Portal Hypertension and Variceal Hemorrhage

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Portal hypertension, a major hallmark of cirrhosis, is defined as a portal pressure gradient exceeding 5 mm Hg [1]. In portal hypertension, portosystemic collaterals decompress the portal circulation and give rise to varices. Successful management of portal hypertension and its complications requires knowledge of the underlying pathophysiology, the pertinent anatomy, and the natural history of the collateral circulation, particularly the gastroesophageal varices.

Hemodynamic principles and causes of portal hypertension

Portal hypertension is a pathologic increase in the portal venous pressure gradient between the portal vein and the inferior vena cava. It results from changes in portal resistance together with changes in portal inflow, as defined by Ohm’s law:

\[ P(\text{pressure}) = Q(\text{blood flow}) \times R(\text{resistance}) \]

The mechanism of the increase in portal pressure depends on the site and the cause of portal hypertension (Box 1), cirrhosis being the most common cause in the Western world [2]. The initial event in the development of portal hypertension in cirrhosis is an increase in resistance to outflow from the portal venous bed. This results from a relatively fixed component from distortion of the intrahepatic vascular bed from the disruption of hepatic architecture and a dynamic component from impaired intrahepatic vasodilation. An estimated 30% of the increased portal resistance is due to the hemodynamic...
changes, characterized by hepatic vasoconstriction and impaired response to vasodilatory stimuli [3,4]. An intrahepatic decrease in the production of the vasodilator nitrous oxide (NO) [5], in combination with an increase in the production of the vasoconstrictor endothelin-1, is the major contributor to the dynamic increase in hepatic vascular resistance [6,7].

Cirrhosis is associated with a hyperdynamic circulatory state that is characterized by peripheral and splanchnic vasodilation, reduced mean arterial pressure, and increased cardiac output. NO-mediated splanchnic vasodilation [8–16] produces an increase in inflow of systemic blood into the portal circulation, which causes an increase in portal pressure [17].

Portal pressure is most commonly determined by the hepatic vein pressure gradient (HVPG), which is the difference between the wedged hepatic venous pressure (reflecting the hepatic sinusoidal pressure) and free hepatic vein pressure [18,19]. In combination with venography, right-sided heart pressure measurements, and transjugular liver biopsy, measurement of the HVPG usually delineates the site of portal hypertension (ie, presinusoidal, sinusoidal, or postsinusoidal).

Collateral circulation

Portal hypertension caused by cirrhosis persists and progresses due to (1) prominent obstructive resistance within the liver, (2) resistance within the

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**Box 1. Causes of portal hypertension**

*Presinusoidal*
- Prehepatic
  - Portal vein thrombosis
  - Superior mesenteric vein thrombosis
  - Sinistral portal hypertension (splenic vein thrombosis)
- Intrahepatic
  - Idiopathic portal hypertension
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis

*Sinusoidal*
- Cirrhosis
- Vitamin A toxicity
- Infiltrative disorders (eg, lymphoproliferative and myeloproliferative diseases)

*Post-sinusoidal*
- Veno-occlusive disease
- Budd Chiari syndrome
- Congestive heart failure
collaterals, and (3) continued increase in portal vein inflow. This hypertension leads to the formation of collaterals that decompress the portal circulation by returning blood to the heart via the systemic venous circulation. The major sites of collaterals are:

Rectum, where the systemic inferior mesenteric vein connects with the portal pudendal vein and results in rectal varices
Umbilicus, where the vestigial umbilical vein communicates with the left portal vein and gives rise to prominent collaterals around the umbilicus (caput medusa)
Retroperitoneum, where collaterals, especially in women, communicate between ovarian vessels and iliac veins
Distal esophagus and proximal stomach, where gastroesophageal varices form major collaterals between the portal venous system and the systemic venous system

The following four zones of venous drainage are involved in the formation of gastroesophageal varices [20]:

The *gastric* zone is 2 to 3 cm below the gastroesophageal junction, where the veins meet at the upper end of the cardia of the stomach, drain into short gastric and left gastric veins, and then drain into the splenic and portal veins, respectively.
The *palisade* zone is 2 to 3 cm proximal to the gastric zone into the lower esophagus, where the veins communicate with extrinsic (periesophageal) veins in the distal esophagus. This zone forms the dominant watershed area between the portal and the systemic circulations.
More proximal to the palisade zone in the esophagus is the *perforating* zone, where a network of submucosal veins in the esophagus connects to the periesophageal veins, which drain into the azygous system and subsequently into the systemic circulation.
The *truncal* zone is approximately 10 cm in length and is located proximally to the perforating zone in the esophagus. It typically has four longitudinal veins in the lamina propria.

