Portal hypertension is diagnosed when the hepatic vein-pressure gradient (HVPG), which reflects hepatic sinusoidal pressure, is more than 6 mm Hg. The elevation in portal pressure results in the development of portosystemic venous collaterals, ascites, and hepatic encephalopathy. Each year, approximately 40,000 deaths within the United States are related to complications of cirrhosis, and the vast majority of these patients will die from complications of portal hypertension or hepatocellular carcinoma.

Pathogenesis of Portal Hypertension

As in all vascular systems, portal pressure is a product of portal blood flow and resistance to portal flow. Portal hypertension may, therefore, result from increases in portal blood flow, increases in portal vascular resistance, or a combination of these factors. Increased portal blood flow is an uncommon cause of portal hypertension. In the majority of cases, the initiating event in portal hypertension secondary to cirrhosis is increased resistance to portal blood flow. The site of increased portal resistance depends on the etiology of portal hypertension. Although the site of increased portal resistance has been classified broadly as presinusoidal, sinusoidal, and postsinusoidal, this scheme oversimplifies the actual sites of resistance. In fact, multiple levels of resistance exist for various causes of cirrhosis. In alcoholic cirrhosis and cirrhosis secondary to viral hepatitis, the increase in resistance is at the level of hepatic sinusoids, whereas cirrhosis secondary to primary biliary cirrhosis has, in addition, a presinusoidal component. In schistosomiasis, which is the most frequent cause of portal hypertension worldwide, the site of increased resistance is in the presinusoidal portal venules. In extrahepatic portal vein obstruction, the increased resistance is in the portal vein and its tributaries, whereas in Budd-Chiari syndrome, increased resistance is at the level of the hepatic venous outflow tract. In contrast to most patients who develop portal hypertension from chronic liver disease and increased resistance to portal venous blood flow, the initial stage of portal hypertension in patients with an arteriovenous fistula is secondary to increases in portal blood flow.

In cirrhosis, increased resistance to vascular flow may be secondary to mechanical or vascular factors. Mechanical factors include fibrosis and nodularity, which distort the portal vasculature. Vascular factors that contribute to increased intrahepatic portal vasoconstriction include an elevation in the vasoconstrictor endothelin and a decrease in vasodilator substances, such as nitric oxide. These vasoactive substances are potential targets for the development of drugs to decrease portal pressure. The increase in portal venous flow is secondary to splanchnic vasodilatation and an increase in the cardiac output.

Financial disclosure information is located at the end of this chapter before the references.
splanchnic arteriovenous fistula as a cause of portal hypertension, whereas a venous hum in the epigastrium represents collateral flow in the falciform ligament. Alterations in mental status and asterixis, although rarely presenting findings, may be evident also.

Laboratory studies usually reveal evidence of hepatic dysfunction. Hypersplenism associated with cirrhosis is characterized by a mild to moderate thrombocytopenia and leukopenia. Anemia may be present from recent hemorrhage, hemolysis, or malnutrition. Electrolyte abnormalities, including hyponatremia, hypokalemia, azotemia, and acid-base derangements, may also be present. As hepatic dysfunction progresses, coagulation factors synthesized by the liver are reduced, and, consequently, the prothrombin time and international normalized ratio (INR) increase. Similarly, a degree of hyperbilirubinemia occurs with either chronic or acute hepatic decompensation. Serum aminotransferases are elevated variably and partially reflect a degree of hepatocellular necrosis with the underlying liver process. The diagnosis of cirrhosis is not always clear and may require a liver biopsy for confirmation. However, a combination of physical examination, laboratory tests, and radiologic imaging may strongly suggest the diagnosis even without a liver biopsy.\(^5\)

The most accurate method of diagnosing portal hypertension is measuring the HVPG, which is the gradient between the wedged hepatic vein pressure (WHVP) and the free hepatic vein pressure (FHVP).\(^7\) Measurement of the HVPG requires passage of a balloon catheter under fluoroscopic guidance into the hepatic vein. Measurement of the pressure with the balloon inflated and occluding the hepatic vein represents the WHVP, and the pressure with the balloon deflated represents the FHVP. The HVPG may be used to monitor portal pressure in patients on pharmacologic treatment, as a prognostic marker; to assess the risk of hepatic resection in patients with cirrhosis; and to determine the cause of portal hypertension, that is, presinusoidal, sinusoidal, or postsinusoidal.

In selected circumstances, direct measurement of the portal vein pressure may be carried out through a percutaneous transhepatic route when HVPG cannot be measured, as in patients with Budd-Chiari syndrome, in whom the hepatic veins are occluded, or in patients with an intrahepatic presinusoidal cause of portal hypertension, where the HVPG is normal.

