Recent Approaches in Portal Hypertension Involving Risk Stratification and Medical Management

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Abstract: Portal hypertension leads to the formation of portosystemic collaterals that divert portal blood to the systemic circulation and bypass the liver, resulting in multiple severe complications. Portal hypertension has classically been diagnosed using invasive methods to calculate the hepatic venous pressure gradient. There has been a recent evolution in portal hypertension pathology emphasizing dynamic changes and integrated pathophysiology, as well as concurrent changes in medical management. There is now a focus on using less-invasive approaches to diagnose portal hypertension and novel treatments that target the various components of evolving portal hypertension pathophysiology. This article details the latest techniques in diagnosing and treating portal hypertension that are becoming cornerstones of portal hypertension management.

Keywords
Portal hypertension, liver disease, medical management, pathophysiology

Portal hypertension (PHTN) is characterized by a pathologic increase in portal venous pressure that ultimately leads to the formation of portosystemic collaterals diverting portal blood to the systemic circulation and bypassing the liver.[1] The gold standard of diagnosing PHTN is the hepatic venous pressure gradient (HVPG), which is defined as the difference between the wedged and the free hepatic venous pressures. Pressures higher than 5 mm Hg define the presence of PHTN.[2] PHTN can lead to devastating complications; the development of gastroesophageal varices and variceal hemorrhage are two of the most direct consequences.[3] To better manage this condition and help prevent complications, it is crucial to understand PHTN pathophysiology, especially as it evolves. Previously, PHTN was considered a fundamentally linear pathology, primarily involving fibrosis and vascular remodeling.[4] In recent years, PHTN has been viewed as a more dynamic disease involving complex interactions between inflammation and endothelial dysfunction.[5] With this development come corresponding advances in guidelines and management surrounding the disease process. Medical management previously focused on targeting the prevention of bleeding; however, with a better understanding of the complexity of PHTN,

