Management of Portal Hypertension

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Portal hypertension is the cause of the clinical complications associated with cirrhosis. The primary complications of portal hypertension are ascites, acute variceal bleed, and hepatic encephalopathy. Hepatic venous pressure gradient measurement remains the gold standard test for diagnosing cirrhosis-related portal hypertension. Hepatic venous pressure gradient more than 10 mmHg is associated with an increased risk of complications and is termed clinically significant portal hypertension (CSPH). Clinical, laboratory, and imaging methods can also aid in diagnosing CSPH non-invasively. Recently, deep learning methods have been demonstrated to diagnose CSPH effectively. The management of portal hypertension is always individualized and is dependent on the etiology, the availability of therapies, and the degree of portal hypertension complications. In this review, we discuss the diagnosis and management of cirrhosis-related portal hypertension in detail. Also, we highlight the history of portal hypertension and future research areas in portal hypertension. (J Clin Exp Hepatol 2022;12:1184–1199)

Portal Hypertension

Portal hypertension is an increase in portal venous pressure above 5 mm Hg. Cirrhosis is the most common cause of portal hypertension. Non-alcoholic fatty liver disease (NAFLD), alcohol misuse, and viral hepatitis are the common causes of cirrhosis.[1,2] In cirrhosis, a structural component driven by liver fibrosis and a dynamic component characterized by increased hepatic vascular tone leads to increased intrahepatic resistance, which in turn causes portal hypertension. Portal hypertension leads to the release of vasodilators such as nitric oxide (NO), which consequently leads to splanchnic vasodilation, decrease in effective arterial blood volume and blood pressure, activation of the renin-angiotensin-aldosterone system, and sodium and water retention. A hyperdynamic circulation ensues, further worsening portal pressure.

Keywords: history, ascites, acute kidney injury, vasoconstrictors, hemodynamics

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Abbreviations: ACLF: acute-on-chronic liver failure; AKI: acute kidney injury; APRI: AST to platelet ratio; AST: aspartate transaminase; BB: Beta blocker; BRTO: balloon occluded retrograde transvenous obliteration; CKD: chronic kidney disease; CSPH: clinically significant portal hypertension; CT: computed tomography; GFR: glomerular filtration rate; GOV: gastrpoesopahegal varices; HE: hepatic encephalopathy; HRS: hepatorenal syndrome; HVPG: hepatic venous pressure gradient; ICG: indocyanine green; LOLA: L-ornithine L-aspartate; NAFLD: Non-alcoholic fatty liver disease; SBP: spontaneous bacterial peritonitis; SGLT2I: sodium glucose co-transporter 2 inhibitors; SSM: splenic stiffness measurement; TE: transient elastography; TIPS: transjugular intrahepatic portosystemic shunt; VITRO: von Willebrand factor to platelet counts

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The main clinical complications due to these pathophysiological changes are:[3]

- Ascites and associated complications such as hepatic hydrothorax, spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome (HRS)
- Variceal hemorrhage
- Hepatic encephalopathy (HE)

The cause of portal hypertension can be pre-hepatic (portal vein thrombosis, idiopathic portal hypertension, or non-cirrhotic portal fibrosis) or post hepatic (Budd-Chiari syndrome and heart failure). In this review, we will focus on the diagnosis and management of portal hypertension, which develops as a result of cirrhosis.

History of Portal Hypertension

Andreas Vesalius was the first to demonstrate the pictorial graphic of the portal circulation. Rene Laennec coined the term cirrhosis in 1819. Didier Lebrec published the first trial on propranolol for portal hypertension. Since then, there has been significant progress in the management of portal hypertension. Some of the landmark years in the history of portal hypertension are described in Table 1.

DIAGNOSIS OF PORTAL HYPERTENSION

In patients with compensated cirrhosis, the diagnosis of portal hypertension and risk stratification based on portal pressure is necessary for prognostication and to determine the therapeutic approach to prevent hepatic decompensation. We will discuss the hepatic venous pressure gradient (HVPG), the gold standard for the diagnosis of portal hypertension, and other non-invasive and invasive surrogates.

Table 1 History of Portal Hypertension.

Andreas Vesalius in Latin, (Bruxelles, 1514— Zante, 1564)- Bleeding hemorrhoids and dilated portal veins-first picture of the portal venous system.
1665, Marcello Malpighi and Francis Glisson: Anatomy of portal venous circulation
1761, Giovan Battista Morgagni-GI hemorrhage from stomach in a patient with altered liver
1819, Renè Laennec-coined the term cirrhosis
1903, Rutherford Morssion: Omentopexy for ascites
1906, Nicolas Augustin Gilbert and Maurice Villaret, introduced the term portal hypertension
1930, K Westfal and 1947, LG Rowntree: Direct pressure on bleeding varices using balloon catheter
1936, Clarence Crafoord and Paul Frenckner: Sclerotherapy for esophaegal varices. Later popularized by J Terblanche in 1979
1937, WP Thompson and AO Whipple demonstrated portal hypertension as a cause of varices in cirrhosis
1937, Nicholas Eck: Side to side portocaval shunt
1945, Allen O Whipple: Splenorenal shunts.
1974, HH LeVeen L Peritoneo-venous shunt
1950, RW Sengstaken and AH Blakemore balloon tamponade for bleeding esophageal varices.
1967, Warren: Distal splenorenal shunt for bleed
1969, Josep Rosch-Transjugular portal venography and radiologic portocaval shunt
1980, Didier Lebrec: Propranolol for portal hypertension
1982, R.F. Colapinto: Balloon dilated TIPS using Gruntzig catheter
1983, Guido Banti: Splenomegaly is the cause of cirrhosis and anemia
1984, E. Olson Transrenal-Vein Reflux Ethanol Sclerosis for gastric varices
1986, JC Palmaz: Created stents for intrahepatic portocaval shunts
1989, G. M Richter:Palmaz stents for TIPS
1990, First BAVENO Consensus
1992, GV Stiegmann and JS Goff: Ligation for esophaegal varices.
1996, ZA Saeed: Multiband ligator for ligation of varices
1996, H. Kanagawa coined the term BRTO for fundal varices obliteration

Abbreviations: BRTO, balloon occluded retrograde transvenous obliteration; TIPS, transjugular intrahepatic portosystemic shunt.

HVPG

HVPG is a surrogate for portal pressure and is the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP). WHVP is a measure of hepatic sinusoidal pressure and is measured by extending a balloon catheter to the farthest branches of the hepatic vein. Here, occluding the vein with balloon inflation results in a column of blood with equal pressure to the preceding vascular territory, i.e., hepatic sinusoids. WHVP should be measured in triplicate for one minute without instability for 20 s. WHVP correlates well with portal pressure, especially in viral and alcohol-related cirrhosis. FHVP is a measure of systemic pressure and is subtracted from WHVP to obtain HVPG. FHVP should be measured within 2–3 cm of hepatic vein-inferior vena cava confluence.