### Determination of the Severity of Liver Disease

The two most commonly used methods to assess the severity of liver disease are the Child-Turcotte-Pugh (CTP) class and the Model for End-stage Liver Disease (MELD) score. The components of the CTP class and the CTP score are shown in Table 1. The MELD score is derived based on a patient’s bilirubin, INR, and creatinine level: \( \text{MELD} = 3.78[\ln \text{serum bilirubin (mg/dL)}] + 11.2[\ln \text{INR}] + 9.57[\ln \text{serum creatinine (mg/dL)}] + 6.43; \) http://www.mayoclinic.org/meld/mayomodel5.html. The MELD score is currently used to prioritize allocation of organs for liver transplantation within the United States and many other countries. The advantages of the MELD score over the CTP score are that it uses only objective variables (the CTP score includes ascites and hepatic encephalopathy, which have a subjectivity in determination), has no ceiling or floor effects (e.g., in the CTP system, a serum bilirubin level of > 3 mg/dL and a bilirubin level of 30 mg are both given the same score, and albumin levels of 2.8 g/dL and 1.8 g/dL are also given the same score), and has extensive prospective validation. However, the CTP score is used more commonly in stratifying perioperative risk, especially as it relates to surgery for portal hypertension. Importantly, both the CTP class and MELD score are predictive of operative risk of death in patients with cirrhosis undergoing any major operation.\(^8,9\) However, only the MELD score is predictive of long-term survival, which can be calculated using the following website: http://www.mayoclinic.org/meld/mayomodel9.html.\(^8\) Serum Na+, when added to the other MELD parameters, improves the predictive accuracy of the model and is calculated as follows:

\[ \text{MELDNa} = \text{MELD} – \text{Na} – [0.025 \times \text{MELD} \times (140 – \text{Na})] + 140 \]\n
### Detection of Varices

Upper gastrointestinal endoscopy is the most common method used to detect varices. All patients with cirrhosis of the liver who are potential candidates for prophylactic treatment with either endoscopic variceal ligation or nongenetic beta blockers should be screened for esophageal varices by upper endoscopy. When patients with newly diagnosed cirrhosis are screened by endoscopy, large varices are seen in about 15 to 20% of patients. If no varices are detected at the initial endoscopy, then a repeat endoscopy should be carried out in 2 to 3 years. On the other hand, if only small esophageal varices are noted, then the procedure should be repeated in 1 to 2 years. Endoscopic grading of varices is subjective. The most acceptable classifications of varices at endoscopy are small (< 5 mm in diameter) and large (< 5 mm in diameter) [see Figure 1 and Figure 2]. The risk of bleeding within 1 year is the highest in patients with large esophageal varices, Child-Pugh class C, and red-colored signs on varices [see Figure 2 and Figure 3].

### Table 1 Child-Turcotte-Pugh Classification of Severity of Liver Disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>1</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Absent</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt; 3.5 g/dL</td>
</tr>
<tr>
<td>Prothrombin time (seconds over control)</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>INR</td>
<td>&lt; 1.7</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
</tbody>
</table>

\[ A \text{ total score of 5 to 6 is graded as class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease).} \]
Platelet counts and the platelet-to-spleen diameter ratio are not sensitive enough to determine which patients are at high risk for developing varices. Ultrasound examination has been used to confirm splenomegaly and detect thrombosis in the portal venous system. Fibroelastography, using either ultrasonography or magnetic resonance imaging, is a new technique to study liver stiffness and may be helpful in detecting portal hypertension but cannot be used to monitor changes in portal pressure. Multidetector row computed tomography is an emerging modality for the detection of esophageal varices, as is capsule endoscopy. However, liver biopsy is still the gold standard for the diagnosis of cirrhosis, and upper endoscopy is the standard for grading of varices.

Large esophageal varices are seen in approximately 15 to 20% of patients with cirrhosis screened by upper endoscopy. In patients who do not have esophageal varices at the initial endoscopy, the annual rate of development of new varices is approximately 5%. In patients in whom small varices are noted at initial endoscopy, progression to large varices occurs at a rate of about 10% per year. The rate of progression in variceal size is related to increases in portal pressure related to changes in liver fibrosis in liver function. On the other hand, improvement in liver function in patients with alcoholic liver disease may be associated with a decrease in or even disappearance of varices. Without prophylactic treatment, the risk of bleeding in patients with small varices is 7% at 2 years, whereas the risk of bleeding in patients with large varices is 30% at 2 years. Bleeding is virtually absent when the HVPG is below 12 mm Hg. In patients who bleed, the risk of death with acute variceal bleeding is 5 to 8% at 1 week and about 20% at 6 weeks. Patients with a higher MELD score and those who require greater than 4 units of packed red blood cell transfusions are at the highest risk of death.

Modalities for Treatment of Portal Hypertension–Related Bleeding

Treatment of portal hypertension is traditionally aimed at decreasing portal pressure by decreasing portal blood flow with pharmacologic agents or through the creation of portosystemic shunts, using radiologic or surgical techniques as a means of decreasing resistance to portal blood flow. Treatment may also be focused on obliteration of the varices using endoscopic techniques. Rarely, surgical devascularization is used in isolated segments of the gastrointestinal tract with varices to control bleeding when other alternatives have been exhausted.
PHARMACOLOGIC THERAPY

The pharmacologic agents that decrease splanchnic blood flow are vasopressin and its analogues, somatostatin and its analogues, and nonselective beta-adrenergic blockers. Vasopressin and somatostatin and their analogues are given parenterally and are used only in the acute situation. Vasopressin, a splanchnic vasoconstrictor, can control acute bleeding in nearly half of patients but is not currently used because of an increased risk of cardiovascular ischemia. The semisynthetic analogue of vasopressin, terlipressin, has been used extensively in Europe because of its superior safety profile but is not currently available in the United States. The agent most commonly used within the United States is the somatostatin analogue octreotide because of its safety profile. Octreotide reduces portal pressure by decreasing portal blood flow through arteriolar splanchnic vasoconstriction. Octreotide is administered intravenously as a bolus of 50 µg followed by a continuous infusion at the rate of 50 µg/hr.

