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Portal Hypertension and Related Complications: Diagnosis and Management

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CME Activity

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Abstract

Portal hypertension is a major complication of cirrhosis, and its consequences, including ascites, esophageal varices, hepatic encephalopathy, and hepatorenal syndrome, lead to substantial morbidity and mortality. The past several decades have seen major improvements in the clinical management of complications of portal hypertension, resulting in substantial gains in patient outcomes. However, important challenges remain. This review focuses on the pathophysiology and diagnosis of portal hypertension and discusses general approaches in the management of patients with ascites as a result of portal hypertension.

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DEFINITION AND PATHOPHYSIOLOGY OF PORTAL HYPERTENSION

Portal hypertension can be simply defined as abnormal venous pressure elevation in the portal system. Portal vein pressure normally ranges from 7 to 12 mm Hg at rest and in fasting conditions.[1] Direct portal pressure measurement, however, is invasive and requires direct cannulation of portal or umbilical veins. Alternatively, portal hypertension can be accurately diagnosed by the pressure

gradient between the portal vein and the inferior vena cava, defined as the hepatic venous pressure gradient (HVPG). The HVPG represents the actual liver portal perfusion pressure, and it ranges from 1 to 4 mm Hg.[2] Values greater than 5 mm Hg indicate portal hypertension, and values greater than 10 mm Hg correspond to clinically significant portal hypertension, that is, when clinical complications ensue.

According to the hydraulic analogy of Ohm's law ($\Delta P = Q \times R$), the main determinants of portal pressure (ΔP) are blood flow (Q) and vascular resistance (R). Thus, portal hypertension results from an increase in resistance or blood flow in the portal venous system. In cirrhosis, the most common cause of portal hypertension, the formation of scar tissue and regenerative nodules leads to an increase in intrahepatic vascular resistance and, consequently, portal pressure. These structural changes are observed in the early stages of cirrhosis-related portal hypertension and are followed by compensatory splanchnic vasodilation, which, in turn, results in increased portal blood flow, further aggravating the portal pressure (Figure 1).

In addition to permanent architectural distortion of the liver parenchyma in cirrhosis, a dynamic and potentially reversible component has also been reported that accounts for 30% of the total increase in intrahepatic vascular resistance.[3] This modifiable feature is a result of exaggerated production of vasoconstrictors and deficient release of vasodilators in cirrhosis, resulting in increased vascular tone in the intrahepatic capillary bed (sinusoids).

Extensive research has identified the molecular and cellular mechanisms involved in the development and progression of liver fibrosis as well as vascular remodeling, the main drivers of portal hypertension. Chronic hepatocellular injury promotes activation of perisinusoidal cells, known as hepatic stellate cells (HSCs), which acquire a fibrogenic myofibroblast phenotype, resulting in collagen production and sinusoidal constriction. Transdifferentiation from quiescent to activated HSCs is a complex process modulated by various extracellular signals originating from resident liver cells, such as hepatocytes and sinusoidal endothelial cells, as well as inflammatory cells, including macrophages, lymphocytes, and platelets.[4] Increased understanding of HSC biology has led to the development of stellate cell–targeting drugs, which are currently in phase 2 and 3 human clinical trials, including Cenicriviroc (dual CCR2–CCR5 receptor antagonist),[5] GR-MD-02 (galectin-3 inhibitor),[6] and ND-L02-s0201 (vitamin A–coupled lipid nanoparticle–containing

