study assessed intermittent administration of parathyroid hormone (hPTH 1–34) in bile duct-ligated rats, showing that PTH restores BMD as well as trabecular thickness. Therefore, PTH 1–34 can be a potential therapy for osteoporosis in patients with liver disease [72].

Conclusions and Future Prospects

Osteoporosis and the subsequent development of bone fractures are common complications in patients with advanced cirrhosis, regardless of the etiology, and especially prevalent in chronic cholestatic diseases. These complications are associated with high morbidity and represent a further problem in patients eligible for liver transplantation. Accordingly, clinicians must be aware of this frequent and detrimental complication in patients with cirrhosis.

The main mechanism involved in the development of osteoporosis is the decreased bone formation resulting from the harmful effects of substances retained in cholestasis, such as bilirubin and bile acids or by the toxic effect of alcohol or iron on osteoblasts. Osteomalacia infrequently occurs in patients with chronic liver disease despite low circulating vitamin D.

There is no specific treatment for osteoporosis, although different bisphosphonates increase bone mass in patients with chronic cholestasis. The efficacy of these antiresorptive agents in patients with cirrhosis remains to be confirmed, although they have positive effects after liver transplantation. The development of larger trials with bisphosphonates and the assessment of new drugs for osteoporosis may change the future.

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Part III

Cost, Quality and End-of-Life Care in Cirrhosis

The Economic Cost of Cirrhosis

32

Fasiha Kanwal and Michael L. Volk

Cirrhosis of the liver is a common condition with high rates of morbidity and mortality [1, 2]. In addition, the economic consequences of cirrhosis—both direct health-care expenditures in caring for the disease and indirect costs related to lost income from premature death or disability—are substantial. These costs represent an important component of the burden that cirrhosis imposes on society (Table 32.1). The practicing clinician should be cognizant of the financial impact of cirrhosis on health-care systems as well as individual patients and their families.

To prepare this chapter, we reviewed original research reports published in peer-reviewed journals over the past 10 years (from January 1, 2003 through March 31, 2014) that described cost burden in patients with cirrhosis regardless of the etiology of underlying liver disease. We focused on studies that reported the value of resources used for medical care of cirrhosis and its related complications (direct costs) and/or resources lost owing to foregone income from premature death or disability (indirect costs). Although we reviewed studies that examined the cost-effectiveness of preventive or therapeutic strategies in patients with cirrhosis to determine the source of cost estimates, this chapter does not detail the results from these economic models. Moreover, given the differences in clinical practices, insurance coverage, and reimbursement policies, cost estimates may vary across different countries and geographic regions (i.e., Asia, Europe, North America). We mostly describe studies that reported on the cost for care of cirrhosis in North America, although studies have found similar trends in other parts of the world [3].

This chapter is divided into four sections: (1) direct cost of cirrhosis, (2) direct cost of cirrhosis-related complications (variceal bleeding, hepatic encephalopathy, and hepatocellular cancer, HCC), (3) indirect costs associated with cirrhosis, and (4) clinical implications.

Direct Costs of Cirrhosis

The most recent data on the cost of liver disease (including cirrhosis) in the USA are summarized in a recent report commissioned by the National Institutes of Health [4]. This report used the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS); National Ambulatory Medical Care Survey, National Hospital Ambulatory Medical Care Survey, and Medicare reimbursement rates; Verispan data; National Nursing Home Survey; and National

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Table 32.1 Burden of cirrhosis

Frequency
Prevalence (pool of existing cases)
Incidence (occurrence of new cases)
Impact on
Longevity (premature death)
Morbidity (in- and outpatient care, quality of life)
Finance (direct and indirect costs to society)

The burden of cirrhosis not only encompasses the frequency of cirrhosis but also reflects how it affects other aspects of the health of a population. These include the negative impact of cirrhosis on longevity (such as premature death and years of lost life), morbidity (pain and impaired health-related quality of life), as well as the economic consequences of cirrhosis (such as direct health-care expenditures in caring for the disease and indirect costs related to lost income from premature death or disability)

Home and Hospice Care Survey to estimate the direct liver disease-related costs for hospital services, physician services, prescription, and over-the-counter drugs, nursing home care, home health care, and hospice care, respectively. The exact methodology used to derive cost estimates is beyond the scope of this chapter and is detailed elsewhere [5].

Based on this report, in 2004, total direct costs related to liver disease approximated US$ 2.5 billion in the USA. Because etiology and severity of liver disease are not always clearly identifiable from administrative data, this report could not separate cirrhosis—from non-cirrhosis-related health-care utilization. However, one can assume that a significant proportion, if not the majority, of hospital admissions and ambulatory visits related to liver disease was attributable to cirrhosis. Of note, the hospital facility costs and physician charges for hospital and ambulatory care in this report included only non-federal hospitals and physicians, and, therefore, underestimated the total costs of hospital care and ambulatory care for liver disease in the USA. Furthermore, despite being comprehensive, these estimates are outdated by a decade. The economic burden of cirrhosis has likely increased substantially in the last 10 years as a result of an aging chronic hepatitis C cohort and the rising prevalence of nonalcoholic fatty liver disease (NAFLD). Indeed, based on publically available data from the Agencies for Healthcare Research in Quality, the estimated number of emergency department visits with cirrhosis as one of the listed diagnoses (cirrhosis ICD-9 codes 5713, 5715, 5716) increased from 411,869 in 2006 to 548,092 in 2011 [6]. Similarly, the number of hospital discharges with cirrhosis as a diagnosis increased from 436,901 in 2006 to 576,573 in 2011 [6]. These trends show that the cost of caring for cirrhosis has likely increased substantially compared to the estimates provided from 2004.

Several recent studies have quantified the financial impact of cirrhosis related to chronic hepatitis C virus (HCV) infection (Table 32.2) [7–9]. HCV remains the leading cause of cirrhosis in the USA. Given this, data from these studies can be used to approximate the overall cost burden of cirrhosis. Information from private and public third-party payers identified HCV infected patients with and without cirrhosis (defined by the International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9] codes). Gordon et al., used a US private insurance database (from January, 2002 to August, 2010) to estimate all-cause health-care costs in 2010 US dollars for HCV patients with non-cirrhotic liver disease, compensated cirrhosis, and end-stage liver disease (ESLD; cirrhosis-related complications including HCC and liver transplantation (LT)) [7]. Mean all-cause per-patient-per-month health-care costs were 32 and 247% higher for patients with compensated cirrhosis and ESLD compared to those without cirrhosis (US$ 1870 and US$ 4931 vs. US$ 1420; $P<0.001$) and were independent of age or comorbid conditions (Table 32.2). The annual all-cause health-care costs were estimated to be US$ 22,752 for patients with compensated cirrhosis and US$ 59,995 for patients with ESLD [7].

Table 32.2 Studies reporting the economic burden of chronic hepatitis C virus-related cirrhosis. Complications include decompensated cirrhosis, hepatocellular cancer, and liver transplantation in three studies. *PPPM* per patient per month, *PPPY* per patient per year, *AIDS* acquired immune deficiency syndrome, *CC* compensated cirrhosis, *HCV* hepatitis C virus, *LT* liver transplantation, *SD* standard deviation

	Gordon 2012 [7]	McAdam-Marx [7]	Menzin 2012 [9]
Year	*2002–2010*	*2001–2010*	*1998–2008*
Patient population	Patients with HCV in a large US private insurance database	Patients with HCV in a large US private insurance database	Patients with HCV in Florida Medicaid database
Definition of cases	Diagnosis or procedure codes associated with cirrhosis and its complications	Diagnosis or procedure codes associated with cirrhosis and its complications	Diagnosis or procedure codes associated with complications of cirrhosis
Number of cases	3718 with compensated cirrhosis 8200 with complicated (end stage) cirrhosis	1521 with compensated cirrhosis 6099 with complicated (end stage) cirrhosis	1193 with complicated (end stage) cirrhosis
Controls	41,858 with HCV	330,435 matched controls without HCV	1193 matched controls with diagnosis of HCV alone
Costs measured	Direct (amounts paid by the health plans)[a] reported as PPPM costs adjusted to 2010 US dollars	Direct (amounts paid by the health plans)[a] reported as PPPM costs adjusted to 2009 US dollars	The total unadjusted all-cause medical costs over the 12-month follow-up adjusted to 2009 US$
Interval (follow-up period/time interval)	PPPM all cause[b,c]	PPPY all-cause	PPPM all cause[c]
Adjustment variables	Age, gender, geographic region, index year, Charlson comorbidity score, other HCV-related comorbidities, baseline health-care utilization, medications	Gender, age, hospital referral region state, pre-index health-care costs, alcoholism, HIV/AIDS, and a modified Charlson Comorbidity Index	NA
Cost estimates point (interval) mean (SD)	*PPPM costs* decompensated cirrhosis = US$ 4931 (US$ 11,911) CC ~ US$ 1870 (US$ 4448) HCV ~ US$ 1420 (US$ 4689)	*PPPY costs* decompensated cirrhosis ~ US$ 41,943 (US$ 1129) HCC = US$ 58,208 (US$ 2912) LT ~ US$ 113,282 (US$ 4908) CC ~ US$ 16,911 (US$ 659) HCV ~ US$ 14,915 (US$ 196)	*PPPM costs* decompensated cirrhosis ~ US$ 4937 (US$ 5236) HCV ~ US$ 1730 (US$ 2309)

[a] Costs paid by other health plans and Medicare were not included
[b] Study also reported hepatitis C specific costs. Data not included in the table
[c] Study also reported annual costs. Data not included in the table

Using similar data, McAdam-Marx et al. estimated the annual cost of care for patients with advanced liver disease to be US$ 41,943 [8]. The differences between the two estimates are likely due to the codes used to define the populations and differences in the index dates. In a study using Florida State Medicaid data, Menzin et al. estimated the total unadjusted all-cause annual medical costs in a cohort of patients with HCV-related advanced cirrhosis at US$ 37,424 (adjusted to 2009 US dollars); somewhat lower than those encumbered by patients with private insurance [9].

Building on the cost data from McAdam-Marx et al [8], a modeling study estimated that the total cost associated with HCV cirrhosis at ~US$ 6 billion in 2014 (~US$ 3 billion for decompensated cirrhosis; ~US$ 1.8 billion

for compensated cirrhosis, ~US$ 1.2 billion for HCC) [10]. The total cost associated with HCV is expected to peak in 2024 in the USA at US$ 9.1 billion (95% confidence interval US$ 6.4–US$ 13.3 billion); the majority of peak cost will be attributable to more advanced liver diseases—decompensated cirrhosis (46%), compensated cirrhosis (20%), and HCC (16%). These data represent the cost burden related to cirrhosis from HCV alone and demonstrate that the financial impact of cirrhosis from all etiologies may indeed by higher now than the US$ 2.5 billion estimate in 2004 [4]. In fact, as discussed below the costs of complications related to cirrhosis exceed US$ 3 billion when combined together.

Direct Cost of Cirrhosis Complications

Several studies have estimated the financial impact of specific complications of cirrhosis on the US health-care system (Table 32.3). Most of these have relied on the NIS of the Healthcare Cost and Utilization Project (HCUP). The NIS is the largest publicly available all-payer inpatient database in the USA. Using the NIS 2002, Adam et al. estimated that, on average, the cost of an inpatient stay for patient with variceal bleeding was US$ 6612 (standard deviation (SD) US$ 5488) in 2005; this estimate increased to US$ 23,207 (SD US$ 14,538) in patients with complicated variceal hemorrhage (defined as an admission with a length of stay longer than 9 days). Based on the study by Stepanova et al., the cost of caring for patients with hepatic encephalopathy (HE) was US$ 17,812 (SD US$ 764) per case in 2009. This translated into a total national cost related to inpatient care of HE exceeding US$ 2billion in 2009. Using the similar data source, the average cost of caring for patients with HCC was US$ 15,828 per inpatient admission in 2009 with the total annual HCC-related cost of approximately US$ 1 billion in 2009.

