CLINICAL CONSEQUENCES OF PORTAL HYPERTENSION

Part of "11 - PORTAL HYPERTENSION"

The portal hypertensive syndrome is responsible for many of the manifestations of advanced, decompensated liver disease. Some of these complications are a direct consequence of portal hypertension: gastrointestinal bleeding resulting from ruptured gastroesophageal varices, PHG, and colopathy; hyperkinetic syndrome; hypersplenism; and an increased systemic availability of drugs and endogenous compounds with rapid hepatic uptake (5). In other complications, portal hypertension plays a key role, although it is not the only pathophysiologic factor in their development. These include ascites, abnormalities of renal function, hepatorenal syndrome, spontaneous bacterial peritonitis, hepatopulmonary syndrome, and hepatic encephalopathy. This chapter focuses on gastrointestinal bleeding; the other complications are dealt with elsewhere in this book.

Collateral Circulation

The most important clinical consequences of portal hypertension are related to the formation of portal-systemic collaterals; these include gastroesophageal varices, which are responsible for the main complication of portal hypertension, massive upper gastrointestinal bleeding (91).

Collaterals develop in areas where anatomic connections exist between the portal venous and systemic circulation. These are vascular channels that are functionally closed in normal conditions but become dilated in portal hypertension as a consequence of increased intravascular pressure and blood flow. It should be noted that the grossly dilated portal-systemic collaterals characteristic of portal hypertension are not merely passively dilated vessels; a marked hypertrophy and hyperplasia of the collateral walls suggest that angiogenic factors activated in portal hypertension contribute to their formation.

The portal system and the systemic venous circulation are connected at several locations (91). Gastroesophageal collaterals develop from connections between the short gastric and coronary veins and the esophageal, azygos, and intercostal veins; the result is the formation of esophageal and gastric varices. Other collaterals may develop as follows: between the superior hemorrhoidal vein and the middle and inferior hemorrhoidal veins, giving rise to anorectal varices; between the portal and epigastric veins through the reopening of remnants of the umbilical or paraumbilical veins, forming a vascular net that is at times apparent on the abdominal wall as a *caput medusae* and causing a murmur over the umbilicus (the Cruveilhier-Baumgarten syndrome); between the portal system and the posterior abdominal wall through the liver capsule and diaphragm; and between the portal system and the left renal vein, forming spontaneous splenorenal shunts. In instances of portal vein thrombosis, “hepatopetal” collaterals develop between the splenic vein and the coronary vein via the short gastric veins, giving rise to gastric varices, and between the mesenteric or portal vein and the intrahepatic vena porta through the veins of Sappey,

causing pseudocavernomas of the portal vein (91). Ectopic varices may develop at other locations, depending on local anatomic factors. Most ectopic varices develop in the duodenum (primarily associated with extrahepatic portal hypertension) and in the colon and small intestine (more frequent in patients who have previously undergone abdominal surgery). Overall, these ectopic varices account for between 1% and 5% of all episodes of variceal bleeding (92,93).

Lymph flow is also increased in portal hypertension. Enlargement of the hilar lymphatics and lymph nodes has been demonstrated. Increased hepatic lymph flow contributes to the formation of ascites (94).

Natural History and Clinical Manifestations of Portal Hypertension

Information on the natural history and clinical manifestations of portal hypertension is primarily drawn from patients with liver cirrhosis, the best-studied disease causing portal hypertension. It is generally accepted that this information is applicable to most of the other causes of portal hypertension, although some differences may be identified in specific diseases. These differences are outlined wherever appropriate.

Esophageal Varices

Portal hypertension is an almost unavoidable complication of cirrhosis. The prevalence of esophageal varices is very high; when cirrhosis is diagnosed, varices are present in about 40% of compensated patients and in 60% of those who present with ascites (95,96).