Nonselective beta-adrenergic agents are the preferred treatment for long-term use in decreasing portal pressure. A nonselective beta blocker is essential because blockade of beta-1-adrenergic receptors in the heart decreases cardiac output, whereas blockade of beta-2-adrenergic receptors results in a decrease in portal blood flow. Of the two nonselective beta blockers, nadolol is preferred to propranolol because it is excreted predominantly by the kidney and has lower lipid solubility, which is associated with a lower risk of central nervous system side effects. The initial starting dose of nadolol is 20 mg daily and that of propranolol is 40 mg daily as a long-acting preparation. The dose of the agents is titrated upward every 3 to 5 days until a target heart rate of 55 to 60 beats per minute is reached or a decrease in resting heart rate by 25% is achieved. Recently, carvedilol, a nonselective beta blocker with additional alpha blocking activity, has been introduced for the prevention of variceal bleeding. The effect of alpha blockade is to decrease intrahepatic vascular resistance. Thus, carvedilol causes further decrease in portal pressure than do nonselective beta-blockers alone.15 Carvedilol is currently recommended in patients with portal hypertension who, in addition, have coronary artery disease or systemic hypertension but, in future, may be recommended for the majority of patients with portal hypertension. Nitrates act by causing venous dilatation and decreased portal blood flow because of the resulting reflex splanchnic vasoconstriction. Nitrates are seldom used within the United States because of the inability of most patients to tolerate the medication for prolonged periods because of headaches.

ENDOSCOPIC THERAPY

Endoscopic therapy is the only modality that can be used to prevent variceal bleeding, control variceal bleeding, and prevent variceal rebleeding. The preferred endoscopic technique is variceal ligation [see Figure 4]. Multiband devices are available that can apply several bands without withdrawal of the endoscope. The procedure involves suctioning of the varix into the device at the end of the endoscope. A band is then deployed around the varix, which strangulates the vessel and causes thrombosis. Banding the varices is started at the gastroesophageal junction and, moving more proximally in a spiral fashion, at approximately 2 cm intervals. Care should be taken to avoid applying the bands at the same level because of the risk of triggering esophageal strictures. Complications of variceal ligation include esophageal ulceration and esophageal strictures. Pulmonary aspiration may also occur. Gastric varices and ectopic varices may be treated using cyanoacrylate glue, which obliterates the varices. These glues are used off label in the United States.

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNTS

A transjugular intrahepatic portosystemic shunt (TIPS) functions effectively as a side-to-side portocaval shunt [see Figure 5]. The technique involves creating a communication in the intrahepatic portion of the liver between the hepatic vein and a portal vein. Because TIPS functions like a side-to-side portocaval shunt, it may be used to treat not only acute or recurrent variceal bleeding but also refractory ascites, Budd-Chiari syndrome, and hepatic hydrothorax. The TIPS placement is usually performed with the patient under sedation. A platelet count of more than $50 \times 10^3/µL$ and an INR less than 2 are usually recommended. The hepatic vein is cannulated through a transjugular approach by an interventional radiologist. Using a Rosch needle, the portal vein is cannulated through the intervening liver from the hepatic vein. The tract is dilated over a guide wire, and an expandable metal stent is placed across the tract to reduce the portocaval pressure gradient to below 12 mm Hg. The stent may be balloon dilated to reduce the pressure so that the target pressure of less than 12 mm Hg is reached. A coated stent is preferred nowadays. The uncoated portion anchors the stent to the portal vein, whereas the polytetrafluoroethylene-coated portion lines the tract within the liver. Shunt stenosis is reduced when coated stents are used. TIPS can be placed successfully in over 95% of patients and is associated with a procedure-related mortality of approximately 1%.16
Complications may occur early or late. Intra-abdominal bleeding is the most serious immediate complication. Long-term complications are related to shunt stenosis. Survival of patients following placement of a TIPS may be determined using the MELD score. Follow-up ultrasonography at 6-month intervals is recommended as surveillance for shunt patency. The patency of TIPS can usually be maintained through repeated radiographic intervention.

Surgery for Portal Hypertension

Surgical treatment for portal hypertension includes portosystemic shunts, nonshunt procedures, and liver transplantation. Surgical procedures are used infrequently for patients with portal hypertension from cirrhosis because of the efficacy of both TIPS and liver transplantation. In fact, all patients with cirrhosis and variceal bleeding should be evaluated for liver transplantation, but patients with a MELD score less than 15 are not likely to have a survival benefit with liver transplantation. Portal hypertensive bleeding should be managed preferably by nonoperative alternatives as a bridge to transplantation, and only failure of nonoperative management should prompt consideration of operative intervention. When a surgical procedure is being considered, the choice of nontransplant procedure is dependent on the presence or absence of underlying liver disease, the patency of the portal venous system, the acuity of the variceal hemorrhage and its response to nonoperative therapy, and candidacy for liver transplantation. Patients who are CTP class A are the best candidates for nontransplant operations for portal hypertension from cirrhosis. However, patients with portal hypertension and variceal bleeding from portal vein thrombosis should be evaluated for nontransplant operative procedures.