Most patients who have intrahepatic causes of portal hypertension have gastroesophageal varices because this provides the largest collateral flow via the short and left gastric veins.

Varices form only when the HVPG exceeds 10 mm Hg and bleed only when the HVPG exceeds 12 mm Hg [21,22]. Not all patients who have a HVPG greater than 12 mm Hg bleed. Other local factors that increase variceal wall tension are required [23]. The wall tension is defined by Frank’s modification of Laplace’s law [24]:

\[ T = \frac{(P \text{ varices} - P \text{ esophageal lumen}) \times (\text{radius of varix})}{\text{wall thickness}} \]

The varix ruptures when the tolerated wall tension is exceeded because the variceal wall thins and the varix increases in diameter and has an increased pressure. Larger varices at sites of limited soft tissue support, notably the gastroesophageal junction, are
at greater risk for variceal rupture and bleeding in patients who have portal hypertension.

**Diagnosis of varices**

Upper gastrointestinal endoscopy is the most common method to diagnose varices. Various criteria have been used to standardize the description of esophageal varices. The Japanese Research Society for Portal Hypertension described varices in terms of red color signs, color of the varix, form (size) of the varix, and location of the varix [25]. The Northern Italian Endoscopy Club simplified this scheme by classifying varices as F1, F2, or F3 (corresponding to small, medium, or large) with or without red signs. The clinically important decision is whether varices warrant therapeutic intervention. It is therefore useful to evaluate varices in terms of those that require treatment. It is recommended that varices be classified as small, which do not always warrant intervention, or large, which include those that were previously called large [26]. This provides a relatively simple and easily reproducible classification.

Gastric varices are classified by location, which correlates with their risk of hemorrhage. Varices in direct continuity with the esophagus along the lesser and greater curves of the stomach are called gastroesophageal varices (GOV) types 1 and 2, respectively. Isolated gastric varices in the fundus (IGV1) occur less frequently than GOVs (10% versus 90%) but are the most likely to bleed. They may be caused by splenic vein thrombosis or spontaneous splenorenal collaterals.

Endoscopic ultrasound (EUS) has been used to study esophageal varices and to identify a high risk of bleeding by assessment of the cross-sectional area of varices [24]; the size of and flow in the left gastric vein, azygous vein, and paraesophageal collaterals; the changes after endoscopic therapy; and the recurrence of esophageal varices after variceal ligation (collaterals >5 mm are at high risk for recurrent varices) [27]. It is unclear if EUS is superior to standard endoscopy.

Esophageal capsule endoscopy is a promising modality to assess varices. It may provide an accurate, less invasive alternative to EGD for the detection of esophageal varices or portal hypertensive gastropathy [28,29]. A large recent trial, reported only in abstract form, found excellent concordance with endoscopy. The role of capsule endoscopy in the management of varices is still evolving.

**Natural history of gastroesophageal varices**

De novo varices develop in 5% to 15% of patients who have cirrhosis per annum and enlarge by 4% to 10% per annum. Most patients who have cirrhosis develop varices, but only one third of them experiences variceal bleeding. Only 40% to 50% of actively bleeding varices spontaneously stop bleeding.
Risk factors for variceal bleeding are listed in Table 1 [21]. When combined, these factors reasonably accurately predict the risk of bleeding (see Table 1) [30]. Varices with a high risk of bleeding include medium and large varices or small varices in patients who have advanced liver failure (Child-Pugh class C).

It is essential to identify and prophylactically treat high-risk patients because each episode of variceal hemorrhage carries a 15% to 20% mortality, and up to 70% of untreated patients die within 1 year of the initial bleeding episode [31]. All patients who have cirrhosis should undergo diagnostic endoscopy to document the presence of varices and to determine their risk for variceal hemorrhage. Recent data showed that a platelet count greater than 150,000 has a high negative predictive value (>90%) for the presence of high-risk esophageal varices [32] in patients who have hepatitis C and Ishak stage 3, 4, 5, or 6 fibrosis with compensated liver function. These data need to be corroborated in an independent population of subjects who have various causes of cirrhosis before applying them to alter screening strategies.

In patients who have cirrhosis without varices or with varices that do not require intervention, endoscopy must be periodically repeated. Patients who have cirrhosis without varices should be rescreened at 2- to 3-year intervals and at the time of hepatic decompensation; patients who have cirrhosis with small varices that do not warrant therapy should be rescreened at 1- to 2-year intervals [26]. Patients who have Child’s class B or C with varices of any grade or Child’s class A with medium-large varices should be considered for primary prophylaxis of variceal hemorrhage.

