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Review Article

Review Article

Advances in the management of complications from cirrhosis

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Abstract

Cirrhosis with complications of liver decompensation and hepatocellular carcinoma (HCC) constitute a leading cause of morbidity and mortality worldwide. Portal hypertension is central to the progression of liver disease and decompensation. The most recent Baveno VII guidance included revision of the nomenclature for chronic liver disease, termed compensated advanced chronic liver disease, and leveraged the use of liver stiffness measurement to categorize the degree of portal hypertension. Additionally, non-selective beta blockers, especially carvedilol, can improve portal hypertension and may even have a survival benefit. Procedural techniques with interventional radiology have become more advanced in the management of refractory ascites and variceal bleeding, leading to improved prognosis in patients with decompensated liver disease. While lactulose and rifaximin are the preferred treatments for hepatic encephalopathy, many alternative treatment options may be used in refractory cases and even procedural interventions such as shunt embolization may be of benefit. The approval of terlipressin for the treatment of hepatorenal syndrome (HRS) in the USA has improved the way in which HRS is managed and will be discussed in detail. Malnutrition, frailty, and sarcopenia lead to poorer outcomes in patients with decompensated liver disease and should be addressed in this patient population. Palliative care interventions can lead to improved quality of life and clinical outcomes. Lastly, the investigation of systemic therapies, in particular immunotherapy, has revolutionized the management of HCC. These topics will be discussed in detail in this review.

Keywords: liver cirrhosis; hepatocellular carcinoma; liver failure

Introduction

Cirrhosis is the result of chronic liver disease with progressive and diffuse hepatic fibrosis that may lead to hepatocellular carcinoma (HCC) or hepatic decompensation in the form of ascites, hepatic encephalopathy (HE), or variceal bleeding [1, 2]. Advances in procedural techniques and a growing body of evidence in the management of complications in the last decade have led to updates in many areas of cirrhosis and decompensation. In this review, we will discuss advancements in the management of cirrhosis.

Portal hypertension

Pathophysiology of portal hypertension

Portal hypertension in cirrhosis is the culmination of intrahepatic factors such as endothelial cell dysfunction, pro-fibrotic and pro-inflammatory activated hepatic stellate cells, and angiogenesis that ultimately lead to collateral vessel formation and arterial vasodilation [3, 4]. The complex interplay of vasoconstriction, fibrosis, inflammation, and angiogenesis within the liver increases intrahepatic vascular resistance, thus leading to portal hypertension [3, 4]. Once portal hypertension develops, blood from the digestive organs shunts into the collateral vessels that have formed [3]. In order to compensate for the relative lack of portal flow by the shunted blood, splanchnic circulation flow is increased, thereby worsening portal hypertension [3]. An increase in portal blood flow stimulates the production of nitric oxide, leading to both systemic and splanchnic arterial vasodilation [3] (Figure 1).

Measuring the hepatic venous pressure gradient (HVPG) is considered the gold standard in diagnosing portal hypertension, with a value of >5 mmHg indicating sinusoidal portal hypertension [5]. Multiple studies have classified an HVPG of >10 mmHg as clinically significant portal hypertension (CSPH) and, when the HVPG reaches >12 mmHg, the risk of variceal bleeding is much greater [5, 6]. The clinical manifestations of portal hypertension include varices (gastroesophageal, intra-abdominal, and ectopic), ascites, HRS, HE, hepatopulmonary syndrome, portopulmonary hypertension, hepatic hydrothorax, and cirrhotic cardiomyopathy, many of which will be discussed later in this article [7].

Spectrum of liver disease and portal hypertension

The Baveno consensus meetings lay the groundwork for an evidence-based approach to the management of portal hypertension, with the most recent (Baveno VII) convening in October 2021 [5]. Perhaps one of the most significant developments from

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Baveno VII has been the use of non-invasive testing (transient elastography [TE], in particular) to estimate CSPH [5].

Compensated advanced chronic liver disease (cACLD) was a newly introduced term used to represent the spectrum of severe fibrosis and cirrhosis in patients with chronic liver disease and has since also been used in other guidelines [5].

In the Baveno VII consensus meeting, experts noted that a liver stiffness measurement (LSM) of <10 kPa by TE effectively rules out cACLD [5]. Furthermore, the Baveno group suggests the "rule of 5" for LSM by TE (10–15 to 20–25) that indicates an increasingly higher risk of liver decompensation and liver-related death [5]. Additional LSM thresholds that are clinically relevant include LSM by TE of ≤15 kPa and platelets of ≥150 × 10^9/L, which rules out CSPH, and in patients with LSM by TE of ≤20 kPa and platelets of ≥150 × 10^9/L, screening endoscopy for varices may be avoided [5] (Figure 2).

Recently, the new American Association of the Study of Liver Diseases (AASLD) practice guidance on the risk stratification and management of portal hypertension had been accepted for publication in *Hepatology* as of October 2023 and reflect the data and evidence-based approach to portal hypertension presented by Baveno VII [8]. By utilizing TE, CSPH can also be diagnosed based on one of the following, noted in the ANTICIPATE study in patients with viral, alcohol, and/or non-obese metabolic dysfunction-associated steatohepatitis (MASH)-related ACLD: LSM by TE of ≥25 kPa irrespective of platelet count, LSM of 20–25 kPa with platelet count of <150 × 10^9/L or LSM of 15–20 kPa with platelet count of <110 × 10^9/L [5, 8, 9]. Furthermore, CSPH can be diagnosed clinically with the presence of liver decompensation, gastroesophageal varices on endoscopy, portosystemic collaterals, or hepatofugal flow on imaging [8]. In compensated cirrhosis, the presence of CSPH is associated with an increased risk of decompensation [5, 8].

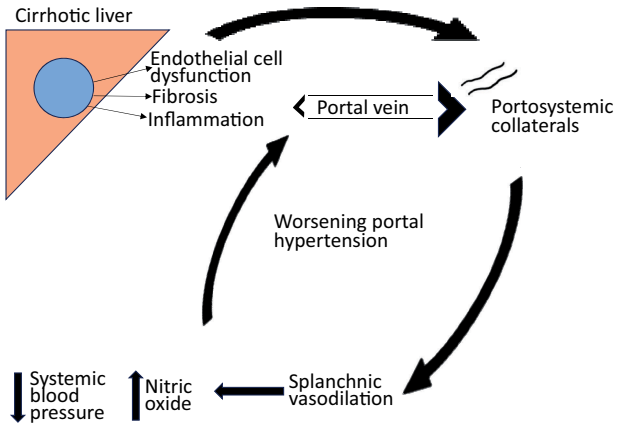


Figure 1. Pathophysiology of portal hypertension in cirrhosis.