Cost of inpatient care is one component of the overall direct cost associated with cirrhosis and its complications. In a population-based study using Ontario Cancer Registry-linked administrative data, Thein et al. calculated the net costs of care due to HCC in Ontario, Canada. The mean (95% CI) 5-year net cost of care was US$ 77,509 (US$ 60,410–US$ 94,607) and the 5-year ag-

Table 32.3 Studies reporting the economic burden of cirrhosis complications

	Viviane 2008 [11]	Stepanova 2012 [12]	Mishra 2013 [13]
Year	2002	2005–2009	2005–2009
Patient population	Patients with variceal bleeding in the NIS	Patients with hepatic encephalopathy in the NIS	Patients with hepatocellular cancer in the NIS
Definition of cases	Variceal bleeding (ICD9-CM) codes 456.0 and 456.20	Hepatic encephalopathy (ICD-9=572.2) listed as the primary or secondary diagnosis	Primary liver cancer (ICD-9 code 155.0) listed as the primary or secondary diagnosis
Number of cases	840	115,814 in 2009	6364 in 2009
Costs measured	Charges and costs expressed in 2004 US dollars	Charges (for the entire hospital stay) Cost estimated	Charges (for the entire hospital stay)
Interval (follow-up period/ time interval)	Hospitalization	Hospitalization	Hospitalization
Cost estimates point (interval) Mean (SD)	Uncomplicated variceal bleeding=US$ 6612 (US$ 5488) in 2005 US$ Complicated variceal bleeding US$ 23,207 (US$ 14,538)	US$ 17,812 (US$ 764) in 2009	US$ 15,828 (cost) in 2009[a]

NIS Nationwide Inpatient Sample, *SD* standard deviation
[a] Cost to charge ratio applied

gregate net cost of care was US$ 106 million (US$ 83–US$ 130 million; undiscounted costs) [14]. Per-patient lifetime costs of HCC care were higher than the per-patient lifetime costs of lung, breast, and colon cancer care (US$ 22,970–US$ 27,890 in 2010 US dollars) in Canada. Inpatient costs accounted for 35–58 % of total costs of HCC care [14].

Lang and colleagues found similar results in their analysis of the US Surveillance, Epidemiology and End Results (SEER) and Medicare dataset [15]. SEER is a premier source for cancer statistics in the USA and collects information on incidence, survival, and prevalence from specific geographic areas representing 26 % of the US population. Medicare is the US government health insurance plan that provides hospital, medical, and surgical benefits for all persons age 65 and older and for people with certain disabilities. The SEER-Medicare data reflect the linkage of these two large population-based sources of data that provide detailed clinical, demographic, health-care utilization, and cause of death information for Medicare enrollees with cancer.

After accounting for inflation, the study estimated that caring for a patient with HCC cost an average US$ 32,907 in 2005. With the estimated prevalence of approximately 14,000 patients with HCC in 2005, the total economic burden of HCC was estimated to be US$ 454.5million. However, the direct costs in this study were based on the frequency of HCC specific health-care utilization in 1999. The treatment repertoire in HCC has changed significantly since 1999. Some of the commonly used treatment modalities for HCC (such as ethanol ablation, radiofrequency ablation, transarterial chemoembolization, sorafenib, and LT) were likely only sparsely used in 1999. HCC incidence and prevalence is expected to increase considerably over the next decade. Thus, the cost estimate presented in this study is likely a conservative one [16]. Nonetheless, inpatient costs represented ~50–60 % of the total cost of HCC care. Combined together, these data combined with the recent estimates of inpatient cost of HCC care suggest that net cost of HCC care may be upwards of US$ 1–2 billion in the USA.

Comparison with Other Diseases

In summary, the direct health-care costs attributable to cirrhosis appear to be approximately US$ 3–5 billion per year in the USA. By comparison, the top ten costliest diseases range from US$ 45 billion/year (heart disease) to US$ 17 billion/year (back problems) [17]. However, since the peak incidence of cirrhosis occurs during the working years, the relative impact on workforce productivity—and thus indirect costs—is proportionally larger than many other diseases.

Indirect Cost of Cirrhosis

Everhart et al. estimated the indirect cost of liver disease to approximately US$ 10.2 billion in 2004 [4]. These estimates consisted of the value of lost earnings or production owing to use of hospital or ambulatory care, premature death, and additional work loss associated with liver disease. Importantly, this US$ 10.2 billion estimate did not account for the earnings forgone by patients' informal caregivers (family or friends). A recent study found that individuals with cirrhosis need more than twice the number of informal caregiving hours per person than age-matched controls without cirrhosis [18], which may add significantly to the indirect cost of cirrhosis.

Clinical Implications

The very high per capita cost of cirrhosis health care has two important implications for the practicing clinician. First, clinicians need to be sensitive to patients' ability to pay for diagnostic testing and treatment. Most clinicians do not routinely discuss health-care costs with patients, but the cirrhotic population tends to be less economically advantaged than average, and may have difficulty paying for their health care

[19]. In fact, a recent study described significant financial stressors associated with cirrhosis and HE [20]. We have found that patients are often relieved to be asked about their financial situation, and such discussions often alter the medical decision making. The second implication relates to the change from fee-for-service to risk-based insurance contracting. Increasingly, hospitals and health-care systems are assuming some financial risk in caring for populations, and patients with cirrhosis represent a well-defined group at high risk for frequent readmissions and excess costs [21, 22]. Thus, clinicians may find that their hospital administrators are willing partners in programs to improve care and prevent readmissions.

Future Challenges

Liver disease is one of the most costly digestive diseases in the USA [4]. Liver disease-related total (direct and indirect) costs topped US$ 13.1 billion in 2004 [4]. This cost estimate would have increased to US$ 16.4 billion if it included the costs associated with viral hepatitis. The recent approval of two new drugs in the USA, sofosbuvir and simeprevir, marked the beginning of a new era for HCV treatment. With these agents, the sustained virologic response rates have increased to more than 90% in many patients. In addition, these therapies have fewer adverse effects, are given for a shorter period of time and require less intense monitoring than the previous standard approach [23]. Given their high efficacy and excellent safety profile, many patients with cirrhosis will now be candidates for these or other soon to be approved HCV drugs. However, the cost of these treatment regimens is as high as US$ 170,000 per patient [24]. The large number of persons infected with HCV needing treatment with the new drugs will likely have an additional (and potentially huge) financial impact on health expenditures related to the care of cirrhosis. This significant burden will add to the cost of cirrhosis placed on individual patients, their families, the health-care system, and society as a whole.

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Delivering Quality Care to Patients with Cirrhosis: A Practical Guide for Clinicians

33

Michael L. Volk and Fasiha Kanwal

Every health-care provider prides him- or herself on delivering quality care, but the days are gone where such a claim could be taken at face value. In the current health-care environment, providers are increasingly being asked to objectively demonstrate *value* (=*quality*÷*cost*). Fee for service is being gradually replaced with pay for performance—whether in a capitated fashion such as accountable care organizations, the use of explicit measures of quality to determine insurance contracts, or by direct bonus payments for reporting quality measures or conducting quality improvement (QI) [1]. Quality measures are increasingly being reported publicly, which may influence patients' choices about where to receive their care. Furthermore, QI is a requirement for maintenance of certification with the American Board of Internal Medicine. This chapter provides the "why" and "how" of quality improvement for clinicians.

Why Cirrhosis?

QI has been defined by the Institute of Medicine as a set of "systematic and continuous actions that lead to measurable improvement in health-care services and the health status of targeted patient groups" [2]. One key feature of this definition is *targeted patient groups*; QI is generally most effective when focusing on a specific group or disease population. In this regard, cirrhosis represents an ideal target because it is a well-defined group of patients at high risk of morbidity and mortality. Additionally, numerous studies have shown that patients with cirrhosis fail to receive proven treatments (Fig. 33.1) [3–6]. These deficits are not caused by a handful of "bad doctors" as many of these reports are from top-tier institutions. Rather, the causes of these failures are systems-based, multifactorial, and differ by location. Common causes of systems failure will be mentioned below, though a detailed analysis is beyond the scope of this chapter.

Measuring Quality

Another key feature of the QI definition is *measurable*. If something cannot be measured, it cannot be improved. A usable taxonomy of health-care quality was first developed by Avedis Donabedian, who divided it into *structure, process,* and *outcome* [7]. Structural elements include, for example, whether all physicians in a practice are board certified, or whether a hospital offers advanced treatments such as transjugular intrahepatic portosystemic shunt (TIPS). Processes reflect evidence-based medical decision making and health-care-related activity, such as prescribing antibiotics for secondary prophylaxis of spontaneous bacterial peritonitis (SBP). Outcomes can be intermediate endpoints such as

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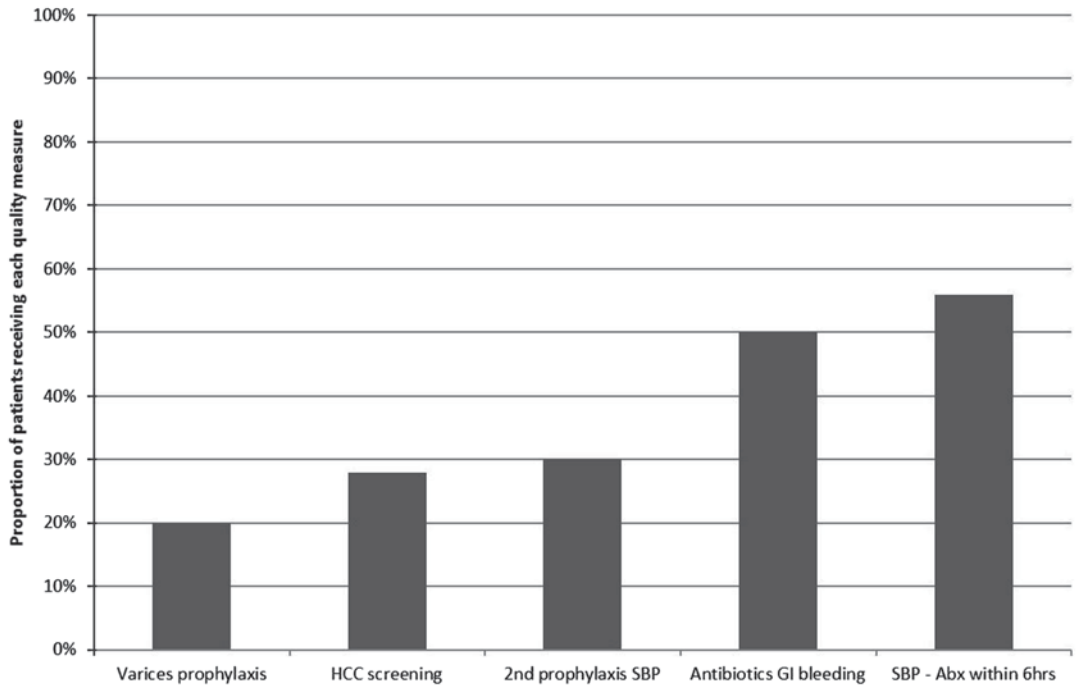

Fig. 33.1 Many patients with cirrhosis fail to receive evidence-based treatments [3–6]. *HCC* hepatocellular carcinoma, *SBP* spontaneous bacterial peritonitis, *Abx* antibiotics

re-bleeding rate after endoscopic hemostasis of varices, or more distal measures such as mortality or health-related quality of life. Although the ultimate goal of medicine is to improve quality and/or quantity of life, outcome measurement is susceptible to confounding variables, statistical error, provider manipulation, and may depend on many factors—many of which are not under the control of health-care providers [8]. In addition, with distal outcomes such as mortality, it is often difficult to determine what changes should be implemented to create improvement. Therefore, most quality measurement focuses on either processes or intermediate outcomes. Kanwal et al. have proposed a set of 41 process measures for cirrhosis [9]. These measures, which were developed from the literature review and input from a multidisciplinary expert panel, provide a useful starting point for QI efforts—some examples are provided in Table 33.1.

Additional quality measures of importance include *patient-centered* measures, such as knowledge, self-efficacy, and satisfaction with care. Most medical interventions require an engaged patient to carry them out, and the extent to which a clinician educates and involves the patient in the decision-making process (i.e., shared decision making) is an important feature of quality care. We surveyed patients in our practice, and found that many lacked the critical basic knowledge to manage their disease; for example, 58 % thought that a low-sodium diet included the use of sea salt! Patients' knowledge about their condition and its management improved significantly after implementing a structured education program in our practice (Fig. 33.2) [10].

How to Improve Quality?

