

LEARNING OBJECTIVES

- Describe the pathophysiology, including specific causes, of portal hypertension
- Explain how portal hypertension is diagnosed
- Discuss the treatment of portal hypertension
- Review interventions that can be used when medical management has failed

The evaluation of liver dysfunction: When to suspect portal hypertension

This condition is a life-threatening disease process. Management largely focuses on treating the complications and avoiding further injury to the liver.

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A 58-year-old man presented to the emergency department in 1997 with an upper GI hemorrhage and was acutely treated for the bleeding. He was found to have esophageal varices caused by cirrhosis-related portal hypertension. Within 3 months, the patient underwent a transjugular intrahepatic portosystemic shunt (TIPS) placement; he was also evaluated and placed on the list to receive a liver transplant. Throughout the years, the shunt was revised seven times because of occlusion; endoscopic banding was performed to treat recurrent variceal hemorrhages on 18 occasions; and the patient developed encephalopathy. Medical management of his condition consisted of propranolol, isosorbide, lactulose, fluid restriction, and dietary changes. A portal vein thrombosis caused by TIPS occlusion removed him from the liver transplant list. Despite this complicated course, however, the patient was 69 years old at the time this article was written and has survived for 11 years with this condition. An understanding of portal hypertension, as well as knowing how to diagnose and adequately manage its complications, can allow PAs to extend the survival of their affected patients.

PATHOPHYSIOLOGY

Portal hypertension is an increase in the portal vein pressure that results in a higher portal vein-systemic venous pressure gradient. Normal pressure gradients between the portal vein and the inferior vena cava are 3 to 6 mm Hg. Portal hypertension is defined as a pressure gradient higher than 10 mm Hg.¹ Certain hepatic conditions cause increased resistance to portal blood flow, which elevates the portal vein pressure (see Table 1, page 40).

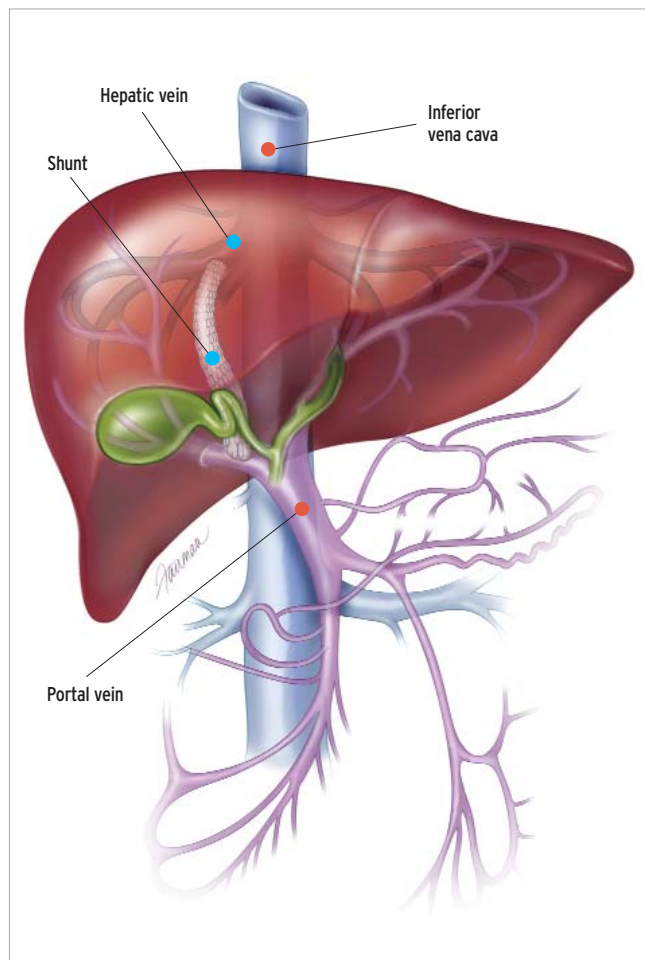


FIGURE 1. Transjugular intrahepatic portosystemic shunt

Prehepatic portal hypertension is caused by a portal vein thrombus, a tumor-related obstruction applying extrinsic compression on the portal vein, or congenital stenosis of the portal vein. Notably, prehepatic portal hypertension is usually associated with normal liver function.