Non-selective beta blockers

Non-selective beta blockers (NSBBs) reduce portal and collateral blood flow by decreasing cardiac output (β1 blockade) and splanchnic arterial vasoconstriction (β2 blockade). Carvedilol has the added benefit of anti-α1 adrenergic activity and allows the release of nitric oxide, which leads to intrahepatic vasodilation and improvement in portal flow into the liver [8].

PREDESCI was a landmark randomized–controlled trial from Spain that was published in 2019; it evaluated the impact of beta blockers on the reduction of HVPG and prevention of clinical decompensation in patients with compensated cirrhosis and CSPH [10]. In this study, 201 patients were randomly assigned to placebo or NSBB (propranolol or carvedilol) with a primary endpoint of cirrhosis decompensation (development of ascites, bleeding, or overt encephalopathy) or death. The primary endpoint occurred in 16% of the NSBB group vs 27% in the placebo group (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.26–0.97; $P = 0.041$) and was mostly due to a reduced incidence of ascites (HR, 0.42; 95% CI, 0.19–0.92; $P = 0.03$), with adverse events remaining similar in the two groups. However, the results of this study should be interpreted with caution, as all of the patients had confirmed CSPH with direct HVPG measurements, which is not routinely done in practice. Additionally, most patients had untreated hepatitis C and any ongoing alcohol use was not addressed [8, 10]. Regardless, the results of the study have contributed to the existing body of literature supporting the use of NSBBs in CSPH.

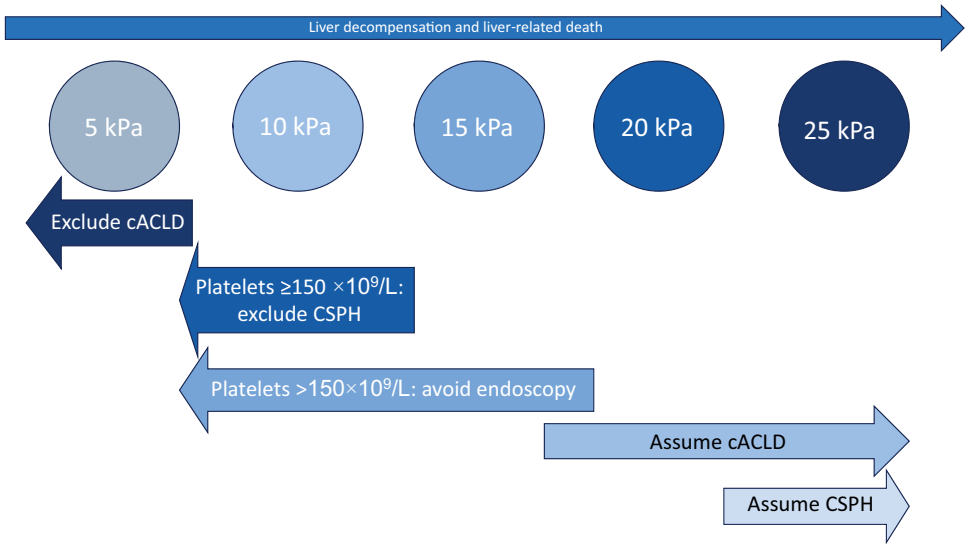


Figure 2. Use of liver stiffness measurement in the diagnosis and management of cACLD. [a]Adapted from reference [5]. cACLD = compensated advanced chronic liver disease, CSPH = clinically significant portal hypertension.

Carvedilol is considered to be superior to other NSBBs given its greater reduction in HVPG and it does not require titration by heart rate [8]. Data also show that carvedilol may portend a survival benefit in patients with compensated cirrhosis and CSPH [11, 12]. Given the available data, recommendations from Baveno VII and AASLD practice guidance suggest considering the use of NSBB (preferably carvedilol 12.5 mg/day) in patients with compensated cirrhosis and CSPH in the absence of contraindications [5, 8]. In patients who develop systemic arterial hypotension with systolic BP of <90 mmHg or serious adverse events, NSBB should be stopped [8]. Absolute contraindications to NSBBs include asthma, second- or third-degree atrioventricular block, sick sinus syndrome, and bradycardia (<50 b.p.m.) [8]. Relative contraindications to NSBBs include psoriasis, peripheral artery disease, chronic obstructive pulmonary disease, pulmonary artery hypertension, insulin-dependent diabetes mellitus, and Raynaud syndrome [8].

Prior data had suggested that the use of NSBBs increased mortality in patients with ascites. However, since then, there have been many studies and meta-analyses that have been conducted showing that NSBBs do not increase mortality in patients with ascites—even refractory ascites [13, 14]. The key factor in determining the therapeutic window of NSBBs in decompensated cirrhosis is maintaining arterial perfusion so as not to precipitate renal hypoperfusion [8, 15, 16]. The use of NSBBs in the primary and secondary prophylaxis of variceal bleeding will be discussed in the next section.

Endoscopic and endovascular management of esophageal, gastric, and ectopic varices

Anatomy and blood supply of esophageal and gastric varices

Collaterals in the gastro-intestinal tract are considered varices, with the most common location in the distal esophagus and proximal stomach [17]. The supply and drainage of the varices depend on their location. Esophageal varices are supplied by the left gastric vein (LGV) and drained by the azygos and hemiazygous vein into the superior vena cava (SVC) [17]. GOV1 are gastroesophageal varices that are contiguous with esophageal varices into the lesser curvature of the stomach, supplied by the LGV and drained by the azygos and hemiazygous vein into the SVC [17]. This type of varices can be managed similarly to esophageal varices [8]. GOV2 are gastroesophageal varices that are contiguous with esophageal varices into the greater curvature of the stomach, supplied by the LGV and posterior gastric vein, and draining into the SVC as well as into the left renal vein (through a gastrorenal shunt) and inferior vena cava as a gastrocaval shunt [17]. Other types include isolated gastric varices, rectal varices, duodenal varices, and stomal varices [17].

Primary prophylaxis for variceal bleeding

Primary prophylaxis refers to those patients who have never had variceal bleeding. The use of NSBB obviates the need for screening endoscopy for varices [8]. However, in those patients with compensated ACLD and CSPH who have a contraindication or intolerance to NSBB, screening endoscopy for varices should be performed [8]. If no varices are present, endoscopy may be repeated every 2 years if the underlying liver disease is uncontrolled or every 3 years if controlled [8]. If varices are present without a history of variceal hemorrhage and there is a contraindication or intolerance to NSBB, screening endoscopy should be repeated every year if underlying liver disease is uncontrolled or every 2 years if controlled [8]. In patients with high-risk varices without NSBB use, endoscopic variceal ligation (EVL) may be performed and repeated every 2–4 weeks until varices have been eradicated [8]. The algorithm is depicted in Figure 3.

