

Portal hypertension: the management of esophageal/gastric varices, portal hypertensive gastropathy or hypertensive colopathy

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Portal hypertension is one of the main consequences of cirrhosis. Esophageal varices are most often a consequence of portal hypertension, although they can also be formed in other areas of the body, including the stomach, duodenum, colon and/or rectum. Patients with esophageal varices have a strong tendency to develop bleeding. Conversely, varices do not bleed if the hepatic venous pressure gradient is below 12 mmHg. Approximately 30–50% of patients with esophageal varices will bleed within the first year of diagnosis. Once a patient experiences bleeding, the risk of rebleeding is high, reaching 80% within 1 year. The mortality rate for esophageal variceal bleeding, on the first event, is between 40 and 70%. Endoscopy can be useful in searching for varices with respect to primary prophylaxis and treatment of bleeding in cirrhotics. The treatment of esophageal varices can be pharmacologic, endoscopic or surgical. Three different clinical situations must be distinguished: in primary prophylaxis of esophageal variceal bleeding, the use of β -blocker treatment is only recommended in patients at high risk; in treatment of acute variceal hemorrhage, combining pharmacotherapy for 3–5 days with endoscopic therapy reduces rebleeding compared with either measure alone; in secondary prophylaxis of esophageal variceal bleeding, the treatment of choice is eradication of esophageal varices with band ligation. When the bleeding is refractory, the use of balloon tamponade may stop hemorrhage at least temporarily. If bleeding is uncontrolled, transjugular intrahepatic portosystemic shunt or nonselective portosystemic shunt may be suitable in patients with cirrhosis, provided that the liver dysfunction is not too severe. None of these measures, while being effective in stopping bleeding, have been shown to affect surveillance.

Portal hypertension is one of the main consequences of cirrhosis. It results from a combination of increased intrahepatic vascular resistance and increased blood flow through the portal venous system. Major complications of portal hypertension include the development of esophageal, gastric or colonic varices. Esophageal varices are dilated blood vessels within the wall of the esophagus. The most common cause of portal hypertension is alcoholic or postviral liver disease. Other etiologies of portal hypertension include portal vein thrombosis, schistosomiasis, and inferior vena caval obstruction by tumor or thrombus [1–3].

Cirrhosis is the most common cause of portal hypertension. In cirrhosis, both intrahepatic vascular resistance and portal flow are increased. The hyperdynamic circulation of cirrhosis results from an imbalance between vasoconstrictor and vasodilator mechanisms, leading to decreased resistance in the splanchnic and systemic circulation. As a consequence, the adrenergic and renin–angiotensin systems

are activated as counter-regulatory mechanisms. Portal venous pressure (P) is the product of vascular resistance (R) and blood flow (Q) in the portal bed ($P = Q \times R$). A normal hepatic venous pressure gradient (HVPG) is less than 5 mmHg. A HVPG of 12 mmHg is necessary, but not sufficient, for varices to form. They form preferentially in the submucosa of lower esophagus. The lower esophagus is a site of portosystemic anastomosis, meaning that venous blood flow in the portal circulation (i.e., draining into the portal vein) and the mesenteric circulation mix freely. When portal pressures increase, there is dilation of veins in the anastomosis, leading to esophageal varices. Varices can also be formed in other areas of the body, including the stomach, duodenum, colon and/or rectum. These blood vessels continue to dilate until they become large enough to rupture [4].

Patients with esophageal varices have a strong tendency to develop bleeding. Approximately 30% of cirrhotic patients have esophageal

Keywords: esophageal varices, gastric varices, gastrointestinal bleeding, hypertensive colopathy, portal hypertension, portal hypertensive gastropathy

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varices at the time of diagnosis; this proportion increases with time and reaches 90% after approximately 10 years. Diagnosis of esophageal varices requires endoscopy. Rupture and bleeding from esophageal varices is a major complication of portal hypertension and carries a high mortality. Varices rupture if the wall tension becomes too large. Clinical risk factors for an initial bleeding episode include poor liver function and continuing alcohol consumption. Endoscopic predictors of bleeding include the size of the varices and the presence of red color signs or red wale markings corresponding to areas of thinning of the varix wall owing to high wall tension. The rupture and bleeding is again proportionate to the HVPg. Conversely, there is not bleeding if the HVPg is below 12 mmHg. Approximately 30–50% of patients with esophageal varices will bleed within a year of diagnosis. Despite advances in intensive care, bleeding episodes still carry a high mortality, which mainly depends on the severity of the underlying liver disease. Once a patient has bleeding, the risk of rebleeding is high, reaching 80% within 1 year [5].