### Prophylactic treatment of esophageal varices

**Pharmacologic therapy**

Nonselective beta-blockers (nadolol and propranolol) are the first-line treatment for primary prophylaxis. They block vasodilatory beta-adrenergic

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Risk factors for variceal hemorrhage</th>
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<tbody>
<tr>
<td>Portal pressure</td>
<td>HVPG &gt; 12 mm Hg</td>
</tr>
<tr>
<td>Varix size and location</td>
<td>Large esophageal varices</td>
</tr>
<tr>
<td>Variceal appearance on endoscopy (&quot;red signs&quot;)</td>
<td>Red wale marks (longitudinal red streaks on varices)</td>
</tr>
<tr>
<td>Degree of liver failure</td>
<td>Child-Pugh class C cirrhosis</td>
</tr>
<tr>
<td>Presence of ascites</td>
<td>Tense ascites</td>
</tr>
<tr>
<td>Isolated cluster of varices in fundus of stomach</td>
<td>Cherry-red spots (red, discrete, flat spots on varices)</td>
</tr>
<tr>
<td>Diffuse erythema</td>
<td>Hematocystic spots (discrete, red, raised spots)</td>
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</tbody>
</table>

*Abbreviation: HVPG, hepatic vein pressure gradient.*
receptors, permitting unopposed alpha-adrenergic vasoconstriction in the mesenteric arterioles, thereby reducing portal venous inflow and pressure. They also decrease cardiac output, which further decreases the portal inflow. Meta-analysis of clinical trials shows that the risk of bleeding is reduced by beta-blocker therapy versus placebo from 25% to 15% [33]. The effectiveness of beta-blockers is most accurately assessed by the HVPG. The best predictor of success is a sustained decrease in the HPVG to less than 12 mm Hg, whereas patients who have a sustained 20% decrease in HPVG to greater than 12 mm Hg have a risk of bleeding of less than 10% [34,35]. This approach is not widely applied to clinical practice. The efficacy of beta-blockers is clinically monitored by a decrease in the resting heart rate greater than 25% but not to a rate less than 55 beats/min. Only 20% to 30% of subjects achieve these endpoints, and 15% to 20% of subjects cannot tolerate and require discontinuation of this therapy.

Short-acting (nitroglycerin) or long-acting (isosorbide mononitrates) nitrates cause venodilatation, rather than arterial dilatation, and decrease portal pressure predominantly by decreasing portal venous blood flow. The effect on intrahepatic resistance is not impressive, and nitrates are no longer recommended for primary prophylaxis due to discrepant results of clinical trials.

Other agents that may decrease intrahepatic resistance include α1-adrenergic blockers and angiotensin II receptor antagonists. Prazosin, an α1-adrenergic blocker, caused worsening of the systemic hyperdynamic circulation and was associated with portal hypertension and consequent sodium retention and ascites [36]. Losartan, an angiotensin II receptor antagonist, caused a reduction in portal pressure without significant effects on the systemic circulation [37]. It did not significantly reduce portal pressure in randomized controlled trials, but it worsened the renal function [38,39]. Endothelin receptor blockers and liver-selective NO donors that target intrahepatic vascular resistance are promising investigational therapies [40].

**Endoscopic sclerotherapy**

Prophylactic endoscopic sclerotherapy (EST) was used in the 1980s. Although controlled trials initially reported that it significantly reduced the risk of a first variceal bleed and improved survival [41–43], subsequent trials did not show a survival benefit. EST may provoke bleeding that is difficult to control and may increase the mortality [44,45]. A meta-analysis showed a marked reduction in the risk for a first episode of bleeding, but the mortality was higher in certain studies [46]. Consequently, EST is not recommended for prophylaxis of esophageal varices.

**Endoscopic variceal ligation**

Endoscopic variceal ligation (EVL) is associated with fewer procedure-related complications than EST. EVL significantly reduces the risk of the
first bleeding compared with no treatment [47–49] or compared with propranolol [50–52], with a relative risk reduction of almost 40% (Fig. 1). No survival benefit was seen compared with propranolol. One study did not reveal any benefit of EVL and propranolol versus EVL alone; however, given the low risk of bleeding after variceal eradication and the use of EVL when varices recurred, the investigators likely missed any chance of demonstrating a benefit of combined therapy because beta-blockers would be expected to prevent varices as their main effect.