In decompensated cirrhosis, the AASLD practice guidance on portal hypertensive bleeding has classified high-risk varices as moderate/large varices, varices with red wale signs, or any patient with Child–Turcotte–Pugh (CTP) class C [8]. Patients who have a contraindication or intolerance to NSBBs should have annual screening endoscopy for varices. Approaches to the primary prophylaxis of esophageal variceal bleeding in patients with decompensated cirrhosis include NSBB and EVL.

One meta-analysis published in 2019 reviewed 32 randomized–controlled trials including 3,362 patients with cirrhosis and high-risk varices [18]. The analysis demonstrated that the EVL monotherapy group showed decreased overall mortality when compared with that in the placebo group (OR, 0.48; 95% CI, 0.28–0.80). However, EVL monotherapy resulted in a higher risk of overall mortality than NSBB monotherapy (OR, 1.35; 95% CI, 0.98–1.86) [18]. Of the NSBBs that were reviewed in the studies, carvedilol was superior in decreasing the risk of variceal bleeding but did not demonstrate a mortality benefit compared to other NSBBs [18]. This meta-analysis contributed to existing literature highlighting the benefit of NSBBs in the survival of patients with cirrhosis. Therefore, in patients with high-risk varices, primary prophylaxis of variceal bleeding may be achieved with NSBBs such as carvedilol given the additional survival benefit or EVL may be performed [8, 18].

Approach to variceal bleeding

The endoscopic approach to acute variceal hemorrhage has remained standard over the years, with early endoscopy, the use of vasoactive drugs, and antimicrobial therapy [8]. In recent years, more data have advocated the use of an early transjugular intrahepatic portosystemic shunt (TIPS) as an adjunct for the secondary prophylaxis of variceal bleeding [8, 17].

TIPS procedure

TIPS is an endovascular shunt used to treat the complications of portal hypertension such as variceal bleeding and refractory ascites. TIPS is performed by interventional radiology using fluoroscopy and ultrasound guidance to create a tract between the hepatic vein and the portal vein, thus directing flow to the systemic circulation [17]. This procedure dates back to the 1980s when the first metal stent was used in a human [19]. TIPS itself has undergone many iterations and, most recently, the polytetrafluoroethylene-covered (PTFE) stent has been endorsed by society guidelines as the stent of choice, given its improved patency and survival, with lower rates of rebleeding [17, 20]. Additionally, data show that a PTFE-covered stent with a smaller

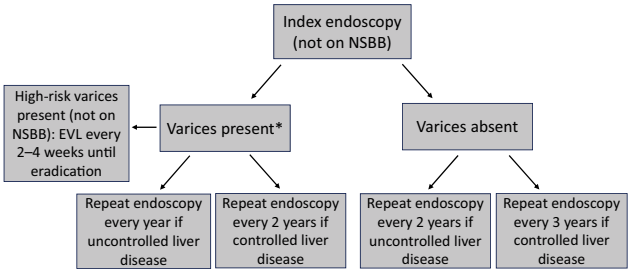


Figure 3. Algorithm for variceal surveillance in patients with cirrhosis and portal hypertension. [a]Without prior variceal hemorrhage. NSBB = non-selective beta blocker, EVL = endoscopic variceal ligation.

diameter of 8 mm is sufficient to prevent rebleeding and decreases the risk of HE and liver dysfunction [21, 22].

Role of TIPS in secondary prophylaxis for variceal bleeding

Studies conducted in recent years have demonstrated a benefit of early TIPS (within 72 h) in the secondary prevention of variceal bleeding. One key trial published in 2010 randomized 63 patients with acute esophageal variceal bleeding who were CTP class C or CTP class B with persistent bleeding on endoscopy to either pharmacotherapy (with NSBB) and EVL or early TIPS [23]. The primary end-point was a composite outcome of failure to control acute bleeding or failure to prevent clinically significant variceal bleeding within 1 year of enrollment [23]. Fourteen out of 31 patients in the pharmacotherapy-EVL group achieved the primary end-point vs 1 out of 32 in the early TIPS group ($P = 0.001$). Other studies have since demonstrated that early TIPS can prevent rebleeding, even though there may not be an impact on mortality [23–26].

Thus, AASLD recommends pre-emptive TIPS in patients presenting with acute variceal hemorrhage (AVH) who are CTP class C score 10–13 or CTP class B >7 with active bleeding on endoscopy [8]. If patients are unable to undergo TIPS, then the recommendation is to initiate NSBB and ongoing EVL with the goal of variceal eradication [8]. For indication of variceal bleeding, the goal is to achieve post-TIPS HVPG of <12 mmHg or a reduction of ≥50% from pre-TIPS to post-TIPS HVPG [17]. If the gradient is not reduced to <12 mmHg, then TIPS dilation to maximum of 10 mm may be performed or NSBBs may be added to further reduce the portal pressure [17].

Absolute contraindications to TIPS include congestive heart failure (stage C/D or ejection fraction (EF) <50%), severe pulmonary hypertension with mean pulmonary arterial pressure (mPAP) of >45 mmHg, severe uncontrolled HE, or uncontrolled sepsis [17]. Complications of TIPS are rare (<5%) and include intraperitoneal bleeding, arterial injury, hepatic infarct, puncture of the liver capsule, hemobilia, TIPS thrombosis, or stenosis, and procedure-related deaths are exceedingly rare, at <1% [17].

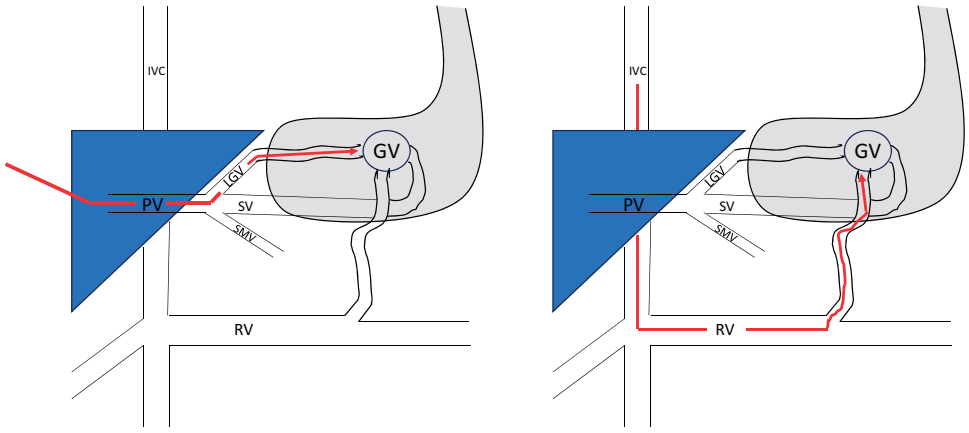
TIPS function and patency can be followed with Doppler ultrasonography at regular intervals: 1–4 weeks, 3 months, 6 months, and then every 6 months thereafter [17]. Discussion of the prevention and management of post-TIPS HE will be discussed in a later section.