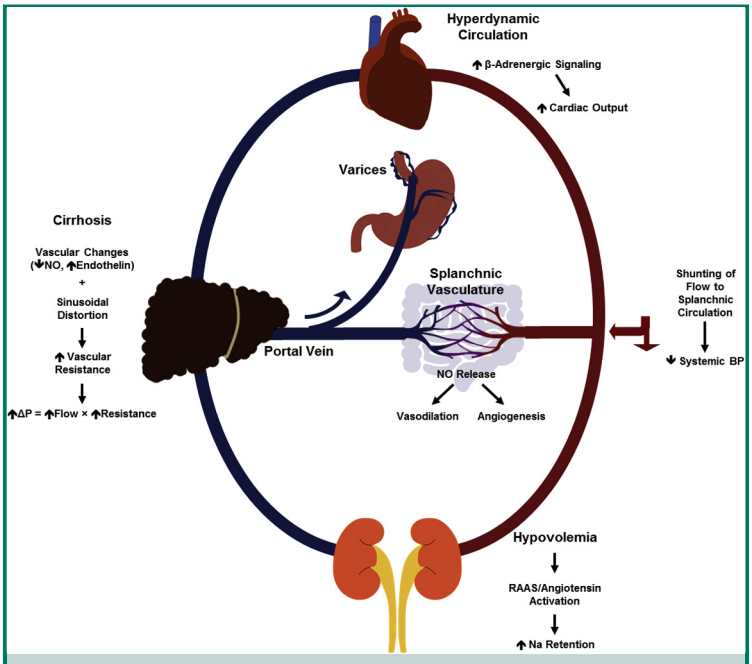

FIGURE 1. Pathophysiology of portal hypertension. Multiple organ systems are involved in the maladaptive responses that characterize portal hypertension. Liver cirrhosis increases vascular resistance of the liver through mechanical distortion of liver sinusoids and vasoconstriction driven by decreased vasodilator availability (nitric oxide [NO]) and increased vasoconstrictor production (endothelin). Increased portal pressure signals to the splanchnic system to promote vasodilation and increase portal flow. Nitric oxide is recognized as a major player in mediating splanchnic vasodilation and angiogenesis. Increased vascular resistance in the liver and augmented flow from the splanchnic system result in elevated portal pressure. Portal hypertension, in turn, feeds portal-systemic collaterals and underlies the development of varices and ascites. Another consequence of splanchnic vasodilation is shunting of cardiac output from the systemic circulation to the mesentery, leading to systemic hypotension and relative renal hypoperfusion. Activation of the renin-angiotensin-aldosterone system (RAAS)/angiotensin system leads to sodium (Na) and fluid retention, causing systemic volume overload. Hyperdynamic circulation driven by activation of the β-adrenergic system is another compensatory response to systemic hypotension. BP = blood pressure; P = pressure.

siRNA against HSP47) (ClinicalTrials.gov [https://clinicaltrials.gov/ct2/show/NCT02421094]). These agents may result in fibrosis regression through "deactivation" of HSCs back into a quiescent state and may potentially lead to resolution of portal hypertension.

CAUSES OF PORTAL HYPERTENSION

Any condition that interferes with blood flow or vascular resistance in the portal venous system can lead to portal hypertension. Cirrhosis remains the most common cause in western countries, and all other etiologies account for less than 10% of cases.[7] The causes of portal hypertension can be classified according to their anatomical location: prehepatic, intrahepatic, or posthepatic (Table).

Prehepatic Portal Hypertension

Although cirrhosis and portal hypertension are the most common causes of portal vein thrombosis (PVT), isolated PVT may result in prehepatic portal hypertension due to impaired blood flow in the portal venous system.[8] In the absence of cirrhosis, PVT is often a consequence of prothrombotic conditions (congenital or acquired), local complications (eg, neonatal omphalitis, pancreatitis, abdominal trauma, surgery), or both. Despite extensive investigation, the etiology of PVT cannot be identified in approximately 15% to 30% of patients.[9,10]

Intrahepatic Portal Hypertension

Intrahepatic portal hypertension is driven by high vascular resistance at the presinusoidal, postsinusoidal, or sinusoidal capillaries. The main causes of presinusoidal portal hypertension include nodular regenerative hyperplasia, schistosomiasis, sarcoidosis, primary biliary cholangitis, autoimmune cholangiopathy, congenital hepatic fibrosis, and adult polycystic disease. Cirrhosis is the most common cause of sinusoidal portal hypertension, which can also be caused by infiltrative conditions such as amyloidosis, mastocytosis, and Gaucher disease. Finally, postsinusoidal portal hypertension is usually caused by veno-occlusive disease or sinusoidal obstruction syndrome.[11]

Posthepatic Portal Hypertension

Posthepatic portal hypertension is generally caused by venous outflow impairment resulting in increased vascular resistance to hepatic blood flow. The most common causes are Budd-Chiari syndrome and right-sided heart failure resulting from conditions such as constrictive pericarditis, restrictive cardiomyopathy, complex congenital heart diseases, and Fontan physiology.[12]

DIAGNOSIS OF PORTAL HYPERTENSION

Although the definitive diagnosis of portal hypertension requires the use of invasive methods, an accurate diagnosis can still be

TABLE. Etiologies of Portal Hypertension

Prehepatic	Hepatic			Posthepatic
	Presinusoidal	Sinusoidal	Postsinusoidal	
Portal vein thrombosis	Schistosomiasis	Cirrhosis	Veno-occlusive disease	Budd-Chiari syndrome
Splenic-arteriovenous fistula	Nodular regenerative hyperplasia	Acute hepatitis/alcoholic hepatitis	Sinusoidal obstruction syndrome	Congestive heart failure
	Cholangiopathy	Acute fatty liver of pregnancy		
	Liver metastasis	Amyloidosis		
	Sarcoidosis	Mastocytosis		
	Amyloidosis	Gaucher disease		
	Polycystic liver disease			
	Congenital hepatic fibrosis			

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made based on the presence of portal hypertension–related complications and exclusion of other potential causes. Ascites, gastroesophageal varices, splenomegaly, hypersplenism-related thrombocytopenia, portosystemic encephalopathy, and hepatopulmonary syndrome are common manifestations of clinically significant portal hypertension. One or more of these complications, combined with clinical, biochemical, or radiologic features of cirrhosis, is sufficient to make a diagnosis. Because cirrhosis accounts for 90% of all causes of portal hypertension, invasive assessment of portal pressure is rarely needed in clinical practice for diagnostic purposes. Invasive measurements, however, also assess for severity of portal hypertension and can still be of value for prognostication.