In summary, nonselective beta-blockers or EVL are recommended first-line treatments for primary prophylaxis of variceal hemorrhage. EVL may be used in subjects who cannot tolerate beta-blockers. The authors use EVL in patients who are likely not to tolerate beta-blockers (eg, patients who have low blood pressure or asthma) and who have medium-large varices, whereas they preferentially use beta-blockers when the varices are small and technically difficult to band. This practice is based on evidence that up to 6% of subjects undergoing EVL may experience potentially life-threatening iatrogenic hemorrhage.

Management of acute variceal bleed

The management of acute variceal bleeding includes hemodynamic resuscitation, general treatments, prevention of complications, and achievement of hemostasis. Intravenous access must be promptly secured (Box 2). Airway intubation is indicated in patients who are bleeding severely or who have mental status changes that preclude their ability to protect their airway. Intravascular volume loss is estimated and replaced with crystalloids

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and packed red cells. The systolic blood pressure should be maintained at least at 90 to 100 mm Hg, and the heart rate should be maintained below 100 beats/min, with a hemoglobin level around 9 g/dL (hematocrit of 25–30), because overtransfusion can cause a rebound increase in portal pressure and precipitate early rebleeding [53,54]. Fresh frozen plasma and platelets (particularly for a platelet count < 50,000/ml) are often used to correct a coagulopathy. They do not adequately correct the coagulopathy and can induce volume overload and rebound portal hypertension [55]. The use of recombinant factor VII has been shown to improve hemostasis rates, but it did not improve survival [56].

Bacteremia is often present on admission for acute variceal hemorrhage. Common bacterial infections include spontaneous bacterial peritonitis, urinary tract infection, and pneumonia. Infections are associated with an increased risk of rebleeding and higher mortality, likely secondary to a further increase in resistance to portal flow, further splanchnic arteriolar dilatation, and further coagulopathy [57,58]. A complete microbiological work-up,
including blood cultures and diagnostic paracentesis when appropriate, should be performed. Empiric therapy with a third-generation cephalosporin (eg, ceftriaxone) should be uniformly instituted because several clinical trials have shown improvement in control of bleeding and in patient outcomes (Fig. 2) [59].

Pharmacologic therapy

Vasopressin and its analogs

Vasopressin is an endogenous nonopeptide that causes splanchnic vasoconstriction by acting on V1 receptors located in arterial smooth muscle, reduces portal venous inflow, and reduces portal pressure [60]. It has severe toxicity, including bowel necrosis from vasoconstriction. Terlipressin, a semisynthetic analog of vasopressin, has a lower rate of systemic side effects. It increases survival in patients who have variceal bleeding. It is not available in the United States [61].

Somatostatin and its analogs

Somatostatin has a half-life in the circulation of 1 to 3 minutes. It decreases portal pressure and collateral blood flow by inhibiting the release of glucagon [62]. It also decreases portal hypertension by decreasing postprandial blood flow (blood perfusion of the gastrointestinal tract after a meal) [63]. Somatostatin is not available in the United States.

Octreotide, a somatostatin analog, has a half-life in the circulation of 80 to 120 minutes. Its effect on reducing portal pressure is not prolonged. Moreover, continuous infusion of octreotide does not decrease the baseline

Fig. 2. A meta-analysis of studies of empiric antibiotic use in active variceal bleeding. Each data point reflects the odds ratio for the benefit of one treatment versus another for a given study. Horizontal bars represent the confidence limits for the data. There was a significant advantage for use of antibiotics (pooled odds ratio, 0.09). (From Bernard B, Grange JD, Khac EN, et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology 1999;29(6):1655–61; with permission.)
portal pressure despite decreasing the postprandial increase in portal pressure [64]. Although some studies failed to prove the superiority of somatostatin or its analogs compared with placebo in the control of acute variceal bleeding [65], other studies showed efficacy [66]. Early administration of vапреотид may be associated with improved control of bleeding but without a significant reduction in mortality [67].

**Endoscopic therapy**

*Endoscopic sclerotherapy*

EST has largely been supplanted by EVL, except when poor visualization precludes effective band ligation of bleeding varices. Current evidence does not support emergency EST as first-line treatment of variceal bleeding [68]. The technique involves injection of a sclerosant into (intravariceal) or adjacent to (paravariceal) a varix. Complications of EST occurring during or after the procedure include chest discomfort, ulcers (and ulcer-related bleeding), strictures, and perforation. The risk of ulcers can be reduced by prescribing sucralfate after EST [69].