Few studies have assessed the incidence of esophageal varices in cirrhosis. Available information has been recently reviewed in a large consensus conference (93). According to the best available estimate, the incidence of esophageal varices in patients with cirrhosis increases about 5% per year. Therefore, if it is assumed that approximately 40% of patients already have varices when first seen, the estimated risk for varices is about 65% at 5 years after the diagnosis of cirrhosis (Fig. 11.16).

FIGURE 11.16. The incidence of esophageal varices among 1,159 cirrhotic patients without varices at diagnosis. Cumulative data from two studies of the natural history of cirrhosis.

Cross-sectional studies have shown that esophageal varices do not develop below the threshold HVPG value of 10 to 12 mm Hg (1). However, not all patients with an HVPG above this threshold have esophageal varices, and the relationship between the incidence of varices and an HVPG above this level is poorly understood. Worsening liver function and continued exposure to alcohol are clinical factors associated with an increasing risk for the development of varices. The HVPG frequently increases with worsening liver function and continued alcohol abuse and may decrease when liver function improves and alcohol is discontinued (97). Therefore, an increased HVPG is presently considered the most important risk factor for the development of esophageal varices.

Progression of Esophageal Varices from Small to Large

Once developed, varices increase in size from small to large before they eventually rupture and bleed. Studies assessing the progression from small to large varices are controversial, and available data are not conclusive. Five such studies show variable rates of progression of varices ranging from 5% to 30% per year (93). The most likely reason for such variability is the different patient selection across studies. It is worth noting that the only inception cohort study (i.e., including only patients with newly diagnosed cirrhosis) reported a variceal progression rate of only 5% per year (98). When all the available studies are considered, the median rate of progression of varices from small to large is about 12% per year during the first 2 years following the endoscopic diagnosis of small varices.

Improvement in liver function and abstinence from alcohol may result in the regression or even disappearance of varices (97). As already stated, this change may be related to a decrease in the HVPG. It has been shown that changes in the HVPG (either “spontaneous” or caused by drug therapy or TIPS) are usually accompanied by parallel changes in the size of esophageal varices, which are significantly reduced when the HVPG decreases below 12 mm Hg or when it decreases more than 15% from the baseline value (97,99). Thus, an increase in the HVPG plays a key role in both the formation and progression of varices. It will probably become a major means of monitoring the response to treatment to prevent variceal bleeding or rebleeding.

A striking association has been noted between an increased size of esophageal varices and a poor prognosis in cirrhosis. The risk for bleeding increases nearly fourfold from absent to small varices and twofold from small to large varices (Fig. 11.17). A similar increase in risk may be shown for the development of ascites and for mortality.

FIGURE 11.17. Survival of cirrhotic patients according to the presence and size of esophageal varices at diagnosis. Cumulative data from two studies of the natural history of cirrhosis. *Absent,* no esophageal varices at diagnosis; *small,* small esophageal varices at diagnosis; *large,* medium or large varices at diagnosis.

Incidence of First Bleeding from Esophageal Varices and Indicators of Risk

The incidence of variceal bleeding is about 4% per year in nonselected patients who have never bled at the time of diagnosis (100,101). The risk is much lower (between 1% and 2%) in patients without varices at the first examination; it increases to about 5% per year in those with small varices and to 15% per year in those with medium or large varices at diagnosis (102).

The importance of the size of varices determining the risk for bleeding is further discussed below.

Clinical and Endoscopic Indicators of Risk.

Among patients with esophageal varices, the incidence of bleeding is significantly lower in Child-Pugh class A patients than in class B or C patients, and in patients without ascites versus those with ascites, independently of variceal size (102).