The mortality of any bleeding episode may range from 10% or less in well compensated Child–Pugh A to 70% or over in advanced Child–Pugh C cirrhotics, respectively. The mortality rate for esophageal variceal bleeding, on the first event, is between 40 and 70%. The treatment of esophageal varices can be pharmacological, endoscopic or surgical and three different clinical situations must be distinguished [6]:

- Primary prophylaxis of esophageal variceal bleeding (prevention of a first variceal bleed)
- Treatment of acute variceal hemorrhage
- Secondary prophylaxis of esophageal variceal bleeding (prevention of rebleeding)

Primary prophylaxis of esophageal variceal bleeding (prevention of a first variceal bleed)

Any patients with portal pressure greater than 12 mmHg is at risk of esophageal varices, thus they should be screened endoscopically for the presence of varices and, if varices are present, measures should be taken to reduce the change of hemorrhage [7]. Upper gastrointestinal endoscopy is usually recommended for the evaluation of esophageal varices in patients with liver cirrhosis. The possibility of identifying cirrhotic patients with esophageal varices by noninvasive means is attractive and the

recently proposed platelet count:spleen diameter ratio appears to be the best noninvasive predictor of esophageal varices developed to date. The platelet count:spleen diameter ratio may be proposed as a safe and reproducible means to improve the management of cirrhotic patients; however, the available evidence is not yet sufficient to allow for the modification of the current policy of screening cirrhotic patients by endoscopy [8]. For some years, the use of wireless capsule endoscope to study the gastrointestinal tract has been proposed but, only recently, a new video capsule has been proposed specifically to view the inner lining of the esophagus. The capsule is equipped with miniature cameras and the patient swallows the capsule lying down, before it travels through the esophagus by normal peristaltic waves, capturing images of the esophagus. The images captured may identify potential abnormalities, such as esophagitis, esophageal ulcers and also esophageal varices. This new capsule endoscopy is safe, highly acceptable and preferred by patients, although it may prove to be more cost-effective than conventional endoscopy [9].

Propranolol was shown to reduce the incidence of variceal bleeding in patients who had no previous bleeding, therefore cirrhotics who have varices, regardless of their size, should receive primary prophylaxis with nonselective β -blockers. The aim of pharmacotherapy is to reduce HVPg and, thus, collateral blood flow and pressure through/in the varices. Reducing portal pressure by 20% from baseline reduces the risk of rebleeding from over 60% to less than 10% at 3 years; if HVPg is lowered below 12 mmHg there is no bleeding. Nonselective β -blockers reduce cardiac output, splanchnic arterial inflow, portal venous flow and pressure and, thus, variceal flow and pressure. In cirrhotics with esophageal varices, both propranolol and nadolol have been demonstrated to reduce the risk of an initial bleeding episode by 40–50%, while there was a trend only in reducing mortality. Approximately 30% of patients will not respond to nonselective β -blockers with a reduction in HVPg, despite adequate dosing. These nonresponders can only be detected by invasive measurements of HPVG. Bleeding may occur when nonselective β -blockers are abruptly discontinued, thus this therapy should be lifelong if tolerated. Nonselective β -blockers may cause side effects, such as bradycardia, brocospasm, hypoglycemia, fatigue and impotence [10,11].