Portal hypertension can be determined by the gradient between the sinusoidal pressure (wedged hepatic venous pressure) and the hepatic vein pressure (free hepatic venous pressure), which corresponds to the HVPG.[13] Measurement of the HVPG is performed by an interventional radiologist under local anesthesia and conscious sedation (Figure 2). Fluoroscopic guidance is used to advance a balloon-tipped catheter into the main right hepatic vein via the internal jugular, antecubital, or femoral vein. Wedged hepatic venous pressure is obtained through balloon occlusion of the hepatic vein, and free hepatic venous pressure is measured by maintaining the tip of the catheter floating freely approximately 2 to 4 cm distal to the inferior vena cava. Note, however, that measurement of the HVPG does not reflect portal pressure in prehepatic causes of portal hypertension.

As mentioned previously herein, a normal HVPG ranges from 1 to 4 mm Hg, and values greater than 10 mm Hg are associated with the development of complications such as gastroesophageal varices and ascites. Variceal bleeding typically ensues when the HVPG is greater than 12 mm Hg,[14] and HVPG values greater than 20 mm Hg within 48 hours of a variceal bleeding episode are associated with high mortality rates in patients with cirrhosis.[15]

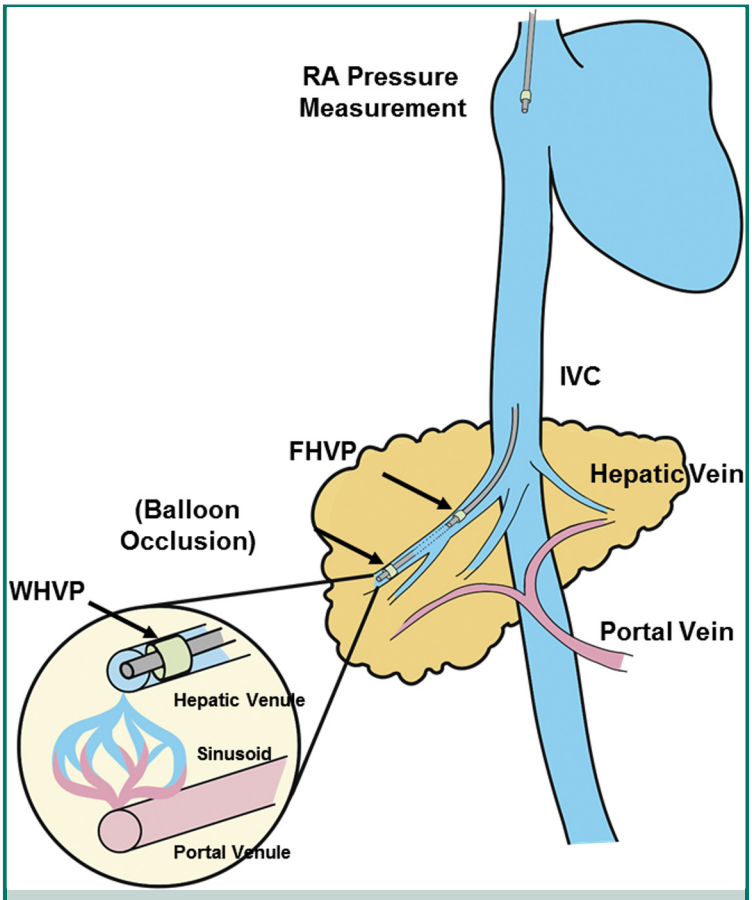

FIGURE 2. Measurement of portal pressure. Through direct access to the systemic venous system, a branch of the hepatic vein can be reached under fluoroscopic guidance, and free hepatic venous pressure (FHVP) can be obtained. Balloon occlusion of a small branch of the hepatic vein measures the static pressure of liver sinusoids, which is termed *wedged hepatic venous pressure* (WHVP). The hepatic venous pressure gradient is the difference between WHVP and FHVP and is often used as a surrogate measurement of portal pressure in patients with cirrhosis. IVC = inferior vena cava; RA = right atrium.

Even after adjusting for model for end-stage liver disease (MELD) score, decompensating events, and age, the HVPG remains an independent prognostic variable with a 3% increase in mortality risk for each 1–mm Hg gradient increase.[16]

TREATMENT OF PORTAL HYPERTENSION

Effective reduction in portal pressure may decrease the incidence of complications in patients with cirrhosis and potentially improve survival. Unfortunately, currently available therapeutic options have limited

efficacy or carry substantial risks. Therefore, the search for more potent and safer alternatives continues. The effect of drugs or interventions on portal pressure can be indirectly assessed through clinical outcomes, such as incidence of variceal bleeding, or directly measured by the HVPG. Achieving a gradient of less than 12 mm Hg or a 20% reduction from baseline has been associated with a significant decrease in the incidence of complications and a sustained long-term reduction in the risk of first variceal bleeding.[17]

Pharmacologic Therapy

Nonselective β-blockers are the first class of drugs found to decrease portal pressure, through inhibition of β_2-induced splanchnic vasodilation, thereby reducing portal venous inflow. Carvedilol, a nonselective β-blocker (NSBB) with anti−α_1-adrenergic activity, promotes greater reduction of portal pressure compared with other NSBBs[18] through additional α_1 blockage and reduction of the intrahepatic and portocollateral vascular resistance.