The risk for variceal bleeding is significantly associated with variceal size (Fig. 11.18), the severity of liver dysfunction as expressed by the Child-Pugh classification, and red weal marks (vessels newly formed on the variceal wall). These risk indicators have been combined in the New Italian Endoscopic Club (NIEC) index (61,62), which allows us to classify patients in different classes with a predicted 1-year risk for bleeding ranging from 6% to 76%. Although this index has been validated recently (62), its predictive accuracy is far from satisfactory. In fact, the best operative characteristics of the NIEC index in the prediction of risk for bleeding are a 74% sensitivity and a 64% specificity, with a positive predictive value of 33% and a negative predictive value of 91% (62). Another recently proposed endoscopic index combining variceal size, the presence of PHG, and the presence of gastric varices has similar unsatisfactory

operative characteristics for predicting the risk for bleeding (103). Whether these indices can be improved by incorporating additional parameters related to portal hypertension (i.e., spleen size, platelet count) remains to be determined.

FIGURE 11.18. Incidence of variceal bleeding in cirrhotic patients according to the presence and size of esophageal varices at diagnosis. Cumulative data from two studies of the natural history of cirrhosis. *Absent,* no esophageal varices at diagnosis; *small,* small esophageal varices at diagnosis; *large,* medium or large varices at diagnosis.

Hemodynamic Indicators of Risk.

Cross-sectional and prospective studies have shown that esophageal varices do not bleed below a threshold HVPG level of 11 to 12 mm Hg (1,97,99). Importantly, it has also been demonstrated in prospective studies that variceal hemorrhage does not occur if the HVPG is reduced, either spontaneously or pharmacologically, to levels below 12 mm Hg (4,97,99) or more than 20% from baseline (104). The reduction in risk for bleeding occurs despite the continued demonstration of varices in the majority of patients. However, variceal size is significantly decreased when the HVPG is reduced below threshold values (4,99).

Variceal pressure is significantly related to variceal size, red signs, and the severity of liver dysfunction (3,105); moreover, a prospective study showed variceal pressure to be significantly associated with the risk for bleeding and death (106).

The relationship between variceal pressure and risk for bleeding reflects the increase in variceal wall tension associated with increases of variceal pressure and size (3,105). Variceal wall tension cannot be measured accurately because the endoscopic evaluation of variceal diameter is only approximate, and it is not possible to measure variceal wall thickness with sufficient accuracy. However, endosonography or high-resolution

endoluminal probe sonography allows a more precise and reliable measurement of variceal diameter than endoscopy (107,108) and may allow an estimation of wall thickness. If a reliable measurement of variceal wall tension becomes possible, it will probably contribute to further improvements in the assessment of risk for variceal bleeding (88).

Ultrasonographic Indicators of Risk.

Although considerable effort has been made to identify hemodynamic indicators noninvasively by Doppler flowmetry, only the so-called congestion index (the ratio between the cross-sectional area of the portal vein and the mean blood flow velocity) has been reported to be related to the risk for variceal bleeding (109). However, its sensitivity and specificity in detecting patients at risk for bleeding are far from satisfactory (93).

Assessment of Risk for First Bleeding from Esophageal Varices in Clinical Practice

The estimated size of varices at endoscopy is the most widely used indicator of risk for first variceal bleeding. Patients with medium-sized to large varices are considered to be at considerable risk for bleeding, and they should receive therapy to prevent variceal bleeding (100,110). Other clinical and hemodynamic indicators are used only in clinical research.

Screening for Esophageal Varices.

In a recent large consensus conference, it was agreed that all patients with cirrhosis should be screened for the presence of esophageal varices at the time of initial diagnosis (93).

Although several studies indicate that noninvasive tests (particularly platelet count and data obtained from abdominal ultrasonography) may be of potential use in selecting patients at high risk for varices, so far none of these has proved accurate enough that endoscopy can be safely omitted in patients with negative noninvasive indicators (93). Very recently, a simple prediction rule based on a platelet count lower than 100,000/mL, prothrombin activity lower than 70%, and portal vein diameter greater than 13 mm on abdominal ultrasonography was found to provide satisfactory accuracy in predicting the presence of varices (95). This prediction rule has been validated in an independent cohort of patients, showing a diagnostic accuracy of nearly 80%. However, the clinical consequences of the 20% diagnostic error should be reliably evaluated before such a prediction rule is accepted for clinical practice.