Intrahepatic portal hypertension is caused by cirrhosis, schistosomiasis, or congenital hepatic fibrosis. Liver function test results for patients with cirrhosis-related portal hypertension generally indicate abnormal liver function.

Posthepatic conditions that can cause portal hypertension include venous outflow obstruction or Budd-Chiari syndrome and constrictive pericarditis. These conditions are initially associated with normal liver function.

Alcoholic cirrhosis and hepatitis-induced cirrhosis are the two most common causes of portal hypertension in the United States.² In the cirrhotic liver, greater resistance to blood flow through the hepatic sinusoids and increased splanchnic blood flow elevate the portal pressure. Resistance is caused by injury to or fibrosis in the liver cells. Splanchnic arteriolar vasodilation caused by higher levels of glucagon and nitric oxide, which reduce sensitivity to vasoconstrictors, increases portal blood flow. This is why portal pressure remains high, even when collateral blood vessels develop and divert as much as 80% of the portal blood flow.³ Collateral vessels partially decompress the portal system; however, it is these varices that are at risk for bleeding. The risk increases with the severity of liver disease.⁴

Schistosomiasis is the most common cause of portal hypertension outside the United States. This parasitic infection is contracted through skin contact with fresh water in which certain types of snails are present. An immune response to the presence of *Schistosoma* eggs in the liver results in a progressive buildup of fibrous tissue. The granulomatous reaction compresses the hepatic venules, eventually causing portal hypertension.⁵

Portal vein thrombosis is the most common cause of portal hypertension in children.⁶ Although the exact incidence is not known, The Office of Rare Diseases for the National Institutes of Health lists portal hypertension as a rare disease; prevalence is estimated to be fewer than 200,000 affected persons in the United States.⁷

DIAGNOSIS

Portal hypertension is generally not diagnosed until symptoms of progressive hepatic dysfunction or cirrhosis develop. When portal hypertension is suspected, initial laboratory tests need to focus on identifying the potential cause and the stage of hepatic dysfunction. Tests include a hepatitis panel, hepatic enzymes, lipid panel, tuberculosis test, prothrombin time (PT)/international normalized ratio (INR), and albumin level. An endoscopy is also performed to document the presence of esophageal or gastric varices. A Doppler ultrasound of the liver is used to visualize liver morphology, verify the presence of ascites, detect most masses or portal vein thrombi, and measure the diameters and blood flow velocities of the portal vein and inferior vena cava. Invasive procedures, such as transfemoral cannulation for a venous phase angiogram, can measure the portal vein pressure more accurately but carry a slightly higher risk; however, transfemoral cannulation can determine if the patient is a suitable candidate for certain therapeutic procedures. A liver biopsy may be necessary if there is no diagnosable cause of cirrhosis in a patient with cirrhosis-related portal hypertension.

Two formulas commonly used to determine liver disease severity based on laboratory test results and simple clinical parameters are the model for end-stage liver disease (MELD) score and the Child-Pugh classification.^{2,8} The MELD score was developed to predict the prognosis of patients with end-stage liver disease undergoing the TIPS procedure, but its use has been expanded to include prioritizing patients for liver transplant. The calculation gives a numeric score based on serum bilirubin, creatinine, and INR levels⁹ (see Table 2, page 40). Generally, scores higher than 14 correspond to advanced liver disease. The Child-Pugh classification was designed to predict hepatic reserve and mortality associated with a cirrhotic liver based on serum bilirubin, albumin, PT, and the presence of ascites and encephalopathy² (see Table 3, page 41). Disease severity is determined to be class A, B, or C; class C corresponds to the most severe liver disease.