Activation of the renin-angiotensin-aldosterone system (RAAS) plays an important hemodynamic role in cirrhosis and portal hypertension.[19] Angiotensin receptor blockers (ARBs) have also been found to inhibit HSC contraction and reduce portal pressure in animal models.[20] Several small studies have investigated the effect of ARBs on portal hypertension and prevention of related complications. Although a mild reduction in portal pressure has been observed, inhibition of the RAAS results in a clinically significant decrease in systemic arterial pressure and higher rates of renal dysfunction.[21-24] Therefore, ARBs, either as monotherapy or combined with NSBB, is not recommended in the management of portal hypertension. Transient portal pressure reduction has also been observed with administration of octreotide, a somatostatin analogue with potent splanchnic vasoconstrictive effects.[25,26] However, long-acting octreotide does not result in sustained portal pressure reduction and is associated with high rates of serious adverse events.[27]

Animal studies have suggested a role for nitric oxide derivatives in the treatment of portal hypertension through selective vasodilatory effects on the intrahepatic circulation.[28] However, a benefit could not be confirmed in human trials.[29,30] On the other hand, simvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, has been found to increase nitric oxide release in the liver and decrease hepatic sinusoidal resistance in patients with cirrhosis and portal hypertension.[31-33] Although no effect on prevention of variceal bleeding has been reported, simvastatin may confer a survival benefit to patients with Child-Pugh class A or B cirrhosis.[34] Further studies are needed however, before simvastatin can be routinely recommended for this indication.

Finally, overweight/obese patients with cirrhosis and portal hypertension may also derive benefit from lifestyle changes (diet and exercise) and consequent weight loss. An intensive 16-week program of diet and moderate exercise led to a significant reduction in portal pressure in overweight/obese patients, independent of the liver disease etiology.[35]

Portosystemic Shunting Procedures

Although pharmacologic therapies have limited efficacy in portal hypertension, portosystemic shunting procedures are highly effective in reducing portal pressure. Transjugular intrahepatic portosystemic shunt (TIPS) is a procedure performed by an interventional radiologist via the internal jugular vein, and it entails the creation of an intrahepatic shunt between the portal and hepatic veins (Figure 3). With the advent of TIPS, surgical procedures such as portocaval, mesocaval, and splenorenal shunts are now reserved for noncirrhotic patients with contraindications to TIPS, such as extensive PVT. TIPS is recommended for the management of refractory or recurrent gastroesophageal variceal bleeding, diuretic-intolerant and diuretic-refractory ascites, or hepatic hydrothorax.[36] Data also suggest a benefit of TIPS in hepatorenal[37] and hepatopulmonary syndromes[38,39]; however, the available data

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are insufficient to support the routine use of TIPS for these indications.

One of the hemodynamic consequences of TIPS is increased cardiac venous return, which leads to elevation of end diastolic volume.[40] Therefore, TIPS is contraindicated in patients with congestive heart failure, severe pulmonary hypertension, and tricuspid regurgitation. TIPS should also generally be avoided in patients with underlying hepatic encephalopathy, particularly if not medically controlled. Hepatic encephalopathy is one of the most dreaded complications of TIPS, reported in as many as 45% of patients.[41] However, medically refractory encephalopathy requiring TIPS occlusion or downsizing is less common. Moreover, the widespread use of polytetrafluoroethylene-covered stents has resulted in a decreased incidence of hepatic encephalopathy and improved shunt patency.[42,43]

In addition to the palliative benefits of TIPS, a meta-analysis of individual patient data found a significant increase in transplant-free survival of cirrhotic patients with refractory ascites undergoing TIPS compared with large-volume paracentesis (LVP).[44] A recent multicenter randomized trial comparing polytetrafluoroethylene-covered TIPS vs LVP, not included in the previous meta-analyses, also found a significant survival benefit with TIPS (1-year transplant-free survival of 93% vs 52%, respectively).[45]