There are numerous approaches to QI, such as Six Sigma or Lean [11]. Most of these philosophies come from the manufacturing sector, and consultants can be hired to advise physicians and practices on QI. However, not only can this be costly but hiring external consultants also goes against the principles that QI needs to be *continuous* and driven by those doing the daily work. Therefore,

Table 33.1 Types of quality measures

Type of measure	Examples	Advantages	Pitfalls
Structure	Proportion of physicians in a group who are Board-certified	Easily understood by patients	Weak correlation with outcomes
Process	(1) Proportion of cirrhosis patients receiving ultrasound surveillance for HCC in a 12-month period (2) Proportion of those with medium/large varices who receive nonselective beta-blockers and/or endoscopic banding (3) Proportion of those with prior SBP who are on antibiotics for secondary prophylaxis	Evidence-based, actionable	Numerator and denominator exclusions, criteria are sometimes subjective (e.g., size of varices), often requires chart review to ascertain
Intermediate outcome	Re-bleeding rates after variceal hemostasis	Intermediate link between medical management and distal outcomes	Confounded by risk factors
Distal outcome	Mortality, quality of life	Ultimate goal in medicine is to improve these	Influenced by multiple confounders, other diseases, difficult in most situations to identify necessary changes to medical management
Patient-centered measures	Knowledge, satisfaction	Patients' involvement is necessary to implement most outpatient care plans, patients can identify service flaws that may be invisible to clinicians	Will vary by socioeconomic status, not completely within clinicians' control
Practice variation	Use of TIPS for ascites	Identify high-impact areas where group consensus is needed	Avoid "profiling" outliers

HCC hepatocellular carcinoma, *SBP* spontaneous bacterial peritonitis, *TIPS* transjugular intrahepatic portosystemic shunt

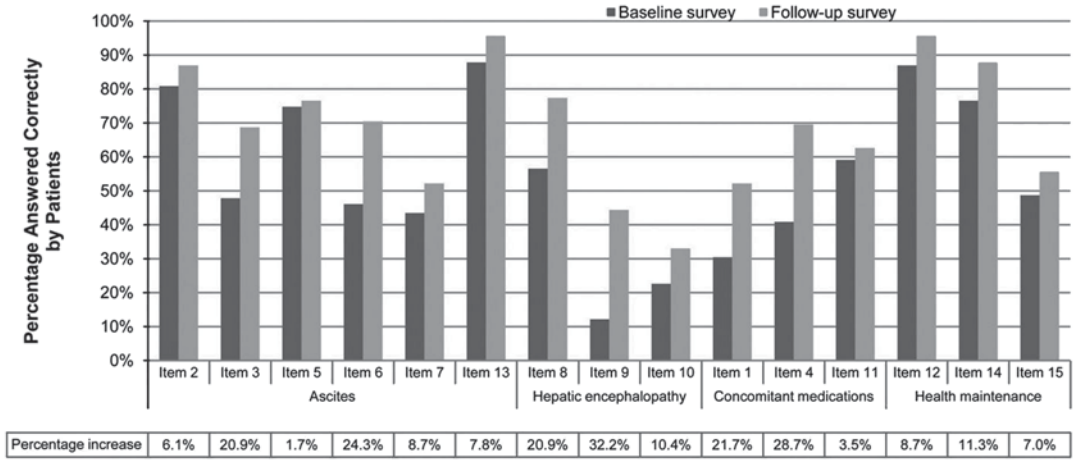

Fig 33.2 Patient's knowledge about disease self-management, before and after a structured educational intervention. Knowledge improved significantly across all domains ($p < 0.001$). (Reprinted with permission from reference [10])

in many instances, a provider group may be better served to develop their own system. The following steps outline a practical approach:

1. *Identify the population*
   The first step is to be able to identify patients with cirrhosis on an ongoing basis, for inclusion in a continuously updated clinical registry. One method available in the USA is to develop an automated feed from the billing database, using ICD-9 codes 571.5 and 571.2. The advantage of this method is the automation, while its disadvantage is ascertainment error—these codes have fairly good positive predictive value at 80 and 87%, respectively, but less robust negative predictive value at 52 and 46% [12]. Another method is prospective clinician-driven identification. In our practice, when a clinician sees a patient with cirrhosis in the clinic (diagnosed by liver biopsy or imaging/laboratory evidence), he or she notifies the support staff to enroll the patient in the registry. This method takes additional time, but is more precise. A decision is then required as to how to store registry data. The options range from simple computer programs such as Excel, to more complex disease management systems—we use a program called Avitracks, which links to our electronic medical record (EMR) and provides reminders when laboratory or imaging tests are due. Epic, an EMR used by many health-care systems, can also support disease registries in some versions of its software.
2. *Measure quality*
   The next step is to decide on quality measures. For reasons discussed above, a combination of process and intermediate outcome measures is recommended. Each measure will need a clearly defined denominator (e.g., patients with prior SBP), numerator (in the example of SBP, those prescribed antibiotic prophylaxis), and denominator exclusions (e.g., those who no longer have ascites). In addition to the evidence base supporting the measures, several other factors should be considered. One is the reliability and ease of data collection. For example, a measure focusing on management of variceal bleeding will suffer from poor interrater reliability of the denominator as many patients stop bleeding by the time the endoscopy is performed, and no "nipple sign" is present. Descriptive data that require a skilled chart review for collection will pose greater measurement burden than discrete data which can be gathered in an automated fashion. Another important consideration is to generate data that are *actionable*. The data should be current, and permit clinicians to drill down to the individual patient level to remedy any deficits. It is also important to measure areas that affect a large proportion of patients, and areas where less-than-optimal quality is suspected (if performance is already 100%, then no improvement is required). Finally, it may sometimes be useful to measure practice variation in the absence of an explicit quality measure [13]. An example would be the utilization of TIPS for patients with refractory ascites—although it may be difficult to discern appropriateness of TIPS for this indication, a finding of large practice variation could lead to efforts at developing consensus and standardization. In the manufacturing world, this consensus is called a "shared baseline." Conversely, processes with very little variation are probably constrained by nonremediable factors, and thus may not be readily amenable to improvement.
3. *Identify root causes for inadequate quality*
   Root cause analysis involves developing an understanding of the sequence of actions that led to an event. Like other areas in medicine, this means developing hypotheses and gathering data to test them. A critical component of this process involves going to see where the work is done, called a "gemba walk" in Lean terminology. The investigator should talk to all people involved, and ask why repeatedly (often as many as five times). It is important to maintain a nonjudgmental attitude and take the position that all medical errors are systems errors—humans will inevitably make mistakes, so backup systems should be put in place to prevent patient harm. Additionally, in most clinical scenarios, quality measures lack

sufficient statistical power to accurately discriminate between individual clinicians. For this reason, QI experts distinguish between "measurement for selection" versus "measurement for improvement" [14]. Measurement for improvement focuses less on individuals and more on processes of care. Common process failures include lack of duplicative systems in place to act on test results, confusion about who is supposed to be responsible for each step of the process, and breakdown of communication (between providers, providers and support staff, and/or with patients). For example, we found that many of our patients were not receiving timely screening for hepatocellular carcinoma (HCC) because the test was ordered when they were seen in clinic, to be done at a local hospital. Oftentimes, the patient did not understand that they needed to call and schedule the test, or it was actually performed but no results made it back to our clinic—and no health-care provider realized this until their return visit 6 months later.

4. *Implement corrective action*
   Once the root causes are identified, the lead individual on the project typically presents the findings to the rest of the group. This is where a consensus should be developed about the appropriate steps—if many people in the group disagree on the action to be taken, it will not happen. It is also important to make the changes as simple as possible. For example, in partnership with our nursing staff, we improved our HCC screening rates from 74 to 93%, by (a) encouraging clinicians to schedule ultrasounds in conjunction with clinic visits, so they occurred at our institution, (b) including the importance of HCC screening in our educational booklet, (c) establishing a reminder system, and (d) writing out a clinical protocol and empowering the nurses to order a screening test when due without the need for a physician order (while still allowing opt-out for certain patients) [15].
5. *Re-measure and adjust*
   QI is a continuous process, for several reasons. First, QI interventions are often mini experiments: it is not practical to conduct a randomized trial for each change, so follow-up is needed to determine whether the change worked as intended. This is the basis behind the "plan-do-study-adjust" cycle popularized by W. Edwards Deming [16]. Second, clinical medicine changes: what was appropriate care at one time may become outdated. Third, the individuals in an organization change and "institutional memory" about process changes can wane over time. Finally, a continuous focus on quality makes it an appropriate focus of emphasis in the culture of an organization.

Summary

Patients with cirrhosis represent an ideal population for QI efforts; health-care providers at all levels are facing increasing demands to participate in such efforts. A downside to QI is that it requires time, a commodity that few clinicians possess in surplus. However, most of the work occurs prior to and at the initiation of a QI project, with less time being needed once the infrastructure is established. Furthermore, these efforts can sometimes provide a return on investment by improving efficiency in a practice. Finally, clinicians will benefit from the satisfaction that their efforts will result in an immediate positive impact on patient care. Delivering quality care remains fundamental to the practice of medicine now and in the future.

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Quality of Life Issues for Patients with Cirrhosis

34

Zobair M. Younossi and Linda Henry

In recent years, evaluating the impact of chronic liver disease and the success of its treatment has expanded beyond only measuring clinical outcomes. These assessments now include measuring patients' perspective of their disease, and the effect treatment has on their quality of life [1–13]. In this context, health-related quality of life (HRQOL) has become a very important outcome for measuring patient's perspective about their health and treatment.

HRQOL falls under the broader category of quality of life which accounts for many other aspects of a person's life besides simply health, including the influence of environment, freedom, economy as well as aspects of their culture, values, and spirituality [2, 5, 6, 14, 17, 18, 19]. Therefore, HRQOL has been very succinctly defined as a broad multidimensional concept that includes self-reported measures of physical and mental health as well as the ability to be socially active (social well-being) [1–13].

Although HRQOL and patient-reported outcomes (PROs) can be interchangeable terms, PROs may include other outcomes reported by and important to patients. Alternative terms that are commonly used to define a patient's perspective (self-report) of their physical, mental, and social functioning include health status and well-being [20–22]. In general, HRQOL tools or instruments are divided into general measures (generic instruments) and disease-specific instruments [1–24]. In the following paragraphs, we describe some of the most common generic and disease-specific instruments used to measure HRQOL in patients with cirrhosis.

Tools Used to Measure HRQOL (Tables 34.1 and 34.2)

The Short Form-36 Version 2 (SF-36v2)

The Short Form-36 version 2 (SF-36v2) is a widely used instrument for HRQOL evaluation [6]. It assesses eight HRQOL scales (ranging 0–100 with higher values corresponding to a better health status): physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The two summary scores summarize the physical and mental health components of the SF-36: the Physical Component Summary score (PCS) and Mental Component Summary score (MCS). The SF-36 scales and summary scores are calculated

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Table 34.1 Health-related quality of life tools for patients with chronic hepatitis C virus

Name of tool	Health domains measured	Number of items	Strengths and limitations	Generic or disease specific	How administered
SF-36	Eight domains measuring functional health and well-being: general health, vitality, role emotional, role physical, social well-being, mental health, and physical functioning. Two summary scales of physical composite and mental composite scores	36 items	Most widely used tool worldwide. Established population norms for comparison. It is generic and disease specific. Asks for recall of how the patient is feeling over past week/month	Generic-general health	Self-administered or can be done in person or over the telephone. Takes 5 to 10 minutes to complete
Sickness impact profile (SIP), also the SIP-68	Investigates a change in behavior as a consequence of illness, Covers 12 categories of daily living sleep and rest, eating, work, home management, ambulation, mobility, body care and movement, social integration, alertness behavior, emotional behavior and communication	136 items/68 items	Items are scored on a numeric scale with higher scores reflecting greater dysfunction. An aggregate psychosocial score is derived from four categories and an aggregate physical score from three categories	Generic-general health	Paper and pencil takes approximately 30–40 min for the full survey and 15–20 min of the SIP-68
Chronic liver disease questionnaire (CLDQ) and CLDQ-HCV	The CLDQ has six domains (abdominal symptoms, activity, emotional function, fatigue, systemic symptoms, and worry). CLDQ applies to all patients with chronic liver disease CLDQ-HCV is specific for HCV patients and measures four domains: activity and energy, emotional, worry, systemic. CLDQ-HCV assesses HRQOL in patients with HCV	Both CLDQ and CLDQ-HCV have 29 items with scores ranging from 1 to 7; higher scores indicate better health-related quality of life (HQRL)	Widely used and validated tool; translated into many languages—see website	Disease specific	Paper and pencil: self-administered Electronic version: e-CLDQ
Post–liver transplant quality of life (pLTQ)	8 domains which include: emotional function, worry, medications, physical function, healthcare, graft rejection concern, financial, pain	32 items with the first 28 items scored on a scale of 1–7 and higher scores reflect better HRQOL	Stable over time but a relatively new measurement	LT	Self-administered

Table 34.1 (continued)

Name of tool	Health domains measured	Number of items	Strengths and limitations	Generic or disease specific	How administered
Liver disease quality of life (LDQOL)—short form	9 domains and measures symptoms of liver disease and the effects of liver disease. Shown to correlate highly with SF-36 scores, symptom severity, disability, days and global health	36 items	Translated into several languages to include Spanish and Korean	Disease specific	Self-administered
Hepatitis quality of life questionnaire (HQLQv2)	Two-part survey to assess functional health and well-being of patients with chronic HCV, Includes the SF-36v2® Health Survey (36 questions) and 15 additional questions which measure generic health concepts relevant to assessing the impact of hepatitis (health distress, positive well-being) and disease-specific concepts (e.g., hepatitis-specific functional limitations, hepatitis-specific distress)	51 items	Is available in a fixed form or interview (telephone/face-to-face) format	Disease specific	It can be administered in clinical settings, at home or in other locations
Liver disease symptom index 2.0 (LDSI 2.0)	Measures symptom severity and symptom hindrance in the past week	18 items	Measures symptom severity and symptom hindrance in the past week. Considered an additive tool when researching HRQOL with the liver disease population. Responses are on a five-point scale from "not at all hindered" to "hindered a high extent." Translated into several languages	Disease specific	Self-administered
Multidimensional fatigue inventory	Measures that cover: general fatigue, physical, fatigue, mental fatigue, reduced motivation and reduced anxiety	20 items use a 5-point Likert scale from 1 to 5 (yes that is true to no that is not true). Higher scores mean less fatigue	Valid and reliable tool	Generic for fatigue	Self-report