Portal pressure is useful in the risk stratification of cirrhosis and has therapeutic implications. Clinically significant portal hypertension (CSPH) or HVPG ≥10 mmHg, is a key event in patients with compensated cirrhosis as it is associated with increased risk of decompensation, death, development of varices, and hepatocellular carcinoma.[4] It is in patients with CSPH, non-selective beta-blockers (NSBBs) are indicated to increase decompensation-free survival. Despite the wide applicability of the concept of CSPH as a prognosticator in compensated cirrhosis, it is important to note that patients with NAFLD and PBC may decompensate at lower HVPGs. Severe portal hypertension (≥12 mm Hg) and very severe portal hypertension (≥16 mmHg and above) have been linked to worse outcomes including acute variceal hemorrhage, encephalopathy, ascites, and postsurgical decompensation.[5,6] Changes in portal pressure have additional prognostic importance. A decrease in HVPG in response to NSBBs has been shown to prevent the first variceal hemorrhage, development of ascites and death. Changes, as small as 1 mmHg in HVPG, are associated with increased or decreased risk of decompensation and death. The demonstration of decrease in portal pressure is the principal end point used in studies to show the effect of portal pressure-lowering drugs. Though HVPG is accepted as the gold standard for portal pressure measurement, it has limitations. First, it correlates well with portal pressure in viral and alcohol-related cirrhosis (R = 0.92) but not as well in fatty liver disease (R = 0.61). Second, in 10% of patients with histologic cirrhosis, HVPG is normal. And lastly, HVPG is invasive, expensive, requires a specialized operator, and is available only in select centers, limiting its practical clinical utility. Thus, the diagnosis of portal hypertension and CSPH with non-invasive methods is of immense practical significance and is widely used clinically.

Non-invasive Tests in Patients With Compensated Cirrhosis

Spider nevi, splenomegaly, and visible abdominal portosystemic collaterals are clinical signs of CSPH. CSPH can also be diagnosed by the presence of porto-systemic collaterals or reversal of blood flow in the portal vein on imaging modalities. However, the absence of these features does not rule out CSPH.[7] In the past decade, there has been significant progress in the development of non-invasive tests for the diagnosis of portal hypertension (Figure 1). Depending

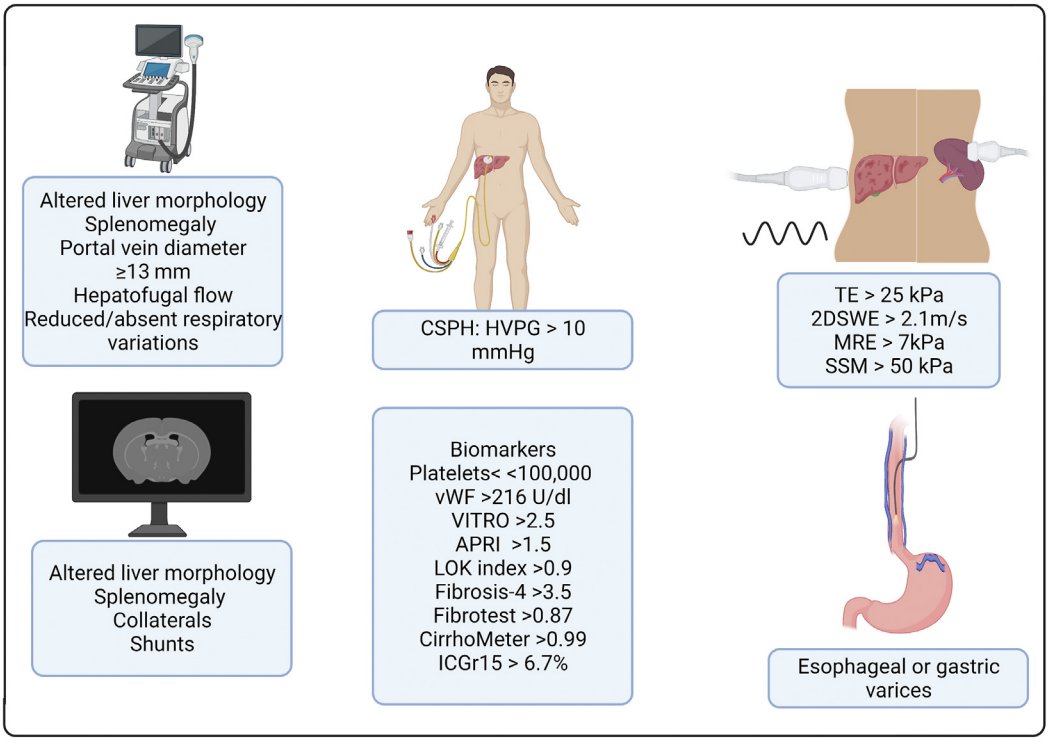

Figure 1 Non-invasive methods for diagnosis of portal hypertension. HVPG, hepatic venous pressure gradient; APRI, AST to platelet ratio; ICGr, indocyanine green retention test; TE, transient elastography; SWE, shear wave elastography; MRE, magnetic resonance elastography; SSM, splenic stiffness measurement; CSPH, clinically significant portal hypertension; vWF, Von Willebrand factor.

upon their availability, several elastographic and laboratory tests have been incorporated into clinical practice.

Elastography

Liver stiffness (LS) as measured by transient elastography (Fibroscan) is widely used in clinical practice and can aid in diagnosing CSPH. In a meta-analysis of 11 studies, the sensitivity of LS as measured by TE was 87.5% and the specificity was 85.3% for the diagnosis of CSPH with an area under the curve (AUROC) of 0.9.[8] A cut-off of 21 kPa has more than 90% specificity to diagnose CSPH.[9] A liver stiffness below 15 kPa and platelet count above 150,000 can definitely rule out CSPH in most etiologies. Based on Baveno VII criteria, in patients with virus-related, alcohol-related, and NAFLD (non-obese) compensated advanced chronic liver disease, LS measured by transient elastography above 25 kPa is sufficient to rule in CSPH.[10] However, as demonstrated in the ANTICIPATE study, liver stiffness measured by transient elastography between 20 and 25 and platelet count below 150,000 would also be sufficient to rule in CSPH.[11] However, in obese patients with NAFLD, liver stiffness cut off of 25 kPa has only a 62.8% positive predictive value in ruling in CSPH. For these patients, a new model incorporating body mass index and a nomogram to better predict CSPH has been proposed.[12]

Other elastographic techniques, such as two-dimensional shear wave elastography have an excellent sensitivity and specificity for diagnosing CSPH.[13] However, their use is limited by considerable heterogeneity in cut-offs, techniques, and protocols for diagnosis at each center.[13]

Significant changes in splenic architecture have been utilized to assess the degree of portal hypertension.[14] Spleen stiffness measurement (SSM) correlates well with the presence of esophageal varices and CSPH, as demonstrated recently in a meta-analysis of 32 studies.[15] This is particularly helpful when liver stiffness is between 15 and 20 kPa.[14] A spleen stiffness <21 kPa rules out CSPH while a value ≥ 50 kPa rules in CSPH.[10] However, SSM requires a dedicated device and may not replace the well-validated liver stiffness measurement that is readily available at most major centers.

Common Laboratory Measures

In portal hypertension, the splenic sequestration of platelets and suppression of thrombopoietin by tumor necrosis factor leads to thrombocytopenia, which is the most common sign of portal hypertension.[16] While a normal platelet count cannot be used to rule out the presence of portal hypertension.[3] A platelet count <100,000/mL is strongly associated with the presence of CSPH.[17] Several other serum biomarkers like aspartate transaminase to platelet ratio index, LOK index, fibrosis-4 score, and fibrotest, can accurately predict cirrhosis but are less sensitive to diagnose portal hypertension.[18–21] These tests should be

used in combination with others, and relying solely on these blood tests to rule out CSPH is not currently recommended.