Retrograde transvenous obliteration and antegrade transvenous obliteration in gastric or ectopic variceal bleeding

Variceal embolization or obliteration through retrograde transvenous obliteration (RTO) or antegrade transvenous obliteration (ATO) may be necessary in cases of variceal bleeding in which TIPS is contraindicated [8, 17]. The ATO and RTO techniques are depicted in Figure 4. Endoscopic therapies for the treatment of gastric variceal bleeding are limited to band ligation, cyanoacrylate, and endoscopic coiling. Cyanoacrylate may be more superior to band ligation in the prevention of rebleeding gastric varices, though studies are small and at risk of bias [27]. Recently, a randomized–controlled trial published by Luo *et al.* [28] in 2021 demonstrated that cyanoacrylate resulted in a higher risk of gastric variceal rebleeding than balloon-occluded retrograde transvenous obliteration (BRTO) ($P = 0.024$).

The RTO and ATO techniques have significantly advanced over the years, from the introduction of the first BRTO in 1996 by Kanagawa *et al.* [29, 30]. In the original BRTO procedure, a balloon was inflated within the gastrorenal shunt and a sclerosant was injected into the shunt [17]. Other procedures such as plug-assisted RTO (PARTO) and coil-assisted RTO (CARTO) use Gelfoam and/or coils to obliterate the collateral vessels [17].

Complications of RTO may be related to embolization of sclerosant leading to portal vein and/or renal vein thrombosis, anaphylactic shock, stroke, and disseminated intravascular coagulation, with rare complications including gross haematuria, cardiac arrhythmia, pulmonary embolization, and renal failure. Perhaps the most clinically relevant complication is that of worsening portal hypertension, which has been noted in the literature [31, 32]. This worsening of portal hypertension may lead to exacerbation of esophageal or ectopic varices with or without bleeding and ascites/hepatic hydrothorax [17]. Therefore, endoscopic surveillance of varices is indicated within 1–2 months of the RTO procedure [17]. A potential solution for the worsening of portal hypertension after RTO is the use of TIPS as an adjunctive treatment (Saad WE 2021). While there is a growing body of evidence



A Anterograde transvenous obliteration (ATO) directly through portal vein.

B Retrograde transvenous obliteration (RTO) through IVC and RV.

IVC: inferior vena cava. PV: portal vein. LGV: left gastric vein. SV: splenic vein. SMV: superior mesenteric vein. GV: gastric varices. RV: renal vein.

Figure 4. ATO and RTO techniques for the treatment of gastric varices

to suggest the benefit of combined TIPS and RTO, more robust data are warranted to routinely recommend concomitant TIPS and RTO to prevent the worsening of portal hypertension (Saad WE 2021) [33].

Bleeding ectopic varices, such as duodenal, jejunal/intestinal, stomal, or rectal, may be treated with endoscopic measures [17]. However, TIPS and/or ATO/RTO are considered more definitive in the management of ectopic variceal bleeding [17].

Management of HE

Pathophysiology of HE

HE is defined as cerebral dysfunction as a result of liver insufficiency and/or portosystemic shunting [34]. The clinical manifestations vary widely, from subclinical signs and symptoms to a comatose state [34]. HE can be classified into three types: type A is seen in acute liver failure, type B occurs in patients with a portosystemic shunt, and type C refers to HE in patients with cirrhosis who may or may not have a portosystemic shunt [35]. HE can further be subclassified as overt HE (OHE) or minimal HE (MHE), with MHE manifesting as abnormalities on psychometric testing [35].

HE represents a pathogenic hyperammonemic state from inadequately cleared ammonia by the hepatic urea cycle [36]. Ammonia subsequently crosses the blood–brain barrier, where cerebral astrocytes convert ammonia into glutamine [36]. Glutamine subsequently causes an osmotic effect within the cerebral astrocytes, causing edema, generation of reactive oxygen species, and altered neurotransmission [36, 37].

Gut microbiome and HE

The gut microbiome is intimately involved in ammonia production and metabolism. Dysbiosis and intestinal permeability play a central role in the development of HE [37–42]. Bajaj *et al.* [40] discovered that certain bacteria such as *Alcaligenaceae*, *Porphyromonadaceae*, and *Enterobacteriaceae* are associated with poor cognitive performance, worsening inflammation, and Model End Stage Liver Disease (MELD) in patients with cirrhosis.

Diagnosis of HE

The West Haven criteria are most commonly used in the diagnosis of HE, especially in cases of OHE, but are subject to variability between providers [43]. MHE often warrants diagnosis with psychometric testing, for which multiple objective and reliable tools exist [43]. The Psychometric Hepatic Encephalopathy Score (PHES) is a standard diagnostic tool used in many countries across the world and is the sum score of five subtests: Number Connection Tests A and B, Digital Symbol Test, Serial Dotting Test, and Line Tracing Test [43].

First-line therapies for HE

First-line treatment is non-absorbable disaccharides (lactulose and lactitol), with at least four therapeutic benefits in HE. Lactulose catabolism acidifies the colonic pH, converting ammonia into ammonium, which is impermeable [37, 44, 45]. It is also a laxative, shortening gut transit time, which leads to less absorption of ammonia and an increase in its excretion [37, 44, 45]. Lactulose promotes the uptake of nitrogen by bacteria in the colon for protein synthesis [37, 44, 45]. Lastly, lactulose promotes non-urease producing *Lactobacillus* in the gastro-intestinal tract [37, 44, 45].

Rifaximin is well established as an adjunctive therapy with lactulose in the treatment of HE or in patients who are intolerant of lactulose. A key study from 2010 by Bass *et al.* [46] demonstrated the superiority of rifaximin over placebo in maintaining remission from HE and reducing the risk of hospitalization with HE. Many trials have been conducted over the last several years showing that rifaximin is superior to placebo in the treatment of HE (in particular, MHE) and that the use of rifaximin with non-absorbable disaccharides improves HE and recurrence [47]. Additionally, a recent randomized–controlled trial published in 2021 by Bureau *et al.* [48] found that rifaximin use 14 days prior to TIPS resulted in reduced risk of OHE post-TIPS when compared with placebo (OR, 0.48; 95% CI, 0.27–0.87). Given these data, it is reasonable to initiate rifaximin prophylaxis 2 weeks prior to TIPS to reduce the risk of post-TIPS and maintain therapy for 6 months [17].