Table 34.1 (continued)

Name of tool	Health domains measured	Number of items	Strengths and limitations	Generic or disease specific	How administered
Multidimensional fatigue symptom inventory- short form (MFSI-SF)	Assesses global, somatic, affective, cognitive, and behavioral manifestations of fatigue	30 items	Shorter version of the original 83 items—Multidimensional fatigue symptom inventory. Takes less time but maintains the integrity of original survey	Generic	Self-report
Quality well-being scale	Combines preference-weighted values for symptoms and functioning. Symptoms are assessed by questions that ask about the presence or absence of different symptoms (yes or no). Functioning is assessed by a series of questions designed to record functional limitations over the previous three days, within three separate domains (mobility, physical activity, and social activity). The four domain scores are combined into a total score that provides a numerical point-in-time expression of well-being that ranges from 0 for death to 1 for asymptomatic optimum functioning	3 pages—58 questions	Can be self-administered, used in a face-to-face interview, answered by proxy and administered online	Generic	Self-administered (see strengths and limitations)
Health utilities index (HUI)	A generic multi-attribute preference-based measure of health status and HRQOL	HU13 consists of eight attributes/dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Scores range from highly impaired to normal	Can be used in clinical studies, population-based surveys, in the estimation of quality-adjusted life years and economic analysis	Generic	Self-administered then scored by investigator

Table 34.1 (continued)

Name of tool	Health domains measured	Number of items	Strengths and limitations	Generic or disease specific	How administered
Short form-6D (SF-6D)	To calculate the true value of a treatment, the scores from the SF-36v2® or the SF-12v2® Health Surveys can be converted into a utility index, called the SF-6D, which considers not only how many years a medical intervention can add to a patient's life, but also the quality of that life	–	Get a better understanding of a patient's real preference for a treatment. Helps select the best course of action for a patient. Compares two interventions based on quality-adjusted life years and cost. Assesses the cost effectiveness of a medical product, procedure, or health and wellness program. Allocates health-care resources most efficiently	Generic for quality of years added. Used for the economic impact of a disease	The SF form is self-administered then the investigator will convert the scores to a utility score
Euro-QOL (EQ-5D)	A standardized instrument for use as a measure of health outcome	Measures five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems, extreme problems. Incorporates a visual analog scale to obtain the respondent's self-rated health on a vertical, visual analog scale where endpoints are labeled 'best imaginable health sate' and 'worst imaginable health state	Cognitively simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire	Generic	Self-completion by respondents and is ideally suited for use in postal surveys, in clinics and face-to-face interviews

HCV hepatitis C virus, *HRQOL* health-related quality of life, *LT* liver transplant, *HU13* health utilities index mark 3

Table 34.2 URLs for health-related quality of life tools used for patients infected with the hepatitis C virus (www.cldq.org)

Name of tool	Short name	URL	URL2
SF-36 (ware)	SF36	http://www.sf-36.org/tools/SF36.shtml#VERS	–
Sickness impact profile (SIP) also the SIP-68	SIP/SIP-68	http://www.outcomes-trust.org/instruments.htm	http://www.sciepro-ject.com/outcome-
Chronic liver disease questionnaire (CLDQ)	CLDQ	https://www.cldq.org/	–
Post-liver transplant quality of life (pLTQ)	pLTQ	http://onlinelibrary.wiley.com/doi/10.1002/lt.22267/full	–
Liver disease quality of life (LDQOL)- short form	LDQOL SF	http://www.ncbi.nlm.nih.gov/pubmed/11151892	–
Hepatitis quality of life questionnaire (HQLQv2)	HQLQv2	http://www.qualitymetric.com/WhatWeDo/DiseasespecificHealthSurveys/HepatitisQualityofLifeQuestionnaireHQLQv2/tabid/193/Default.aspx	–
Liver disease symptom index 2.0 (LDSI 2.0)	LDS!2.0	http://www.ncbi.nlm.nih.gov/pubmed/15503842	–
Multidimensional fatigue inventory	Multidimensional fatigue inventory	http://www.ncbi.nlm.nih.gov/pubmed/7636775	–
Multidimensional fatigue symptom inventory-short form (MFSI-SF)	MFSI-SF	http://www.cas.usf.edu/~jacobsen/HANDOUT.FSI&MFSI.pdf	–
Quality well-being scale	Quality well-being scale	http://www.healthmeasurement.org/pub_pdfs/_QUESTIONNAIRE_QWB-SA,%20version%201.04.pdf	–
Health utilities index (HUI)	HUI	www.researchgate.net/utilityhealth_utilities_index/d9	–
Short form 6D (SF-6D)	SF-6D	–	–
Euro-QOL (EQ-5D)	EQ-5D	www.euroqol.org	–

URL uniform resource locator

using the QualityMetric Health Outcomes Scoring Software 4.5 (Lincoln, RI, USA) and the 2009 US population norms [6].

Sickness Impact Profile (SIP)

The SIP is a generic health measurement tool that is used to investigate a change in behavior as a consequence of illness. It contains a 136 items divided by 12 categories covering activities of daily living (sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behavior, emotional behavior, and communication). Items are scored on a numeric scale with higher scores reflecting greater dysfunction. In addition to individual category scores, an aggregate psychosocial score is derived from four categories, and an aggregate physical score is calculated from three categories [5, 12, 14].

Chronic Liver Disease Questionnaire (CLDQ)

The CLDQ is another widely used and validated HRQOL instrument developed specifically for assessment of HRQOL in chronic liver disease

patients [7, 13, 14, 18]. It includes 29 items and 6 HRQOL scales: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry. CLDQ has a summary score, CLDQ total score [7]. These scales are averaged to the total CLDQ score that ranges 1–7 with higher values representing better HRQOL [7, 17, 18]. In addition to CLDQ, a hepatitis C-specific version was also developed and validated (CLDQ-hepatitis C virus (HCV)). CLDQ-HCV consists of four scales that measure: activity/energy (AE), emotion (EM), worry (WO), and systemic (SY) as well as a CLDQ-HCV total score (CLDQ-HCV Tot) [25]. Both CLDQ and CLDQ-HCV are now widely used throughout the world to assess HRQOL for patients with liver disease and HCV [15, 20, 26–32].

Liver Disease Quality of Life (LDQOL)

The short form of liver disease quality of life instrument (SF-LDQOL) is a questionnaire that comprises 36 disease-targeted items representing nine domains, symptoms of liver disease, and the effects of liver disease. The SF-LDQOL has been shown to correlate highly with SF-36 scores, symptom severity, disability days, and global health [6, 14].

Post-Liver Transplant Quality of Life (pLTQ) Instrument

The pLTQ instrument is a relatively new measurement tool developed to measure health-related quality of life in posttransplant patients. After 12 liver experts and transplant recipients were interviewed, a thorough literature search was conducted, and factor analysis and testing in more than 200 liver transplant (LT) patients was performed, the pLTQ was formulated. The tool includes 32 items which covers eight domains (emotional function, worry, medications, physical function, health care, graft rejection concern, financial, and pain) and has been determined to be stable over time [35–39].

Hepatitis Quality of Life Questionnaire (HQLQv2)

The Hepatitis Quality of Life Questionnaire™ Version 2 (HQLQv2™) is a two-part survey designed to assess the functional health and well-being of patients with chronic hepatitis C. It includes the SF-36v2® Health Survey and 15 additional questions that measure other generic health concepts particularly relevant in assessing the impact of hepatitis (e.g., health distress, positive well-being), and disease-specific concepts (e.g., hepatitis-specific functional limitations, hepatitis-specific distress) [5, 14].

The HQLQv2 was developed to help patients and clinicians monitor the effects of hepatitis C and its treatment as well as screening and monitoring changes in disease impact. The HQLQv2 is available in a fixed form or interview (telephone/face-to-face) format. It can be administered in clinical settings, at home, or in other locations. The HQLQv2 is intended for adults 18 years of age and older, and is available in multiple language translations with a standard 4-week recall period [5, 14].

Liver Disease Symptom Index 2.0 (LDSI 2.0)

The Liver Disease Symptom Index 2.0 (LDSI) developed in a Dutch cohort of patients includes 18 items that measure symptom severity and symptom hindrance in the past week [5, 11, 14] Through convergent and divergent construct validity, the investigators determined that the information from the LDSI provided complementary information to the information gleaned from the SF-36 and the multidimensional fatigue inventory (MFI)-20 and it should be considered an additive tool when researching HRQOL in a population with liver disease [5, 11, 14].

Quality of Well-Being Scale (QWB)

The QWB-self-administered (SA) combines preference-weighted values for symptoms and

functioning. Symptoms are assessed by questions that ask about the presence or absence of different symptoms or conditions. Functioning is assessed by a series of questions designed to record functional limitations over the previous 3 days, within three separate domains (mobility, physical activity, and social activity). The four domain scores are combined into a total score that provides a numerical point-in-time expression of well-being that ranges from zero (0) for death to one (1.0) for asymptomatic optimum functioning [5, 14].

Health Status/Utility Assessment (The Health Utilities Index (HUI), EuroQol-5D (EQ-5D), and the Short Form-6D (SF-6D))

One of the most important applications for quality of life assessment is in economic analysis. In fact, outcomes, such as life years gained or lost by an intervention, are usually qualified in terms of the quality-adjusted years of life gained or lost. Health utility assessment is the method used to obtain quality-of-life adjustments. The direct assessment of health utilities uses the technique of time trade-off or standard gamble, while the indirect assessment utilizes questionnaires designed to assess health status. Some of the important questionnaires that are available to assess health utilities are discussed below [5, 14].

To calculate the true value of a treatment, the scores from the SF-36v2® or the SF-12v2® Health Surveys can be converted into a utility index, called the SF-6D, which considers not only how many years a medical intervention can add to a patient's life, but also the quality of that life. The SF-6D can then be used to obtain a better understanding of a patient's real preference for a treatment, select the best course of action for a patient, compare two interventions based on quality-adjusted life years (QALYs) and cost, assess the cost-effectiveness of a medical product, procedure, or health and wellness program, and allocate health-care resources most efficiently [5, 6].

The approach most commonly used in the European community is the EQ-5D, which has been advanced by a collaborative group from Western Europe known as the EuroQol group. This group, originally formed in 1987, comprises a network of international, multidisciplinary researchers, originally from seven centers in England, Finland, the Netherlands, Norway, and Sweden. More recently, researchers from Spain as well as researchers from Germany, Greece, Canada, the USA, and Japan have joined the group. The intention of this effort is to develop a generic currency for health that could be used commonly across Europe. The original version of the EuroQol had 14 health states in six different domains. More current versions of the EuroQol, the EQ-5D, are now in use in a substantial number of clinical and population studies [5, 14].

HRQOL Findings in Patients with Chronic Liver Disease

Patients with chronic liver disease (CLD) report significant impairment of their HRQOL [1–22]. Although this impairment is applicable to most patients with CLD, patients with HCV, primary biliary cirrhosis (PBC) and non-alcoholic fatty liver disease (NAFLD) seem to have more impairment [1, 2]. In fact, several recent studies have reported that patients with HCV have a dramatically reduced HRQOL due to extreme fatigue and depression [2, 7, 18, 19, 25]. A number of studies of patients living with PBC report impairment of the physical health component related to fatigue. In fact, fatigue in PBC is so overwhelming that some have questioned whether it should be an indication for LT in this group of patients [39]. Carbone and group found that LT improved the HRQOL in patients with PBC; however, fatigue, though improved, persisted 2 years posttransplant calling into question the appropriateness of this symptom as an indication for transplant given the scarcity of donated organs [40]. Patients with cirrhosis have also demonstrated a significantly reduced HRQOL related

to numerous clinical and demographic features in addition to suffering from depression and anxiety [1–25].

Specific Studies of HRQOL in Cirrhotics

In addition to etiology of CLD, severity of liver disease accounts for the majority of impairment in patients' HRQOL. There are multiple publications suggesting that patients with compensated cirrhosis have more impairment than CLD patients without significant hepatic fibrosis. Worsening hepatic dysfunction in patients with cirrhosis, as documented by higher model for end-stage liver disease (MELD) scores, and the development of complications, such as ascites and hepatic encephalopathy, account for severe impairment of HRQOL [2, 3, 4, 9, 17, 20, 23, 30, 40–44].