*Endoscopic variceal ligation*

EVL is the preferred endoscopic modality for control of acute esophageal variceal bleeding and for prevention of rebleeding. Varices at the gastro-esophageal junction are banded initially, and then more proximal varices are banded in a spiral manner at intervals of approximately every 2 cm. Varices in the middle or proximal esophagus do not need to be banded. EVL is associated with similar but fewer complications [70] than EST and requires fewer sessions to achieve variceal obliteration.

In summary, the first-line treatment for active esophageal variceal hemorrhage is a combination of pharmacologic treatment (ie, octreotide) and endoscopic treatment (EVL or EST) (Fig. 3) [71]. About 80% to 90% of patients achieve hemostasis with first-line therapy; the remaining patients fail to achieve hemostasis or experience early rebleeding [72].

Within the first 6 hours, failure to control bleeding is recognized by [73] (1) transfusion requirement of more than four units of packed red cells and (2) the inability to maintain the systolic blood pressure greater than 70 mm Hg or to raise it by 20 mm Hg or to reduce the resting pulse to less than 100/min or to decrease it by 20 beats/min.

After 6 hours, early rebleeding is defined by hematemesis together with (1) reduction in systolic blood pressure by 20 mm Hg from the level at 6 hours, (2) increase in pulse rate by 20/min from the rate at 6 hours on two consecutive readings 1 hour apart, or (3) the need to transfuse two or more units of packed red cells to increase the hematocrit to more than 27% or the hemoglobin to more than 9 g/dL.
Bleeding that occurs more than 48 hours after the initial admission for variceal hemorrhage and is separated by at least a 24-hour bleed-free interval is considered as rebleeding. Specific factors have been associated with failure to control active bleeding and early rebleeding[74], including spurring varices, high Child-Pugh score, HPVG greater than 20 mm Hg [75], infection, and portal vein thrombosis (Box 3).

In patients who have uncontrolled active bleeding or early rebleeding, definitive salvage therapy must be performed before the onset of complications related to the bleeding. Balloon tamponade effectively produces hemostasis in 80% to 90% of cases [76]. Balloon tamponade requires airway protection, is associated with a high incidence of rebleeding when the balloon is deflated, and can cause pressure necrosis of the mucosa if the balloon remains inflated for more than 48 hours. It is therefore used to temporize until definitive treatment is instituted. EVL can be attempted once more for early rebleeding, but this decision must be individualized because of an absence of controlled trials in this setting. The salvage treatment in these patients is portal decompression, with transjugular intrahepatic portosystemic shunts (TIPS) being the procedure of choice.

**Transjugular intrahepatic portosystemic shunts**

TIPS reduces elevated portal pressure by creating a communication between the hepatic vein and an intrahepatic branch of the portal vein. It produces hemostasis in more than 90% of cases [77,78]. Once complications from bleeding of aspiration pneumonia or multiorgan failure occur, the prognosis is dismal regardless of the achievement of hemostasis, as demonstrated by a 10% survival at 30 days in patients who have aspiration pneumonia [79]. In the absence of aspiration pneumonia, a 90% survival can be achieved. The best predictor of mortality after TIPS is the MELD (Model of End Stage Liver Disease) score.
Contraindications to TIPS include severe congestive heart failure, severe pulmonary hypertension, severe hepatic failure, portal vein thrombosis with cavernomatous transformation, and polycystic liver disease. In a decision in an individual patient, the risk of exsanguination must be weighed against the type of contraindication. Although hemostasis may be achieved with TIPS, patients who have multiorgan failure have a dismal prognosis in the authors’ experience. After consultation with the next of kin, provision of only palliative care may often be appropriate in such patients.

Surgical decompression of the portal system via portosystemic shunts is another salvage modality. The use of surgical shunts has declined markedly due to the increasing availability of TIPS, the high morbidity of surgery, and the decline in the number of surgeons trained to perform these procedures.

### Box 3. Factors affecting risk of continued bleeding or recurrent bleeding

*Factors associated with failure to control acute hemorrhage*
- Spurting varices
- High Child-Pugh score
- High hepatic venous pressure gradient
- Infection
- Portal vein thrombosis

*Factors associated with early rebleeding*
- Severe initial bleeding
- Overly aggressive volume resuscitation
- Infection
- High hepatic venous pressure gradient
- Complications of endoscopic therapy
- Renal failure

*Factors associated with late rebleeding*
- High Child-Pugh score
- Large variceal size
- Continued alcohol use
- Hepatocellular carcinoma

Based on data from pooled sources.