Timing of Subsequent Evaluations.

In patients without varices on initial endoscopy, a second (follow-up) evaluation should be performed to detect the development of varices before they bleed (93). Because the expected incidence of new varices is about 5% per year, the general consensus is that endoscopy should be repeated after 2 to 3 years in patients without varices at the first endoscopy (93). In patients with small varices on initial endoscopy, the aim of subsequent evaluations is to detect the progression of small to large varices because of the important prognostic and therapeutic implications. Based on an expected 10% to 15% annual rate of progression of variceal size, endoscopy should be repeated every 1 to 2 years in patients

with small varices (93,102).

Acute Bleeding from Esophageal Varices: Definitions and Time Intervals

Ruptured esophageal varices cause 60% to 70% of all episodes of upper gastrointestinal bleeding in patients with portal hypertension (102). Variceal bleeding is diagnosed at emergency endoscopy. The diagnosis is based on observing one of the following: (a) blood spurting from a varix (nearly 20% of patients); (b) white nipple or clot adherent to a varix; (c) presence of varices without other potential sources of bleeding. Because variceal bleeding is frequently intermittent, it is difficult to assess when bleeding stops and when a new episode of hematemesis or melena should be considered an episode of rebleeding. Several consensus conferences have addressed this issue and set definitions for the events and timing of events related to episodes of variceal bleeding (89,111). According to these definitions, the index bleeding episode is separated from the first episode of rebleeding by at least a 24-hour

interval without bleeding, during which no new hematemesis or melena occurs and all the following criteria are verified: stable hemoglobin levels, systolic blood pressure above 100 mm Hg or a postural change of less than 20 mm Hg, and a pulse rate below 100/min. When these criteria are used, the median duration of an acute episode of variceal bleeding is nearly 10 hours (102). Data from placebo-controlled clinical trials have shown that variceal bleeding ceases spontaneously in 40% to 50% of patients. Active treatment achieves control of bleeding within 24 hours after admission in nearly 80% of episodes (112). Active bleeding on endoscopy (112), bacterial infection (113), and an HVPG above 20 mm Hg are significant prognostic indicators of failure to control bleeding (114). Immediate mortality from uncontrolled bleeding is in the range of 5% to 8%.

Early Rebleeding.

Early rebleeding is significantly associated with a risk for death within 6 weeks, which suggests that the prevention of early rebleeding should be a primary objective of the therapeutic approach to variceal bleeding. The incidence of early rebleeding ranges from 30% to 40% in the first 6 weeks. The risk peaks in the first 5 days, with 40% of all episodes of rebleeding occurring in this very early period, remains high during the first 2 weeks, and then declines slowly during the next 4 weeks. After 6 weeks, the risk for further bleeding becomes virtually equal to that before bleeding (115).

Active bleeding at emergency endoscopy, gastric varices, low albumin or high blood urea nitrogen level, and HVPG above 20 mm Hg have been reported as significant indicators of a risk for early rebleeding (116).

Six-Week Mortality.

Because it may be difficult to assess the true cause of death (i.e., bleeding vs. liver failure or other adverse events), the general consensus is that any death occurring within 6 weeks after hospital admission for variceal bleeding should be considered a bleeding-related death. Six-week mortality after variceal bleeding is about 30%. Almost 60% of deaths are

caused by uncontrolled bleeding, either during the initial episode or after early rebleeding. Like the risk for rebleeding, the risk for mortality peaks during the first days after bleeding, slowly declines thereafter, and after 6 weeks becomes constant and virtually equal to that before bleeding (115,116).

Accurate indicators of a risk for early death would allow the selection of patients for emergency shunting or TIPS before their conditions deteriorated and hampered further therapy. Unfortunately, the indicators of risk so far identified are mainly indicators of poor liver or renal function, which are also associated with a high operative risk and consequently are of limited clinical value.