When compared with the national norm for healthy subjects, HRQOL, as measured by SF-36 [6], shows severe impairment of HRQOL in patients with cirrhosis. In fact, this impairment occurs in every aspect of their well-being [17, 19, 45]. Marchesini and colleagues assessed HRQOL using 2 generic HRQOL tools (SF-36 and the Nottingham Health Profile) in a large cohort of Italian patients with cirrhosis and compared their results to norm-based results [46]. They found that the cirrhotic group had significantly lower HRQOL than the Italian population norms as a result of muscle cramps and pruritus associated with cirrhosis. It was noted that clinicians' and patients' perceptions of the importance of certain symptoms on well-being may differ [18]. Therefore, it is imperative that clinicians spend sufficient time to determine what is causing the most problems for patients so that an appropriate intervention plan will be developed [18].

Other investigators have explored the role of HRQOL in predicting mortality. Kenwal and associates administered the SF-LDQOL questionnaire to 156 patients who were awaiting LT [29, 47]. Using Cox proportional hazard modeling to measure the independent effect of baseline HRQOL on survival after adjusting for MELD scores and other covariates, they found that higher-baseline HRQOL predicted lower mortality (hazard ratio, 0.96; 95% confidence interval, 0.94–0.99). Specifically, for each one-point increase in HRQOL, there was a 4% decrease in mortality. These results did not change after adjusting for MELD scores, patient demographics, or psychosocial characteristics [47]. It was also interesting to note that the MELD score accounted for only 1% of the variation in HRQOL scores ($p=0.18$). Survival was most strongly predicted by activities of daily living, health distress, sleep disturbance, and perceived disease stigma. Based on these results, the authors concluded that measuring HRQOL may have a role in predicting survival of patients with advanced liver disease [47].

Sleep disturbances have long been associated with patients living with cirrhosis [48]. These changes are a multifactorial phenomenon [48]. Recently, Mostacci et al. evaluated daytime somnolence and sleep complaints in a group of 178 patients with cirrhosis compared to a control group using the Basic Nordic Sleep Questionnaire (BNSQ) and the Epworth Sleepiness Scale (ESS). Compared to controls, patients with cirrhosis complained of more daytime sleepiness ($p<0.005$), sleeping badly at least three times a week ($p<0.005$), difficulties falling asleep ($p<0.01$) and frequent nocturnal awakening ($p<0.005$). The study authors concluded that insomnia and daytime sleepiness are major complaints for this group of patients [48].

Studies assessing the feasibility and effectiveness of measuring HRQOL in daily clinical practice have been performed, generally showing positive results regarding the discussion of HRQOL-related topics, but mixed results regarding the added value to clinical practice of any actual improvement in HRQOL. In one study, which assessed the use of computerized measurement and feedback of HRQOL in the daily clinical practice of an outpatient hepatology department, results demonstrated that there was no improvement in HRQOL for the entire group of chronic liver patients. However, HRQOL showed an improvement in the mental subscale of older patients and male patients with CLD, which had an effect on patient management of this subgroup

of patients [21]. Logistic and attitudinal barriers also seem to impede successful implementation of measuring HRQOL in clinical practice settings [22]. However, despite these, HRQOL remains important and relevant in helping to guide clinical decision making.

Cirrhosis Complications and HRQOL

Hepatic Encephalopathy and HRQOL

Hepatic encephalopathy (HE) impacts patients' level of consciousness, intellect, personality, neuromuscular activity and survival, thus affecting their ability to carry out activities of daily living and so influencing their HRQOL [41–45, 49, 50]. Recent investigators have studied the impact on HRQOL of new cirrhosis treatments in patient suffering with HE. In one study, investigators reported the outcomes of a clinical trial where patients with HE were randomized to receive either rifaximin or a placebo twice daily for 6 months or until they had a breakthrough episode of HE [51]. Using the CLDQ, patients' HRQOL was followed for the duration of the study. Taking rifaximin significantly improved patients' HRQOL. However, within the group that had a breakthrough of HE, there was a decrease in scores prior to the appearance of HE. The authors concluded that a decrease in HRQOL in patients with a history of HE can signal the onset of a new episode of HE. Therefore, consideration should be given to using a quality of life tool to track a patients' progress [51].

Other investigators have also found that the degree of HE was an independent predictor impacting a patients' HRQOL—the more severe the HE, the lower the HRQOL scores. Results from some studies suggest that complete resolution of an episode of HE may not occur, so over time HRQOL will continue to decrease despite the normal functioning of the patient [41–45, 49–51]. HRQOL results have also helped investigators to determine resolution of the impact of clinically overt HE on a patient's quality of life. Results have indicated that despite the patient appearing to function normally in all areas of daily activities, their HRQL scores have not returned to baseline. This may indicate that a number of these patients may suffer from covert HE, which may not completely resolve. However, further work is necessary to substantiate this finding [41–45, 49–51].

Ascites and HRQOL

Studies examining the impact of ascites caused by cirrhosis on patients' HRQOL have noted similar findings to those found in patients suffering from HE. Sola and colleagues determined that having severe ascites, leg edema, and low serum sodium were all independent predictors for a low HRQOL [9]. Les et al. determined that several potentially treatable variables (ascites, hypoalbuminemia, minimal HE, and anemia) if corrected may positively alter a patients' HRQOL [10].

In another study, Bhogal and Sanjay investigated the impact of using transjugular intrahepatic portosystemic shunts (TIPS) to correct cirrhosis induced complications [51]. Though the TIPS procedure carried potentially significant risks for HE, shunt induced hemolysis, and infection, its success in reducing portal hypertension was superior to paracentesis. However, in a meta-analysis, Albillos et al. found that better control of ascites by TIPS did not translate into improved survival and was associated with worsening of encephalopathy if present [52].

HCV-Related Cirrhosis and HRQOL

Work completed by Younossi et al. and Spiegel et al. suggest that patients infected with HCV have an already diminished quality of life even before reaching the stage of cirrhosis [18, 19, 20, 34, 35, 53]. In fact, Younossi et al. found that assessing HRQOL can be challenging as many of these patients suffer from the indirect effects of fatigue and psychological issues, namely depression and cognitive impairment, which are present early in the disease course [18, 19]. Another issue confounding the assessment of HRQOL is stigmatization resulting from the HCV diagnosis,

creating the potential for a psychological disturbance, as well as acting as a barrier to treatment and eroding a patient's social support network [54–56].

Speigel et al. found that achieving a sustained virologic response (SVR) with HCV treatment (i.e., being HCV RNA negative 6 months after completing therapy) was associated with an increase in HRQOL scores as well as a change of 4.2 points in the vitality score from the SF-36, representing a minimally important difference in HRQoL [53]. They also noted that HRQOL in patients with HCV was impaired regardless of the severity of the disease and attributed this impairment to extra hepatic manifestations related to HCV. Their results also confirmed previous observations that patients with HCV had impaired cognitive functioning as well as an increase in symptoms of their comorbid psychosocial issues after contracting HCV, making it difficult to assess the true of effects of cirrhosis alone [53].

The information gleaned from these studies has become invaluable as new treatments are developed for HCV. Recognizing the impact on patients beyond the biologic effects of the virus is now mandatory—therefore, obtaining a baseline HRQOL score prior to treatment is necessary to ensure any changes in the score will be associated with the correct variable(s), including treatment. Several recent studies on new treatment medications called direct acting antiviral agents (DAAs) have been completed [20, 33, 34]. Patients with HCV and cirrhosis who participated in recent phase III clinical trials using DAA's demonstrated decreased scores in their PROs prior to the initiation of treatment. However, during treatment, the researchers found that interferon-free regimens were associated with minimal PRO decrements. On the other hand, PROs were substantially impacted in both cirrhotics and non-cirrhotics by the inclusion of interferon in sofosbuvir-based treatment regimens. The short duration of treatment (12 weeks) appeared to be advantageous, as the decrease in PROs during treatment disappeared and scores returned to baseline after termination of therapy. Finally, patients with cirrhosis who achieved an SVR 12 weeks after stopping treatment, especially with the interferon-free sofosbuvir-based regimens, enjoyed significant improvement in many areas of their PRO scores [20, 33, 34].

Cirrhosis and Liver Transplantation

Five-and ten-year patient survival after LT is now around 70 and 60 %, respectively. This improvement in life expectancy has shifted the emphasis on follow-up from simple clinical indicators to focusing on how patients cope with everyday life— physically, mentally, and socially [39]. Several studies have investigated the impact of LT on patients' HRQOL [35–40].

Younossi and group determined that patients who underwent LT for complications of cirrhosis had significantly impaired HRQOL [35]. However, after transplantation, their mental health scores rose significantly and were the same or higher than the population norms, while their HRQOL physical component also rose significantly but did not surpass the population norms. They found that HRQOL was clearly associated with the amount of health-care resources expended during their transplant hospitalization such that the more expenses they were perceived to have used, the lower their HRQOL perhaps indicating that patients with a shorter length of stay were healthier [35].

Nutrition has also been found to play a role in patients HRQOL following transplantation. Urano and colleagues determined that after LT, it took at least 6 months for nutritional status, based on laboratory data and energy metabolism, to normalize [37]. Once these parameters normalized, the physical component HRQOL scores improved. They, therefore, concluded that long-term nutritional support is necessary for LT patients in order for them to obtain an optimal level of physical functioning [37]. Others who have studied HRQOL in LT recipients found that patients who were sicker, as noted by their MELD and quality-of-life scores pre-transplant, continued to have low HRQOL scores over time, although their scores improved from baseline [36].

Conclusions

The HRQOL in patients suffering from cirrhosis is significantly decreased when compared to patients without liver disease/cirrhosis. Many tools have been developed to measure the impact of cirrhosis on HRQOL. The most commonly used tools include the CLDQ, the SF-36, the LDQOL, and the EU 5D—for cost-effectiveness studies. HRQOL is influenced by the type of complications arising from cirrhosis. The net overall effect is lower scores, whether such scores are a result of mental impairment or a limitation that had been placed on patients' ability to perform an activity of daily living. Collecting information on HRQOL is helpful in guiding and evaluating the impact of treatment on patients and will be particularly valuable as the management of cirrhosis continues to evolve. Measuring HRQOL in the clinical setting has never been more timely or important.

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Palliative Care in Cirrhosis

35

Maria L. Yataco, Robert Shannon and Andrew P. Keaveny

"May I never see in the patient anything but a fellow creature in pain" Maimonides

The development of complications related to cirrhosis portends a significant change in mortality risk [1]. In addition, any superimposed acute deterioration, often due to infection, can be associated with a high risk of short-term mortality [2]. While some patients have the potential for improvement in their condition, for example with alcohol cessation, many more die from progression of their liver disease. A select group of patients cope with the complications of cirrhosis while waiting for liver transplantation (LT), which is an intervention that also carries significant risk for morbidity and mortality. Various national and center-specific selection criteria affect a patient's candidacy for LT beyond medical issues, including age and social support [3]. Even when listed for LT, there is no guarantee of success. The demand for organs far exceeds the supply; in the USA in 2012, the United Network for Organ Sharing (UNOS) reported 2187 patients died, while 815 were removed from the waiting list as they were deemed "too sick for transplant" [4]. Thus, the complications of cirrhosis and its treatment options weigh heavily on patients, family members, and the community [5]. Affected individuals seek care within a health delivery system that may not be optimized to meet their needs [6]. Palliative care focuses on the prevention and relief of suffering, providing a framework to address many deficiencies of care in patients dying from end-stage liver disease (ESLD) [7].

The Impact of Decompensated Cirrhosis

Insights into the last phase of life for patients suffering with decompensated cirrhosis have been obtained from a limited number of studies. Over a decade ago, data on 575 such patients who met the Study to Understand Prognoses and Preference for Outcomes and Risk of Treatments' inclusion criteria were collected [8]. In the study group, 29 % died during the index hospitalization and 29 % died within the following year. There was greater resource utilization among those who died during the index hospitalization compared with those who survived to discharge. High rates of poor quality of life (QOL) and functional impairment were reported pre-hospitalization. Patients reported substantial pain, with serious pain afflicting about one third of patients. Confusion increased as the patients' condition deteriorated. The financial impact of illness on the families was considerable. Hospitalized patients expressed a consistent preference for cardiopul-

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monary resuscitation (CPR); regrettably, none of the 22 patients who received CPR survived. One third of the study group expressed a preference for do not resuscitate (DNR) orders. As death approached, written DNR orders increased from 21% between 1 and 3 months before death to 78% in the last month of life.

In a study conducted at a large-volume US transplant center, goals of care discussions, palliative care consults, and comfort care orders were all less common in patients considered for LT [9]. Another recent retrospective study from a Canadian transplant center highlighted issues with the course and management of patients with ESLD removed from the LT wait list [10]. After removal, 17% of the 102 patients subsequently received renal replacement therapy (RRT) and 48% were admitted to the intensive care unit (ICU). Pain, nausea, anxiety dyspnea, and anorexia were all common symptoms. Only a third of all patients had documentation of DNR status; furthermore, 11% were referred for palliative care. The lack of palliative care access for this group of terminally ill patients was described as "startling" [11].