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### Secondary prophylaxis

Once acute variceal bleeding is controlled, prevention of recurrent bleeding should be emphasized. After an index bleed, 70% of patients experience recurrent variceal hemorrhage within 1 year [80], and these patients have
a 70% 1-year mortality. The risk of rebleeding is greatest within the first 6 weeks, with more than 50% of rebleeding occurring within 3 to 4 days. Risk factors for rebleeding include severe initial bleeding as defined by a hemoglobin level less than 8 mg/dL, gastric variceal bleeding, active bleeding at endoscopy, and a high HPVG [81,82]. Age greater than 60 years, large esophageal varices, severe liver disease, continued alcoholism, renal failure, and the presence of a hepatoma also increase the risk of rebleeding [81,83]. It is important to prevent recurrent hemorrhage, preserve liver function, maintain a normal renal function, prevent ascites, and avoid alcohol consumption to prolong survival.

Orthotopic liver transplant is the only treatment that achieves most of these objectives and prolongs long-term survival. Some patients are unsuitable candidates for liver transplantation, and, even if orthotopic liver transplant is being considered, patients often have to wait several months before a donor liver becomes available. During this time, they are at risk for recurrent variceal hemorrhage and therefore require treatment to prevent this complication.

The first-line therapy for secondary prophylaxis of variceal hemorrhage is EVL and beta-blocker therapy (Fig. 4). A randomized controlled trial evaluated this combination therapy versus EVL alone [84]. After a median follow-up of 21 months, combination therapy was associated with a significantly lower rate of rebleeding (12% versus 29%) and of variceal recurrence (26% versus 50%). A meta-analysis of 13 studies of EVL versus EST demonstrated that EVL reduced the relative risk of rebleeding by 37% [70]. EVL does not provide a survival advantage over EST. On the other hand, nonselective beta-blockers alone reduce the risk of rebleeding from 63% to 42%, for a 33% relative risk reduction [33]. For mortality, the absolute risk reduction is 7%. Pharmacotherapy with beta-blockers and nitrates cannot be recommended due to discrepant results from clinical trials [84–86].

Fig. 4. The outcomes of a clinical trial of endoscopic variceal ligation and nadolol versus endoscopic variceal ligation alone. Combination therapy was associated with a significantly lower rebleeding rate, although survival was not significantly affected. (Data from de la Pena J, Brullet E, Sanchez-Hernandez E, et al. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial. Hepatology 2005;41(3):572–8.)
A meta-analysis of 12 clinical trials of TIPS versus endoscopic treatment indicates that TIPS is superior to endoscopic treatment for the prevention of rebleeding (19% versus 47%) [87], but this advantage is offset by its failure to improve survival, its higher morbidity from the development of liver failure and encephalopathy (34% versus 19%), and its lack of a cost benefit [88]. Based on these considerations, TIPS is primarily used as a salvage treatment for patients who experience recurrent bleeding despite adequate endoscopic and pharmacologic treatment. In one recent study, subjects who had bleeding esophageal varices underwent early HVPG measurement after initial stabilization with band ligation. Patients who had a HVPG greater than 20 mm Hg were randomized to TIPS versus band ligation. In this high-risk subgroup, early, elective TIPS dramatically improved outcomes compared with EVL. These results await corroboration from other prospective trials.

In summary, the following regimen is recommended for secondary prophylaxis of esophageal variceal hemorrhage:

1. Eradication of esophageal varices by EVL (every 7–14 days until varices are eradicated) with concomitant use of nonselective beta-blockers (propranolol or nadolol)
2. Long-term endoscopic control and banding of recurrent varices every 3 to 6 months
3. If EVL is unavailable or contraindicated, nonselective beta-blockers can be used alone.
4. TIPS is considered if pharmacologic and endoscopic therapy faild (recurrence of variceal hemorrhage despite at least two sessions of endoscopic treatment performed not more than 2 weeks apart).

Always consider liver transplantation if the patient is Child-Pugh B or C.

**Gastric varices**

Gastric varices most commonly are caused by portal hypertension, usually in patients who have cirrhosis. Patients who have splenic vein thrombosis or spontaneous splenorenal collaterals can develop isolated gastric varices, particularly IG1. GOV1 disappears in approximately 58% and 70% after EST and EVL of esophageal varices, respectively [89,90]. The obliteration of varices at the gastroesophageal junction blocks the shunting veins in the palisade zone, leading to dilatation and the formation of new or secondary gastric varices [91]. These secondary varices occur at a rate of 9.7% to 15.3% [92–94] and have a higher frequency of bleeding compared with primary gastric varices. On the other hand, bleeding from primary gastric varices after endoscopic treatment of esophageal varices is uncommon.