The addition of isosorbide mononitrate to nonselective β -blockers has been evaluated. Isosorbide 5-mononitrate has been shown to lower portal pressure. The mechanism of action of nitrates in portal hypertension is not fully clarified, but may involve vasodilatation in the portal venous bed. Unfortunately, the use of nitrates in cirrhotics is limited by their systemic vasodilatory effects, often leading to a further decrease in blood pressure and potentially in prerenal impairment of kidney function. Thus, nitrates alone are not recommended. Combining isosorbide 5-mononitrate with nonselective β -blockers has been shown to have additive effects in lowering portal pressure and is especially effective in patients not responding to nonselective β -blockers alone. However, these beneficial effects may be outweighed by detrimental effects on kidney function and long-term mortality, especially in those aged 50 years or older.

Patients who are intolerant of nonselective β -blockers and are at increased risk of bleeding (large varices, red signs or severe liver disease) should be considered for alternative prophylactic regimens, such as band ligation, transjugular intrahepatic portosystemic shunt (TIPS) or surgical shunting [12].

However, data on real usefulness of endoscopic or surgical treatment in the prevention of first bleeding are confusing and do not have an accepted role in primary prophylaxis. As with any primary prophylactic measures, overall cost-effectiveness strongly depends on the risk of the event to be prevented in the population pretreated prophylactically. Hence, primary prophylaxis is often performed in patients at a medium to high risk of bleeding only, their selection being based on endoscopic findings.

According to a statement from the international consensus conference [6], at the time, the use of nonselective β -blockers treatment is not recommended for primary prophylaxis, but only in patients at high risk (Box 1).

Treatment of acute variceal hemorrhage

Variceal hemorrhage stops spontaneously in approximately 62–70% of cases but recurrent bleeding occurs in 40% of patients within the next 72 h. In fact, 60% of patients will rebleed within 7 days of their initial bleeding. The manifestation of variceal hemorrhage may vary from a single life-threatening episode of hematemesis and/or melena with cardiovascular collapse to unusual but possible asymptomatic anemia;

however, the patients have gone in hospital. Initial measures are directed at general resuscitation and at stabilization of the circulation.

Bacterial infections are a frequent complication in patients with cirrhosis and gastrointestinal bleeding. Antibiotic prophylaxis appears to decrease the incidence of bacterial infections. Oral antibiotics, active against enteric bacteria, have been most often used as antibiotic prophylaxis in cirrhotic patients with gastrointestinal bleeding and bacterial infections. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding is well tolerated, efficacious in reducing the number of deaths and bacterial infections and should be advocated [13,14].

Pharmacotherapy with octreotide, a synthetic somatostatin analog, or terlipressin, a synthetic vasopressin analog, has been shown to be effective in stopping bleeding, at least temporarily, in up to 80% of patients. These compounds inhibit the release of vasodilator hormones, causing splanchnic vasoconstriction and decreased portal inflow. Both somatostatin and octreotide are safe medications with very few side effects. Endoscopic sclerotherapy and variceal ligation are effective in stopping bleeding in up to 90% of patients [13]. Endoscopic band ligation is as effective as sclerotherapy but has fewer side effects. However, in severe active bleeding, endoscopic band ligation may be more difficult to apply than sclerotherapy. Combining pharmacotherapy for 3–5 days with endoscopic therapy reduces rebleeding compared with either measure alone. If the bleeding is refractory, the use of balloon tamponade may stop hemorrhage, at least temporarily.

If the bleeding is uncontrolled, a TIPS that, through a jugular route, connects the hepatic and portal veins in the liver can be useful. The goal is to reduce portal pressure and, thus, prevent variceal bleeding. TIPS diverts portal blood flow from the liver; however, it increases the risk of encephalopathy. In most cases, encephalopathy responds to standard therapy but, in some cases, the calibre of the shunt has to be reduced; rarely, when encephalopathy does not respond to treatment, the shunt should be occluded. Thrombosis and stenosis are other complications that can cause TIPS dysfunction. In cases of refractory bleeding and when TIPS is technically impossible, creation of a nonselective portosystemic shunt may be suitable in patients with cirrhosis, provided that the liver dysfunction is not too severe (Child–Pugh class A or B).