Nonshunt Surgical Procedures

Nonshunt procedures include esophageal transection and gastroesophageal devascularization. Gastroesophageal devascularization is generally reserved for patients with extensive portal venous thrombosis in whom the absence of a suitable patent branch of the portal vein precludes portosystemic shunting.

Esophageal Transection

Esophageal transection involves division and anastomosis of the esophagus, usually by stapling, to disrupt esophageal varices. Often splenectomy is performed to further reduce portal blood flow. The Sugiura procedure has been the primary transection procedure employed and is usually coupled with selective vagotomy. Importantly, this operation attempts to maintain patency of paraesophageal collaterals to permit the development of additional portoazygos collaterals, thus diverting the hypertensive portal blood flow from the esophagogastric junction. Esophageal transection has reportedly been safe and highly effective in controlling variceal bleeding and is associated with a lower risk of encephalopathy than that for portosystemic shunts in the East but not in the West. Patient selection and modifications in the originally described technique likely account for the differences in outcome. Esophageal transection typically has been undertaken when patients continued to bleed from esophageal varices despite two endoscopic sessions within a 24-hour period. With the increasing use of emergency TIPS to control acute variceal bleeding, esophageal transection is seldom used.

Devascularization Procedures

Devascularization procedures are performed to prevent recurrent variceal bleeding in patients with CTP class A in whom a portosystemic shunt is precluded, either surgically or radiologically. Typically, these procedures are employed in patients with extensive splenic and portal venous thrombosis. As originally described by Sugiura, a combined thoracotomy and laparotomy approach was required, but, subsequently, the operation has been carried out through an abdominal approach combined with a splenectomy. Total

Figure 5 Transjugular intrahepatic portosystemic shunt (TIPS). (a) Portogram demonstrating gastroesophageal varices and portal perfusion of the liver. (b) Portogram following creation of TIPS. Note the absence of portal hypertension.
The rate of recurrent bleeding following this procedure depends a great deal on the extent of devascularization and may be as high as 40% if devascularization is incomplete.

**PORTOSYSTEMIC SHUNTS**

Surgical portosystemic shunts are divided into selective shunts, partial shunts, and total portosystemic shunts.

**Selective Shunts**

Selective shunts isolate and decompress only a portion of the portal venous system, that is, only the gastroesophageal junction, proximal stomach, and spleen. The most widely used selective shunt is the distal splenorenal shunt or Warren shunt [see Figure 7]. Portal hypertensive blood flow is maintained to the liver through the uninterrupted superior mesenteric and portal veins, and hepatic sinusoidal pressure remains elevated; therefore, selective shunts are ineffective in treating ascites. The distal splenorenal shunt is constructed by anastomosing the distal end of the splenic vein from the preserved spleen to the side of the left renal vein. The right and left gastric and right epiploic veins and greater curve perforating branches to the gastroepiploic vein are ligated, but the short gastric veins are preserved to decompress the gastroesophageal junction through the shunt. Additionally, all pancreatic branches to the splenic vein from the splenic hilus to the portal vein are divided to prevent the late loss of selectivity of this shunt. In expert hands, the distal splenorenal shunt can prevent variceal bleeding in more than 90% of patients with low operative mortality and morbidity and a low risk of hepatic encephalopathy, approximately 25% have two episodes of hepatic encephalopathy requiring hospitalization, and approximately 50% have one episode at 5 years.

**Partial Portosystemic Shunts**

A partial portosystemic shunt is actually a type of side-to-side portocaval shunt, but the shunt is calibrated by the size of the synthetic interposition graft placed between the portal vein and the inferior vena cava. Shunt diameters of 8 mm usually reduce the portal pressure to less than 12 mm Hg and maintain most antegrade portal blood flow to the liver. Construction of a partial shunt is technically simpler than construction of a distal splenorenal shunt. Although partial shunts are nonselective because they do not selectively decompress an isolated portion of the portal system, their efficacy in terms of reduction of variceal bleeding and the rate of encephalopathy is similar to that seen with a distal splenorenal shunt.

**Figure 6** By extensively devascularizing the esophagogastric junction, this procedure may provide means of interrupting esophagogastric varices without portosystemic shunting.
Nonselective Portosystemic Shunts

Nonselective shunts effectively decompress the entire portal venous system and divert portal blood flow from the liver to a significant degree. Nonselective portosystemic shunts include the end-to-side and side-to-side portocaval shunts, the central splenorenal shunt [see Figure 8a], and the mesocaval shunt [see Figure 8b]). The end-to-side portocaval shunt [see Figure 8c]), which was an excellent procedure for preventing variceal bleeding but which could not be used to treat ascites because hepatic sinusoidal pressure was maintained, is no longer used. Nowadays, the side-to-side portocaval shunt is used predominantly [see Figure 8d]). Any portocaval shunt more than 12 mm in diameter results in almost total shunting of portal blood flow. These shunts are very effective in controlling bleeding and ascites because the hepatic sinusoids are decompressed, but hepatic encephalopathy occurs in about 40% of patients followed long term. Moreover, these shunts may be associated with increased morbidity and intraoperative transfusion requirements in those patients who undergo liver transplantation.