CirrhoMeter, a composite score of platelet count, prothrombin index, aspartate transaminase, α2-macroglobulin, hyaluronate, urea, age, and sex with a coefficient different from FibroMeter can also diagnose large esophageal varices, which in turn is a surrogate for CSPH.[22] A CirrhoMeter score >0.99 would predict high-risk esophageal varices, and a score ≤0.21 would rule out high-risk varices.

Other Laboratory Tests

The ratio of von Willebrand factor to platelet counts (VITRO) has been studied as another non-invasive laboratory-based marker for portal hypertension. A VITRO ≥2.5 is a significant predictor of decompensation and mortality in patients with compensated cirrhosis irrespective of the etiology.[23] However, in patients with hepatitis C-related compensated cirrhosis who achieve sustained virologic response, a VITRO score ≥2.1 increases the risk of decompensation. Indocyanine green (ICG), a water-soluble dye, is exclusively removed by the liver after an active uptake. ICG clearance correlates with the hepatocyte blood flow and function. ICG retention at 15 s (ICG-r15) ≥ 6.7% can rule in CSPH, while a value < 10% can rule out large esophageal varices and values ≥ 23% can predict long-term decompensation events.[24,25]

Endoscopic Techniques

As previously discussed, an HVPG of 10–12 mm Hg is necessary for the development of gastroesophageal varices. Thus in patients with cirrhosis, the diagnosis of varices establishes the presence of CSPH. Esophageal capsule endoscopy can help in the diagnosis of esophageal varices. However, capsule endoscopy is not economical and ubiquitously available.[22]

Imaging Modalities

Computed tomography (CT)-based liver surface nodularity (LSN) score is another imaging modality to detect CSPH.[26] It is hypothesized that cirrhotic nodules visible on CT imaging progressively increase in size and number in cirrhosis and correlate with CSPH. The LSN score is the average distance between each pixel of the detected surface of the liver and a mathematically smoothened line derived from the detected surface that is designed to mimic a normal smooth liver surface. In the validation cohort of this study, an LSN score of 2.8 showed a positive predictive value of 86% for the detection of CSPH.[26]

The use of subharmonic aided pressure estimation (SHAPE), a form of contrast-enhanced ultrasonography, has shown promise in the diagnosis of portal hypertension in patients with chronic liver disease. In a small study, the SHAPE gradient between hepatic and portal vein has been shown to have a good agreement with HVPG (R = 0.82).[27]

Recently, artificial intelligence (AI) has been harnessed to diagnose CSPH. In a deep convolutional neural network (CNN) analysis of CT and magnetic resonance images of liver and spleen, the AUROC to diagnose CSPH was 0.9.[28] This needs to be validated in further studies. Other examples are AI algorithms using platelet count, portal vein diameter, and splenic width to diagnose esophageal varices and 3D reconstruction of portal vein models and computational fluid dynamics from computed tomographic angiography to determine virtual HVPG.[29–31] Further studies are needed to validate these findings.

Key message: HVPG is the gold standard test for the diagnosis of cirrhosis-related portal hypertension. LS measurement and platelet counts are the simplest non-invasive surrogates of portal hypertension commonly used in practice.

MANAGEMENT OF ACUTE COMPLICATIONS OF PORTAL HYPERTENSION

In this section, we will discuss the management of acute, life-threatening complications or portal hypertension, namely variceal hemorrhage, hepatorenal syndrome-acute kidney injury (HRS-AKI) and HE.

Variceal Hemorrhage

Variceal hemorrhage, mainly from esophageal or gastric varices, is a life-threatening acute decompensating event associated with 10%–20% mortality at six weeks.[32–34] The main goals in the management of acute variceal hemorrhage are to control bleeding and prevent early rebleeding and death. Varices outside the gastroesophageal region such as the rectum, duodenum, and at surgically created sites (e.g. stomal) are uncommon (<5% variceal bleeding) and are referred to as ectopic varices. The management of ectopic varices is determined by the anatomy of varices and availability of angiographic and/or endoscopic skills on a case-by-case basis.

As in any gastrointestinal bleeding, the initial steps involve adequate volume resuscitation with consideration to patient age, ongoing blood loss, cardiovascular disorders, and hemodynamic stability. Excessive volume resuscitation can increase portal pressure in variceal bleeding, which can worsen bleeding or cause early rebleeding.[35] Unique to the management of variceal bleeding in cirrhosis is thus a cautious, restrictive transfusion strategy of 7–9 gm/dL, which is associated with improved survival.[36] Elevated INR in cirrhosis is not an accurate reflection of bleeding tendency and does not warrant additional blood products.[37,38] The use of fresh frozen plasma or factor VII transfusion to correct the elevated prothrombin time has shown to have no additional benefits in variceal

bleeding and can be potentially harmful.[34,39] No specific data are available to guide platelet or cryoprecipitate administration in the management of acute variceal bleeding.[37]

Bacterial infections are very common in patients with cirrhosis and gastrointestinal bleeding and are associated with poorer clinical outcomes, including 6-week mortality.[40] Short-term (maximum 7 days) and early initiation of broad-spectrum antibiotics (such as ceftriaxone 1 gm IV every 24 h) is associated with decreased risk of rebleeding and death, especially in patients with advanced (Child C) cirrhosis.[5,41] Local resistance patterns and antimicrobial policies should be considered in determining adequate antibiotic coverage.

The early initiation of vasoactive peptides (before endoscopy) is associated with improved outcomes in variceal hemorrhage.[42] Somatostatin and its analogue octreotide, and terlipressin, a vasopressin analogue is the main vasoactive peptides used in the management of variceal hemorrhage. These should be continued for 2–5 days. A meta-analysis of 30 randomized controlled trials investigating the use of somatostatin, vasopressin, and their analogs in variceal hemorrhage found that their use is associated with improved survival, decreased transfusion requirements, improved control of bleeding, and shorter hospital stay.[43] Somatostatin, octreotide, and terlipressin are comparable in efficacy and safety in the control of variceal hemorrhage defined by five-day treatment failure.[44]

Upper GI endoscopy is definitive in diagnosing and managing suspected variceal hemorrhage.[3] Patients with suspected variceal hemorrhage should undergo an endoscopy after hemodynamic resuscitation within 12 h. Prior to endoscopy, the infusion of 250 mg IV erythromycin to clear the stomach of blood is suggested. Intubation in patients with altered mental status should be considered with the goal of extubation as soon as the bleeding is controlled. Band ligation is the definitive therapy for esophageal varices and gastroesophageal varices (GOV) type 1. Sclerotherapy is recommended for bleeding from isolated gastric varices and GOV type 2. All patients should undergo contrast-enhanced cross-sectional imaging to exclude portal vein thrombosis and hepatocellular carcinoma. This imaging study will also be useful for planning pre-emptive transjugular intra-hepatic portosystemic shunt (pTIPS). Patients with Child-Pugh class C (<14 points) or Child-Pugh class B (>7 points) with active bleeding or HVPG >20 mmHg during variceal bleed have a high risk of rebleeding and should be considered for the placement of pTIPS in 24–72 h.[10] pTIPS does not increase the risk of hepatic encephalopathy or worsening of ascites.[45] ACLF, HE, and hyperbilirubinemia at admission should not be considered as a contraindication for pTIPS as per the recent guidelines[10] (Figure 2).