Assessing Prognosis

Over the last two decades, two prognostic tools have been intensively studied in patients with ESLD—the Child–Turcotte–Pugh (CTP) and the model for end-stage liver disease (MELD) scores; strengths and weaknesses of these tools are discussed elsewhere in this textbook. Table 35.1 lists proposed general indicators to provide a prognosis for terminal disease [12]. A 6-month median survival has been associated with the presence of at least two of these factors. Other investigators have suggested that the MELD score could be used along with clinical indicators as a quantitative metric to guide hospice referral [13]. More recently, through a collaborative European effort, diagnostic criteria for "acute-on-chronic liver failure" were established that identified hospitalized patients with cirrhosis who had a significant risk of mortality within 28 days [2].

Table 35.1 Universal set of prognostic factors indicating progression to terminal disease [12]

Poor performance status (palliative performance scale and Karnofsky scale)
Advanced age
Malnutrition
Comorbid illness
Increasing organ dysfunction
Hospitalization for acute decompensation

Principles of Palliative Care

Palliative care is rooted in the interdisciplinary hospice model of care, which focuses on holistic and team-based care [14]. The interdisciplinary palliative care team creates a care plan congruent with the wishes and values of patients and families treating symptoms appropriately, addressing bio-psychological, social, cultural, and spiritual issues to maximize the QOL of patients and their family members along the entire trajectory of the illness including bereavement. The trained interdisciplinary team has the required skills, access, and expertise to provide patient-centered and family-focused care to reach their goals which often includes transition to hospice care. Key tenets of palliative care as put forth by the World Health Organization (WHO) are summarized in Table 35.2 [7].

Hospice is a system, a philosophy, and place of care designed to provide a comprehensive multidisciplinary care, mostly at home, for dying patients with an identifiable short prognosis [6]. In the USA, hospice services are delivered in a model established by statue in federal law. The Medicare Hospice Benefit is largely restricted to patients with conditions that have a prognosis of 6 months or less, if the disease follows its natural course. These patients agree to forgo therapies with curative intent, focusing on maximizing comfort and QOL; however, treatment including radiation therapy, chemotherapy, and surgery may be provided, when the intent is truly palliative. The distinction between palliative care and hospice is unique to the USA, while these

Table 35.2 Key tenets of palliative care (modified from the World Health Organization) [7]

Relief from pain and other distressing symptoms
Affirmation of life, regarding dying as a normal process
Neither hasten or postpone death
Integration of the psychological and spiritual aspects of patient care
A support system to help patients live as actively as possible until death
A support system to help the family cope during the patient's illness
A team approach to address the needs of patients and their families, including bereavement counseling
Enhance the quality of life and positively influence the course of illness
Offer palliative care early in the course of illness, along with other therapies and investigations that are intended to manage distressing complications and prolong life

two terms are often used interchangeably in other countries.

The National Consensus Project for Quality Palliative Care advocates the incorporation of the palliative care philosophy and delivery throughout the illness trajectory across all settings in patients with progressive chronic conditions [14]. While the concurrent care model is now accepted as the ideal palliative care model, there are insufficient palliative care specialists to be the exclusive providers of such services [11]. Basic palliative care expectations and behaviors have been identified that could be provided by all health-care providers, including hepatologists and gastroenterologists [15]. Table 35.3 outlines the skill sets for "primary" and "specialty" palliative care proposed by Quill and Abernethy, which could form the basis for the improvement in the scope of palliative care provided to patients with ESLD. Further research will be required to define the requirements or conditions that are required to engage palliative care specialist involvement [11].

Barriers to the provision of palliative care may be physicians themselves [16]. Practice patterns may delay referral [17]. Some have cited the lack of established metrics to guide physician referral to hospice for patients with ESLD, although the concurrent care model of palliative care de-emphasizes the requirement to define a precise prognosis [13]. Therefore, concern about premature palliative care referral is likely misplaced [18]. During the initial encounters when treating patients with ESLD, especially those being considered for LT, a significant amount of information is imparted which can be overwhelming for patients and their families, generating significant stress and uncertainty [19]. Given the high prevalence of hepatic encephalopathy (HE), which compromises a patient's cognitive status, early identification of a health-care proxy or surrogate is very important in order to address the needs and perceptions about the care plan [20]. A collaborative approach involving primary providers

Table 35.3 Skill sets for primary and specialty palliative care. Reproduced with permission from Quill and Abernethy [15]. Copyright © (2013) Massachusetts Medical Society

Primary palliative care	Basic management of pain and other symptoms
	Basic management of anxiety and depression
	Basic discussion about
	Prognosis
	Goals of treatment
	Suffering
	Code status
Specialty palliative care	Management of refractory pain and other symptoms
	Management of more complex depression, anxiety, grief, existential distress
	Assistance with conflict resolution regarding goals or methods of treatment
	Within families
	Between staff and families
	Among treatment teams
	Assistance in addressing cases of near futility

and palliative care specialists can effectively manage concerns across the spectrum of the decompensated state [19]. As the disease progresses, an in-patient palliative care consultation may facilitate integration and transition of care [13]. Advance care planning and clarification of code status, as well as discussions about the futility of additional interventions may be less difficult if effective communication has been established among patient, family and providers.

The literature regarding the value of palliative care in ESLD is scant. Early referral may reduce the burden on health-care system and providers and improve patient and family satisfaction. In the context of ESLD, this could result in care rendered in a more appropriate outpatient setting [10]. Whether early palliative care in ESLD will result in an improvement in QOL and longer median survival, as was noted in patients with non-small-cell lung cancer, remains to be determined [21].

Management of Specific Complications of End-Stage Liver Disease

The following is a review of treatments for specific and common complications associated with patients who are terminally ill with cirrhosis. All treatments must be congruent with the patient's goals as determined by a thorough discussion of his or her understanding of the diagnosis and prognosis. Furthermore, the priorities of the patient drive the plan, i.e., if he or she wishes to extend life at all costs, strict adherence to practice guidelines may be appropriate. Alternatively, if QOL is the principle concern, then the treatment should reflect the patients' and families' goals of care.

Ascites

Ascites, the most common complication of cirrhosis, develops in up to 50 % of patients within 10 years of the diagnosis of cirrhosis [22]. Patients with newly diagnosed ascites have a 1-and 5-year survival of 85 and 56 %, respectively [23]. Ascites can cause dyspnea, orthopnea, limited mobility, abdominal discomfort, anorexia, nausea, and vomiting.

Initial management includes a sodium-restricted diet while avoiding drugs that cause sodium retention, such as nonsteroidal anti-inflammatory agents [22]. For oral diuretic therapy, an aldosterone antagonist (spironolactone or amiloride) may be used alone [24]. However, patients with recurrent ascites usually require a combination of a loop diuretic (such as furosemide) with an aldosterone antagonist [25]. In the terminal phase of liver disease, the use of diuretics to manage ascites is often limited by hypotension, hyponatremia, and renal insufficiency. Midodrine can be added to treat hypotension, which may allow the continuation of diuretics [25]. Vasopressin antagonists such as tolvaptan have been prescribed to treat hypervolemic hyponatremia but are expensive and have shown no clinical benefit in the long-term management of ascites while mortality could be increased in patients with cirrhosis [26]. As a consequence, they have not gained widespread use in any setting. Beta-blockers should be prescribed very cautiously in patients with refractory ascites, given their adverse impact on systemic hemodynamics while causing fatigue and lethargy [27, 28]. Large-volume paracentesis can be performed as required to provide symptomatic relief. Intravenous albumin replacement with 6–8 g/l of fluid removed is recommended when more than 5 liters (l) are removed, to decrease the risk of renal impairment and adverse circulatory changes [22, 25]. The continued administration of albumin to a patient in a hospice setting is debatable since albumin has not been demonstrated to improve long-term patient survival [24]. The placement of a transjugular intrahepatic portosystemic stent shunt (TIPS) is a very effective intervention to control ascites [29]. The most common complication of TIPS is new onset or worsening HE, which is usually controlled with medical treatment and rarely requires occlusion of the shunt to control symptoms. Contraindications to TIPS placement include pulmonary hypertension, heart failure, and advanced decompensated cirrhosis. Therefore, proceeding to TIPS placement in an individual with a prognosis of less than 3 months should only be done after careful consideration given its risks.

The insertion of a peritoneovenous shunt, such as the Denver or Le Veen shunt, has declined significantly over the last two decades due to their high incidence of complications including shunt occlusion and sepsis [30]. Such shunts are rarely acceptable options now.

Implanted peritoneal drainage catheters have been used for the treatment of malignant and nonmalignant refractory ascites; they allow convenient drainage of ascitic fluid for symptom relief on an as needed basis. The drainage can be done at home; if small volumes (less than 5 l) are removed, albumin replacement is not required which can minimize the need to travel to a hospital while reducing the cost associated with repeated large-volume paracentesis [31]. Complications include catheter malfunction, leakage of ascites at the incisional site, cellulitis, and peritonitis. Lungren et al. recently reported that the complication event rate for tunneled peritoneal drainage catheters in patients with malignant and nonmalignant ascites was 0.43 events per year [32]. Other studies have shown that peritoneal catheters were safe, practical, and offered symptomatic improvement for most patients with refractory ascites [33, 34]. Prophylactic oral antibiotics may be an appropriate adjunctive therapy to minimize the risk of sepsis associated with an indwelling catheter.

Recently, a multicenter nonrandomized trial evaluated the safety and efficacy of an implanted automated pump from the peritoneal cavity into the bladder for the removal of ascites in patients with cirrhosis. The ascitic fluid was then eliminated through normal urination. The pump was able to remove 90 % of the ascites and reduce the number of large-volume paracentesis. The rate of complications was moderate and included infection, HE, and renal dysfunction [35]. Further evaluation is required before recommending this procedure as a means to control ascites in patients with advanced liver disease.

Hepatic Hydrothorax

Pleural effusions occur in 5–12 % of patients with ESLD; they are most often right-sided (65–85 % of cases) and are commonly seen in conjunction with ascites, although may be present alone [36]. The most likely mechanism for the development of a pleural effusion is the movement of ascitic fluid transdiaphragmatically through minute diaphragmatic defects because of a pressure gradient between the peritoneal space and pleural cavity [37]. Due to the limited compliance of the pleural space, even small to moderate amounts of pleural fluid can cause significant respiratory symptoms including dyspnea, chest pain, and hypoxia.

Similar to the management of ascites, the initial treatment of hepatic hydrothorax is dietary sodium restriction and diuretic therapy. Thoracentesis may be necessary for the rapid relief of dyspnea. This procedure is relatively safe and can be repeated as needed, but there is a small risk of complications including pneumothorax and hemothorax [38]. Evacuation of more than 2 l of pleural fluid is usually not recommended, because of the risk of pulmonary edema and hypotension, although patients with cirrhosis may be able to tolerate the removal of larger volumes of fluid [38]. Albumin replacement is not necessary after a thoracentesis due to the relatively small volume of fluid removed [38].

When frequent thoracenteses are required, alternative treatments must be considered. TIPS placement effectively manages refractory hydrothorax [39, 40]. However, as in the case of patients with refractory ascites, TIPS is often not a viable option in patients with advanced liver dysfunction. Pleurodesis is not an effective therapy for hepatic hydrothorax, probably due to the rapid re-accumulation of pleural fluid, while being associated with significant morbidity and mortality [41]. In addition, incomplete pleurodesis can create loculated pleural effusions, complicating potential subsequent thoracenteses. Chest tube placement has not been recommended for the management of recurrent pleural effusions because of a high rate of complications including bacterial empyema, pneumothorax, hemothorax, electrolyte imbalance, and renal insufficiency [42]. However, in the palliative setting, tunneled pleural catheters have a role in managing respiratory distress associated with malignant and nonmalignant pleural effusions. Several studies have reported complete or partial symptom

improvement with low-complication rates [43, 44]. While only a small number of patients with ESLD were included in these studies, given the limited options, we believe that these catheters are an appropriate treatment option for patients with refractory hepatic hydrothorax [36, 45].

