Variceal bleeding is one of the dreaded complications of portal hypertension. Although its prognosis has improved over the last several decades, it still carries substantial mortality. Although most portal hypertensive bleeds result from the ruptured distal esophageal varices, bleeding from other sources such as gastric varices, portal hypertensive gastropathy, and ectopic varices can lead to clinically significant bleeding. The following sections review management of acute variceal bleeding, prevention of rebleeding, bleeding from gastric varices and portal hypertensive gastropathy, and the prevention of first variceal bleeding.

**MANAGEMENT OF ACUTE VARICEAL BLEEDING**

Variceal bleeding typically presents as massive gastrointestinal (GI) bleeding with hematemesis, melena, or hematochezia. In general, the therapeutic aims of management are to initially correct hypovolemic shock, to control bleeding, to prevent complications of bleeding, such as infection and renal failure, and to prevent early rebleeding.

**INITIAL MANAGEMENT**

Hemodynamic instability related to hypovolemia is a common presentation of acute variceal bleeding. Therefore, patients require prompt resuscitation, hemodynamic support, and correction of hemodynamic dysfunction, which usually requires intensive care unit monitoring. Lung aspiration of gastric contents and blood is a major concern, especially in encephalopathic patients. Furthermore, patients who are actively consuming alcohol can be combative and difficult to sedate for endoscopic procedures. Therefore, endotracheal intubation for airway protection should be considered in anyone who is at risk for aspiration or is uncooperative. Judicious transfusion of blood products is necessary.
In animal studies, 100% volume replacement in portal hypertensive rats led to a rebound increase in portal pressure [1]. In another study, following a variceal bleed in animal models, rapid blood transfusion to correct arterial pressure led to an increased risk of further bleeding [2]. Therefore, one should aim for target hemoglobin between 9 and 10 g/dL when transfusing cirrhotic patients who have variceal bleeding.

Renal failure is a common complication of cirrhotic patients hospitalized for variceal bleeding [3]. The cause of acute renal failure in this setting is typically multifactorial, including prolonged hypovolemia, overuse of diuretics, infection, and hepatorenal syndrome. In a retrospective study by Cardenas and colleagues [3], hypovolemia and poor liver function were the only independent risk factors for renal failure in patients who had cirrhosis presenting with upper GI hemorrhage. Furthermore, in this study, renal failure was an independent risk factor for in-hospital mortality. Therefore, every effort should be made to avoid the development of renal failure by early aggressive resuscitation of patients and by avoiding nephrotoxic agents such as aminoglycosides and nonsteroidal drugs.

Recent studies have shown the importance of using prophylactic antibiotics in cirrhotic patients with bleeding. Bacterial infections are more common in cirrhotic patients with variceal bleeding (35% to 66%) than in noncirrhotic hospitalized patients (5% to 7%) [4]. Two factors have been identified to increase the risk of bacterial infections in patients who have cirrhosis: severity of the liver disease and GI hemorrhage [5,6]. Several studies have shown that mortality is significantly higher in infected cirrhotic patients versus noninfected cirrhotic patients [7,8]. Furthermore, a study by Bernard and colleagues demonstrated that infected cirrhotic patients had a higher rate of variceal rebleeding (43%, 10 of 23 patients) than noninfected patients (10%, 4 of 41 patients) [9]. This is likely because of the endotoxins and cytokines as a consequence of the infection, which induces hematologic abnormalities, including platelet dysfunction and activation of coagulation and fibrinolytic systems [10]. Therefore, the current body of knowledge strongly suggests that, in patients who have cirrhosis with variceal hemorrhage, prophylaxis against a bacterial infection reduces variceal rebleeding and improves survival. A meta-analysis by Bernard and colleagues [11] demonstrated that prophylactic use of antibiotics significantly increased survival (9.1% mean improvement, $P = .004$). A recent randomized study by Hou and colleagues [12] showed that early rebleeding (within the first 15 days) was significantly lower in patients who received ofloxacin for 7 days compared with those who received on-demand antibiotics (8% versus 38%, $P < .05$). In prospective studies, the most common causes of bacterial infections in patients who had cirrhosis with variceal bleeding included spontaneous bacterial peritonitis, urinary tract infection, and pneumonia. Typically gram-negative organisms are isolated [6,13]. Therefore, antibiotics (oral quinolones or intravenous cephalosporins) should be given for 7 days in patients who have cirrhosis with bleeding.