This classification system is felt to adequately establish the degree of liver dysfunction; however, it has been criticized because the extent of ascites or encephalopathy can be subjective.⁹ Both the MELD score and the Child-Pugh classification

KEY POINTS

- Normal pressure gradients between the portal vein and the inferior vena cava are 3 to 6 mm Hg. Portal hypertension is defined as a pressure gradient higher than 10 mm Hg. An increase in the resistance to portal blood flow caused by certain hepatic conditions elevates the portal vein pressure.
- Alcoholic cirrhosis and hepatitis-induced cirrhosis are the two most common causes of portal hypertension in the United States. In the cirrhotic liver, greater resistance to blood flow through the hepatic sinusoids and increased splanchnic blood flow elevate the portal pressure.
- Portal hypertension is generally not diagnosed until symptoms of progressive hepatic dysfunction or cirrhosis develop. When portal hypertension is suspected, initial laboratory tests need to focus on identifying the potential cause and the stage of hepatic dysfunction. Tests include a hepatitis panel, hepatic enzymes, lipid panel, tuberculosis test, prothrombin time/international normalized ratio, and albumin.
- Effective treatment of portal hypertension is based on identifying the underlying cause, treating the complications, and avoiding further injury to the liver.
- The goal of surgical intervention is to decompress the portal system by diverting blood to the systemic circulation. Which procedure is appropriate for a specific patient depends on the patient's status, portal vein patency, and the availability of resources.

are proven similar in their predictive power of short-term, 1-year, and long-term survival.¹⁰ These scores are employed to determine the most appropriate therapeutic options for a given patient and whether the patient's survival potential justifies the allocation of resources.⁸

TREATMENT

Patients with portal hypertension are at risk for ascites, coagulopathy, hypoproteinemia, jaundice, variceal bleeding, and liver failure. Effective treatment is based on identifying the underlying cause, treating the complications, and avoiding further injury to the liver.

Varices Initial medical treatment is aimed at preventing the formation of esophageal or gastric varices and preventing the first bleeding episode. Observation may be sufficient for patients with portal hypertension who have not had a variceal bleeding episode. An acute upper GI hemorrhage is managed with blood volume replacement, vasoactive drug therapy with somatostatin or octreotide, prophylactic antibiotics, and immediate endoscopy for assessment and, possibly, definitive management of the bleeding.¹¹ Hepatic function following an initial hemorrhage, as determined by Child-Pugh class or MELD score, will factor into whether the patient will require surgical intervention. Studies have shown that approximately 90% of patients with cirrhosis will develop esophageal varices, and 30% of those patients will experience a bleeding episode. Although gastric varices are less common, patients who develop gastric varices bleed more profusely, have a higher risk of rebleeding, and have a higher mortality rate.¹² As long as there are no contraindications, patients who have had variceal bleeding should initially be started on a beta-blocker such as propranolol. Nonselective beta-blockers may prevent variceal progression as they lower portal pressure by reducing portal blood flow.¹³ Patients may then be followed with repeat endoscopy based on the extent of varices. Repeat endoscopy

should be done within 3 years if no varices are present, 2 years if the patient has grade I esophageal varices, and 1 year if the patient has alcoholic cirrhosis regardless of whether varices are present. Patients with varices larger than grade I need to be treated and not monitored.¹⁴

Endoscopic band ligation is the first-choice treatment for esophageal varices. This involves placing an elastic band on the varix and aspirating it. Recommended therapy for acute gastric varices includes endoscopically injecting tissue adhesive into the variceal lumen to harden it and arrest the bleed.¹¹ Endoscopic sclerotherapy is another treatment option. Intravariceal or paravariceal injection of a sclerosing agent is used to induce thrombosis of the vessel.¹³ In very rare cases, balloon tamponade is employed to control active hemorrhage from varices in an emergency setting. This procedure provides a temporary solution for patients not amenable to or not responding to endoscopic treatment.