Alternative treatments for HE

Table 1 includes a list of alternative treatments for the treatment of HE by mechanism of action. Probiotics, prebiotics, and synbiotics have been studied extensively in the treatment of HE, by theoretically promoting a more favorable gut microbiome [49]. Multiple randomized controlled trials (RCTs) and meta-analyses have been conducted; however, the overall quality of the majority of studies was low with a high risk of bias. Thus, probiotics, prebiotics, and synbiotics are not routinely recommended.

Fecal microbiota transplant (FMT) has also been introduced as a potential treatment approach for patients with HE. The first RCT that evaluated the effect of FMT in patients with HE was conducted in 2017 by Bajaj *et al.* [50]. Twenty patients with at least two episodes of OHE were randomized 1:1 to FMT enema or standard of care [50]. Compared with the standard-of-care arm, patients in the FMT group had improvement in PHES score ($P = 0.003$) and the EncephalApp Stroop ($P = 0.01$) [50]. Long-term analysis at 12 months demonstrated fewer hospitalizations ($P = 0.05$), no HE events ($P = 0.03$), and sustained improvement in cognitive function in the FMT arm compared with standard of care [51]. Subsequent trials have been performed to evaluate the efficacy of FMT in HE and large-scale trials are needed to endorse routine use.

Other alternatives to detoxify ammonia and treat HE include branched chain amino acids, L-ornithine L-aspartate, glycerol phenylbutyrate, zinc, and sodium benzoate. While multiple studies have been performed to assess these agents as viable treatments for HE, their use is not routinely recommended by society guidelines and they should be utilized on a case-by-case basis.

Artificial liver support systems, such as the Molecular Adsorbent Recirculating System, have been studied in the treatment of OHE. A study published in 2007 randomized 70 patients with grade 3 or 4 (according to West Haven criteria) OHE to extracorporeal albumin dialysis (ECAD) plus standard medical therapy or standard medical therapy alone [52]. Improvement of HE was higher in the ECAD group than in the standard medical therapy (34% vs 18.9%, $P = 0.044$) [52]. A subsequent randomized–

Table 1. Alternative treatments for the management of hepatic encephalopathy

Mechanism of action	Treatments
Gut microbiome modulation	Probiotics, prebiotics, synbiotics Fecal microbiota transplant
Ammonia detoxification	Branched chain amino acids L-ornithine L-aspartate Glycerol phenylbutyrate Zinc Sodium benzoate
Procedural	Liver support devices Liver transplantation Shunt embolization

controlled trial demonstrated similar findings of improvement in HE, though this was not statistically significant [53]. While liver support devices may be a viable option for the treatment of HE, its limited availability and high cost may prohibit routine use.

Embolization of portosystemic shunts has become a more recent procedural advancement for the treatment of refractory HE. In a retrospective study of 20 patients with refractory HE from portosystemic shunts who underwent shunt embolization, all experienced immediate improvement [54]. At 1 year, most patients (92%) experienced durable improvement without recurrent HE [54]. As discussed in the section regarding RTO and variceal bleeding, the recommendation after shunt embolization is to monitor signs of worsening portal hypertension, such as varices and ascites.

General management of ascites and spontaneous bacterial peritonitis

Ascites and terminology

Ascites is often the first decompensating event in liver disease and occurs at a rate of 5%–10% per year in patients with compensated cirrhosis [55]. An increase in lymph production and lymphangiogenesis in cirrhosis leads to an imbalance in the volume of lymph and the amount of lymph that can be returned to the systemic circulation [56]. This imbalance leads to the accumulation of fluid in the peritoneum [56]. Ascites is graded based on the amount of fluid accumulation [55]. Grade 1 is mild ascites detected on imaging alone and considered responsive to therapy and/or dietary sodium restriction, though treatment may not be necessary [55]. Grade 2 is moderate ascites, also termed recurrent ascites, which recurs on at least three separate occasions within a 12-month period despite dietary sodium restriction and adequate diuretics [55]. Grade 3 is large ascites that is refractory in nature and cannot be prevented with medical therapy alone, thus requiring paracentesis [55].

Management of ascites

Dietary sodium restriction of 2 g per day or 90 mmol per day should be employed in all patients with cirrhosis and grade 2 ascites [55]. Aldosterone antagonists—most commonly spironolactone used at doses of 100–400 mg per day—are considered the backbone of diuretic therapy [55, 57]. Loop diuretics, such as furosemide, can also be added in cases of long-standing ascites at dosages from 40 to 160 mg per day [55]. Finally, large-volume paracentesis is first-line therapy for the treatment of refractory ascites with or without albumin [55].

Albumin is routinely recommended in paracenteses with >5 L removed to prevent post-paracentesis circulatory dysfunction (PPCD) [55]. PPCD is the result of splanchnic vasodilation after paracentesis, which leads to an increase in plasma renin activity and subsequently retention of free water and sodium [58]. This underlying pathophysiology can subsequently precipitate renal injury, HE, and even death.

Albumin in refractory ascites

The most established indications for the use of albumin in decompensated cirrhosis include spontaneous bacterial peritonitis (SBP), PPCD, and HRS [59]. However, long-term albumin use may also portend a survival benefit in patients with refractory ascites. Multiple studies have been done to evaluate the role of albumin in patients with decompensated cirrhosis and ascites [59].

In the ANSWER trial, the authors randomized 440 patients with cirrhosis and medically controlled ascites to receive standard medical therapy or standard medical therapy and albumin (40 g twice weekly for 2 weeks and then 40 g weekly) [60]. Overall, the 18-month survival rate was higher in the group receiving albumin than in the group receiving standard medical therapy alone (77% vs 66%, $P = 0.028$) [60].

Another study, by Di Pascoli *et al.* [61], followed 70 patients with cirrhosis and refractory ascites, with 45 patients non-randomly assigned to 20 g of albumin twice weekly in addition to standard of care or only standard of care. The authors found that, at 24 months, mortality was lower in the group that had received chronic albumin infusions (41.6% vs 65.5%, $P = 0.032$), with a longer period without emergent hospitalization ($P = 0.008$) [62]. Patients receiving albumin also had a lower incidence of OHE, ascites, SBP, and non-SBP infections [61]. Additionally, there was a non-significant trend towards a lower risk of HRS in patients receiving albumin [62].

Long-term albumin administration may play a role in patients with refractory ascites but more data are needed to employ this in regular clinical practice.