In case of failure to control bleeding or refractory bleeding despite pharmacologic and endoscopic therapy, tamponade with Sengastaken-Blakemore or Minnesota tube can be considered as a bridge to more definitive therapies such as TIPS. Balloon occluded retrograde transvenous obliteration (BRTO) can be considered for GOV2, isolated gastric varices or ectopic varices depending on variceal anatomy and availability of local expertise.

Key message: Endoscopy should be performed after initial hemodynamic resuscitation and pharmacotherapy with vasoactive peptides.

HRS

HRS is a form of kidney injury due to a decrease in renal blood flow occurring in patients with cirrhosis and ascites.[46] HRS portends poor survival and represents a state of further decompensation in patients with decompensated cirrhosis (history of uncomplicated ascites, variceal hemorrhage or encephalopathy).[47,48] HRS can be classified as HRS-AKI and HRS-non-acute kidney injury. HRS-AKI is a rapidly developing AKI defined as an increase in serum creatine by ≥ 0.3 mg/dl within two days or ≥50% from baseline value and/or decrease in urinary output ≤0.5 ml/kg in ≥6 h in patients with cirrhosis and ascites with no other evident cause for acute renal injury such as shock or nephrotoxins.[46] Liver transplantation is the definitive therapy for HRS. Pharmacologic therapy aiming at HRS reversal, i.e., improvement in serum creatinine, has been typically used to bridge liver transplantation. Vasoconstrictors and albumin are the primary pharmacological agents for the treatment of HRS.[46,48] Vasoactive peptides -terlipressin, octreotide, and noradrenaline are three vasoconstrictors used in the treatment of HRS. Albumin is an essential adjunct to vasoconstrictor therapy that acts as a plasma expander, improves cardiac index, binds to nitrous oxide and other deleterious cytokines, and reduces plasma renin and aldosterone level.[49] Vasoactive peptides for HRS should be initiated early as the most significant positive predictor of response to therapy is lower baseline creatinine.[50,51]

Terlipressin is the most investigated drug for HRS and is the preferred first-line treatment for HRS-AKI.[47] Multiple clinical trials and metanalyses have demonstrated the efficacy of terlipressin and albumin in HRS reversal (reduction in serum creatinine to < 1.5 mg/dL).[52] Terlipressin is associated with improved overall short-term survival, and responders to terlipressin have improved survival compared to non-responders.[53,54] A recent landmark trial that compared terlipressin to placebo demonstrated higher efficacy of terlipressin in improving renal function.[55] However, serious, adverse events, including respiratory failure, were noted in the terlipressin arm compared to placebo, probably due to a higher dose of albumin used in the trial.[55,56] In addition, terlipressin in patients with a high model for end-stage liver disease (MELD) scores is known to cause ischemic adverse events which may be life-

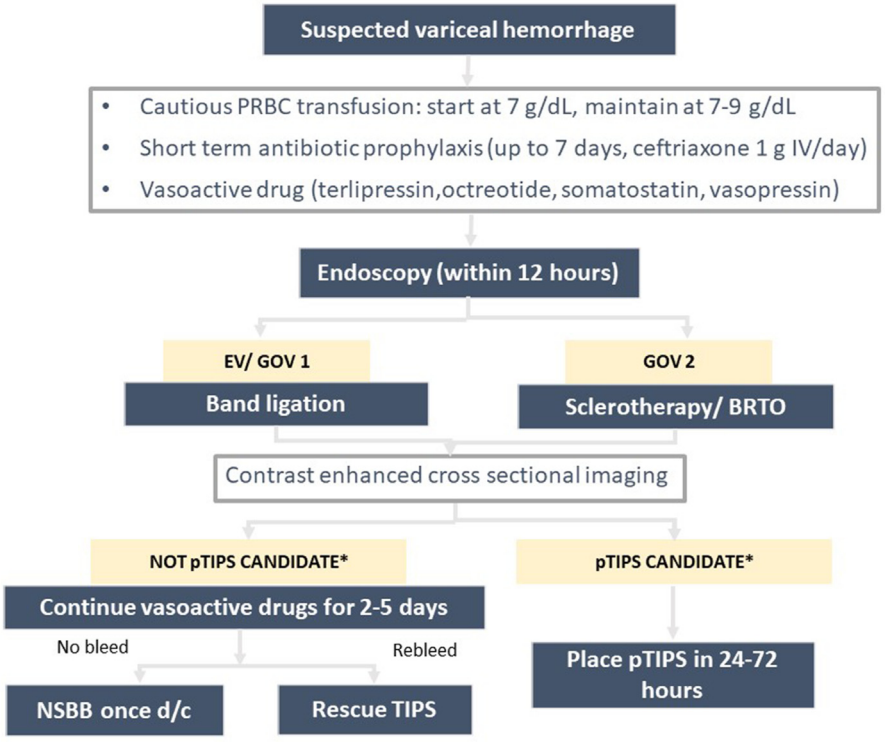

Figure 2 Management of acute variceal bleed. Patients with HVPG >20 mmHg or patients with a Child-Pugh score of 10–13 (Child class C) or Child-Pugh score of 7–9 (Class B) with active bleeding at endoscopy are high risk patients who may benefit from pTIPS. PRBC, packed red blood cells; EV, esophageal varices; GOV, gastrpoesopahegal varices; BRTO, balloon occluded retrograde transvenous obliteration; pTIPS, pre-emptive TIPS; TIPS, transjugular intrahepatic portosystemic shunt.

threatening.[56,57] Norepinephrine can be used as an alternative to terlipressin to increase the mean arterial pressure. Octreotide is used in combination with midodrine, an alpha agonist that increases blood pressure and renal perfusion. Though octreotide/midodrine is administered via the oral/subcutaneous route in a non-intensive care setting and has a favorable safety profile, it is less effective in reversing HRS than terlipressin[58].

Key message: The early recognition of HRS-AKI and initiation of treatment is critical in reversing HRS-AKI. Terlipressin is the recommended drug of choice. Octreotide/midodrine and noradrenaline are alternatives to terlipressin.

HE

HE is defined based on the underlying disease (as type A- acute liver failure; B- shunting; C- cirrhosis), grade (using West-Haven criteria), time course (as episodic; recurrent; persistent), and the presence or absence of precipitating factor.[59] The incidence of covert HE increases gradually as the disease progresses, reaching up to 80%, while overt HE is seen in up to 40% of patients with cirrhosis during illness.[59] Therefore, identifying and correcting the precipitant of HE is the most important aspect in the management of HE. Non-absorbable disaccharidases are the first-line therapy for overt HE. A recent study has demonstrated that the addition of polyethylene glycol may lead to early and sustained improvement in HE with improved survival.[60] Currently, rifaximin and intravenous L-ornithine L-aspartate (LOLA) are not recommended for overt HE treatment. However, few trials have demonstrated the efficacy of these drugs in overt HE management.[61,62] The management of HE is depicted in Figure 3.

Key message: Identifying the precipitant of HE is the key to management.

MANAGEMENT OF CHRONIC COMPLICATIONS OF PORTAL HYPERTENSION

In cirrhosis, portal hypertension can lead to chronic complications such as the development of varices, ascites, and HE. The main goals of management are to prevent recurrent variceal bleeds, control ascites, prevent further decompensation (refractory ascites, HRS or SBP), and prevent exacerbations of hepatic encephalopathy.