On hospital admission, the most consistently reported indicators of the risk for death are the Child-Pugh classification or components thereof, blood urea nitrogen or creatinine level, age of the patient, presence or absence of active alcohol abuse, presence or absence of active bleeding on endoscopy, and the HVPG (102). Bacterial infection (113) and an HVPG above 20 mm Hg (114) have been reported as significant indicators of treatment failure. Conceivably, they are also associated with a higher risk for death, although their prognostic role for 6-week mortality has not been assessed.

Early rebleeding is the most important and most consistently reported late prognostic indicator of 6-week risk for death.

Long-Term Recurrent Bleeding from Esophageal Varices and Mortality

Patients surviving a first episode of variceal bleeding have a very high risk for rebleeding and death. The median incidence of rebleeding within 1 to 2 years in untreated controls in randomized controlled trials (RCTs) of nonsurgical treatment to prevent recurrent bleeding reported after 1981 is 63% (116). The corresponding mortality figure is 33% (Fig. 11.19). Because of these high risks, all patients surviving an episode of variceal bleeding should be treated to prevent rebleeding independently of other indicators of risk (117).

FIGURE 11.19. Survival after an episode of variceal bleeding according to early rebleeding. Cumulative proportion of survivors among a cohort of 477 patients with esophageal variceal bleeding observed consecutively at the Medical Department of V. Cervello Hospital, Palermo, Italy, between 1984 and 1992. The survival of patients who experienced early rebleeding was significantly worse.

RCTs of the prevention of rebleeding suggest that indicators of a risk for rebleeding and death are large variceal size, Child-Pugh class, continued alcohol abuse, and the presence of hepatocellular carcinoma. An HVPG above 20 mm Hg is significantly associated with a higher risk for 1-year mortality. Reduction of the HVPG to below 12 mm Hg totally prevents recurrent bleeding (104).

Gastric Varices

The natural history of gastric varices is not as well-known as that of esophageal varices.

According to the most widely used classification (118), gastric varices may be found as a continuation of esophageal varices along the lesser curve of the stomach (GOV-1) or in the fundus (GOV-2); more rarely, *isolated gastric varices* (i.e., not connected with esophageal varices) may be found in the fundus (IGV-1) or in the rest of the stomach (IGV-2). These are more frequent in patients with prehepatic portal hypertension. Overall, the prevalence of gastric varices in patients with portal hypertension is about 20% (14% GOV-1, 4% GOV-2, 2% IGV-1 or IGV-2) (119). Sometimes, it is difficult to differentiate gastric varices from plicae; endoscopic ultrasonography may be helpful in these cases.

Gastric varices are commonly fed through the short or posterior gastric veins. They are frequently associated with a lower portal pressure than esophageal varices and with large gastrosplenorenal shunts. The risk for bleeding in patients with gastric varices is thought to be lower than that of patients with esophageal varices, but the incidence of portal-systemic encephalopathy is higher in patients with gastric varices.

Gastric varices are the source of 5% to 10% of all episodes of upper gastrointestinal bleeding in patients with cirrhosis. The incidence of bleeding from gastric varices has been assessed in few studies and is on the order of two or three cases per 100 patients annually (118). However, in a recent prospective cohort study including 117 patients with fundal varices (GOV-2 or IGV-1), the cumulative proportions of patients who bled from fundal varices at 1, 3, and 5 years after their detection were 16%, 36%, and 44%, respectively. As in esophageal varices, the risk for bleeding was significantly related to variceal size, Child class, and the presence or absence of red color signs. A higher incidence of bleeding from fundal (GOV-2 or IGV-1) than from junctional (GOV-1) varices has been confirmed in a large survey.

The effect of sclerotherapy or banding ligation of esophageal varices on gastric varices is still unsettled; regression, no change, and “de novo” appearances of gastric varices have all been reported.

Bleeding-related mortality after a first episode of gastric variceal bleeding is about 20%, and rates of long-term recurrent bleeding and mortality are similar to those for esophageal varices.