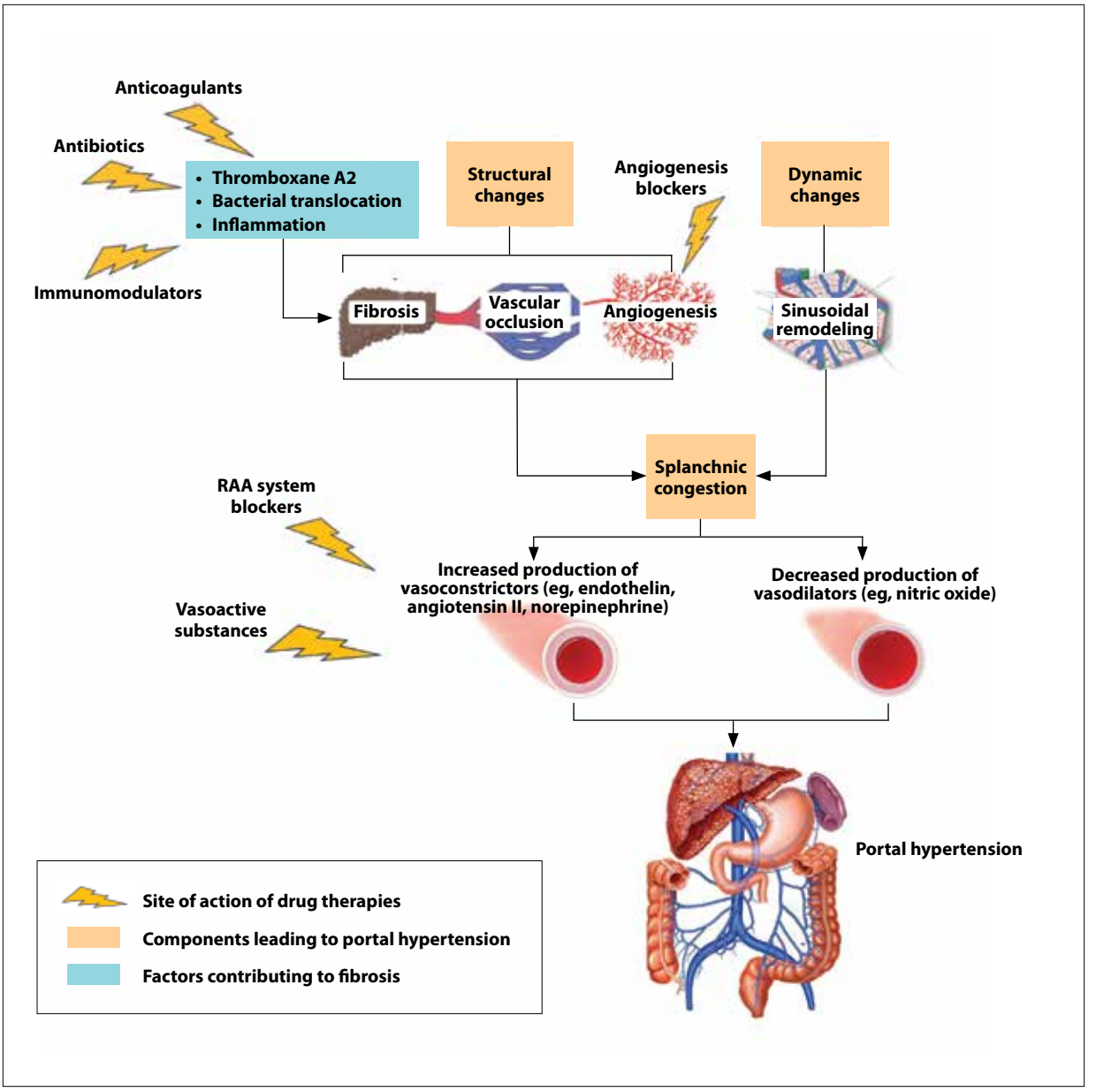

Figure. Overview of portal hypertension pathophysiology. Portal hypertension is driven by an increase in intrahepatic vascular resistance secondary to structural and dynamic changes in the liver. There are several potential novel treatments for medical management of portal hypertension, including renin-angiotensin-aldosterone (RAA) system blockers, immunomodulatory drugs, antibiotics, anticoagulants, angiogenesis blockers, and vasoactive substances.

newer targets of therapy are coming to light. Specifically, treatments are now aimed at the various substrates playing a role in PHTN, including the renin-angiotensin-aldosterone (RAA) system, inflammation, bacterial translocation, thrombosis, angiogenesis, and vasodilation. This article will highlight recent developments in PHTN diagnosis and the corresponding newest advances in its guidelines and management.

Established Understanding of Portal Hypertension Physiology

The primary cause of PHTN, particularly in cirrhosis, is an increase in intrahepatic vascular resistance secondary to structural and dynamic changes in the liver (Figure). Fibrosis, nodule formation, angiogenesis, and vascular occlusion cause structural distortion of the liver. Fibrosis

Table. Noninvasive LSM in Relation to Estimated HVPG and Clinical Correlate

LSM by TE[a]	LSM by TE clinical correlate	HVPG estimate	HVPG clinical correlate
5-9.9 kPa	Rules out cACLD (in absence of other clinical/imaging signs); possible liver fibrosis	1-5 mm Hg	Normal
10-14.9 kPa	Suggestive of cACLD No CSPH	6-9 mm Hg	Mild or preclinical sinusoidal PHTN
15-19.9 kPa	Certain cACLD Probable CSPH	≥10 mm Hg	CSPH
20-24.9 kPa	Certain cACLD High likelihood of CSPH	≥10 mm Hg	CSPH
≥25 kPa	Certain CSPH	≥10 mm Hg	CSPH

BMI, body mass index; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; kPa, kilopascals; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; PHTN, portal hypertension; TE, transient elastography.

[a]In patients with virus- and/or alcohol-related cACLD and nonobese (BMI <30) MASH cACLD, a LSM value by TE ≥25 kPa is sufficient to rule in CSPH.