Ascites One of the most common complications is ascites, which is associated with a significant decline in nutritional status and poor quality of life. Half of patients with advanced cirrhosis who are under medical surveillance for at least 10 years will develop ascites. Of those patients, 50% will die within 2 years unless they receive a liver transplant.¹⁵ Management of ascites includes sodium restriction (2 g/d), fluid restriction, and diuretics, including spironolactone and furosemide. If the ascites persists, diuretic dosages are progressively increased to a maximum of 400 mg/d of spironolactone and 160 mg/d of furosemide, unless the patient cannot tolerate the side effects.¹⁵ The goal of the diuretics and sodium restriction is to decrease the intravascular volume.¹⁶ For ascites refractory to pharmacologic therapy, large-volume paracentesis may be necessary. Refractory ascites develops in 10% of patients, and transplant needs to be considered promptly.¹³

Encephalopathy Hepatic encephalopathy is a neuropsychiatric syndrome characterized by a change in neurologic function that is usually the result of declining hepatic function. Management focuses on reducing the amount of ammonia generated. Most patients are treated with lactulose to prevent confusion. A change to neomycin tablets or dietary changes, such as reducing the amount of animal protein consumed, may be necessary. Refractory or recurring encephalopathy generally indicates a very poor prognosis, and these patients must be evaluated for a liver transplant.¹⁷

Hepatorenal syndrome This complication is characterized by renal failure and reduced circulation in the setting of liver failure. Hepatorenal syndrome is diagnosed by ruling out all other causes of renal failure, as the kidneys themselves are physiologically normal. Impaired systemic hemodynamics and activation of the renin-angiotensin system results in

TABLE 1. Hepatic causes of portal hypertension

Budd-Chiari syndrome
Cirrhosis
Congenital hepatic fibrosis
Congenital stenosis of the portal vein
Constrictive pericarditis
Extrinsic compression of the portal vein caused by a tumor
Schistosomiasis
Thrombus in the portal vein

TABLE 2. MELD score equation

$$3.8 \times \log_e (\text{bilirubin [mg/dL]}) + 11.2 \times \log_e (\text{INR}) + 9.6 \times \log_e (\text{creatinine [mg/dL]}) + 6.4 \times (\text{etiology: 0, if cholestatic or alcoholic; 1, otherwise})$$

Key: MELD, model for end-stage liver disease.
Data from Kamath PS et al.⁹

severe reductions in renal function. Treatment is a combination of vasoconstrictors and plasma volume expansion with albumin.¹⁸

SURGICAL INTERVENTIONS

Several surgical interventions are available for patients with portal hypertension when medical management has failed. The goal of these procedures is to decompress the portal system by diverting blood to the systemic circulation.¹⁶ Which procedure is appropriate for a specific patient depends on the patient's status, portal vein patency, and the availability of resources.

Transjugular intrahepatic portosystemic shunt The TIPS procedure is performed in the radiology suite with the patient under local anesthesia or conscious sedation. A stent is placed into the liver via the jugular vein to create a connection between a branch of the portal vein and the hepatic vein (see Figure 1, page 38). TIPS may be utilized as a salvage procedure for patients with acute bleeding that cannot be controlled with medications or endoscopic therapy. The other indication is as a temporary bridge to imminent transplant. TIPS does not impair the patient's ability to receive a transplant,¹⁹ and the procedure is proven effective for esophageal and gastric variceal bleeding and prevention of rebleeding.^{12,20} Some drawbacks are that shunting diverts blood flow from the liver; therefore, it may worsen liver failure and increase the risk of encephalopathy. The procedure is also plagued by dysfunction from stenosis and thrombosis.¹³ The rate of shunt occlusion after TIPS is reported to be 10% to 60% at 1 year and 70% to 85% at 2 years. Polytetrafluoroethylene-covered stents are expected to reduce the occlusion rate; however, patients who have undergone TIPS still require close follow-up and repeat interventions to maintain stent patency.^{1,21}