Varices

Primary Prophylaxis

Beta-blockers (BBs) and endoscopic variceal ligation are the mainstay of therapy to prevent the first variceal bleed.[3]

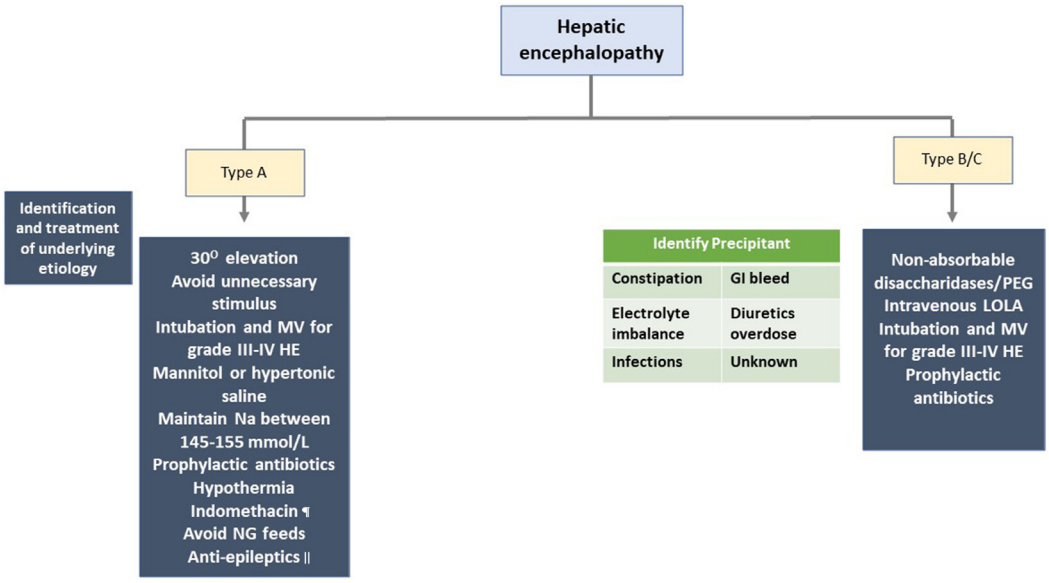

Figure 3 Management of hepatic encephalopathy. ¶ A bolus intravenous indomethacin (0.5 mg/kg) may be considered for raised intracranial hypertension and cerebral hyperemia, which does not respond to mannitol and hypertonic saline. ‖ For patients with increased intracranial pressures and progressive encephalopathy, an electroencephalogram is suggested to evaluate seizure activity and start antiepileptics accordingly. MV, mechanical ventilation; HE, hepatic encephalopathy; Na, sodium; NG, nasogastric; PEG, polyethylene glycol; LOLA, L-ornithine L-Aspartate.

BBs are economical and can prevent bacterial translocation and SBP.[63] BBs can also prevent decompensation (ascites) in patients with compensated cirrhosis and CSPH.[64] Furthermore, BB therapy may prevent the progression of portal hypertensive gastropathy, while variceal ligation is deemed to be associated with accentuation of portal hypertensive gastropathy.[65] The major concern with BB is the need for life-long therapy and regular monitoring to prevent hypotension. Carvedilol is preferred over traditional BB due to its multiple benefits. Carvedilol is 2–4 times more potent than propranolol.[66] Carvedilol has intrinsic antioxidant properties and prevents vascular smooth muscle cell proliferation. Beta-2 blockade leads to vasoconstriction in the splanchnic circulation and due to intrinsic α1-adrenoceptor blockade causes precapillary vasodilatation leading to a reduction in resistance in hepatic and portosystemic collaterals. Due to its low β1 blockade, the decrease in heart rate and cardiac output is less pronounced. Carvedilol reaches a peak plasma concentration within 60–120 min unless consumed with food when the absorption is delayed by another 60–120 min.[67] Nearly 98% of the drug is plasma protein-bound in circulation. The terminal half-life of carvedilol is 7–10 h. Carvedilol is cleared by oxidative metabolism, and the conjugates of these metabolites are excreted in feces. Only 16% of conjugates are eliminated through the renal route. Carvedilol is also effective in delaying the progression of small to large esophageal varices.[68] The recommended target to prevent variceal bleeds is a 25% reduction in heart rate or a 55–60/minute resting heart rate. The addition of ivabradine to BB can improve the hemodynamics and achieve the target heart rate with a reduced incidence of kidney injury and encephalopathy.[69] However, the role of ivabradine in preventing variceal bleed needs further studies.

Nearly 20% of variceal bleeds are due to gastric varices. GOV-1 needs to be managed similarly to esophageal varices. The management of acute gastric variceal bleed from GOV-2 and isolated gastric varices (IGV-1) is complicated, and the mortality in these patients is higher.[70] For GOV-2 and IGV-1, BB and endoscopic cyanoacrylate obliteration are the mainstay of therapy to prevent bleeds.[3,71] BB is the recommended therapy for the primary prevention of GV bleed.[47,70] However, few studies have demonstrated endoscopic cyanoacrylate obliteration to be superior to BB.[71] The data to support BRTO/TIPS for primary prevention is sparse. Recently, a study from Korea demonstrated that both BRTO and endoscopic obliteration are equally effective in preventing gastric variceal bleeds than no treatment.[72] However, this retrospective study had several concerns. Less than 30% of patients in each group were treated with BB. The study also included patients with GOV-1 for BRTO and endoscopic obliteration. The study had significant deviations from the current standard of care recommended by the American Association for the Study of the Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL).[5,47]

Key message: Patients with small high-risk varices (red signs) or small varices in Child-Pugh Class C require primary prophylaxis with BB. In contrast, those with medium to large varices can be treated with BB or EVL. BB can

prevent the decompensation and progression of varices. BB and endoscopic obliteration are equally effective for primary prophylaxis against GV bleed.

Secondary Prophylaxis

Surgical portosystemic shunting was the only effective modality in the early 1950s to prevent recurrent variceal bleeds in patients with cirrhosis. However, shunt surgery was associated with high morbidity and mortality. Propanolol was the first drug demonstrated to be effective in preventing recurrent bleeds from esophageal varices.[73] Since then, BBs have become the standard of care for preventing recurrent variceal bleeds. Reduction in HVPG by ≥ 20% from baseline or reduction to <12 mmHg leads to reduced incidence of variceal rebleeding, ascites, SBP, HRS, and hepatic encephalopathy.[74] Endoscopic variceal ligation with BB (propranolol and nadolol) is the recommended therapy to prevent recurrent variceal bleeds.[3] A small trial has compared carvedilol + EVL vs. propranolol + EVL for secondary prevention of AVB.[75] A higher number of patients in the carvedilol group achieved HVPG response though the incidence of recurrent bleed was similar in both groups.[75] BBs are also associated with reduced waitlist mortality in patients with refractory ascites and variceal bleeds.[76] However, the safety of beta-blockers in patients with advanced cirrhosis is still contentious.