is the primary determinant of intrahepatic resistance; however, dynamic and vascular components also play a role. Dynamic changes involve smooth muscle cells of the hepatic vasculature and sinusoidal remodeling through activation and contraction of endothelial cells and stellate cells, respectively.[4] The resulting splanchnic congestion leads to angiogenesis, in which the newly formed blood vessels bypass sinusoids and fail to provide oxygen and nutrients to the tissues, thus worsening the progression of PHTN.[6] Coupled with this, there is an excessive production of vasoconstrictors (eg, endothelin, angiotensin II, norepinephrine, leukotrienes, thromboxane A2) and depletion of vasodilatory substances (eg, nitric oxide). As PHTN progresses, hyperdynamic circulation and increased splanchnic blood flow begin to play a larger role.[7] The hyperdynamic circulation leads to the formation of portosystemic collateral vessels and subsequent arterial vasodilation.[8] Blood from the digestive organs diverts into the collateral vessels, and the pressure of portal blood from the splanchnic circulation increases to compensate. Arterial vasodilation occurs in the splanchnic and systemic circulations in response to local release of splanchnic vasodilators to increase blood flow to the portal vein.[8] This leads to decreased effective arterial blood volume, low mean arterial pressure, heightened activation of neurohumoral systems, increased sodium retention, and expansion of plasma volume, resulting in elevated portal pressure and circulatory dysfunction.[7] Ultimately, these effects result in multiple complications of cirrhosis, including esophageal varices, hepatic encephalopathy, and ascites. Circulatory dysfunction also results in various organ maladaptations, including hepatorenal syndrome, portopulmonary syndrome, cirrhotic cardiomyopathy, and hepatopulmonary syndrome.[5]

Updates in the Understanding of Portal Hypertension Physiology

Recent findings demonstrate that PHTN is not solely a linear process involving progressive fibrosis and the development of complications, but also a dynamic process composed of complex interactions between innate inflammatory responses and endothelial dysfunction. This process is increasingly seen in patients with superimposed inflammation, especially those with acute-on-chronic liver failure.[9] In particular, there is a strong correlation between inflammatory markers and the HVPG for reasons that are currently unclear.[10] It is, however, noted that inflammation contributes to a feed-forward cycle in which hepatocyte cell death induces inflammation, which in turn leads to further oxidative stress and vascular dysfunction. These effects eventually contribute to liver fibrosis and splanchnic angiogenesis, as liver sinusoidal endothelial cells and hepatic stellate cells increase collagen deposition around sinusoids.[9] Additionally, the gut microbiota plays an important role in PHTN. Patients with cirrhosis commonly have dysbiosis and bacterial overgrowth, partly owing to damaged intestinal barriers increasing portal translocation.[11] The microbiota affects the progression of liver disease, as gut-derived bacterial products stimulate hepatic stellate cells and Kupffer cells leading to fibrogenesis.[12] In addition, PHTN is now considered to be

a prothrombotic and prohemorrhagic condition, rather than solely prohemorrhagic as previously thought.[13] Thrombin and factor Xa activate hepatic stellate cells contributing to fibrogenesis and worsening PHTN.[14,15] With this improved understanding of the disease process, novel therapies that target these mechanisms are being introduced in this patient population.

Paradigm Shift in Terminology and Classification of Portal Hypertension Stages

As the lens used to view pathobiology of PHTN has started to shift, guidelines surrounding its diagnosis have also begun to change. The term *advanced chronic liver disease* (ACLD) is now used to refer to patients with late stages of chronic liver disease. ACLD is also used as a substitute for the term *cirrhosis*, a histologic concept that is rooted in diagnosis through an invasive procedure.[16] The determination of compensated ACLD (cACLD) is based on noninvasive tests (NITs) and is used to help predict the development of complications of cirrhosis.[17] Thus far, the gold standard of diagnosing PHTN has been the HVPG. Although pressures higher than 5 mm Hg define the presence of PHTN, pressures higher than 10 mm Hg define clinically significant portal hypertension (CSPH), in which patients may develop esophageal varices, clinical decompensation, postsurgical decompensation, and a higher risk of hepatocellular carcinoma.[16]

Advances in Diagnostic and Prognostic Methods for Detection of Portal Hypertension

The Baveno VII consensus workshop brought to light the shifting nature of PHTN management from a primarily bleeding-centric view (prevention of bleeding and rebleeding) to a more comprehensive preventive view that focuses on avoiding decompensation.[16] This entailed using NITs as HVPG surrogates, including liver stiffness measurement (LSM), biomarkers, and spleen stiffness measurement (SSM). LSM by transient elastography (TE) allows for risk stratification regardless of histologic stage. Studies have shown that LSM correlates well with the HVPG up to values of 10 to 12 mm Hg.[18]