Hepatic Encephalopathy

Hepatic encephalopathy is characterized by reversible neuropsychiatric disorders ranging from subtle disturbances and cognitive deficiency to obvious confusion, ataxia, and somnolence progressing to stupor and coma [46]. This entity can cause significantly disability and a negative effect on patients' QOL. Avoiding precipitating or aggravating factors, such as narcotics and sedatives, can be particularly challenging in the terminally ill patient. A nonabsorbable disaccharide, such as lactulose, is the first line of treatment and can be administered orally or per rectum. The goal of lactulose therapy is to achieve three to five soft bowel movements per day. Excessive administration of lactulose may result in diarrhea, dehydration, and electrolyte imbalance that can precipitate or worsen HE. In patients who cannot tolerate or are refractory to the treatment with lactulose, nonabsorbable antibiotic therapy should be considered. In the past, neomycin was used for the treatment of HE but nephrotoxicity and ototoxicity limited its use [47]. In 2010, rifaximin received approval in the USA for the secondary prevention of HE. This medication can effectively reverse HE and is generally well tolerated, but is expensive [48]. Advance care planning must occur prior to the onset of symptoms for obvious reasons.

Hepatocellular Carcinoma

The 5-year cumulative risk for the development of hepatocellular carcinoma (HCC) in patients with cirrhosis ranges between 5 and 30%; the 5-year survival rate for HCC is dismal at less than 12% [49]. Surgical resection is the first-line treatment option for patients with a solitary tumor without clinically significant portal hypertension and who have preserved liver function [50, 51]. LT is the preferred and most effective treatment for selected individuals. For patients who are not eligible for resection or LT, nonoperative treatment modalities are available that provide effective short-term palliation, including ablation with radiofrequency (RFA) and percutaneous ethanol injection (PEI) [52–54]. Arterial chemoembolization has been shown to improve survival among patients with unresectable HCC [55]. The most common adverse events associated with chemoembolization are fever, abdominal pain, nausea, and anorexia. Contraindications include main portal vein thrombosis, decompensated liver disease, macroscopic tumor invasion, and the presence of extra-hepatic metastasis. Systemic chemotherapy, tamoxifen, immunotherapy, anti-androgen, and herbal drugs are not recommended for the clinical management of HCC due to their side effects, dose-limiting hepatotoxicity, and poor efficacy [51]. Sorafenib, an oral multi-tyrosine kinase inhibitor, was shown to have a modest survival benefit in patients with advanced HCC; it is approved for use in the USA for patients with well-compensated liver function who have advanced tumors or tumors that progress after failing locoregional therapies [51, 56]. The most frequent adverse events include diarrhea, hand–foot–skin reaction, fatigue, and weight loss. Its use in terminally ill patients is tempered by its cost and limited benefit. Radiotherapy can be considered to alleviate pain in patients with bone metastasis [51].

Pruritus

Pruritus is a common symptom in patients with liver disease. Generalized pruritus can cause significant distress, leading to sleep deprivation and depression. The initial management includes adequate treatment of the underlying cause of cholestasis, including the drainage of biliary obstruction when possible. An oral antihistamine may be particularly helpful, especially if administered at bedtime exploiting its sedative effect [57]. Current evidence-based guidelines recommend a stepwise approach to the treatment using cholestyramine, rifampin, naltrexone, and sertraline [58].

Cholestyramine, an oral nonabsorbable bile acid exchange resin, prevents the uptake of bile acids in the terminal ileum. Other oral medications must be taken at least 4 hours (h) apart

because cholestyramine can interfere with their absorption [58]. Rifampin is a second-line therapy for pruritus; it may improve symptoms by decreasing hepatocyte uptake of bile acids. Significant hepatotoxicity has been reported within 3 months of initiating rifampin in up to 12% of patients who have cholestatic liver disease [59]. Naltrexone, an oral opioid antagonist, and a third-line treatment for pruritus should only be considered when cholestyramine or other resins and rifampin lack efficacy or when intolerance and adverse effects manifest [58]. Possible withdrawal-like symptoms have been reported in some patients who take naltrexone; logically, it is not recommended in those taking opioid analgesics for pain [57]. While rifampin has not been recommended for use in patients with advanced liver dysfunction, we believe that it has a role in treating pruritus in the palliative setting [58]. Recent studies support the use of sertraline, a serotonin reuptake inhibitor, for cholestatic pruritus [60]. Experimental treatments such as ultraviolet phototherapy, extracorporeal albumin dialysis and nasobiliary drainage can be considered when standard treatments have failed to alleviate severe pruritus. However, debilitated patients may not have access to or be able to undergo such interventions.

Other Symptoms

Depression is common in patients with cirrhosis and is closely associated with the severity of liver disease [61]. It is particularly difficult to evaluate in patients with HE. There are not enough data to recommend any specific agents for depression in patients with cirrhosis.

Insomnia, delayed sleep habits, and excessive daytime sleepiness are frequently encountered in patients with cirrhosis. The etiology of these sleep disturbances has been attributed to HE and impaired hepatic melatonin metabolism [62]. Limited data suggest that hypnotics should be carefully used in patients with advanced liver disease. The ideal agent should have negligible hepatic metabolism, short half-life, and no active metabolites [62].

Fatigue is most likely multifactorial; possible factors include underlying liver disease, muscle wasting, the use of beta-blockers and diuretics [63]. This symptom frustrates both patients and providers alike. The psychostimulant methylphenidate which is used in advanced cancer patients may be beneficial for patients with vegetative symptoms (fatigue); however, its use in ESLD has not been studied [64].

Muscle cramps are a frequent complaint in patients with cirrhosis but the etiology is unknown [63]. They are not always associated with electrolyte imbalance or the use of diuretics. No specific therapy for cramps is recommended. Quinine sulfate and tonic water have been used; however, their safety and efficacy have not been evaluated.

Cachexia in cirrhosis is secondary to increased metabolism, protein loss from frequent paracentesis and decreased caloric intake due to gastroparesis and intra-abdominal pressure from ascites [65]. Protein restriction is not recommended, even in patients with HE. A study by Marchesini et al. reported that branched-chain amino acid (BCAA) supplementation delayed progression of liver disease and improved anorexia and health-related QOL, but long-term compliance with BCAA was poor [66]. Further studies are needed to evaluate treatment options for cachexia in patients with ESLD.

Anorexia in cancer patients responds to metoclopramide, dexamethasone, megestrol, and dronabinol; however, it has not been studied in ESLD; anecdotal evidence suggests success with all these agents, including nonmedicinal marijuana use [67].

Future Directions

The needs of patients can be effectively addressed by providers versed in managing complications of cirrhosis by the implementation and integration of the principles of palliative care in standard hepatology care. Patients with ESLD and their families suffer from significant physical and emotional distress [13]. “Prognostic paralysis” based on the uncertainty of a patient’s life expectancy should not impede the holistic assessment and management by a multidisciplinary and integrated care team [68]. Even in the absence of such a team, providers can provide valuable

"primary" palliative care, dealing with basic symptom control and initiating discussions about prognosis, code status, and goals of therapy [15, 19]. Integration of palliative care into basic and specialty training will facilitate an earlier and more widespread adoption of these principles. Physician skill in communicating bad news is another important aspect of care that will require a particular focus in training [19]. This can be especially challenging in patients with significant HE, which only reinforces the benefit of early advanced care planning. Another frequently overlooked aspect germane to the care of terminally ill patients is teaching coping skills to health-care professionals while providing emotional support for staff [14].

A decade ago, Rossaro et al. advocated a combined transplant and palliative care team approach emphasizing a shift away from the current sequential model (too sick to transplant precipitating referral) to a simultaneous provision model of care which allows concomitant advanced care planning [69]. An integrated management approach involving primary and specialist providers that includes palliative care may improve QOL and result in higher rates of advanced planning and more appropriate utilization of services for patients with ESLD [6, 70, 71]. Palliative care should no longer be seen as a failure of conventional therapies but as an essential component of managing decompensated cirrhosis.

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Ethical Issues in End-Stage Liver Disease: A Framework for Assessment and the Challenges

36

Stephen Chris Pappas

Ethics is knowing the difference between what you have a right to do and what is right to do

Judge Potter Stewart

Patients with end-stage liver disease (ESLD) can present complex ethical issues. Despite the increasing numbers of these patients being admitted with acute, critical illness and advanced age, the established treatment role of liver transplantation (LT), and the underlying settings of alcohol, drug abuse, and socioeconomic disadvantage, it is perhaps surprising that there is a paucity of data and consensus policy to help us assess and manage the inevitable ethical dilemmas that arise. This chapter reviews a practical framework for the assessment of ethical issues in patients with ESLD, presents challenges to the evaluation of ethical issues, and briefly reviews specific areas where ethical problems have arisen or are about to become more complex.

Frameworks for Assessment of Ethical Issues

The initial assessment of ethical issues has historically started with the traditional four pillars of medical ethics: respect for autonomy, beneficence, nonmaleficence, and justice [1]. Autonomy refers to the moral right to decide, and act, on one's own free will related to all aspects of medical care.[1] An important core of autonomy includes informed consent, the basis on which free-will decisions are made. Beneficence is the moral imperative of doing what is best for the patient. This should arise from the health-care professional's competence and the patient's wishes (autonomy). Nonmaleficence embodies the principle of doing no harm; it implies that the health-care professional has met a standard of competence of knowing what can go wrong and a duty to warn (also a legal duty in most situations). Finally, justice, arguably the most complex and variably defined of the pillars, attempts to focus considerations of equity (similarly situated patients should have access to similar care), fairness (does an act inherently appear to be fair both to the individual who may benefit from it and any individuals who may be affected by it?), and utility (the efficient use of resources, particularly scarce resources, to maximally benefit an individual patient or to benefit the maximal number of patients).[2]

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[1] As such, it has an important legal counterpart constitutionally enshrined in the law of most countries of the world.

[2] Justice is the most difficult principle to express succinctly and is not surprisingly the most variably defined. While equity can be determined relatively easily, as in law, the concept of fairness can be vague, often coming down to a subjective assessment of what seems right, as in, "what might your Mother say?"

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While the four main principles of medical ethics are the starting point for identifying and managing clinical ethical dilemmas, as noted by Alfrande and Schumann [1], "…it is important to caution readers that reducing decisions to the four principles may fail to address some of the complexity inherent in many ethical dilemmas…." This is particularly true for ethical analyses that involve policies for patient populations (e.g., those awaiting LT, patients with alcoholic liver disease). For example, organ allocation for transplant, the archetypal complex ethical dilemma, includes ethical principles of efficiency, quality of life, maximum benefit, economical responsibility, and minimum corruptibility [2]. These specific principles might not fit cleanly into one of the four pillars (or might fit into more than one pillar) and for purposes of an ethical analysis, might be identified as a critical "free-standing" principle to be discussed.

To address the problems with translating the four principles of medical ethics into a practical approach for ethical case analysis, Jonsen, Siegler, and Winslade [3] described the "four topic" approach (not to be confused with the four pillars/principles) for clinical ethical case analysis. The four topics method (also known as the "four quadrant" or "four boxes" approach) "…was developed to provide clinicians with a framework for sorting through and focusing on specific aspects of clinical ethics cases…" while recognizing and preserving adherence to the four pillars of medical ethics [4]. The four topics and the principles they include are:

1. *Medical indications*—beneficence and nonmaleficence
2. *Patient preferences*—respect for patient autonomy
3. *Quality of life*—beneficence, nonmaleficence, and respect for patient autonomy
4. *Contextual features*—justice

The four topics analysis begins with filling in each of the "boxes" with the facts of the case, starting with the one most familiar to clinicians, the medical indications. In addition to the usual details of the patient's medical problems such as might appear in the patient's chart, this topic includes the goals of treatment, the probability of success (prognosis) and contingency plans in the event treatment is not effective (or becomes futile). This information is critical to aligning the medically indicated treatment with patient preferences, the next topic assessed. For this topic, anchored in autonomy, beyond a recording of what the patient has expressed either recently or in the past, it is necessary to explore whether the patient is truly competent and has been provided with, and understood, the information required for informed decision making. It is in this box that a surrogate decision maker is identified if the patient is incapacitated; this frequently involves reference to appropriate legal standards and establishing whether the patient has a legally valid advance directive. The importance of the patient preferences topic is underscored by the observation that a conflict between medical indications and patient or surrogate preferences may be the most common reason for formal ethics consultation and involvement of the courts.

The quality-of-life topic serves to focus the ethical analysis on the effects of any treatments and patient preferences on the patient's assessment of quality of life, the default position being that a patient is best able to assess their quality of life. Considerable deference is given to this aspect of autonomy and it is for this topic that the health-care professional must be prepared to provide information about futility of care, options for palliative care, and withdrawal of all or large portions of care. Finally, the contextual features topic attempts to place the facts of the ethical analysis in the context of the case. Context includes, but is not limited to, religious, cultural, socioeconomic, resource allocation, and financial factors. It is these factors that focus our analysis on justice, including fairness, utility, and on occasion, maximum benefit. This makes the contextual features topic arguably the most uncomfortable one for health-care providers. They are generally taught not to include financial or resource considerations in clinical and ethical decisions, but are now under increasing pressure to do so.

Table 36.1 Strategy to identify, manage, and avoid clinical ethical dilemmas. A stepwise approach to the identification, management, and potential avoidance of clinical ethical issues for the management of patients with end-stage liver disease. The steps in the two columns should be carried out in parallel.