As a part of the initial stabilization, balloon tamponade with a Sengstaken-Blakemore tube may be necessary to control brisk bleeding. Balloon tamponade
successfully achieves hemostasis in 90% of cases of bleeding varices, but it has a high recurrence rate for rebleeding once the balloon is deflated. Therefore, balloon tamponade should be reserved as a rescue procedure, so that patients are stabilized for a more definitive therapy.

**MANAGEMENT OF BLEEDING**

**Vasoactive Agents**

Vasoactive agents for treating bleeding esophageal varices first were described in 1962. Vasopressin was the first agent studied [14] because of its ability to induce splanchnic vasoconstriction, which leads to a decrease in portal inflow and portal pressure. A meta-analysis by D’Amico and colleagues of 157 patients demonstrated a significant reduction in failure to control bleeding from 82% to 50%, with no difference in mortality [15]. Vasopressin, however, leads to systemic vasoconstriction in addition to splanchnic vasoconstriction. Vasopressin’s cardiovascular adverse effects, such as myocardial ischemia and infarction, has limited its use. Combining glyceril-trinitrate with vasopressin has reduced adverse effects and improved efficacy over vasopressin alone [16,17]. Because of the significant adverse effects of vasopressin-based therapy, future research has been aimed at developing more effective and safer agents.

Somatostatin is a natural peptide that induces splanchnic vasoconstriction, which leads to a decrease in portal pressure. It lacks most of the cardiovascular adverse effects seen with vasopressin. In four unblinded randomized studies, compared with placebo, somatostatin showed a trend toward benefit, with an overall risk reduction by 17% [18]. One study by Avgerinos and colleagues [19] observed that somatostatin given before urgent sclerotherapy made the endoscopic procedure easier in the acute setting. None of these studies, however, demonstrated an improvement in overall survival compared with placebo. When compared with vasopressin [18], somatostatin was equivalent in terms of efficacy in controlling bleeding but had significantly fewer adverse effects. When somatostatin was compared with emergency sclerotherapy in 367 patients from four randomized controlled trials [20–23], there was no difference between the two groups in terms of failure to control bleeding, rebleeding, and mortality. On the other hand, the somatostatin group had fewer complications. A study by Villaneuva and colleagues [24], however, compared somatostatin alone (n = 50) with combined therapy of somatostatin and sclerotherapy (n = 50). This study observed a higher rate of therapeutic failure in the somatostatin alone group in terms of failure to control bleeding, transfusion requirements, and rebleeding. Therefore, the data suggest that the greatest benefit of somatostatin is when it is used in conjunction with endoscopic therapy. Unfortunately, somatostatin is not available in the United States.

Octreotide, a somatostatin analog, is available in the United States. It has similar properties as somatostatin, but with a longer biological half-life. Results regarding its efficacy compared with placebo, sclerotherapy, and balloon tamponade have been inconsistent. Many of the studies were small, low quality,
and unblinded. A recent meta-analysis [25] demonstrated that octreotide was superior to other alternative therapies (placebo, vasopressin/terlipressin, or sclerotherapy) in controlling acute variceal bleeding (relative risk 0.63; 95% confidence interval [CI] 0.51 to 0.77). Because of its excellent safety profile, octreotide has an added benefit that it can be administered outside of the intensive care unit setting.

Terlipressin is a long acting triglycyl-lysine derivative of vasopressin. It is transformed slowly to vasopressin by enzymatic cleavage. Because of this slow release to the active agent, terlipressin has significantly fewer adverse effects than vasopressin. Also, because of its long half-life, terlipressin can be administered at home or the emergency room with significant reduction in failure to control bleeding [26]. Furthermore, in a study by Brunati and colleagues [27] comparing terlipressin with terlipressin plus sclerotherapy, the combination group had significantly better control of active bleeding and less transfusion requirements. Currently terlipressin is the only pharmacologic therapy that has been shown to reduce mortality in acute variceal hemorrhage compared with placebo (relative risk 0.66, 95% CI 0.49 to 0.88) [28]. Unfortunately, terlipressin is not available in the United States.