The prevalence of gastric varices is 5% to 33% in patients who have portal hypertension, with an overall incidence of bleeding ranging from 3% to 30% [95,96]. Mortality associated with gastric variceal hemorrhage is 30% to 53%, with a 30% rebleeding rate.
Because GOV1 constitutes an extension of esophageal varices along the lesser curvature of the stomach, it is managed like esophageal varices. IGV1 secondary to splenic vein thrombosis is treated by splenectomy. There is no consensus on primary prophylaxis of bleeding GOV2 or IGV due to limited data.

EST controls active bleeding in 40% to 100% of cases of GOV1 [97–103]. The primary drawback is the high risk of recurrent bleeding. EST is frequently associated with ulceration, which bleeds in approximately 50% of cases [97,102,103]. Rebleeding rates have been reported to be 5.5% in GOV1, 19% in GOV2, and as high as 53% in IGV1 [102].

In prospective uncontrolled studies, EVL has been shown to achieve hemostasis rates of up to 89%, with a rebleeding rate of 18.5% [104]. These studies included all types of gastric varices. The major concern after gastric EVL is the potential of partial ligation of large gastric varices, which may produce bleeding [105,106]. EVL is generally not recommended for IGV1.

Compared with EST or EVL, endoscopic variceal occlusion with tissue adhesives, such as N-butyl-cyanoacrylate, isobutyl-2-cyanoacrylate, or thrombin, is more effective for acute fundal gastric variceal bleeding (Table 2). Successful obliteration leads to better control of the initial hemorrhage and lower rebleeding rates [107,108]. A prospective randomized trial of gastric variceal occlusion (GVO) with N-butyl-cyanoacrylate versus EVL in patients who had acute gastric variceal hemorrhage demonstrated that the control of active bleeding was similar in both groups but that rebleeding occurred significantly less frequently in the GVO group (23% versus 47%), with an average of only 1.5 therapy sessions (range 1–3) during a follow-up period of 1.6 to 1.8 years [109]. Therefore, GVO is preferred; however, no tissue adhesive is licensed for use in the United States. In an uncontrolled pilot study, 2-octyl cyanoacrylate, an agent approved for skin closure in the United States, has been described as effective for achieving initial hemostasis and preventing rebleeding from fundal varices [110].

TIPS is the major salvage or, perhaps, is even a primary therapeutic modality for gastric varices in the United States [111], with bleeding control rates greater than 90%. Balloon-occluded retrograde transvenous obliteration is a newly developed transvenous sclerotherapy technique performed for treating gastric fundal varices from spontaneous gastrorenal shunts.

Table 2
Outcomes of trials of gastric variceal occlusion for gastric varices

<table>
<thead>
<tr>
<th>Author</th>
<th>Study comparison (n/n)</th>
<th>Control bleed (%)</th>
<th>Varices obliterated (%)</th>
<th>Rebleed (%)</th>
<th>AE (%)</th>
<th>Mortality (%)</th>
</tr>
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<tbody>
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<td>Tan 2006</td>
<td>GVO/EVL (48/49)</td>
<td>93/93</td>
<td>62/67</td>
<td>22/44</td>
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<td>Lo 2001</td>
<td>GVO/EVL (31/29)</td>
<td>87/45</td>
<td>51/45</td>
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<td>29/48</td>
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<tr>
<td>Sarin 2002</td>
<td>GVO/AA (8/9)</td>
<td>89/62</td>
<td>100/44</td>
<td>22/25</td>
<td>—</td>
<td>11/25</td>
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Abbreviations: AA, Alcohol; AE, Adverse Events; EVL, esophageal variceal ligation; GVO, gastric variceal occlusion.
Shiba and colleagues recently showed that balloon-occluded injection sclerotherapy is safe and effective even in patients who do not have gastrorenal shunts. Surgical shunts also control bleeding gastric varices and prevent recurrent bleeding.

Ectopic varices

Ectopic varices are defined as portosystemic shunts, resulting from portal hypertension, that occur at any site in the gut or abdomen except in the gastroesophageal region. These sites include the duodenum, jejunum, ileum, colon, rectum, biliary tree, and ostomy sites. It is important to differentiate anal varices from hemorrhoids: Anal varices collapse with digital pressure, whereas hemorrhoids do not.

Ectopic varices account for 1% to 5% of all variceal bleeding. Patients who have ectopic variceal hemorrhage typically present with sudden, profuse melena or hematochezia. Because brisk upper gastrointestinal (UGI) bleeding can result in hematochezia, all subjects who have suspected variceal hemorrhage should initially undergo emergency upper endoscopy. If the upper endoscopy fails to reveal a source of UGI hemorrhage, colonoscopy is performed after a rapid colonic purge. If the colon looks normal and bleeding continues, angiography may be useful to identify varices or to localize a nonvariceal source of hemorrhage.