Management of Specific Causes of Portal Hypertension–Related Bleeding

ESOPHAGEAL VARICES

Treatment of esophageal variceal bleeding is classified as either (a) primary prophylaxis to prevent the first bleeding [see Figure 9]; (b) control of acute variceal bleeding [see Figure 10]; or (c) secondary prophylaxis to prevent rebleeding in patients in whom the initial bleeding is controlled [see Figure 11].

Primary Prophylaxis

Either nonselective beta blockers or endoscopic variceal ligation should be considered in patients with large varices. In patients with CTP class C cirrhosis, small varices should also be considered for treatment with a beta blocker. The benefit of primary prophylaxis is greatest in patients with large varices, with the prevention of variceal bleeding in approximately one of 10 patients treated. Either nadolol or a long-acting preparation of propranolol may be used. In
Nonselective portosystemic shunts either immediately or eventually divert all portal blood flow from the liver into the systemic venous circulation. Shown are the four main variants: (a) conventional (proximal) splenorenal shunt, (b) interposition shunt (portacaval [1], mesocaval [2], and mesorenal [3]), (c) end-to-side portacaval shunt, and (d) side-to-side portacaval shunt.

Figure 8

approximately 15% of patients, the drug is discontinued because of side effects. The physiologic goal of treatment with beta blockers is a resting heart rate of between 55 and 60 beats per minute, provided that the systolic blood pressure is more than 90 mm Hg. If patients are started on pharmacologic treatment, follow-up endoscopy is not required unless gastrointestinal bleeding occurs.

Endoscopic variceal ligation is an alternative treatment. Variceal ligation is associated with a lower risk of bleeding and bleeding-related mortality than therapy with beta blockers, but overall mortality is similar. Complications of variceal ligation include esophageal ulcers and strictures, which may be severe but are infrequent with careful technique. Beta blockers are cheaper and convenient to use and may also reduce the risk of bleeding from gastric varices and portal hypertensive gastropathy, but side effects such as fatigue, erectile dysfunction, and cold extremities are more frequent. Moreover, in patients with refractory ascites on beta blockers, long-term survival may be reduced. Therefore, the choice of therapy should be individualized.

Control of Acute Esophageal Variceal Bleeding

The aims of treatment in a patient with active esophageal variceal bleeding are resuscitation of the patient, control of hemorrhage, and prevention of complications such as infections and liver-specific conditions such as ascites and hepatic encephalopathy. Two large-caliber intravenous access catheters should be inserted as the patient is evaluated. Red blood cells are transfused with the goal of maintaining the hematocrit around 25%, and coagulopathy is corrected as indicated. There are no data to guide the use of platelets and fresh frozen plasma during an episode of
**Figure 9** Esophageal variceal bleeding: primary prophylaxis. EGD = esophagastroduodenoscopy.

**Figure 10** Management of acute variceal bleeding: (a) initial management; (b) subsequent management. Early transjugular intrahepatic portosystemic shunt (TIPS) (within 24 to 72 hours) is recommended in patients with Child-Turcotte-Pugh class C or active bleeding at endoscopy.
variceal bleeding. Endotracheal intubation is advisable in the presence of active bleeding. Antibiotics should be administered to all patients to prevent bacteremia. Norfloxacin 400 mg orally twice daily, intravenous ciprofloxacin 400 mg every 12 hours, ceftriaxone 1 g every 24 hours, or levofloxacin 500 mg every 24 hours for 7 days is recommended. Pharmacologic therapy with vasoactive agents should be started as early as possible. Within the United States, the vasoactive agent most commonly used is octreotide. Endoscopic treatment is undertaken as soon as the patient is hemodynamically stable and the vasoactive agent has been infused for at least 30 minutes. Esophageal variceal bleeding is confirmed if active bleeding is seen from the varices or a white fibrin plug or red blood clot is noted over a varix. Esophageal varices are considered the site of bleeding if blood is seen in the stomach and no other bleeding source is identified.

Acute variceal bleeding cannot be controlled by endoscopic variceal ligation and pharmacotherapy in approximately 10% of patients. When two endoscopic sessions within a 24-hour period fail to control variceal bleeding, TIPS should be considered. Balloon tamponade with either a Minnesota tube or a Sengstaken-Blakemore tube may be used to control bleeding until TIPS is undertaken. The Minnesota tube has a suction port in the esophagus that decreases the risk of aspiration. Both have a gastric balloon and an esophageal balloon, but most operators prefer to inflate only the gastric balloon because inflating the esophageal balloon increases the risk of esophageal necrosis. Under no account should the gastric balloon be kept inflated for greater than 12 to 24 hours and the esophageal balloon for greater than 6 hours. Endotracheal intubation greatly reduces the risk of pulmonary aspiration. Patients with CTP class C and a MELD score of 11 to 13, patients with CTP class B with active bleeding at endoscopy, and patients with a MELD score greater than 18 who require transfusion of more than 4 units of red cells to maintain a hematocrit greater than 25% are patients considered at high risk for early rebleeding. Early TIPS (within 24 to 72 hours of control of bleeding) should be considered in these patients. Emergency surgical shunts have largely been abandoned.