TIPS in refractory ascites

Many comprehensive reviews and meta-analyses have highlighted the benefit of TIPS in the management of refractory ascites [62–65]. Data even support that there may be a transplant-free survival benefit in patients who receive TIPS [65–66]. Patients who have a relatively lower frequency of paracenteses may even benefit more from "early" TIPS with improved ascites control post-TIPS and transplant-free survival [66].

Additionally, TIPS does not worsen survival in patients with sarcopenia and, in fact, may even improve muscle mass in patients with decompensated cirrhosis [67–69]. Generally speaking, since the median survival drops significantly in patients with cirrhosis who decompensate, liver transplantation should be considered in patients with ascites.

Although hepatic hydrothorax is not discussed in detail in this review, its management mirrors that of ascites, with medical therapy including dietary sodium restriction and diuretics, consideration of TIPS, and/or referral for liver transplantation [55].

Primary and secondary prophylaxis of SBP

SBP is the result of bacterial translocation in a patient with cirrhosis and ascites, which ultimately leads to a bacterial infection within the peritoneum [70]. Other mechanisms that may precipitate SBP include intestinal bacterial overgrowth, impaired function of the intestinal mucosal barrier, and dampened host immune response [70]. As up to a third of patients may be asymptomatic of SBP, it is recommended that all hospitalized patients with ascites undergo a diagnostic paracentesis to rule out SBP [55, 70].

The diagnosis of SBP is made when the polymorphonuclear (PMN) count exceeds 250/mm^3. Patients with a diagnosis of SBP should be treated with IV antibiotics and, traditionally, third-generation cephalosporins have been recommended. However, multidrug resistant organisms should be considered when patients—especially those who may have a nosocomial infection—are treated [55]. As acute kidney injury is considered the greatest risk factor for predicting mortality in patients with SBP, albumin should be administered on Days 1 and 3 [55].

Secondary prophylaxis, usually with a fluoroquinolone such as norfloxacin or ciprofloxacin, is indicated, as one study demonstrated that the use of antimicrobial prophylaxis dramatically decreased the recurrence of SBP [71].

Primary prophylaxis may be considered in three particular groups of patients, as depicted in Figure 5 [55]. Spontaneous

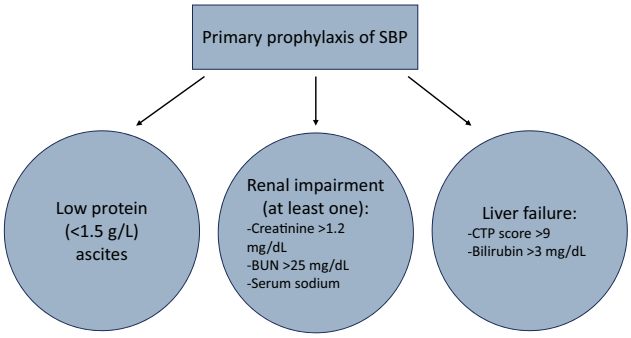


Figure 5. Indications for primary prophylaxis in spontaneous bacterial peritonitis (SBP).

bacterial empyema refers to an infection of the fluid within a hepatic hydrothorax and is managed similarly to SBP [55].

Treatment of HRS

Pathophysiology and definitions in HRS

Acute kidney injury (AKI) is a well-known predictor of mortality in patients with cirrhosis, with a 30-day mortality of ≤58% [72]. Although multiple definitions of AKI exist in the literature, the International Club of Ascites (ICA) proposed a standardized definition of AKI in patients with cirrhosis: an increase in serum creatinine of ≥0.3 mg/dL within 48 h or a percentage increase in serum creatinine of ≥50% from baseline, which is known or presumed to have occurred within the prior 7 days [73]. The incidence of AKI varies from 27% to 53% in patients with cirrhosis who are admitted for cirrhosis-related complications [74]. Of the prerenal causes of AKI, hypovolemia and HRS are the most common in patients with cirrhosis [74].

Splanchnic vasodilatation is key in the development of HRS, as this leads to effective systemic hypovolemia, thereby triggering the renin–angiotensin–aldosterone system and vasoconstrictors, ultimately leading to renal arterial vasoconstriction [75].

Previously HRS was classified as type 1 HRS and type 2 HRS but these definitions were revised by the ICA in 2014. HRS-AKI is now defined as follows: (i) diagnosis of cirrhosis and ascites, (ii) diagnosis of AKI according to ICA-AKI criteria, (iii) no response after 2 days of diuretic withdrawal and plasma volume expansion with albumin of 1 g/kg of body weight, (iv) absence of shock, (v) no current or recent use of nephrotoxic drugs, (vi) no macroscopic signs of structural kidney injury defined as absence of proteinuria (>500 mg/day), (vii) absence of microhematuria (>50 RBCs per high power field), and (viii) normal findings on renal ultrasonography [73].

New biomarkers to estimate renal function

Creatinine has been shown in multiple studies to overestimate the glomerular filtrate rate in patients with cirrhosis [76, 77]. Thus, the need for more accurate biomarkers in patients with renal impairment and cirrhosis is warranted.

One biomarker in particular—urinary neutrophil gelatinase-associated lipocalin (NGAL)—has shown quite promising results in studies in which NGAL has been increased in patients with acute tubular necrosis (ATN) compared with that in patients with hypovolemia or HRS [74]. However, its limited availability in different parts of the world has impacted its routine use.

Other biomarkers that have been studied include IL-18, albumin, KIM-1, and L-FABP, with higher values noted in patients with ATN as compared with hypovolemia and HRS [74]. Plasma levels of cystatin C may also be a predictor of the development of AKI and mortality in patients with cirrhosis [78, 79].

Management of HRS

First-line treatment for HRS is albumin, which expands the effective volume in the systemic circulation and may improve cardiac output [75, 80]. Vasoconstrictors are considered standard in the treatment of HRS-AKI, as they directly target the splanchnic arterial vasodilation [74]. There are three types of vasoconstrictors to consider: terlipressin, noradrenaline, and a combination of octreotide and midodrine [74]. The data are weakest for the use of midodrine and octreotide, as a randomized–controlled trial found that there was a much higher rate of renal recovery in patients treated with terlipressin than in patients treated with midodrine and octreotide (70.4% vs 28.6%, $P = 0.01$) [81].