Box 1. Recommended scheme.**Primary prophylaxis of esophageal variceal bleeding (prevention of a first variceal bleed)**

- Selection of patients with at least medium-sized esophageal varices and/or red color signs.
- Nonselective β -blockers (propranolol or nadolol) starting at a low dose, if necessary increasing the dose step by step until reaching a reduction of resting heart rate by 25%, but not lower than 55/min.
- Endoscopic band ligation is indicated in patients who do not tolerate or have contraindications to β -blockers.

Treatment of acute variceal hemorrhage

- General resuscitation measures.
- Start pharmacotherapy, octreotide 50 μ g intravenous bolus, followed by 50 μ g/h intravenous for 3–5 days (or terlipressin).
- Administer antibiotics, third generation cephalosporine.
- Emergency endoscopy to verify diagnosis and to perform band ligation or sclerotherapy.
- In case of early (within 5 days of index-bleed) rebleeding: repeat endoscopic therapy once, if possible.
- Recurrent or uncontrolled bleeding or endoscopic treatment failure (early rebleeding after two endoscopic attempts): place balloon tamponade, consider transjugular intrahepatic portosystemic shunt (TIPS).

Secondary prophylaxis of esophageal variceal bleeding (prevention of rebleeding)

- Eradication of esophageal varices by endoscopic band ligation; long-term endoscopic control and banding of recurrent varices every 3–6 months.
- If endoscopic band ligation is not available or contraindicated, use nonselective β -blockers starting at low dose, if necessary increasing dose step by step until reaching a reduction of resting heart rate by 25%, but not lower than 55/min; in younger patients with less advanced cirrhosis (Child–Pugh A), addition of isosorbide 5-mononitrate (starting with 2×20 mg/day and increasing to 2×40 mg/day) may be considered.
- If sclerotherapy or pharmacotherapy failed, consider TIPS, especially in candidates for liver transplantation; in selected cases (well preserved liver function or stable liver disease) a calibrated H graft or a distal splenorenal shunt according to Warren may be considered.
- Always consider liver transplantation if patient is Child–Pugh B or C.

However, none of these measures, while being effective in stopping bleeding, have been shown to affect surveillance. Acute variceal hemorrhage is often associated with bacterial infection due to gut translocation and motility disturbances, therefore a prophylactic antibiotic therapy has been recommend [15–18].

Secondary prophylaxis of esophageal variceal bleeding (prevention of rebleeding)

Endoscopic eradication of varices after bleeding is highly effective in reducing the risk of recurrent bleeding, the annual incidence decreasing from approximately 80 to 20–30%. Variceal band ligation has a better efficacy than sclerotherapy and is the endoscopic treatment of choice for eradication of esophageal varices. Endoscopic eradication of esophageal varices requires several sessions, varices may recur and regular endoscopic controls are mandatory long-term in order to detect and enable eradication of recurrent varices prior to rebleeding [17,18]. In cirrhotics with esophageal varices, nonselective β -blockers have been shown to reduce the risk of rebleeding by approximately 50%. About 30% of patients, however, will not respond to nonselective β -blockers with a reduction in HVP, despite adequate dosing. Isosorbide

5-mononitrate has been shown to lower portal pressure and the use of nitrates in cirrhotics is limited by their systemic vasodilatory effects, often leading to a further decrease in blood pressure and potentially in prerenal impairment of kidney function. Thus, nitrates alone are not recommended. The combination of nonselective β -blockers and isosorbide 5-mononitrate has been shown to more effectively decrease the risk of rebleeding than sclerotherapy and even variceal ligation. However, pharmacological therapy appears to be largely effective in Child–Pugh A and B patients. While it seems logical to combine pharmacological and endoscopic strategies for secondary prophylaxis of bleeding, at least until varices have been completely eradicated by endoscopy, this combination remains controversial.