Several studies have reported successful therapy of duodenal varices with sclerosant injection or with an occluding agent. There are no data regarding band ligation of ectopic varices. The next treatment option is embolization. Unlike arterial embolization for gastrointestinal hemorrhage, the goal in this setting is to occlude the feeding vein (on the portal venous side) to the ectopic varices rather than to occlude the bleeding site. Balloon-occluded retrograde transvenous obliteration has been successfully used in several reported cases. If the patient continues to bleed despite embolization, options include TIPS or surgery. At our center, TIPS is the preferred approach for the treatment of bleeding ectopic varices.

Gastric antral vascular ectasia

Gastric antral vascular ectasia (GAVE), or watermelon stomach, describes a vascular lesion of the gastric antrum that consists of ectatic and sacculated antral mucosal vessels radiating toward from the pylorus. Its cause is unknown, but it has been proposed that gastric peristalsis causes prolapse of the loose antral mucosa into the duodenum with consequent elongation and ectasia of the mucosal vessels. Microscopic features include dilated capillaries with focal thrombosis, dilated and tortuous submucosal venous channels, and fibromuscular hyperplasia of the muscularis mucosa. Most cases are idiopathic, but it has been associated
with cirrhosis, achlorhydria, atrophic gastritis, and the CREST syndrome and has occurred after bone marrow transplantation [122]. The association with cirrhosis and portal hypertension is considered unreliable because GAVE with coexisting portal hypertension does not generally respond to reduction of the portal pressure [123].

GAVE may cause acute hemorrhage or chronic occult bleeding. It frequently occurs in middle-aged or older women. Treatment consists mainly of endoscopic coagulation with heater probe, Gold probe, argon plasma coagulator, or laser therapy. Chronic cases sometimes require periodic transfusions and iron therapy. Portal decompression with TIPS does not reduce the bleeding. Antrectomy prevents recurrent bleeding but is usually reserved for patients who fail endoscopic therapies.

**Portal hypertensive gastropathy**

Portal hypertensive gastropathy (PHG) is characterized endoscopically by three patterns: (1) fine red speckling of gastric mucosa; (2) superficial reddening, especially on the tips of the gastric rugae; and, most commonly, (3) the presence of a mosaic pattern with red spots (snake-skin appearance) in the gastric fundus or body. Histologically, the stomach in PHG contains dilated, tortuous, irregular veins in the mucosa and submucosa, sometimes with intimal thickening, usually in the absence of significant inflammation.
PHG is correlated with the severity of liver disease. It is diagnosed by endoscopy. It is an uncommon cause of significant UGI bleeding in patients who have portal hypertension. In one study, acute bleeding from PHG was observed in only 2.5% of patients.

Treatment is directed at decreasing portal pressure. Propranolol has been shown to significantly reduce the rate of recurrent bleeding compared with placebo (35% versus 62% at 1 year). Vasopressin, terlipressin, somatostatin, and octreotide have not been studied for this indication. TIPS is the next therapy. It is associated with significant improvement in the endoscopic findings and a decrease in the transfusion requirements. If bleeding continues, surgical portal decompression is performed. Liver transplantation is indicated for decompensated liver disease. Endoscopic thermal coagulation is not effective for controlling or preventing this diffuse form of bleeding.

**Downhill varices**

Esophageal veins form a plexus on the outer surface of the esophagus. The lower part drains into the short and left gastric veins of the portal system, whereas the upper part drains into the azygous, thyroid, and internal mammary veins and then into the superior vena cava. “Downhill” esophageal varices (DEV) form in the upper third of the esophagus as collateral branches directing blood flow “downward” to bypass superior vena cava (SVC) obstruction via the azygous vein or to drain the systemic superior venous system via the portal vein when the SVC and the azygous vein are obstructed.

DEV are mostly due to SVC syndrome secondary to mass effects (external compression of the SVC) from lung cancer, intrathoracic goiter, mediastinal lymphoma, thyroid carcinoma, thymoma, or mediastinal lymphadenopathy secondary to head and neck cancers. DEV usually disappear after treatment of the underlying condition. Several cases have been associated with gastrointestinal hemorrhage, which can be life threatening. Due to its rarity, neither controlled trials nor a general consensus exists on the best therapeutic approach. Isolated case reports have suggested success with EST, EBL, or balloon tamponade.

**References**