Terlipressin is the most studied in HRS, though many studies were performed prior to the new definition of HRS-AKI with data suggesting that noradrenaline may be similarly efficacious [74, 82, 84]. The study that ultimately contributed to FDA approval of terlipressin for the treatment of HRS was the CONFIRM trial, published by Wong *et al.* [83] in 2021. In this trial conducted at 60 sites in the USA and Canada, a total of 300 patients with cirrhosis, HRS, ascites, and progressive renal failure were randomized 2:1 to receive terlipressin plus albumin or placebo plus albumin [83]. The primary end-point was reversal of HRS, defined as two consecutive serum creatinine measures of ≤1.5 mg/dL at least 2 h apart up to Day 14 and survival without renal replacement therapy for at least an additional 10 days [83]. The primary end-point was achieved in 32% of the terlipressin group as compared with 17% in the placebo group ($P = 0.006$) [83]. HRS reversal was noted in 39% of patients receiving terlipressin and 18% of the placebo group ($P < 0.001$) [83]. Of note, there was a higher risk of respiratory failure in the terlipressin group than in the placebo group in the trial. Thus, albumin should be cautiously used so as not to precipitate respiratory complications in patients on terlipressin [83]. Eventually, in September 2022, the FDA granted the approval of terlipressin for the treatment of hospitalized adults with HRS and rapid reduction in kidney function.

Renal replacement therapy may be considered in select patients, especially as a bridge to liver transplantation. Liver transplantation is deemed curative for HRS but consideration of simultaneous liver–kidney transplantation may be necessary in those patients who are not expected to have renal recovery after liver transplantation alone [55].

Malnutrition, frailty, and sarcopenia

Nomenclature and definitions of malnutrition, frailty, and sarcopenia

Definitions of malnutrition, frailty, and sarcopenia have now been standardized, which is a key development in addressing these syndromes that are known to have an impact on outcomes and survival in patients with cirrhosis [85]. Malnutrition results from the imbalance (deficiency or excess) of nutrients that impact body form or function, regardless of body mass index (BMI) [85]. Frailty refers to a state of decreased physiologic reserve and predisposes to adverse outcomes from health stressors [85]. Sarcopenia is defined as a progressive skeletal muscle disorder resulting in the loss of muscle mass, regardless of BMI [85].

Outcomes in frailty and sarcopenia

There are substantial data in the literature showing that frailty as assessed by tools such as the Karnofsky Performance Status (KPS) and liver frailty index (LFI) predicts waitlist mortality and

graft and patient survival post-liver transplantation [86–88]. Frailty may also have an impact on other measures such as readmissions and patient-reported outcomes such as falls, depression, and quality of life [85]. Similarly, sarcopenia is associated with worse outcomes both pre- and post-liver transplantation, including increased waitlist and post-liver transplant mortality, liver decompensation, reduction in quality of life, increased risk of infection, and prolonged hospitalization [85]. Sarcopenic obesity refers to patients with decreased muscle mass in the setting of increased fat mass and is increasingly important to address, with rising rates of metabolic dysfunction-associated steatotic liver disease (MASLD) [85].

Screening tools for malnutrition, frailty, and sarcopenia

In assessing malnutrition, many tools may be utilized; however, the Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT) has consistently demonstrated a diagnosis of malnutrition in patients with cirrhosis, which may predict outcomes [89, 90]. Frailty assessment may be accomplished by using a multitude of screening tools including the KPS, LFI, handgrip strength, and 6-min walk test [85]. Sarcopenia can be more challenging to diagnose but, currently, the gold standard for diagnosing is with computed tomography (CT) [85]. Muscle mass is reported as skeletal muscle index on CT, calculated as the total skeletal muscle area at L3 normalized to height [85, 91]. Bioelectrical impedance analysis may also be used in diagnosing sarcopenia in patients with cirrhosis [85]

Management of malnutrition, frailty, and sarcopenia

Micronutrient deficiencies in cirrhosis are common and should be routinely evaluated on laboratory analysis [92]. Vitamins A, D, E, and K, thiamine, niacin, pyridoxine, folic acid, B12, C, and other nutrients such as zinc, selenium, and copper should be monitored and supplemented in patients with cirrhosis [85]. Frailty and sarcopenia may require similar interventions to improve the conditions and are centered on a combination of aerobic and resistance exercises as well as tailored recommendations from exercise programs [85].

Finally, caloric needs must be met in order to counteract the catabolism that is inherent in decompensated cirrhosis [85]. In non-obese patients with a BMI of <30 kg/m^2, the target caloric intake is 35 kcal/kg per day. Patients with a BMI of 30–40 kg/m^2 should consume 25–35 kcal/kg per day. Patients with a BMI of >40 kg/m^2 should have a target caloric intake of 20–25 kcal/kg per day. Protein intake is also of crucial importance, with a recommended intake of 1.2–1.5 g/kg ideal body weight per day. Patients who are critically ill require even higher amounts of dietary protein, with a recommendation of 1.2–2.0 g/kg ideal body weight per day [85].

Palliative care in end-stage liver disease

Palliative care definitions

Palliative care is defined as multidisciplinary medical care that addresses the physical, spiritual, and psychosocial needs of patients with serious illness and their caregivers [93]. Palliative care can be divided into four distinct care practices, including primary palliative care, specialty palliative care, hospice, and advance care planning [93]. While palliative care may be delivered at any time in the course of a patient's illness, hospice is exclusively geared towards comfort in patients with limited life expectancy [93]. Advance care planning is a domain within palliative care that addresses medical decision-making for patients and their families longitudinally [93].

Palliative care and improved symptoms in decompensated cirrhosis

Data suggest that palliative care involvement in patients with liver disease leads to reduced resource utilization, improvement in symptoms, and clarification of goals of care [93–95]. While the study was stopped early due to reduced enrollment, Shinall *et al.* [96] conducted a randomized–controlled trial that demonstrated that palliative care intervention led to increased time to first readmission and more days alive outside of the hospital in the first 6 months after study enrollment.

Palliative care interventions

Structured communication framework and serious illness conversation prior to decompensation can be leveraged early in the illness trajectory to honor patient values [93]. While multiple pharmacologic therapies may be employed in palliative care, non-pharmacologic therapies may also be introduced to patients with decompensated liver disease such as hot/cold, physical therapy, mindfulness/meditation, behavioral strategies, or acupuncture, amongst many others [93]. Barriers such as a shortage of palliative care physicians, lack of provider training, and stigma surrounding palliative care may impede referrals to palliative care [93]. However, ultimately, palliative care involvement and co-management with hepatology may lead to improved clinical and patient-reported outcomes in patients with decompensated cirrhosis [93].

HCC

The landscape of treatments for HCC is ever evolving, especially in recent years. Though a full review is out of the scope of this article, it would be prudent to discuss major updates in the advancement of HCC management.