The TIPS appears to be a good mid-term option for prevention of rebleeding, for bridging the waiting time until liver transplantation, whereas, in the long term, other options may be more cost-effective. Surgical shunts (in particular the calibrated H graft, but also the distal splenorenal shunt according to Warren) have a place in secondary prophylaxis, especially in patients presenting with portal hypertensive bleeding as their main clinical problem, a well preserved liver function. Patients who survived

and are Child–Pugh B or C should be considered for liver transplantation (Box 1). At present, nonselective β -blockers remain the medical treatment of choice for both primary and secondary prophylaxis.

Variants of esophageal varices are gastric varices. Gastric varices are dilated blood vessels that are found predominantly in the stomach. The true incidence of gastric varices is unknown. However, investigators have reported a wide incidence ranging between 20 and 70% in patients with esophageal varices. When gastric varices are identified without coexisting esophageal varices, a splenic vein thrombosis may be present. Another variant of portal hypertension is portal hypertensive gastropathy [19]. It is present in 50% of patients with portal hypertension. These patients have dilated arterioles and venules (small veins). This abnormality is usually seen in the fundus and cardia of the stomach (approximately two thirds of the stomach). It is rarely seen in the antrum (last third) of the stomach. Increased incidence of portal hypertensive gastropathy has been noted in patients who have undergone sclerotherapy for esophageal varices in the past. Long-term treatment of portal gastropathy and gastric varices is with nonselective β -blockers or argon plasma coagulation, if possible. Recently, the use of thalidomide has been proposed in bleeding from portal hypertensive gastropathy. Thalidomide selectively inhibits tumor necrosis factor- α production by enhancing messenger RNA degradation, and is also a potent inhibitor of angiogenesis. Thalidomide has been shown to reduce portal venous pressure in cirrhotic and noncirrhotic portal hypertension.

Endoscopic mucosal abnormalities in cirrhotics with portal hypertension are well described in the esophagus and/or the stomach. It is reasonable to think that portal hypertension is capable of producing hemodynamic changes not only at the gastroesophageal level, but also in some intestinal districts. Thus, in recent years, some authors have devoted their attention to verifying the possible presence, in the colon of cirrhotic patients, of specific lesions so as to identify a portal hypertensive colopathy [20]. Colonic lesions are frequent in cirrhotics, however, statistical analyses revealed that such lesions are not specific of the disease and not correlated with the etiology and degree of cirrhosis, the endoscopic treatment of esophageal varices and, finally, the bleeding risk from the lower gastrointestinal tract. To date, unfortunately, the features of the portal hypertensive colopathy are not well defined and there is still confusion regarding the diagnostic criteria and clinical significance of this condition.

Conclusion

The mortality rate for esophageal variceal bleeding, on the first event, is between 40 and 70%, therefore a pharmacologic, endoscopic or surgical treatment is indispensable in the prevention of a first variceal bleed, the treatment of acute variceal hemorrhage or in the prevention of rebleeding.

Outlook

Better therapy is β -blocker treatment and/or band ligation, although neither of these measures, while being effective in stopping bleeding, have been shown to affect surveillance, therefore new therapeutic approaches are necessary.

Highlights

- Esophageal varices are most often a consequence of portal hypertension, although varices can also be formed in other areas of the body, including the stomach, duodenum, colon and/or rectum.
- Approximately 30–50% of patients with esophageal varices will bleed within the first year of diagnosis. Once a patient has bleeding, the risk of rebleeding is high, reaching 80% within 1 year. The mortality rate for esophageal variceal bleeding, on the first event, is between 40 and 70%.
- Conversely, varices do not bleed if hepatic venous pressure gradient (HVPG) is below 12 mmHg.
- The treatment of esophageal varices can be pharmacological, endoscopic or surgical.
- In primary prophylaxis of esophageal variceal bleeding, the use of β -blocker treatment is only recommended in patients at high risk.
- In treatment of acute variceal hemorrhage, combining pharmacotherapy with endoscopic therapy reduces rebleeding.
- In secondary prophylaxis, the treatment of choice is eradication of esophageal varices with band ligation.
- If the bleeding is uncontrolled, transjugular intrahepatic portosystemic shunt or nonselective portosystemic shunt may be suitable in patients with cirrhosis provided that the liver dysfunction is not too severe.

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