The Table shows how LSM and HVPG measurements correlate for PHTN diagnosis. Evidence demonstrates that LSM less than 10 kilopascals (kPa) has a very low 3-year risk of liver-related events, and the 3-year risk increases substantially (5-10 times) with LSM greater than 15 kPa irrespective of ACLD etiology.[16] LSM can be repeated annually in cACLD patients for monitoring. A meta-analysis demonstrated that a 1-kPa increase in LSM is associated with an increased risk of hepatic decompensation.[19] LSM has also played a key role in advocating for the use of nonselective β blockers (NSBBs) to help prevent clinical decompensation in patients with cACLD.[16] A drawback to using LSM for PHTN diagnosis, however, is that while the correlation between LSM and HVPG values less than 10 to 12 mm Hg is excellent, it appears to be poorer for higher HVPG values.[19] This can partly be explained by the fact that early-phase PHTN is primarily linked to fibrotic modifications of the liver parenchyma, thus correlating well with LSM; however, in later stages, it is largely driven by hemodynamic changes that are not captured well with LSM.[19]

Biomarkers and radiologic scores, such as the Aspartate Aminotransferase to Platelet Ratio Index and Fibrosis-4 Score, have also been used to noninvasively detect liver fibrosis and predict large varices. Von Willebrand factor and indocyanine green clearance have also been used as indirect correlates for the HVPG. However, these tests have an overall suboptimal performance, as they modestly correlate with the HVPG and therefore are not routinely used for PHTN detection.[19]

Compared with LSM, SSM has proven to be a more direct surrogate for PHTN. SSM reflects intrasplenic congestion owing to splenic outflow obstruction, enlargement of splenic lymphoid tissue, and increased angiogenesis and fibrogenesis from PHTN. Contrary to LSM, which largely accounts for the fixed component of intrahepatic resistance, SSM reproduces the increased portal flow associated with hyperdynamic splanchnic circulation. SSM has been shown to have great capacity for predicting high-risk varices and CSPH while also helping monitor treatment response. Research has shown that SSM values above 50 kPa were associated with CSPH. SSM has even been shown to better predict a first variceal bleed and first clinical decompensation with more accuracy than LSM.[16]

Clinical Use of Transient Elastography for the Diagnosis of Portal Hypertension

TE holds great clinical value as a diagnostic and prognostic marker. LSM by TE can help act as a quick prognostic indicator for risk of decompensation and liver-related death regardless of ACLD etiology through the rule of five (10, 15, 20, 25 kPa), as outlined in the Table.[16,20] LSM and SSM also help tailor the utility of screening endoscopies through risk stratification of patients. Patients with compensated cirrhosis who are not candidates for NSBBs and have a LSM by TE of at least 20 kPa or a platelet count no more than 150×10^9/L should undergo a screening endoscopy for varices. In contrast, a

LSM of less than 20 kPa plus a platelet count of at least 150 × 10^9/L rule out CSPH in patients with cACLD; such patients can be considered to have a low probability for high-risk varices and should avoid an endoscopy.[20] In patients with virus- and/or alcohol-related cACLD and nonobese (body mass index <30) metabolic dysfunction-associated steatohepatitis cACLD, a LSM by TE of at least 25 kPa is sufficient to rule in CSPH. Finally, a clinically significant decrease in LSM, which is associated with a substantially reduced risk of decompensation and liver-related death, can be defined as a decrease in LSM of at least 20%, LSM less than 20 kPa, or any decrease to a LSM less than 10 kPa.

SSM using TE can also be used in cACLD owing to viral hepatitis (untreated hepatitis C virus; untreated or treated hepatitis B virus) to rule out and rule in CSPH (SSM <21 kPa and SSM >50 kPa, respectively). SSM of no more than 40 kPa by TE can also be used to identify patients at low probability of high-risk varices, in whom endoscopy can be avoided. NITs are less costly than the current gold standard for PHTN diagnosis (eg, HVPG), and they also help better risk stratify patients, monitor treatment response, and avoid unnecessary invasive procedures.[16]

