KEY CONCEPTS

Part of "11 - PORTAL HYPERTENSION"

- Portal hypertension is the most common and lethal complication of chronic liver diseases; it is responsible for the development of gastroesophageal varices, variceal hemorrhage, ascites, renal dysfunction, portal-systemic encephalopathy, hypersplenism, and hepatopulmonary syndrome.
- Portal hypertension is defined by a pathologic increase in portal pressure in which the pressure gradient between the portal vein and inferior vena cava (the portal pressure gradient, or PPG) is increased above the upper normal limit of 5 mm Hg. Portal hypertension becomes clinically significant when the PPG increases above threshold values of 10 mm Hg (formation of varices) or 12 mm Hg (variceal bleeding, ascites). PPG values between 6 and 10 mm Hg represent subclinical portal hypertension.
- The PPG is determined by the product of blood flow and vascular resistance within the portal venous system. Portal hypertension is initiated by an increased resistance to portal blood flow and aggravated by an increased portal venous inflow. The site of increased resistance to portal blood flow is the basis for the classification of portal hypertension: prehepatic (e.g., portal vein thrombosis), intrahepatic (e.g., cirrhosis), and posthepatic (e.g., hepatic vein thrombosis, heart disease).
- The increased resistance in cirrhosis represents not only disruption of the liver vascular architecture by liver disease but also a dynamic component resulting from the active contraction of vascular smooth-muscle cells, myofibroblasts, and hepatic stellate cells. Active contraction is caused by decreased production of the vasodilator nitric oxide (NO) and by increased release of endogenous vasoconstrictors. Increased hepatic vascular tone is the basis for the use of vasodilators to treat portal hypertension in cirrhosis.
- Portal inflow is increased by splanchnic vasodilatation, which is caused by an increased release of local endothelial factors (e.g., NO) and humoral vasodilators (e.g., glucagon). Splanchnic vasodilatation can be counteracted with vasoconstrictors and β blockers, which is why these drugs are used to treat portal hypertension.
- The portal pressure is most commonly assessed clinically by measuring the hepatic venous pressure gradient (HVPG), which is the difference between the wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP), at hepatic vein catheterization. The HVPG accurately reflects the portal pressure in both alcoholic and viral cirrhosis.2
- Bleeding from ruptured esophageal or gastric varices is the main complication of portal hypertension and a major cause of death. It is a major indication for liver transplantation in patients with cirrhosis. About 40% of patients with compensated

cirrhosis have varices at the time of diagnosis. The rate of formation of varices is about 6% per year, so varices develop in most patients during long-term follow-up. The risk for bleeding increases as pressure and size of the varices increase and as thickness of the variceal wall decreases. These parameters determine the tension of the variceal wall; rupture and bleeding occur when wall tension increases above the elastic limit of the varices.

- Most drugs used to treat portal hypertension are vasoconstrictors, which act primarily by reducing blood flow. This group includes vasopressin, terlipressin, the somatostatins, propranolol, nadolol, and other β blockers.
- Vasodilators that decrease the portal pressure include isosorbide-5-mononitrate (IMN), which acts as an NO donor; adrenergic antagonists, such as clonidine and prazosin; and antiendothelins. A common problem with vasodilators is that they exert systemic effects that in turn may enhance sodium retention and aggravate renal dysfunction in cirrhotic patients with ascites.
- In combination therapy, a vasoconstrictor and a vasodilator are administered together. The combination prevents most of the adverse effects of the vasodilator and enhances the fall in portal pressure caused by the reduction in blood

flow induced by the vasoconstrictor. Drug combinations with proven clinical efficacy are vasopressin plus nitroglycerin and propranolol or nadolol plus IMN.

- Continued drug therapy with propranolol or nadolol is highly effective and the only accepted therapy to prevent first bleeding in patients with varices. This treatment should be given to all patients with varices more than 5 mm in diameter who have no contraindications to β blockers. Therapy should be maintained indefinitely and is relatively well tolerated; the rate of discontinuation because of side effects or poor tolerance is 15%. Patients with large varices and contraindications to β blockers can be treated with endoscopic band ligation.
- During acute variceal hemorrhage, general supportive therapy (including antibiotic prophylaxis of bacterial infections and a very conservative use of blood transfusion) is essential to reduce mortality. The prognosis is worst in patients with advanced liver failure or with early (first week) rebleeding. Terlipressin has proved effective as a first-line treatment in arresting variceal bleeding and reducing mortality from variceal hemorrhage. The somatostatins are also probably effective. Drug therapy has been shown to be as effective and safer than emergency endoscopic therapy; also, a specialized staff is not required, so that therapy can be started much earlier during the course of bleeding—on arrival at the emergency room or even during transfer to the hospital. Endoscopic procedures can then be performed while drug therapy is maintained. Such a combined (and pragmatic) approach allows a better use of resources.
- Failures of medical treatment should be managed aggressively with emergency surgery or transjugular intrahepatic portosystemic shunting (TIPS). Because of high rates of morbidity and mortality, only low-risk patients (Child-Pugh score <8) should undergo surgery. In contrast, TIPS may be life-saving in Child class C patients with

variceal bleeding refractory to pharmacologic and endoscopic therapy.

- Patients who survive an episode of variceal bleeding are at high risk for rebleeding. Medical therapy with β blockers and endoscopic band ligation are recommended first-line treatments. All Child class C patients should be considered for liver transplantation. Endoscopic treatments attempt to eradicate varices by injecting irritating substances (injection sclerotherapy) or ligating them with elastic bands (band ligation). Both procedures are effective, but band ligation is safer. These procedures are of limited value in patients with gastric varices.
- β Blockers are almost as effective as endoscopic treatment, but safer. The best results are obtained when the HVPG is reduced by at least 20% of the baseline value or below 12 mm Hg. However, this reduction is achieved in only one third of patients. The combination of IMN and propranolol or nadolol significantly increases the number of patients in whom the targeted reduction in portal pressure is achieved. Combined drug therapy is more effective than either nadolol, endoscopic sclerotherapy, or band ligation, and is as useful as TIPS. Patients who fail medical therapy may be treated by combining drug therapy and endoscopic treatment, or by TIPS or surgical portal-systemic shunting.

Portal hypertension is a common clinical syndrome, defined by a pathologic increase in the portal venous pressure in which the pressure gradient between the portal vein and inferior vena cava (portal perfusion pressure of the liver, or PPG) is increased above normal values (1 to 5 mm Hg.) When the PPG rises above 10 to 12 mm Hg, complications of portal hypertension can arise (1,2,3 and 4). Therefore, this value represents the threshold for defining portal hypertension as clinically significant.

The importance of this syndrome is defined by the frequency and severity of complications: massive upper gastrointestinal bleeding from ruptured gastroesophageal varices and portal hypertensive gastropathy (PHG), ascites, renal dysfunction, hepatic encephalopathy, arterial hypoxemia, disorders in the metabolism of drugs or endogenous substances that are normally eliminated by the liver, bacteremia, and hypersplenism (5). These complications are major causes of death and the main indications for liver transplantation in patients with cirrhosis.

This chapter provides a background on the most important aspects of the pathogenesis, evaluation, and treatment of portal hypertension.