Evolving risk factors and surveillance for HCC

Although viral hepatitis represents a large proportion of incident cases of HCC worldwide, increased uptake of hepatitis B vaccination and treatment of hepatitis C have led to a decline in HCC in parts of the world that are known to be endemic for viral hepatitis [97]. However, this has been counteracted by a rise in obesity and metabolic syndrome across the globe with rising rates of MASLD. In fact, approximately one-fourth to one-third of MASLD-associated HCC develops in the absence of cirrhosis [98]. While a shift in demographics is occurring, the special populations that warrant surveillance for HCC have remained similar over the years. Patients who should be enrolled in surveillance for HCC include all patients with cirrhosis of any etiology and certain patients with non-cirrhotic hepatitis B (men aged >40 years from an endemic country, women aged >50 years from an endemic country, persons from Africa at an earlier age, and those with a family history of HCC or PAGE-B score ≥ 10) [98]. The most cost-effective strategy for HCC surveillance is the "tried and true" abdominal ultrasound with the addition of alpha-fetoprotein (AFP) every 6 months, which confers a sensitivity and specificity of 61% and 92%, respectively [98]. There are also emerging biomarkers such as GALAD, which includes patient age, gender, AFP-L3%, AFP, and des gamma carboxy prothrombin (DCP), that may lead to improved early detection of HCC [99]. Additionally, liquid biopsy, which refers to circulating tumor DNA, may be of use in the future to aid in the early diagnosis of HCC [98].

Diagnosis and general principles of management

Multiphase CT or magnetic resonance imaging can often confirm a diagnosis of HCC, obviating the need for a biopsy. The Liver Reporting and Data System (LI-RADS) classification utilizes diagnostic imaging features such as tumor size, arterial phase hyperenhancement, delayed phase washout, and capsule appearance to assign a score based on the probability that the lesion represents HCC [100]. This diagnostic algorithm has only been validated in patients who have warranted HCC surveillance, which includes patients with cirrhosis and those with non-cirrhotic hepatitis B [98, 103].

Potentially curative options for the management of HCC include surgical resection, liver transplantation, and local ablation [98, 101]. Surgical resection is often reserved for cases of non-cirrhotic HCC or those patients with compensated cirrhosis and an absence of portal hypertension [98, 101]. Liver transplantation should be considered in those patients with cirrhosis and portal hypertension who either are within Milan criteria or may be down-staged to being within Milan criteria [98, 101]. Lastly, local ablation techniques include radiofrequency ablation, microwave ablation, and cryoablation; no one technique is recommended over another [98]. Transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and external beam radiation therapy represent alternative management options as either bridging treatment or destination therapy [98].

Systemic therapy for advanced HCC

Perhaps the most profound advancement in the management of HCC has been the ongoing investigation and use of anti-angiogenic therapies and immune checkpoint inhibitors (ICIs) [98]. While many therapies have been studied over the years, FDA-approved first-line therapies for the management of HCC will be discussed here and are summarized in Table 2.

Sorafenib was the first multikinase inhibitor (mTKI) to have demonstrated an improvement in median overall survival in patients with advanced HCC compared with placebo (10.7 vs 7.9 months, respectively; HR, 0.69; 95% CI, 0.55–0.87; $P < 0.001$) [102]. Ten years later, in 2018, Lenvatinib, another oral mTKI, demonstrated non-inferiority to sorafenib in the REFLECT trial (median survival, 13.6 vs 12.3 months; HR, 0.92; 95% CI, 0.79–1.06) [103].

The IMBrave150 trial is considered revolutionary in the advancement of HCC treatment. It combined atezolizumab, an immunotherapy against PD-L1, with bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF) [104]. In this phase 3, open-label, randomized–controlled trial, patients were randomized to receive atezolizumab and bevacizumab or sorafenib [104]. The primary end-points were overall survival and progression-free survival. A total of 501 patients with HCC who were not amenable to curative or locoregional therapies or who had progressed after treatment were randomized: 336 patients to the atezolizumab–bevacizumab group and 165 patients to the sorafenib group. Overall survival at 12 months for the atezolizumab–bevacizumab and sorafenib groups was 67.2% and 54.6%, respectively [104]. The median overall survival for the atezolizumab–bevacizumab group was 19.2 months [104], which surpasses the median survival for all other approved first-line therapies for HCC [98, 104].

In the HIMALAYA phase 3 trials, 1,171 patients were randomized to tremelimumab plus durvalumab (termed STRIDE), durvalumab, or sorafenib groups, with a primary end-point of overall survival for STRIDE vs sorafenib [105]. The median overall survival was 16.43 months (95% CI, 14.16–19.58 months) in the STRIDE group and 13.77 months (95% CI, 12.25–16.13 months) in patients who received sorafenib. Durvalumab monotherapy also demonstrated non-inferiority to sorafenib. There was no significant difference in progression-free survival amongst the three groups [105].

Of note, the clinical trials that were discussed above included patients with good performance status and CTP class A liver disease. However, some patients with CTP class B liver disease may be eligible for the approved systemic therapies [98].

While the discussion on HCC in this review was brief, the investigation and approval of systemic therapies have led to a paradigm shift in the management of HCC. Emerging therapies and sequential treatment are areas of interest within the field and will continue to change the way in which we approach the treatment of HCC.

Table 2. Overall survival for first-line therapies in the treatment of hepatocellular carcinoma

Study, reference	Systemic therapy	Overall survival (months)	Hazard ratio	95% CI
SHARP [102]	Sorafenib	10.7	0.69	0.55–0.87
	Placebo	7.9		
REFLECT [103]	Lenvatinib	13.6	0.92	0.79–1.06
	Sorafenib	12.3		
IMBrave150 [104]	Atezolizumab + bevacizumab	19.2	0.66	0.52–0.85
	Sorafenib	13.4		
HIMALAYA [105]	Tremelimumab + durvalumab	16.43	0.78	0.65–0.93
	Sorafenib	13.77		

CI = confidential interval.

Conclusions

Procedural technique advancements and an introduction of novel concepts in the management of decompensated cirrhosis have advanced the field in end-stage liver disease. Updates have been reflected in new guidelines by AASLD and European Association for the Study of the Liver (EASL) and the adoption of nomenclature to better represent the clinical entities faced by patients with decompensated liver disease. Emerging therapies and techniques in the management of cirrhosis and HCC will contribute to improved care and prognoses for patients with chronic liver disease. Despite the strides made, many areas of study and research remain and warrant further investigation to help our patients with decompensated liver disease.

Authors' Contributions

J.S., S.S.: study concept and design, and analysis and interpretation of data; J.S.: acquisition of data; S.S.: study supervision; J.S., M.E., and S.S.: drafting of the manuscript, critical revision of the manuscript for important intellectual content, and administrative, technical, or material support. All authors read and approved the final manuscript.

Conflicts of Interest

S.S. is in the speaker bureau for Salix, Eisai, Takeda, and AbbVie. He is also a speaker and advisor to Mallinckrodt and Gilead.

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