Secondary Prophylaxis

All patients who have had even a single episode of esophageal variceal bleeding should receive prophylactic therapy to reduce the risk of recurrent bleeding from esophageal varices. In the absence of secondary prophylaxis, nearly 80% of these patients will have recurrent variceal bleeding at 2 years. Pharmacologic therapy with nonselective beta blockers, endoscopic therapy, and portosystemic shunts (both surgical and TIPS) either alone or in combination have been used for secondary prophylaxis.

The preferred initial treatment to prevent variceal rebleeding is a combination of endoscopic variceal ligation and a nonselective beta blocker. Isosorbide mononitrate is seldom used in the United States as patients typically are intolerant of this medication after beta blockade. Endoscopic variceal ligation alone is carried out in patients who are intolerant of beta blockers. Following control of the acute variceal bleeding with variceal ligation, the next session of endoscopic variceal ligation is carried out at 7 to 14 days. Subsequent sessions are repeated every 3 to 4 weeks until esophageal varices are ablated. If patients have recurrent bleeding after endoscopic variceal ligation alone, beta blockers are added. Conversely, if patients are initially started on nonselective beta blockers alone and have recurrent bleeding, endoscopic variceal ligation is added. For those patients with recurrent bleeding after a combination of endoscopic variceal ligation and beta blocker therapy, an evaluation for a portosystemic shunt is recommended. TIPS is the preferred modality in patients with Child-Pugh class B and C cirrhosis. Even in patients with Child-Pugh class A cirrhosis, the TIPS procedure may be as effective as a distal splenorenal shunt, but the choice of therapy depends on local expertise.
GASTRIC VARICES

The two classes of gastric varices are GOVs and isolated gastric varices (IGVs). Type 1 gastroesophageal varices (GOV1) extend below the gastroesophageal junction along the lesser curvature of the stomach and are in continuity with esophageal varices; type 2 gastroesophageal varices (GOV2) extend into the cardia and fundus of the stomach and are also in continuity with the esophageal varices [see Figure 12]. GOV1 varices comprise approximately 70% of all gastric varices and are treated endoscopically similar to esophageal varices. Varices in the stomach in the absence of esophageal varices are called isolated gastric varices. Type 1 isolated gastric varices (IGV1) are in the fundus, whereas varices that occur elsewhere in the stomach in the absence of esophageal varices are termed IGV2. Although splenic vein thrombosis usually causes IGV1, the most common cause of fundic varices overall is probably cirrhosis. Gastric varices occur in association with advanced portal hypertension, and bleeding is more common in patients with GOV2 and IGV1. Gastric varices that bleed tend to be larger than esophageal varices and are likely to bleed only when their diameter is greater than 1 cm.

Primary Prophylaxis

No large studies have evaluated pharmacologic or endoscopic treatment for primary prophylaxis of gastric variceal hemorrhage, although a recent small study suggests that obliteration of the gastric varices with cyanoacrylate glue might be beneficial. In patients with large gastric varices, pharmacologic treatment with nonselective beta blockers may be started to prevent variceal bleeding. Endoscopic therapy is not currently recommended as primary prophylaxis for gastric variceal bleeding.

Control of Bleeding

The principles of treatment for patients with gastrointestinal bleeding from gastric varices again include volume resuscitation, antibiotic prophylaxis, and a vasoactive agent such as octreotide [see Figure 13]. Endoscopic treatment is performed only after endotracheal intubation because these patients typically have large-volume bleeding. A diagnosis of gastric variceal hemorrhage is sometimes difficult because blood pools in the fundus of the stomach, obscuring visualization of the varices. Gastric variceal hemorrhage is suspected whenever bleeding is noted from a gastric varix; if blood is found in the stomach and gastric varices with a white nipple sign are noted; if active bleeding is seen at either the gastroesophageal junction or in the gastric fundus; or if blood is seen in the stomach and gastric varices are noted in the absence of other lesions in the esophagus and stomach.

The preferred endoscopic treatment for fundal gastric variceal bleeding is injection of cyanoacrylate polymers, usually N-butyl-2-cyanoacrylate in the United States. These cyanoacrylate tissue adhesives are not licensed for use in the United States for variceal injection. Varices are obliterated when the cyanoacrylate adhesives harden on contact with blood. Cyanoacrylate glue injection is superior to both endoscopic variceal ligation and alcohol sclerotherapy in the treatment of gastric fundal varices. Pulmonary and cerebral emboli have been reported, especially in patients with spontaneous large portosystemic shunts or intrapulmonary shunts, and may even be associated with mortality.

If endoscopic and pharmacologic therapies have failed to control gastric variceal hemorrhage, TIPS is performed. A Linton-Nachlas tube with a 600 mL volume gastric balloon may be used temporarily to tamponade bleeding from gastric varices in patients requiring TIPS. The Minnesota tube and the Sengstaken-Blakemore tube with only 250 mL gastric balloons may not be as effective.