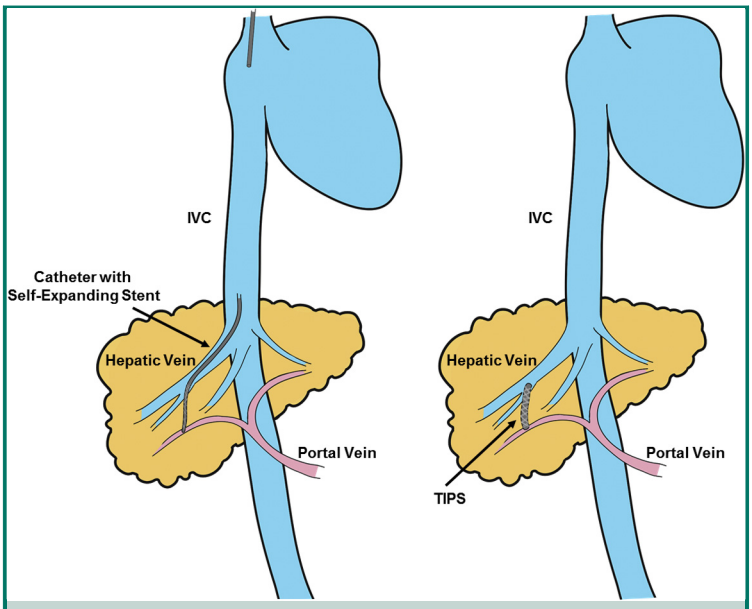

FIGURE 3. Transjugular intrahepatic portosystemic shunt (TIPS). Under fluoroscopic guidance, a balloon catheter is advanced through the jugular vein into the inferior vena cava (IVC) and the liver. Next, a tract connecting a branch of the hepatic vein and a branch of the portal vein is created, and a self-expandable stent is deployed.

COMPLICATIONS OF PORTAL HYPERTENSION

Gastroesophageal Varices

Portal hypertension leads to an increase in the portosystemic collateral flow in an attempt to decompress the portal venous system. The most clinically important site of collateral flow is within the mucosa of the proximal stomach and distal esophagus, resulting in the development of gastroesophageal varices. Screening for gastroesophageal varices with esophagogastroduodenoscopy has been traditionally recommended for all patients with cirrhosis. Recently, however, patients with liver stiffness less than 20 kPa and a platelet count greater than 150 $\times 10^9$/L have been found to carry a very low risk of having varices and can probably avoid a screening endoscopy.[46,47]

The importance of screening for gastroesophageal varices lies in their risk of rupture and potentially life-threatening bleeding. Esophageal varices can be classified as small (<5 mm) or large (≥5 mm) (Figure 4). The risk of bleeding in small varices is approximately 5% per year and as high as 15% in large varices.[48] Thus, pharmacologic or endoscopic treatment for the prevention of first variceal bleeding is recommended for all patients with large varices and those with small varices and significantly decompensated disease (as defined by Child-Pugh class C) or the presence of red wale marks (indicating areas of wall thinning). Use of NSBBs (nadolol and propranolol) results in a decrease in portal flow and, consequently, portal pressure through inhibition of β_2-induced splanchnic vasodilation. These drugs should be titrated to reduce the resting heart rate to 55 to 60 beats/min or to maximal tolerated doses given the poor

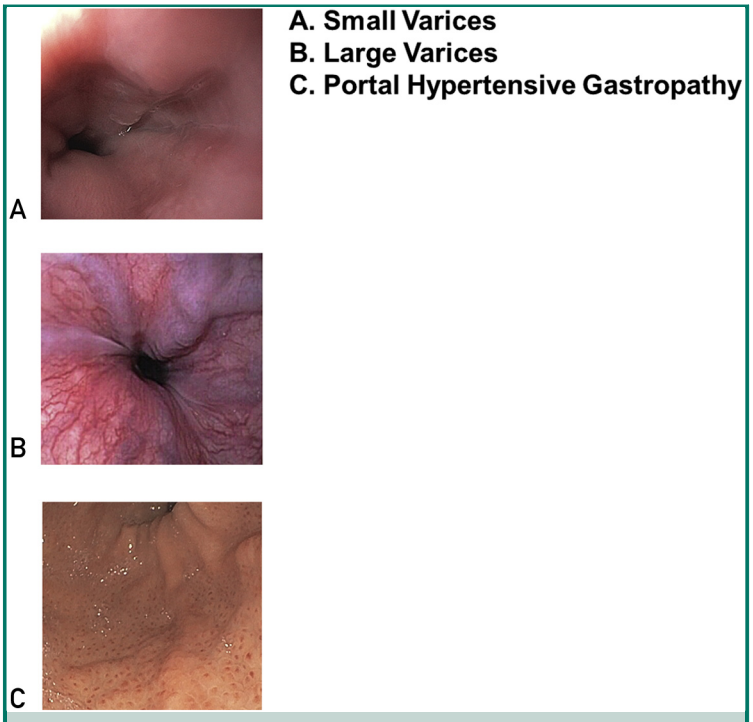

FIGURE 4. Esophageal varices and portal hypertensive gastropathy. A, Endoscopic appearance of small varices. B, Endoscopic appearance of large varices. C, Severe portal hypertensive gastropathy.

correlation between heart rate and HVPG reduction.[49] Carvedilol should be titrated to a recommended dose of 6.5 mg twice daily independent of heart rate response. Alternatively, endoscopic band ligation, which involves the application of rubber bands around the varix, may be used for prevention of variceal bleeding. Patients often require 3 to 4 sessions every 2 to 4 weeks to achieve adequate variceal obliteration.