H-graft portacaval shunt (HGPCS) Surgical shunting with an HGPCS is a major procedure that involves interposing a graft between the portal vein and inferior vena cava at a 90° angle.²² The graft is generally 8 to 10 mm in diameter and helps maintain good perfusion of the liver.²¹ Severity of underlying liver disease and availability of medical resources factor into whether a patient may receive a surgical shunt; the portal vein also must be patent. Whereas some clinicians feel the portacaval shunt has been made obsolete by the introduction of TIPS, HGPCS clearly still has some appropriate applications. Patients with less severe liver disease (Child-Pugh class A or B or MELD score lower than 14) should undergo HGPCS instead of TIPS, based on the availability of a skilled surgeon.^{11,22} Patients are followed up with transfemoral cannulation of the shunt to confirm patency. A few benefits of HGPCS is that the H-graft shunt is less likely to stenose or lose patency following surgery and recurrent variceal hemorrhage is less likely to occur.²³ TIPS is preferred over HGPCS for patients who are not suitable candidates for surgery or when an experienced surgeon is not available.

Distal splenorenal shunt (DSRS) An anastomosis created between the distal end of the splenic vein and the left renal

TABLE 3. Child-Pugh classification system for liver dysfunction

Factors	1 Point	2 Points	3 Points
Albumin	>3.5 g/dL	2.8-3.5 g/dL	<2.8 g/dL
Ascites	None	Controlled	Refractory
Bilirubin	<2 mg/dL	2-3 mg/dL	>3 mg/dL
Encephalopathy	None	Controlled	Advanced
Prothrombin time	1-3 sec	4-6 sec	>6 sec

Score: Class A, 5-6 points; class B, 7-9 points; class C, 10-15 points

Data from Rosemurgy A and Zervos E,² Krige JE and Beckingham IJ,⁶ and Durand F and Valla D.⁸

vein serves to decompress gastroesophageal varices without diverting blood flow to the liver. The occurrence of post-operative encephalopathy is thereby limited, which is especially helpful to patients with recurrent variceal bleeding and good hepatic function.²⁴ DSRS should not be used in patients with intractable ascites because ascites may be worsened if the lymphatics around the renal vein are divided.²¹ A DSRS may be used in patients who have portal vein occlusion. DSRS also does not disturb the right upper quadrant so the patient is in good condition for future transplant.

Devascularization These procedures have lost favor because other options are available; however, they may be useful for patients with portal vein thrombosis that precludes application of TIPS or surgical shunts. The procedure typically involves splenectomy and dividing the mesentery of the upper two-thirds of the lesser and greater curvatures of the stomach and esophagus up to the diaphragm while preserving the left gastric vein. The esophagus is then transected and anastomosed end-to-end to ligate esophageal varices; however, the surgeon may prefer not to perform this part of the procedure. Stringent patient selection has resulted in mortality and rebleeding rates of less than 10%.²¹

Transplantation The best survival rates and most improved quality of life for patients with portal hypertension are achieved through transplantation. The portal vein is decompressed, and the fundamental liver disease is eliminated. Transplantation is particularly beneficial for patients with Child-Pugh class B or C cirrhosis if medical and endoscopic efforts to prevent rebleeding have failed.¹¹ When liver transplantation is performed to treat bleeding, the survival rate is 79% at 1 year and 71% at 5 years.¹⁹ Transplantation is generally not available as an emergency procedure or as treatment for acute hemorrhage.

SUMMARY

Portal hypertension, as a result of cirrhosis or other cause of liver dysfunction, is a life-threatening disease process. The risk of bleeding varices is high. Treatment options have much better outcomes when administered early on. The role of the PA in treating portal hypertension centers on recognizing the complications and understanding the medical

management of those problems. Familiarity with the available treatment options can facilitate initiation of the most appropriate therapy for each patient. The best plan of action is to stabilize the patient and refer him or her to a tertiary center with clinicians who have experience in managing this uncommon problem. **JAAPA**

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DRUGS MENTIONED

Furosemide (Lasix)	Octreotide (Sandostatin)
Isosorbide	Propranolol (Inderal, Inderide, Innopran XL)
Lactulose	Somatostatin
Neomycin tablets	Spirolactone (Aldactone)

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