A. Obtain an advance directive; if not available and the patient is competent, encourage one be executed	1. Identify "up front" whether an obvious ethical issue involving one of the four pillars of medical ethics (autonomy, beneficence, nonmaleficence, justice) is present—if so, proceed to step 6, then return to step 2
B. Begin planning ahead for end-of-life issues	2. Conduct a four-topic analysis
C. Anticipate and schedule regular reevaluation of any plans (at a minimum with each admission or major clinical change)	3. Collect additional information if what is available is not sufficient to complete the analysis
D. If a surrogate medical decision maker is involved, assess the alignment of the surrogate's expressed treatment preferences with those of the patient, if possible	4. Identify the ethical issues present (or are likely to arise), preferably in the form of a question
E. Discuss any plans, issues with all health-care teams and caregivers involved in the patient's care and schedule regular reevaluation of any plans (at a minimum with each admission or major clinical change)	5. Prioritize the issues for management
	6. Prepare a plan to manage or resolve the dilemma(s)
	7. Discuss and refine the plan with all stakeholders, including the patient, family members, surrogate decision makers, and the extended medical team from other specialties, especially critical care
	8. Agree on and institute a consensus plan

Having completed the four topics analysis, the analysis can be used to identify the ethical issue, or issues, guide discussion between the patient or surrogate and the health-care team, identify any missing information that might be required, and formulate some plan. The plan must comport with the four principles of medical ethics and any applicable laws, and respect relevant religious and cultural contexts. As Schumann and Alfrande [4] point out, and as will be demonstrated by considering the special challenges the nature of ESLD imposes, the four topics model is not only helpful for cases with ethical issues but also useful for any clinical encounter. A strategy to identify, manage, and potentially avoid clinical ethical dilemmas in patients presenting with a complication of ESLD is presented in Table 36.1. The steps in the two columns should be carried out in parallel.

The Challenges

The Nature of ESLD

The ethical issues that arise in patients with ESLD are particularly challenging based on the demographics of the patient population. Patients with alcoholism or viral hepatitis, major etiologies for cirrhosis with ESLD, are generally populations with a high proportion of individuals from racial minorities and/or lower socioeconomic status, with substance abuse, or diverse religious and cultural preferences, not indigenous to the areas to which they have immigrated. In addition, the aging cohort of patients with viral hepatitis B and C, particularly in North America and Europe, is resulting in an aging population of patients with ESLD with other comorbidities. This demography makes it difficult for us to conduct our four topics assessment. We have to consider quality of life or contextual features that might include homelessness, single-parent families, and very limited finances, as part of "normal" life, or patient preferences in the setting of foreign cultural standards and unfamiliar religious beliefs.

The ethical issues assessment and plan are further complicated by the frequent presence of hepatic encephalopathy (HE). The complex relationship between HE, cognitive function, and even socioeconomic status [5] makes the patient with ESLD particularly difficult to assess. The impact of HE on higher cognitive functioning involving insight and abstract thinking may make it impossible to engage the patient in discussions of patient preferences, to establish a respect for autonomy. Here, the initial question should be "is the patient competent, meeting both ethical and

legal standards of capacity"? Similar to evaluating testamentary capacity, consideration should be given to ensure that the patient understands exactly what implications arise from their preferences for treatment (analogous to an understanding of the extent and value of property for a will). This may be difficult even for a patient with minimal HE. Furthermore, the fluctuating nature of HE potentially creates a changing platform of the patient's wishes—at one time expressing a need to do nothing, the next time requesting a need to do everything. This reinforces the importance of early advance directives formulated at a time before any HE supervenes (preferably before the onset of any non-HE complication). Unfortunately, this is rarely done and the need for identifying a surrogate medical decision maker, based on local legal requirements, is often executed during an acute crisis. That this occurs frequently and is associated with adverse effects, is suggested by some data indicating that the surrogate may express preferences that do not align with what the patient would have preferred in over one third of cases [6].

The nature of liver disease also interferes with "the quality-of-life box" for patients with ESLD. Patients with ESLD historically have been perceived to have a poor outcome, surrounded by "therapeutic pessimism" [7]. Although it is something every hepatologist has encountered, there is little discussion about the prejudice that may be encountered when transferring a patient to the intensive care unit (ICU) or requesting an advanced therapeutic procedure. While arguably justified in the past, significant advances in the critical care of patients with ESLD have been made and must be incorporated into our four topics ethics discussions [7]. These advances, particularly LT, do create some other problems, however. The opportunity for LT, and the hope springing eternally for its possibility in an individual case, have led to little thought being given to palliative care and end-of-life (EOL) planning in patients with ESLD [8]. Compared to other disease states, patients with ESLD receive more aggressive care towards the EOL when LT is available [9]. It is not clear whether this is appropriate in all cases; there may be futile treatment continuing when transplantation is available but not a realistic possibility. Accordingly, palliative care and EOL planning, an important component of patient autonomy, is overlooked. In contrast to the hope springing eternally when transplant remains a possibility, it appears to be quickly abandoned when a patient is removed from the waiting list—in one study only 10% of patients removed from the wait list were referred for palliative care and EOL planning [10]. Palliative care planning, and often its provision, should be an early part of the care of patients with ESLD, even while they are on the transplant waiting list and certainly when they are not [11, 12]. EOL planning should be discussed at the first complication of ESLD in view of the fact that survival estimates after the first complication are generally in the 6–24 months range [13].

A key component of the information required for optimal clinical ethical case analysis is the ability to provide reliable prognostic information; prognosis touches every one of the four boxes. This information is crucial to allowing the patient to make a decision about treatment preferences (autonomy) and planning for quality of life; it is a cornerstone for a discussion of medical indications (beneficence, nonmaleficence) and has major implications for resource allocations and finances, important components of contextual features (loyalty and fairness). While prognostic models are available, the fluctuating severity of ESLD makes prognostication especially difficult for those patients who are critically ill. In addition to its medical importance, we must improve our ability to "…define the archetypical illness trajectory of ESLD…" [12] to facilitate ethical analysis. Critical analysis of various prognostic scores suggests that that the Child-Pugh-Turcotte score is not adequate, the model for end-stage liver disease (MELD) score is marginally better, and that a liver disease-specific modification of the sequential organ failure assessment (SOFA) score, the chronic liver failure SOFA (CLIF-SOFA) score is the best currently available prognostic score [7, 14]. Reevaluating prognosis after 48 hours of initial intensive care treatment may improve prognostic accuracy [7] and should prompt another discussion with the patient, or usually a

surrogate decision maker, at this time. Prognostication, avoiding the tendency to unrealistically overemphasize the possibility of LT, is crucial for discussions of futility and the withdrawal of care. Limited guidelines exist and suggest that the first 48–72 h in the ICU is the time period after which a review for futility and the withdrawal of care should be considered in certain patients [15]. Full transparency and regular communications between all health-care providers, particularly the critical care staff and the hepatology team, is of paramount importance to see that all clinical information relevant to prognosis is discussed and entered into a regularly updated four topics analysis.

Specific Issues in Patients with ESLD

While it is not clear how often significant ethical issues actually arise during the care of patients with ESLD, or the planning of policies surrounding the delivery of their health care, there have been some particularly challenging specific issues. These include possible bias against ESLD patients with alcoholism and drug abuse, LT for alcoholic hepatitis, legal medical and nonmedical marijuana use in the patient with ESLD and the challenge of developing an equitable efficient system of organ allocation for LT.

ESLD Patients with Alcoholic Liver Disease, Marijuana Use

One of the questions that should be asked as part of the assessment of the quality-of-life "box" during our four topics analysis, is "[a]re there biases that might prejudice the provider's evaluation of the patient's quality of life?" [4]. Health-care providers may harbor conscious or subconscious prejudice against patients who they feel should be morally responsible for their plight when they develop alcoholic liver disease or continue to abuse drugs. These may invoke considerations of social worth based on moral responsibility during the decision-making process. While this is explicitly forbidden by most ethics guidelines, policy discussions have included patients' moral responsibilities as a factor to be considered regarding transplantation for alcoholic liver disease [16]. Although the tension between the ethical responsibility of beneficence for the individual patient and the moral responsibility of responsible stewardship of a value resource (i.e., donor livers) in the setting of transplantation for alcoholic liver disease has been recognized for over 15 years, a consensus policy, widely accepted by the medical community and the general public, adequately addressing this matter has not been developed. Patients with alcoholic liver disease are generally regarded with a lower priority for LT, and probably other aspects of their care, by both the public and health-care providers, compared to patients with nonalcoholic ESLD [7, 17]. There was resurgence in interest in this after the publication of a French report describing early LT in patients with alcoholic hepatitis [18]. Prior to this report, possible transplantation for these patients could be largely ignored since there was no medical evidence to support a benefit from this intervention. The French study provided data that showed that these patients could do quite well with survival approximately 75% at 2 years and low recidivism (approximately 15%). This now introduces an additional ethical–legal wrinkle. If alcoholism is recognized as a disability, there may be a legal basis, based on a claim of discrimination, to prohibit the routine exclusion of patients with alcoholic hepatitis from LT, if they meet evidenced-based selection criteria reasonably imposed by a transplant program. This prohibition could apply to insurers and transplant programs alike. While this would likely apply to only 1 or 2% of liver transplants, a consensus policy on this matter is needed.

Somewhat related, are the ethical issues with nonmedical, "recreational" marijuana use and medical marijuana use in patients with ESLD, particularly those awaiting transplantation. Controversy over this started in 2008 with publicity of the case of Timothy Garon, a patient with hepatitis C related ESLD who alleged that he was kept off the LT list because of bias against his medical marijuana use, legal in Oregon since 1998 [19]. The recent increase in the number

of states in the USA, and countries worldwide, where marijuana is legal for both medical and nonmedical use may lead to an increase in the number of patients with ESLD using marijuana for palliation purposes, including those awaiting transplant. While advocates of policies prohibiting the use marijuana while on the transplant wait list defend these policies with evidence that marijuana users do not experience survival harm by being forced to abstain [20], overall they are less likely to receive a transplant and they may experience a poorer quality of life while awaiting transplant. In the absence of evidence that marijuana in this setting, by these patients, is detrimental, current policies may not comport with fairness and beneficence principles. The issue is further clouded, in the USA at least, by conflict between State law and Federal law; the latter does not recognize the legal use of marijuana, medical or nonmedical. This remains another area where thoughtful, evidence-based consensus policy and further studies are needed.

Organ Allocation for Liver Transplantation

The ethical issues surrounding LT generally fall into one of three categories: procurement, allocation, and payment [16]. One of the questions to be asked in the contextual features section of our four topics approach is "[a]re there problems of allocation of resources?" [4]. While usually focusing on an individual patient and local resources, in patients with ESLD, the question can be broadened to include the effects of the organ allocation system on the likelihood of a patient receiving a transplant. Currently, the USA and many countries follow a liver allocation system based on medical need, the sickest patients first [21]. An alternative that has been proposed is a survival benefit-based liver allocation. Keller, Kwo, and Helft [2] make a persuasive case that this allocation system best aligns with the wide variety of applicable ethical principles, is efficient, and provides maximal benefit, on a population basis, in the era of extended criteria donation (ECD). Deciding between these two allocation systems will involve complex ethical issues. It is not entirely clear at this point how the proposed survival-benefit system will be received by the medical community and the general public. "Sickest first" has long held a respected position in medical ethics. With the scarcity of donor organs, their use for maximal benefit may take priority. The survival-based allocation system may include quality-of-life outcomes (good) but may also prioritize age (not so good from some ethical perspectives). Just as with the four topics approach to an individual clinical ethical analysis, the organ allocation revision is going to require a careful, systematic, transparent analysis based on multiple ethical principles, supported by strong objective evidence of true benefit.

Conclusions

There is no question that complex ethical issues can arise in patients with ESLD. However, there is a paucity of data regarding ethical issues in patients with ESLD. More information is needed on the actual frequency and types of ethical issues arising in patients with ESLD, the use and value of formal ethics consultations in these patients, and the outcomes affected by ethics consultations (do they really help or do they simply make the caregivers feel better?). In the meanwhile, ethical issues in patients with ESLD should be systematically approached within an organized, accepted framework such as the four topics approach. To maximize the value of this approach, we need to be more sensitive to the demographic background of patients with ESLD and improve our ability to assess prognosis and futility of treatment. Advance directives, palliative care, early end-of-life planning and regular, open communication between health-care providers from all medical specialties must become integral parts of the care of patients with ESLD. The hepatology community (which includes caregivers, patients, and their families), in association with other stakeholders, must develop clear and practical consensus policies, based on ethical principles, in several areas. These include addressing bias against patients with alcoholism and drug abuse,

transplantation for alcoholic liver disease, legal marijuana use in patients with ESLD awaiting LT and the system for organ allocation for transplantation.

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