Gastric varices (GV) are present in approximately 20% of patients with portal hypertension.[50] Advanced cirrhosis and variceal diameter greater than 10 mm are the most important predictors of gastric variceal bleeding. Although data are lacking on primary prophylaxis of gastric variceal bleeding, general consensus is to start NSBB therapy in patients with large GV. Although most GV are found in conjunction with esophageal varices, isolated GV (GV type 1) may be seen in patients with splenic vein thrombosis and in the absence of portal hypertension.[51] Splenectomy is considered the treatment of choice in patients with bleeding isolated GV type 1 associated with splenic vein thrombosis.

Portal hypertensive gastropathy (PHG) is another important consequence of portal hypertension, which results from congestion of the gastric mucosal capillaries. Endoscopically, PHG is characterized by a diffuse mosaic pattern of the mucosa and by the presence of red spots in severe cases.[52] Severe PHG may result in chronic gastrointestinal bleeding and, consequently, iron deficiency anemia in patients with portal hypertension. Management also includes the use of NSBB therapy and iron supplementation. Endoscopic therapies have not been found beneficial in the treatment of PHG.

Acute Variceal Bleeding

Variceal bleeding typically presents with painless, effortless, and recurrent hematemesis. The initial step in managing patients with suspected variceal bleeding is hemodynamic assessment and support. Restrictive red blood cell transfusion (when the hemoglobin level drops below 7 g/dL [to convert to g/L, multiply by 10]) lowers the risk of mortality, whereas excessive transfusion may increase portal pressure and the risk of variceal rebleeding.[53] Vasoactive agents that result in a decrease in splanchnic blood flow, such as vasopressin or somatostatin analogues, should be started as early as possible. Octreotide, a somatostatin analogue, is the most commonly used agent in the United States, and continuous infusion for up to 5 days is recommended to prevent early rebleeding.[54] Bacterial infections, including spontaneous bacterial peritonitis and pneumonia, develop in as many as 50% of patients after an episode of variceal bleeding. Prophylactic antibiotics reduce not only the risk of infection but also mortality and should be given to all patients with variceal bleeding, irrespective of the presence of ascites.[55] Quinolones and third-generation cephalosporins are the preferred antibiotic drug choices and should be given for a total of 7 days.

Upper endoscopy should be performed once the patient is hemodynamically stable,

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and typically in a few hours. If active or recent variceal bleeding is confirmed, band ligation is performed. Treatment failure, defined as persistent or recurrent bleeding within 24 hours despite 2 sessions of band ligation, may occur in 10% to 20% of patients.[56] In these patients, TIPS should be performed. Emergency TIPS is often an effective means of controlling variceal hemorrhage, but complications such as infection, renal failure and encephalopathy are common after the procedure, contributing to a high mortality rate (up to 30% within 30 days).[57] When TIPS is not readily available, balloon tamponade or esophageal stenting may be used as a bridging measure for bleeding control. Recent studies favor the use of esophageal stents over balloon tamponade due to greater efficacy and lower risk of serious adverse events.[58]

After an episode of variceal bleeding, the risk of rebleeding can be as high as 60% without prophylactic treatment.[48] The risk can be significantly reduced by a combination of NSBB therapy and endoscopic band ligation to variceal obliteration (performed every 2-4 weeks). Early TIPS may be considered for patients with variceal bleeding and (1) Child-Turcotte-Pugh class C, (2) class B with active bleeding, or (3) MELD score greater than 18 and red blood cell transfusion requirement of 4 U or more.

As opposed to its effectiveness in esophageal varices, endoscopic band ligation for gastric variceal bleeding often fails to achieve hemostasis and is associated with high risk of rebleeding. Obturation of GVs with cyanoacrylate glue, however, is effective in approximately 90% of patients and is the treatment of choice.[59] Obturation with cyanoacrylate glue carries a significant risk of embolization in patients with portosystemic shunting. Therefore, these patients should undergo combined interventional radiology-guided balloon occlusion of the shunt at the time of endoscopic obturation. If bleeding recurs despite endoscopic obturation or this treatment modality is not available, then TIPS should be performed. Coil embolization of GV can also be considered, typically in conjunction with TIPS.[60] Balloon-occluded retrograde transvenous obliteration (BRTO) is another technique that has been increasingly used for the management of GV. It uses threading of a fluoroscopically guided balloon catheter into the gastric varix via a gastrorenal shunt, followed by direct injection of a sclerosing agent to obliterate the GV. In experienced hands, BRTO is highly effective in the management of GV.[61]

Ascites

Ascites represents the pathologic accumulation of fluid in the peritoneal cavity as result of clinically significant portal hypertension and plasma volume expansion. The splanchnic and systemic arterial vasodilation observed in portal hypertension leads to a reduction in effective arterial blood volume, which, in turn, promotes activation of sodium-retaining pathways (RAAS, sympathetic system, and release of antidiuretic hormone) and, consequently, sodium and water retention. Ascites is often the presenting symptom in patients with portal hypertension manifested by abdominal distention, and it should be suspected on physical examination by the presence of flank and shifting dullness.[62] Ascites can be confirmed by abdominal ultrasonography, which can detect as little as 100 mL of intra-abdominal fluid.[63] Ultrasonography may also help assess for other signs of portal hypertension, such as splenomegaly, and when combined with Doppler examination, it also may help rule out portal or hepatic vein thrombosis.