Novel Preventive Medications for Portal Hypertension

With better understanding of PHTN and evolving clinical practice guidance, potential preventive medications such as statins and NSBBs have focused on modifying intrahepatic resistance through modulation of vasoactive substances.[21] In particular, statins, which are medications that were once thought to primarily have negative impacts on the liver through potential drug-induced liver injury, have now come to the forefront as a potential primary preventive treatment to attenuate increases in the HVPG.[11] Statins have pleiotropic effects on patients with cirrhosis. These agents improve nitric oxide availability, decrease portal pressure, and improve liver sinusoidal endothelial dysfunction.[22] These effects, in combination with the potential role of statins in slowing down liver fibrogenesis in vivo and in vitro, have helped solidify the possible use of statins in patients with cirrhotic PHTN.[23] In a large randomized controlled trial (RCT) in patients with cirrhosis and variceal bleeding, the addition of simvastatin to standard preventive therapy (endoscopic vein ligation + NSBBs) did not decrease rebleeding at 2 years but did show a decrease in mortality.[22] The survival benefit, however, was only in patients with Child-Pugh A or B cirrhosis and not in patients with Child-Pugh C cirrhosis. The study also showed that although statins are largely well-tolerated and their side effects are minimal, the risk of significant side effects did increase with higher doses.[22] Thus, statins should be encouraged in patients with cirrhosis who have an approved indication for statins because these agents may decrease portal pressure and improve overall survival. In patients with Child-Pugh B and C cirrhosis, statins should be used at lower doses and patients should be followed closely for muscle and liver toxicity. In Child-Pugh C cirrhosis, the benefit of statins has not been proven yet, and their use should be more restrictive.[20]

NSBBs have also been shown to help reduce portal pressure by decreasing cardiac output and splanchnic blood flow (β-1 receptor blockade)[24] and splanchnic vasoconstriction (β-2 receptor blockade).[25] Carvedilol, specifically, is a NSBB that has additional vasodilating effects through α-1 receptor blockade, which helps reduce portocollateral resistance even further.[26] It also has antioxidant and antifibrotic effects, helping make it the most widely supported NSBB to use in PHTN.[27,28] Studies have also shown that NSBBs, specifically propranolol, can be used for primary and secondary prophylaxis for esophageal varices.[29] Beyond these findings, the PREDESCI RCT showed that clinical decompensation was lower with NSBBs vs placebo in patients who have cACLD and CSPH with no or small varices, owing to a significant reduction in incidence of ascites.[30] In a US study examining a cohort of veterans, new use of carvedilol was associated with reduced hepatic decompensation and liver-related mortality compared with new use of selective β blockers.[31] Although NSBBs have proven to be effective in patients with cirrhotic PHTN, there have also been some notable drawbacks. Selective β-1 blockade can increase portal pressure; thus, carvedilol, through its additional α-1 receptor–blocking effects, has proven to be one of the more effective treatments.[32] NSBBs can increase the risk of arterial hypotension, making them less favorable in patients with decompensated cirrhosis.[33] However, strong data now support screening patients with compensated cirrhosis for CSPH with the goal of starting carvedilol, which can prevent the progression of compensated cirrhosis to decompensation, improving survival and reducing health care burden and cost.[34,35]

Novel Treatments for Portal Hypertension

There are several potential novel treatments for medical management of PHTN, including RAA system blockers, immunomodulatory drugs, antibiotics, anticoagulants, angiogenesis blockers, and vasoactive substances.

Renin-Angiotensin-Aldosterone System Blockers

Beyond NSBBs, RAA system blockers recently have been tested for their effects on PHTN. Plasma renin, in fact,

represents an independent risk factor for mortality and is associated with liver dysfunction in patients with cirrhosis.[36] Additionally, angiotensin II and aldosterone play an integral role in the dynamic changes associated with PHTN as noted earlier. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and aldosterone antagonists have been tested in multiple rodent and human trials and have been shown to have similar effects as NSBBs. The HVPG reduction with ACE inhibitors or ARBs is similar to that of NSBBs, although in decompensated patients, there is an increased risk of hypotension, worsening hyperdynamic circulation, or even renal insufficiency.[37]