Figure 12  Endoscopic image of gastric varix (arrow) in continuity with esophageal varices.

Figure 13  In patients with acute gastric variceal bleeding, initial management consists of transfusion to a hemoglobin of ~8 g/dL, pharmacotherapy with vasoactive agents, and antibiotic prophylaxis. Endoscopic treatment is carried out, but if acute hemorrhage is not controlled, transjugular intrahepatic portosystemic shunt (TIPS) is recommended. If the acute hemorrhage is controlled and cyanoacrylate is available, obliteration of the gastric varices is attempted with cyanoacrylate. If cyanoacrylate is not available, then TIPS is recommended. *A surgical shunt may be considered in patients with Child-Turcotte-Pugh class A cirrhosis.
Secondary Prophylaxis

No control trials have determined the preferred therapy for the prevention of recurrent gastric variceal bleeding. Cyanoacrylate glue injection for secondary prophylaxis has been used, with excellent results. Alternatively, transvenous obliteration of gastric varices can also be undertaken in patients with demonstrable spontaneous splenorenal shunts by interventional radiologists. This technique requires considerable radiologic skill and is currently popular only in some centers in the Far East. TIPS is effective in preventing gastric variceal rebleeding in patients with cirrhosis. However, TIPS does not always result in a decrease in the size of gastric varices even when the HVPG is less than 12 mm Hg; therefore, the target HVPG in these patients is not clear.

Ectopic Varices

Varices that occur at a site other than the gastroesophageal junction and stomach are termed ectopic varices. Ectopic varices account for fewer than 5% of all variceal-related bleeding. Depending on the site of rupture of the varices, clinical manifestations include melena, hematemesis, hemobilia, hematuria, and retroperitoneal or intraperitoneal bleeding. Ectopic varices occur in patients with both extrahepatic portal vein obstruction and cirrhosis. The most common site of ectopic varices is the duodenum. The site of gastrointestinal stomas, particularly in patients with inflammatory bowel disease and primary sclerosing cholangitis who have had an ileostomy following proctocolectomy, is the next most frequent. Peristomal varices present as a bluish halo surrounding the stoma. Anorectal varices are noted in about 10 to 40% of patients with cirrhosis who undergo colonoscopy.

In patients with suspected ectopic variceal bleeding, vasoactive drugs may be used initially to control bleeding. If the ectopic varices are visualized endoscopically, as in the duodenum or colon and rectum [see Figure 14], they are treated with band ligation or glue injection. Colonic varices may require application of hemostatic clips. Stomal varices are initially treated with local compression, but, subsequently, patients require either ultrasound-guided variceal sclerotherapy, transhepatic embolization of the stomal varices, or TIPS.

Ectopic varices that present as intraperitoneal hemorrhage are associated with a poor outcome because the diagnosis is often made late and patients may require a laparotomy.

Portal Hypertensive Gastropathy and Gastric Vascular Ectasia

Portal hypertensive gastropathy is common in patients with cirrhosis and is characterized by a cobblestone appearance of the gastric mucosa on endoscopy. If red spots are superimposed on the cobblestone appearance, the patients are said to have severe portal hypertensive gastropathy [see Figure 15]. Gastric vascular ectasia is an entity in which there are ectatic vessels in the absence of a background mosaic pattern [see Figure 16]. When these vascular aggregates occur in the antrum of the stomach arranged in a linear pattern, the term watermelon stomach is used. If the aggregates are more widely dispersed, the term used is gastric antral vascular ectasia. Portal hypertensive gastropathy responds to beta blockers or TIPS. However, vascular ectasia may require thermoablative therapy and, occasionally, antrectomy. TIPS does not reduce the risk of bleeding from gastric vascular ectasia.

Ascites

The initiating event in the formation of ascites is sinusoidal portal hypertension. The resulting splanchnic vasodilatation results in a decrease in the effective arterial blood volume. As a means of increasing the circulating intravascular volume, there is activation of the renin-angiotensin-aldosterone system, vasopressin, and the sympathetic

Figure 14  (a) Colonic varix (arrow). (b) Rectal varix (arrow) seen on retroflexion of the colonoscope in the rectum.
Figure 15  Endoscopic image of severe portal hypertensive gastropathy. Note the cobblestone appearance (arrow) with red signs on the cobblestone.

nervous system. The net result of these actions is renal retention of sodium and water and renal vasoconstriction. The excess fluid is compartmentalized into the peritoneal space because of portal hypertension. As cirrhosis progresses, there is further splanchnic vasodilatation and renal vasoconstriction. Ultimately, refractory ascites and hyponatremia, both of which are associated with decreased survival, occur. When renal vasoconstriction occurs and the serum creatinine is greater than 2.5 mg/dL, the condition is termed type 1 hepatorenal syndrome, which is associated with a median survival of only 2 weeks without treatment. When the serum creatinine rises above 1.5 mg/dL, patients are said to have type 2 hepatorenal syndrome, the major manifestation of which is refractory ascites. The median survival in patients with refractory ascites is 6 months. Another manifestation associated with increased renal retention of sodium and water is hepatic hydrothorax, that is, pleural effusions in the presence of ascites.