TIPS is currently recommended for patients who fail EVL + NSBB; however, a recent meta-analysis has demonstrated significant mortality benefit with early TIPS defined as placement of the stent within five days after variceal bleed.[77] In addition, early TIPS is also associated with a reduction in the incidence of recurrent variceal bleed (at 1-year) without the added risk of hepatic encephalopathy.[77] Likewise, pTIPS has also been demonstrated to be safe and effective in preventing recurrent variceal bleed and improving mortality in patients with cirrhosis who are at high risk of bleeding (as discussed above).[78] TIPS is also documented to be safe in patients with ACLF. A recent multicenter study demonstrated the safety of pTIPS in patients with ACLF identified by EASL criteria.[79] pTIPS was associated with improved survival and reduced rebleeding rates.[79] However, this retrospective study had several drawbacks.[79,80] Only 6% of patients with ACLF underwent pTIPS. Patients with lower MELD scores and ACLF grades were chosen for TIPS, and the study failed to assess the hemodynamic response to pTIPS in patients with ACLF. Hence, further data are required to assess the safety of pTIPS in patients with ACLF.

TIPS is more effective than cyanoacrylate injection to prevent GV rebleeding, especially in patients with high portal pressure gradients.[81,82] However, TIPS is associated with an increased risk of hepatic encephalopathy and liver failure due to shunting of blood away from the liver. BRTO may be more effective than TIPS in preventing rebleeding from gastric varices and is associated with improved survival.[83] A study is underway comparing endoscopic cyanoacrylate obliteration against BRTO (ClinicalTrials.gov Identifier: NCT02468206). Nearly 20% of patients do not have gastro- (spleno) renal shunts making them less amenable to BRTO.[84] Endoscopic ultrasonography (EUS) guided coiling with or without glue is also effective in preventing rebleeding.[85] However, the expertise to perform these expensive radiological procedures are not available at all centers. Endoscopic obliteration with or without BB is recommended therapy to prevent GV rebleeding in the absence of expertise for TIPS and BRTO.[5,86,87]

Key message: Endoscopic obliteration with BB or BRTO/TIPS is effective for preventing rebleeding from fundal varices. EUS guided coiling can be performed in patients without shunts (Figure 4).

Ascites (Figure 5)

Ascites is the most common decompensation in the natural history of cirrhosis.[47,88] Dietary sodium restriction (5 g salt or 90 mmol of sodium) and oral diuretics are the first-line treatment for uncomplicated ascites. A combination of aldosterone antagonists and loop diuretics is preferred over sequential treatment with aldosterone antagonists followed by loop diuretic.[89] Combination therapy is well tolerated and is associated with better control of ascites than sequential therapy.[89] Early introduction of short-course midodrine can also lead to better control of ascites with lesser incidence diuretic associated complications.[90]

Refractory Ascites

Diagnosis and medical management: A mean weight loss of <0.8 kg over 4 days and urinary sodium less than sodium intake in a patient with cirrhosis on intensive diuretic therapy (furosemide 160 mg/day and spironolactone 400 mg/day) for at least one week is termed as diuretic resistant ascites.[47] Conversely, any patient developing adverse events due to diuretics limiting the further use of diuretics are labeled as diuretic refractory ascites. Hepatocellular carcinoma, portal vein thrombosis, and infection should be ruled out before labeling refractory ascites. Most patients are diuretic intolerant ascites.[91] Furthermore, a full dose of 160 mg of furosemide and 400 mg of spironolactone is rarely tolerated.[90,92] The impaired tolerance, especially in Asian populations, is attributable to sarcopenia and a higher incidence of diuretic-induced complications like acute kidney injury, dyselectrolytemia, or encephalopathy.[90,93]

The incidence of tuberculosis is relatively high in Asian countries.[94] It is suggested to perform adenosine deaminase level testing and tuberculosis nucleic acid testing for all cirrhotic patients before labeling refractory ascites.[93] Recent reports suggest that patients with an ascitic fluid total protein content of >2 g/dl should be evaluated for tubercular ascites.[95]

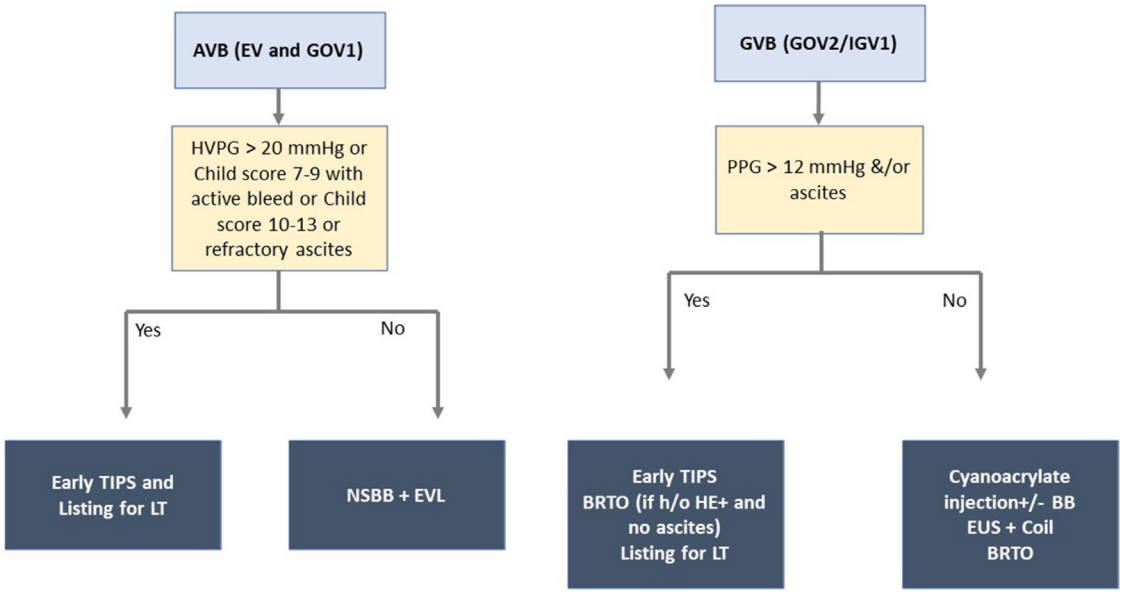

Figure 4 Secondary prophylaxis to prevent rebleeds. AVB, acute variceal bleed; EV, esophageal varices; GOV, gastroesophageal varices; HVPG, hepatic venous pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt; LT, liver transplantation; NSBB, non-selective beta-blocker; EVL, endoscopic variceal ligation; GVB, gastric variceal bleed; PPG, portal pressure gradient; BRTO, balloon occluded retrograde transvenous obliteration; HE, hepatic encephalopathy; EUS, endoscopic ultrasonography.