Portal Hypertensive Gastropathy

The gastric mucosal changes associated with portal hypertension (120,121 and 122) are termed *portal hypertensive gastropathy.* The most frequently observed elementary lesions of PHG are the “mosaic pattern” and “cherry red spots.” The mosaic pattern, which consists of multiple erythematous areas outlined by a white reticular network, is generally considered to be “mild” PHG. Cherry red spots are round, red lesions that are slightly raised over the surrounding hyperemic mucosa. These carry a higher risk for bleeding and are considered to reflect “severe” PHG (89). They vary in severity and have been graded in the NIEC classification (89), although the clinical relevance of such grading is doubtful. The term *portal hypertensive gastropathy* was coined after the relationship of the lesions to portal hypertension was definitively recognized. Histologically, they are characterized by dilatation of the capillaries and venules of the gastric mucosa; mucosal inflammation and *Helicobacter pylori* infection are infrequent (123).

The gastric mucosal changes of PHG are associated with increased gastric mucosal and submucosal perfusion, and therefore they are hyperemic, not “congestive,” changes. The term *congestive gastropathy* is inadequate and should not be used (120,124).

The data on the prevalence, incidence, and natural history of PHG differ widely across studies (119), mostly because patients have been included at different stages of cirrhosis. At the initial diagnosis of cirrhosis, the prevalence of PHG is about 30% and its annual incidence about 12% (102). However, in patients with advanced cirrhosis, these figures may be as high as 70% and 30%, respectively (119). Patients with severe liver dysfunction and large esophageal varices are at higher risk for the development of PHG, whereas large fundal varices may have a protective role, particularly when they are associated with spontaneous gastrorenal shunt. Endoscopic therapy of esophageal varices has been reported as a possible risk factor for PHG, the risk being significantly higher with sclerotherapy than with banding ligation (102). Overall, during the course of cirrhosis, mild PHG may be observed in up to 50% to 70% of patients and severe PHG in 20% to 40% (102). Increasing severity and disappearance of PHG have both been reported (119).

The clinical course of PHG is characterized by overt or chronic gastric mucosal bleeding. The annual incidence of overt bleeding from any source in patients with mild PHG is about 5%, and it is 15% in patients with severe PHG. The source of bleeding is the gastric mucosa in most of these episodes. Overt bleeding from PHG is usually manifested by melena and has a far better prognosis than variceal bleeding, with a mortality rate of less than 5% per episode (102). Mortality is higher in patients with severe PHG, but this has been found to depend on the severity of liver dysfunction (102).

The annual incidence of minor mucosal blood loss, without overt bleeding, is about 8% in patients with mild and up to 25% in patients with severe PHG, in whom severe chronic iron deficiency anemia may develop that requires frequent hospital admissions and blood transfusions. It appears that the wide use of β blockers in cirrhotic patients is reducing both chronic and overt bleeding from

PHG; it has been proved that β blockers significantly reduce the risk for rebleeding in patients who have bled from PHG (125,126).

PHG should be distinguished from gastric antral vascular ectasia (GAVE). This is a distinct entity that may be found in association with conditions other than cirrhosis, such as scleroderma and chronic gastritis. GAVE is characterized by aggregates of red spots, usually in a radial distribution from the pylorus to the antrum of the stomach (this pattern is also called *“watermelon” stomach*). The histology of GAVE is characterized by smooth-muscle cell and myofibroblast hyperplasia and fibrohyalinosis. Clinically, the symptoms of GAVE are as severe as those of PHG, but it may be less responsive to treatment with β blockers.

Portal Hypertensive Lesions in the Gut

Mucosal lesions similar to those of PHG have been described in the duodenum, jejunum, and colon. Like PHG, these lesions tend to cause overt or chronic occult mucosal bleeding. Their incidence and clinical course have not been adequately studied. Their management is

similar to that of PHG.