Immunomodulatory Drugs

Inflammation contributes to liver fibrosis and splanchnic angiogenesis, both of which worsen PHTN through structural and dynamic changes.[9] Thus, modulating inflammation has been a highly researched topic for PHTN treatment. Thalidomide, a first-generation immunomodulatory drug, inhibits the tumor necrosis factor–α/nuclear factor-κB pathway, reducing inflammation and ultimately portal pressure through decreased intrahepatic resistance.[38,39] A small pilot study showed that 2 weeks of thalidomide administration significantly decreased HVPG in patients who have stable alcohol-associated cirrhosis.[40] Emricasan, a caspase inhibitor, is another novel drug that acts further downstream in the inflammation and apoptosis pathway. Its use resulted in decreased inflammation and fibrosis, eventually reducing PHTN in cirrhotic rodent models.[41] Chronic cyclooxygenase inhibition has also been demonstrated to reduce portal pressure through decreased liver fibrosis, angiogenesis, and tortuous hepatic portal venules in cirrhotic rats.[42] Inflammation plays a vital role in the development and progression of PHTN; thus, ongoing research in targeted therapies is vital.

Antibiotics

Beyond inflammation, bacteria also perpetuate PHTN through disrupted epithelial barriers and propagation of bacteria-induced fibrogenesis. Rifaximin, more commonly known to help treat hepatic encephalopathy, has also been shown to decrease the HVPG and improve hemodynamics after being used for a month in patients with alcohol-related decompensated cirrhosis.[43] The use of rifaximin in decompensated patients, however, remains controversial, as not all studies have confirmed its beneficial effects.[44]

Anticoagulants

Given the recently established prothrombotic nature of PHTN, anticoagulation is a new focus for management. Rivaroxaban, a direct factor Xa inhibitor, has been shown to significantly decrease portal pressure in rat models of cirrhosis.[14] The ongoing CIRROXABAN study (NCT02643212) is investigating the effects of rivaroxaban on HVPG, survival, and complications.[11] Given that patients with cirrhosis also have an increased risk of venous thrombotic events, patients who receive anticoagulant therapy have increased recanalization and decreased progression of thrombosis.[45] Thus, in the absence of contraindications, anticoagulants are often now first-line therapy for patients with cirrhosis and portal vein thrombosis.[15]

Angiogenesis Blockers

Angiogenesis also contributes to the progression of PHTN; thus, it is a current focus for novel treatments. Monoclonal vascular endothelial growth factor receptor 2 antibodies have been shown to decrease hyperdynamic splanchnic circulation and portosystemic collateral vessel formation in rodents with PHTN.[46,47] In addition, the administration of placental growth factor antibodies demonstrated a decrease in collateral formation and reduction of portal pressure in mice with PHTN.[48] Specifically, sorafenib, a tyrosine kinase inhibitor that affects multiple angiogenetic pathways, has been shown to decrease the HVPG among patients with alcohol-associated PHTN through the downregulation of proangiogenic factors.[49] For optimal PHTN treatment, antiangiogenic therapies should also be considered, as they help with hepatic tissue repair and fibrosis resolution.[50]

Vasoactive Substances

Vasoactive drugs (terlipressin [Terlivaz, Mallinckrodt Pharmaceuticals], somatostatin, octreotide) are recommended when variceal bleeding is suspected prior to endoscopic therapy.[15] Although the occurrence of ruptured varices does not directly correlate with the degree of PHTN, decreases in portal pressure can reduce the risk of bleeding and treat acute bleeding.[51] Specifically, terlipressin is the only medication that has shown mortality benefit in acute variceal hemorrhage and was recently approved by the US Food and Drug Administration in the United States in Fall 2022.[52]

Conclusion

PHTN is a hemodynamic consequence of cirrhosis and can lead to variceal bleeding, ascites, and hepatic encephalopathy. The framework surrounding management of PHTN has shifted from reactive management of decompensating events to a more prevention-based approach that includes avoiding decompensations and improving risk stratification. Concurrently, there are new guidelines

centered on preventing complications and encouraging less-invasive diagnostic testing, including LSM and SSM, to help guide risk stratification and targeted treatment approaches. NSBBs, specifically carvedilol, are now recommended by guidelines for the prevention of decompensating events in patients with compensated cirrhosis and CSPH. Other treatments that are currently being tested in large studies include statins, anti-inflammatory medications, anticoagulants, angiogenesis blockers, and vasoactive substances. Future directions of novel medical management of PHTN may even include antifibrotic agents and medications improving microvascular function in the initial stages of cirrhosis. As a more comprehensive understanding of PHTN comes to the forefront, expansion of the management of the disease can be expected.

Disclosures

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