EVALUATION

Portal hypertension is responsible for greater than 80% of cases[64]; however, exclusion of other etiologies is recommended for all patients presenting with new-onset ascites. The first test to be performed in such patients is a diagnostic paracentesis. Analysis of the ascitic fluid may provide important clues as to its etiology. The serum ascites albumin gradient (SAAG) is elevated in portal hypertension, with a diagnostic accuracy of 97% to 98% at the cutoff value of 1.1 g/dL[65,66]; SAAG values less than 1.1 g/dL are

observed in peritoneal processes, such as carcinomatosis or tuberculosis. In patients with SAAG values greater than 1.1 g/dL, the total protein level in ascitic fluid can differentiate between intrahepatic and posthepatic portal hypertension. Levels greater than 2.5 g/dL are suggestive of hepatic venous outflow impairment (such as Budd-Chiari syndrome and right-sided heart failure).

MANAGEMENT

The first-line treatment of portal hypertension–related ascites aims to achieve a negative sodium balance through a combination of sodium restriction and diuretics.[67,68] Treatment failure can be divided into diuretic-resistant ascites (persistent ascites despite maximal doses of diuretics and compliance with sodium restriction) or diuretic-intolerant ascites (diuretics cannot be titrated upward due to significant renal impairment or electrolyte disturbances) (Figure 5).

Dietary sodium restriction, limited to 2 g daily, is recommended for all patients with portal hypertension–related ascites. This is often difficult to maintain, and consultation with a dietitian may be helpful to improve compliance. Unfortunately, sodium restriction alone rarely leads to ascites resolution, and the addition of oral diuretics is often required. The preferred regimen is a combination of furosemide and spironolactone. This combination is superior to either alone, and a ratio of 40:100, respectively, helps maintain normokalemia.[69] Dose up-titration every 4 to 5 days with close monitoring of serum electrolytes and renal function is generally recommended. Unfortunately, the use of diuretics is often limited by the development of acute kidney injury (secondary to prerenal azotemia or hepatorenal syndrome) or significant hyponatremia.

Another important reason for diuretic failure is the use of nonsteroidal anti-inflammatory drugs, which blunt the natriuretic effect of diuretics and may predispose to acute kidney injury.[70] This class of drugs should be avoided in patients with portal hypertension–related ascites.

For patients with diuretic-intolerant or diuretic-refractory ascites, therapeutic LVP is required. Usually, LVP is well tolerated and carries a low risk of complications. Post-paracentesis circulatory dysfunction (PCD), manifested by hypotension, renal dysfunction, and high mortality, may develop in as many as 75% of patients without the administration of plasma expanders after LVP.[71] This potentially lethal complication can be prevented by the use of intravenous albumin at a dose of 6 to 8 g per liter of ascitic fluid removed. This approach can reduce the incidence of PCD to less than 20%.[72,73] Albumin administration may not be necessary when less than 5 L of ascites is removed, except in patients at higher risk for PCD, such as those with renal dysfunction or hyponatremia at baseline. In these patients, albumin infusion should be given irrespective of the ascitic volume removed. The risk of bleeding with LVP is low (<1%), and coagulopathy associated with advanced cirrhosis is not a contraindication to LVP.[74] Correction of prolonged prothrombin time is not necessary because the risk of bleeding does not correlate with prothrombin time or international normalized ratio.[75] On the other hand, low platelet counts may increase the risk of complications in patients with sepsis or renal failure, and platelet transfusion is recommended in patients with severe thrombocytopenia.[74]

TIPS is an effective alternative to LVP for patients with refractory ascites, leading to complete ascites resolution in 50% to 75% of patients[45,76,77] and a substantial reduction in LVP frequency in others. Within 6 to 12 months after TIPS, significant improvement is observed in the circulatory dysfunction associated with refractory ascites, resulting in less sodium retention and improved renal function.[77]

Recently, an automated pump device connecting the peritoneal cavity with the bladder has been developed for the management of refractory ascites.[78] The pump is implanted subcutaneously in the abdominal wall, and through internal catheters, it removes the ascitic fluid from the peritoneal cavity into the bladder, from where it is