Large volume paracentesis and paracentesis-induced circulatory dysfunction: Liver transplantation remains the definitive therapy for patients with refractory ascites. However, liver transplantation is not feasible due to organ donor shortage and the financial burden.[96] Large-volume paracentesis with albumin is the recommended therapy to prevent paracentesis-induced circulatory dysfunction. Recently, a network meta-analysis has demonstrated midodrine to be superior to albumin in preventing paracentesis-induced circulatory dysfunction.[97,98] Due to compromised cardiac performance, beta-blockers are contraindicated in patients with refractory ascites and those undergoing large-volume paracentesis.[99–101]

Vasoconstrictors and albumin: Midodrine, an alpha1 agonist, improves urinary sodium excretion and urinary volume and has a beneficial effect in patients with

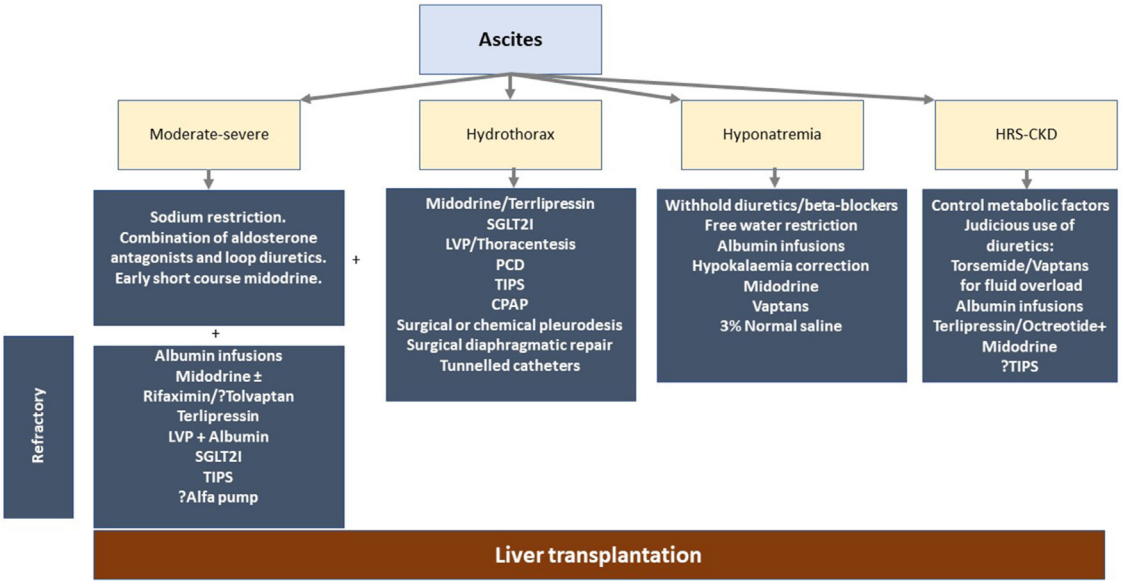

Figure 5 Management of ascites and its complications. LVP, large volume paracentesis; SGLT2I, sodium glucose co-transporter 2 inhibitors; TIPS, transjugular intrahepatic portosystemic shunt; PCD, percutaneous drainage; CPAP, continuous positive airway pressure; HRS, hepatorenal syndrome; CKD, chronic kidney disease.

refractory ascites.[102] The addition of rifaximin in patients with refractory ascites may improve hemodynamics by reducing endotoxemia.[103] Tolvaptan is also reported to improve ascites control and prolong survival.[104] However, tolvaptan depletes vitamin-K-dependent clotting factors and inhibits platelet aggregation increasing the risk of bleeds, hematomas, and ecchymosis.[105] Moreover, tolvaptan has a black box warning due to the risk of liver injury.[106] Hence tolvaptan is suggested only for patients with refractory hyponatremia in grade 3 ascites and/or refractory ascites for a short duration.[48]

Terlipressin has been shown to increase the GFR, urinary sodium excretion and contain the vasodilatory and antinatriuretic systems in cirrhotics with ascites.[53] Terlipressin administration is beneficial in patients with refractory ascites, especially those with AKI.[107,108] Terlipressin administration for a brief period of 3 weeks can improve ascites control and renal function and is suggested as an excellent non-transplant therapy.[53]

Long-term albumin administration in patients with refractory ascites improves survival. In addition, long-term albumin administration is associated with a lesser incidence of hospital admissions for overt hepatic encephalopathy, ascites, SBP, and non-SBP infections.[109] However, the cost of albumin therapy deters one from recommending it, especially in lower socioeconomic countries. A short-term albumin therapy for up to 4–8 weeks may be beneficial in outpatients to overcome the hemodynamic abnormalities.[90]

TIPS: TIPS in carefully selected patients can prolong the transplant-free survival and may be preferred over repeated large volume paracentesis.[110,111] Polytetrafluoroethylene covered stents have patency rates of 90% at two years and are preferred over bare-metal stents.[111] Age <70 years, serum bilirubin <3 mg/dl and MELD score <18 with no history of hepatic encephalopathy are excellent candidates for TIPS.

Newer therapies: The ALFA pump system consists of a subcutaneously implanted battery-powered programmable pump connected to catheters that transfer ascites from the peritoneal cavity to the bladder, from which it is eliminated.[112] Alfa pump is not available worldwide, and the currently available data are limited to suggest its use.[48] Furthermore, alfa pump is associated with higher adverse events.[112] Long-term abdominal drains are a palliative option for patients with malignant ascites and those with end-stage liver disease.[113,114]

Dapagliflozin, empagliflozin, and canagliflozin are three drugs that target Sodium-Glucose Cotransporter 2 (SGLT2) in the proximal tubule of the nephron, promoting increased excretion of both sodium and glucose in the urine.[115] The inhibition of SGLT2 in the proximal tubule promotes glycosuria and natriuresis and attenuates renin secretion, thereby improving glycemic control, reducing salt and water retention.[115,116] Few studies have reported significant improvement in ascites with SGLT2 inhibitors.[116,117] Two major drawbacks with SGLT2I are increased frequency of urinary infections and questionable role in diuretic intolerant ascites.[115,118] However, further research is required to ascertain the role of SGLT2I in patients with cirrhosis and refractory ascites.

Key message: TIPS, large volume paracentesis, and midodrine are suitable alternatives to liver transplantation for the management of ascites and its associated complications.

Hydrothorax

Hydrothorax is common in patients with ascites. The management of hepatic hydrothorax is step-wise.[119] Apart from diuretics and salt restriction, vasoconstrictors such as oral midodrine and intravenous terlipressin can be used to control hepatic hydrothorax.[53,119] Large-volume paracentesis and thoracentesis can improve pulmonary function immediately.[120,121] Alfa pump is a useful measure in controlling ascites and enhancing the quality of life of cirrhotic patients with refractory ascites.[119] Extensive trials with alfa pump should be evaluated in patients with ascites and hydrothorax. Continuous positive airway pressure (>5 cmH20) prevents the reaccumulation of fluid in pleural space. TIPS is an excellent therapeutic option for patients with favorable MELD (<15) and is associated with a response rate of nearly 75%.[122] Although effective, the percutaneous drainage of pleural effusion is associated with infectious complications. Percutaneous drainage with small catheters can be used in hospitalized patients planned for liver transplantation. Approximately 400–500 ml of fluid is drained every 4–6 hourly to prevent respiratory distress. The surgical repair of diaphragmatic defects, surgical or chemical pleurodesis (with talc or tetracycline), have been tried with variable results.[123] However, surgical procedures are poorly tolerated and are associated with higher complication rates. Indwelling catheters are recommended for palliative care.[123]

Hyponatremia

Hypervolemia is the most common cause of hyponatremia in patients with cirrhosis.[124] The first step in the management of hyponatremia is to stop diuretics after a thorough clinical examination for features of hypervolemia. Free water restriction (<1000 ml/day) is recommended only for patients with serum sodium <125 meq/dl. Human albumin solution can increase serum sodium levels in patients with cirrhosis.[125,126] Midodrine and vaptans are beneficial in treating hyponatremia.[105,127] However, the data are limited. Tolvaptan is more effective in treating hyponatremia and is preferred for patients with refractory hyponatremia in grade 3 ascites for a short duration.[48,128–130] Hypertonic saline should be avoided as it may exaggerate ascites. However, in patients with symptomatic hyponatremia with serum sodium <120 mEq/L or serum sodium <110 mEq/L, the cautious use of hypertonic saline is suggested with a target

to increase serum sodium by ≤ 8 mEq per day.[131] The plasma sodium concentration is determined by the ratio of sodium and potassium content to total body water.[132] Therefore, hypokalemia correction may improve hyponatremia.