Treatment of ascites is aimed toward maintaining a negative sodium balance. Specifically, renal sodium losses should exceed sodium intake because extrarenal losses of sodium via perspiration and stooling are more limited and difficult to control. Patients with ascites are typically placed on a 2 g sodium restricted diet (88 mEq of sodium). Spironolactone is the preferred diuretic because it is an aldosterone antagonist. The maximum dose of spironolactone is 400 mg per day. Spironolactone alone can achieve adequate renal sodium losses in 60 to 70% of patients. Furosemide is added in escalating doses if sodium restriction and spironolactone alone do not result in a daily weight loss of more than 500 g per day. The goal of treatment with diuretics is to achieve a daily weight loss of 500 g per day in the absence of lower limb edema and 1 kg a day in the presence of edema. The dose of diuretics is increased every 3 to 5 days if weight loss is less than 200 g per day.

If, in spite of sodium restriction and diuretics, a weight loss of more than 200 g per day is not achieved, the patient has refractory ascites. Most of these patients have diuretic-intractable ascites; that is, ascites persists because further increases in the dose of diuretics are associated with complications such as hyponatremia, renal insufficiency, and hepatic encephalopathy. Patients in whom ascites cannot be adequately immobilized in spite of 400 mg of spironolactone and 160 mg of furosemide per day have diuretic resistance ascites.

Figure 16  Gastric vascular ectasia (arrow), which are ectatic vessels seen in the absence of background mosaic pattern.

When ascites is refractory to diuretic treatment, large-volume paracentesis is recommended. Albumin is infused in a dose of 6 to 8 g per liter of ascitic fluid removed to prevent renal dysfunction and rapid reaccumulation of ascites. If more than two to three large-volume paracenteses are required every month in spite of optimal sodium restriction and maximal diuretics, TIPS is performed [see Figure 17]. TIPS results in better control of ascites in more than 80% of patients but is associated with an increased risk of hepatic encephalopathy and no change in overall survival. A peritoneovenous shunt should be considered in patients with refractory ascites in whom venous anatomy precludes TIPS. Peritoneovenous shunts are avoided in patients who are candidates for liver transplantation because of the risk of procedure-related mortality and, potentially, peritoneal fibrosis around the catheter. Peritoneovenous shunts are associated with frequent shunt occlusion and disseminated intravascular coagulation. The Denver shunt is the only peritoneovenous shunt currently on the market.

spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is caused by infection of ascites in the absence of a perforated viscus. SBP is suspected clinically in patients with ascites who develop fever and, sometimes, abdominal tenderness with associated
Figure 17  Algorithm for management of ascites. TIPS = transjugular intrahepatic portosystemic shunt.

hepatic and renal deterioration without an obvious abdominal source of infection. The diagnosis of SBP is confirmed by an absolute neutrophil count over 250/mL and a positive bacterial culture of the ascites. Unlike secondary bacterial peritonitis, SBP is typically monomicrobial and associated with low ascitic fluid total protein, most often less than 1 g/dL. Treatment for SBP is initiated promptly because the mortality risk approaches 25%. SBP is treated with intravenous cefotaxime 2 g every 8 hours for 5 days and infusion of albumin 1.5 g/kg on day 1 of treatment and 1 g/kg on day 3 of treatment. A repeat paracentesis is carried out in 48 hours to confirm a decrease in the absolute neutrophil count. If the absolute neutrophil count has not decreased by 25%, peritonitis secondary to a perforated vissus or diverticulitis should be suspected. Secondary bacterial peritonitis is also suspected if the cultures are polymicrobial, anaerobic, or fungal. Computed tomography of the abdomen with oral contrast may be required for diagnosis in such patients. Following the resolution of SBP, norfloxacin 400 mg once daily is given indefinitely to prevent recurrence. Fluoroquinolones may also be used to prevent SBP in patients with low-protein ascites who have not previously had SBP. 29

HEPATIC ENCEPHALOPATHY

The neuropsychiatric manifestations of portal hypertension are termed hepatic encephalopathy. Hepatic encephalopathy requires a combination of portosystemic shunting and altered liver function. When hepatic encephalopathy occurs in the absence of significant hepatic dysfunction (MELD score < 15), a large portosystemic shunt should be suspected.

Precipitating factors for hepatic encephalopathy include gastrointestinal bleeding, infection, hypokalemia, dehydration, and excessive intake of animal proteins. Ammonia has been implicated in the pathogenesis of hepatic encephalopathy, but there is a poor correlation between circulating levels of ammonia and the severity of hepatic encephalopathy.

Hepatic encephalopathy is treated initially with oral lactulose given in a dose to produce two to three semiformal stools per day. Antibiotics such as neomycin, metronidazole, or rifaximin in a dose of 550 mg orally twice daily may be used in those patients who are intolerant of lactulose or in whom encephalopathy cannot be controlled in spite of optimal lactulose dosing. 30 Dietary protein restriction is no longer recommended, but some patients may benefit from...
conversion to a predominantly vegetable protein diet. When a large portosystemic shunt can be demonstrated and liver dysfunction is not advanced (MELD < 15), occlusion of the portosystemic shunt can be carried out either radiologically or surgically.

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