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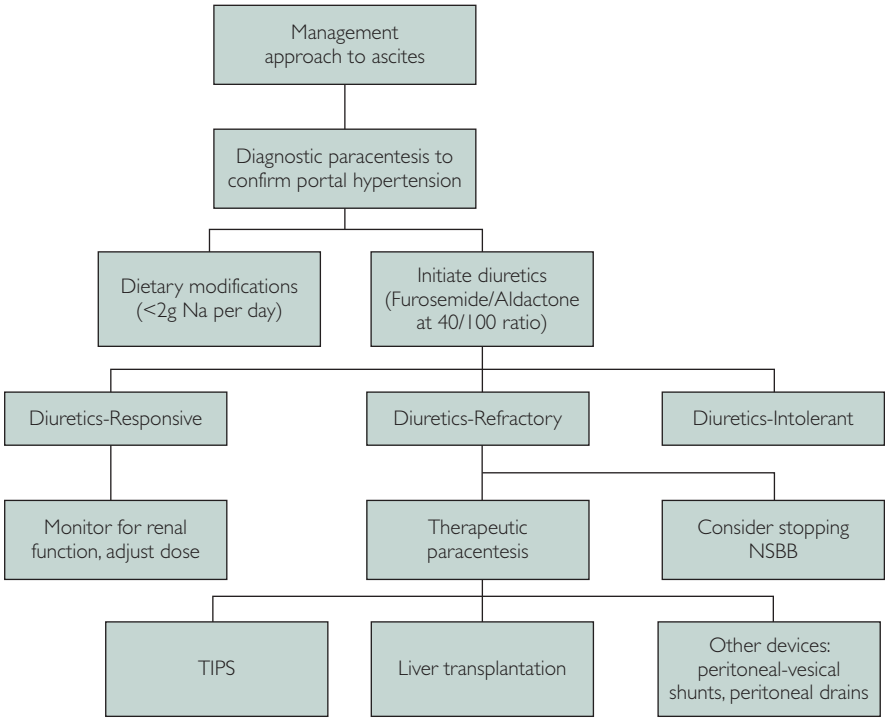

FIGURE 5. Management of ascites. All patients with new-onset ascites should undergo evaluation for potential etiologies. Initial management of portal hypertension–related ascites includes dietary sodium (Na) restriction followed by initiation of oral diuretics. Careful monitoring of renal function is needed with ongoing diuretic use. Diuretic-resistant ascites is defined as persistent ascites despite maximal doses of diuretics and compliance with sodium restriction. Diuretic-intolerant ascites is characterized by significant renal impairment or electrolyte disturbances, limiting up-titration of diuretics. Nonselective β-blockers (NSBBs) may exacerbate circulatory dysfunction related to ascites, and discontinuation may be considered for patients with refractory or intolerant ascites. Large-volume paracentesis is used for persistent ascites as needed. Invasive therapies such as transjugular intrahepatic portosystemic shunt (TIPS), peritoneal-vesical shunt, peritoneal drain, or liver transplant should be considered in appropriate settings.

eliminated through urination. Three prospective studies evaluating the pump in patients with refractory ascites have been completed, including a randomized controlled trial comparing it with serial LVP.[78,79] Although the device is markedly effective in reducing the need for and frequency of LVP, thus improving health-related quality of life, it is not free of risks. Approximately 45% of patients developed pump-related complications requiring repeated intervention, including dislocation of catheters, pump occlusion, as well as pocket hematoma, infection, and wound dehiscence. In addition, a higher rate of acute kidney injury, hyponatremia, and hypoalbuminemia was observed in the pump group compared with the LVP group. No difference in survival has been reported.[79] This procedure is currently investigational and is not available for routine clinical use.

Percutaneous catheter placement for home-based drainage of peritoneal fluid has historically been reserved for patients with malignant ascites and short life expectancy.[80] However, the low incidence of complications with tunneled peritoneal catheters has led to the use of such catheters in patients with portal hypertension–related ascites.[81-83] Although short-term outcomes seem acceptable in this population, prolonged catheter use (>3 months) may increase the risk of peritoneal infections and is not

recommended.[84,85] Until prospective and long-term safety data are available, the use of percutaneous peritoneal catheters should be limited to patients with short life expectancy and who are not transplant candidates.

CONCLUSION

The use of prophylactic antibiotic agents, improvements in endoscopic techniques, increasing availability of TIPS, and the development of implantable devices have significantly changed the clinical management of portal hypertension and ascites during the past 2 decades. Despite these advances, portal hypertension remains largely a progressive disease. With few exceptions, the severity of underlying chronic liver disease, and, therefore, the degree of portal hypertension, increases over time. Given the natural history of this condition, patients with clinically significant portal hypertension, and particularly those with decompensated cirrhosis, should be considered for liver transplant early in their disease course. Transplant remains the only possible cure for many patients with severe portal hypertension, and those who are potential candidates should be referred to a liver transplant center for evaluation.

Abbreviations and Acronyms: **ARB** = angiotensin receptor blocker; **BP** = blood pressure; **BRTO** = balloon-occluded retrograde transvenous obliteration; **GV** = gastric varices; **HSC** = hepatic stellate cell; **HVPG** = hepatic venous pressure gradient; **LVP** = large-volume paracentesis; **MELD** = model for end-stage liver disease; **Na** = sodium; **NO** = nitric oxide; **NSBB** = nonselective β-blocker; **P** = pressure; **PCD** = postparacentesis circulatory dysfunction; **PHG** = portal hypertensive gastropathy; **PVT** = portal vein thrombosis; **RAAS** = renin-angiotensin-aldosterone system; **SAAG** = serum ascites albumin gradient; **TIPS** = transjugular intrahepatic portosystemic shunt

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