HRS-Chronic Kidney Disease

As cirrhosis disease progresses, renal plasma flow and glomerular filtration rate gradually decline in patients with refractory ascites. CKD is in cirrhosis is associated with poor outcomes both pre-and post-transplant.[133,134] If the eGFR is less than 60 mL/min/1.73 m^2 for more than three months in the absence of structural renal disease, then the patient is labeled as HRS-CKD.[135] It is critical to differentiate HRS-CKD (functional CKD) and structural CKD as the treatment is different.[136] However, the differentiation is only by the absence of abnormal urine analysis and normal renal structure.[136] Furthermore, the cut-off of 60 ml is also affected by age and gender and may interfere with the diagnosis of HRS-CKD in elderly patients with cirrhosis. Further studies should assess novel biomarkers to identify HRS-CKD correctly. Patients who do not respond to terlipressin, patients with higher MELD, baseline serum cystatin, albuminuria, and those who develop recurrent AKI episodes progress to HRS-CKD.[137–139]

There are no clear guidelines on HRS-CKD management due to a lack of literature. Diuretic therapy should be avoided in patients with functional renal failure. If deemed necessary for fluid overload, torsemide is preferred due to lower renal clearance. Vaptans have good efficacy but should be used carefully in HRS-CKD with refractory ascites.[128] Terlipressin has excellent efficacy in HRS-CKD; however, the risk of recurrence is high and patients need to be maintained on long-term therapy.[53] Oral midodrine is used at some centers though currently, there is a lack of literature on its efficacy in patients with HRS-CKD. TIPS for HRS is still considered experimental due to the higher incidence of hepatic encephalopathy.[140] However, a recent study demonstrated a significant reduction in in-patient mortality for patients who underwent TIPS for HRS compared to those undergoing dialysis.[141] Fluid overload may be overcome with renal replacement therapy, but the optimal timing is unclear.[48] Patients with GFR <60 ml/min for >90 days and subsequent GFR <30 ml/min or requirement for dialysis are candidates for simultaneous liver-kidney transplant (SLKT). Metabolic diseases (such as hyperoxaluria, atypical hemolytic uremic syndrome, familial non-neuropathic systemic amyloidosis, and methylmalonic aciduria) with CKD, which can be corrected with liver transplant, are also candidates for SLKT.[142] On the contrary, for patients with AKI, the persistence of GFR <25 ml/min for >6 weeks and/or dialysis dependence are candidates for SLKT.[142]

HE

The presence of HE is independently associated with a significant increase in the risk of in-hospital and short-term mortality.[143] Current therapeutic options for the treatment of HE are non-absorbable disaccharides such as lactulose and non-absorbable antibiotics such as rifaximin. Other treatment options such as branched-chain amino acids, probiotics, and LOLA have also been considered. In a randomized trial of patients who had recovered from a recent episode of HE, lactulose vs. placebo for 20 months showed a higher proportion of those in placebo group experiencing recurrence.[144]

Rifaximin was shown to be effective in a study of 299 patients with 2 or more episodes of HE within 6 months. These patients were randomized to receive rifaximin or a placebo. Rifaximin significantly decreased the risk of developing HE with 22.1% in the treatment group compared with 46% in the placebo group. The use of rifaximin decreased the risk of hospitalization (13.6% vs 22.6% P = 0.01).[145] Currently, rifaximin is recommended in addition to lactulose to prevent HE after the second episode of overt hepatic encephalopathy.[146] Norfloxacin is the recommended drug of choice for SBP prophylaxis; however, it is unclear if patients on norfloxacin should also receive rifaximin to prevent HE.[47] A recent study demonstrated that norfloxacin alone effectively reduced the incidence of HE and bacterial infections in patients with ACLF.[147] However, the study reported a higher incidence of fungal infections in such patients.

Probiotics are not currently FDA-approved for the treatment of hepatic encephalopathy. However, a study reported improved recovery and reductions in the development of overt hepatic encephalopathy with VSL#3.[148]

Zinc deficiency is common in patients with cirrhosis. If this is confirmed in a patient with a history of HE, supplementation can be considered, but its role in the management of HE without underlying zinc deficiency is uncertain.[146]

Lastly, LOLA can be considered as an additional agent for the prevention of recurrent HE; however, it is not currently available in the US.[146,149] For patients with persistent HE, BRTO can be performed if there are portosystemic shunts demonstrated on CT scan.[150] For further details on the prevention and management of HE, readers are suggested to refer the review article by Sahney et al[151]

FUTURE DIRECTIONS

Large population-based studies are required to assess the incidence of portal hypertension. EUS guided portal pressure measurements in small trials have been shown to be safe and accurate for diagnosing portal hypertension.[152] However, further studies are required to evaluate its safety and compare it with HVPG. Carvedilol with EVL may be superior to traditional beta-blockers; however, large randomized

Table 2 Future Research Areas.

Population-based study to determine the incidence of portal hypertension.
EUS guided portal pressure measurement
Biomarkers of CKD in cirrhosis
Optimal timing for dialysis in AKI/CKD.
Utility of alfa-pump in clinical practice.
Target weight loss required for ascertaining appropriate diuresis in patients with ascites and hydrothorax.
Role of Artificial Intelligence in the diagnosis of portal hypertension
Simvastatin and Obeticholic acid for prevention of variceal bleeding.
Transient elastography for determining response to beta-blockers.

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; EUS, endoscopic ultrasonography.

controlled trials are needed to ascertain the same. Given the relative rarity of gastric varices compared with esophageal varices, and less robust data regarding endoscopic and clinical predictors of bleeding risk, demonstration of benefit with specific approaches to primary prophylaxis is lacking. There is a significant lack of literature on the management of gastric varices, which needs further well-controlled studies in a homogenous population. Simvastatin has pleiotropic effects and can lower portal hypertension.[153] However, the risk of rhabdomyolysis in advanced cirrhosis is a significant concern. Recent studies suggest that decompensation in NAFLD may occur with lower HVPG and the recent BAVENO guidelines suggest incorporating etiology-based treatment for patients with cirrhosis.[6] Obeticholic acid, a farnesoid X receptor agonist, is relatively safe and effective for NASH.[154,155] Obeticholic acid in preclinical models has been shown to improve portal hypertension.[156] Whether this translates into clinical utility is unknown. In patients with ascites, a weight loss of 0.5–1 kg/day is recommended. However, the amount of weight loss required for ascertaining appropriate diuresis in patients with ascites and hydrothorax is unknown. Some of the research areas in portal hypertension are mentioned in Table 2.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

AVK made the study concept and design; Initial drafting, compilation, and critical revision by AVK, AR, and AM. All members approved the final draft.

CONFLICTS OF INTEREST

The authors have none to declare.

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