There has been recent interest in the use of recombinant factor VIIa (rFVIIa) for managing upper GI hemorrhage in patients with cirrhosis. Cirrhotic patients often will have defects in the coagulation system, in particular factor VII deficiency. Bosch and colleagues [29] performed a randomized control trial of 245 cirrhotic patients presenting with upper GI hemorrhage to evaluate if the addition of rFVIIa to standard therapy improves control of bleeding. Patients either received 8 doses of 100 µg/kg of rFVIIa or placebo. Recombinant factor VIIa did not show advantage over standard therapy in the whole study population. In patients who had decompensated cirrhosis (Child-Pugh class C), however, better 24-hour bleeding control was achieved in the rFVIIa group (P = .01). These findings need to be validated further. In addition, questions such as the optimal dose of rFVIIa and its use as first-line or salvage therapy need to be answered before its routine use can be recommended in this setting.

Endoscopic Management

Both sclerotherapy and band ligation are very effective in controlling acute esophageal variceal bleeding and preventing rebleeding during the index hospitalization. These two modalities are the mainstay of therapy, and they are successful in achieving hemostasis in 80% to 90% of patients with acute variceal bleeding. The advantages of sclerotherapy include its ease of use, especially during massive bleeding, and its lower cost. Sclerotherapy, however, has been associated with ulceration and bleeding, bacteremia, and stricture formation. Band ligation has a lower rate of complication, but it can be difficult to use during acute bleeding. Studies have shown that the two modalities are comparable in achieving initial hemostasis [30]. A more recent study by Avgerinos and colleagues [31] demonstrated that after initial control of bleeding, band ligation had significantly fewer rebleeding rates and complications, and
it achieved eradication with fewer endoscopic sessions than sclerotherapy. Therefore, wherever feasible, band ligation should be the first-line endoscopic therapy for acute variceal bleeding. There are some data regarding the use of endoscopically delivered tissue adhesives, such as cyanoacrylate, for treating esophageal variceal bleeding. A study by Feretis and colleagues [32] observed that cyanoacrylate in combination with polidocanol did not control active bleeding significantly better than polidocanol alone (95% versus 78%). Recurrent bleeding over 2 months, however, was significantly less in the combination group. Sung and colleagues [33] demonstrated that cyanoacrylate was similar to endoscopic band ligation in achieving initial control of bleeding (100% in each group), but cyanoacrylate was inferior to banding for preventing rebleeding over a 7- to 8-month follow up (67% vs. 28%). Because of the sparse data available regarding the use of tissue adhesives for managing bleeding caused by esophageal varices and the inherent difficulties in using these compounds, their use cannot be recommended. In addition, these agents are not approved for use in the United States for managing varices. As mentioned in the previous section, the use of vasoactive agents in combination with endoscopic therapy appears to be more efficacious than either therapy alone.

**Transjugular Intrahepatic Portosystemic Shunt**

Transjugular intrahepatic portosystemic shunt (TIPS) is indicated in situations when acutely bleeding varices are refractory to medical therapy. TIPS has been shown in this situation to control bleeding in 95% of cases with a rebleed rate of only 18% [34]. Furthermore, a study by Vangeli and colleagues [35] reviewed 15 studies involving the use of TIPS to control bleeding when medical therapy failed. Similar to previous reports, bleeding was controlled in 93.6% of patients, and rebleed within 7 days was low (12.4%). The mortality rate, however, is between 30% and 40%. This is likely because patients with continued bleeding tend to be quite ill and have a high mortality rate despite any intervention.

**Surgery**

Surgical options include selective portosystemic shunting, calibrated H grafts, and devascularization procedures. The 30-day mortality rate, however, approaches 80% with these procedures [36]. Therefore, in most situations, surgical intervention for acute variceal bleeding should be reserved for when medical therapy fails and TIPS is not available.

Fig. 1 outlines a reasonable algorithm for the management of acute variceal hemorrhage.

**PREVENTING RECURRENT VARICEAL BLEEDING**

Without further therapy, once initial control of is achieved, variceal bleeding recurs in two thirds of patients within 2 months [37]. Factors associated with increase risk of recurrent bleeding include presence of active bleeding on initial endoscopy, large varices, severity of initial hemorrhage, degree of hepatic
decompensation, impaired renal function, presence of encephalopathy, and severe portal hypertension (as measured by the hepatic venous pressure gradient) [38]. Because of the high risk of recurrent hemorrhage, secondary prophylaxis should be initiated shortly after an episode of bleeding.

**Pharmacologic Therapy**

The main goal of pharmacologic is to significantly reduce portal hypertension, ideally to reduce the hepatic venous pressure gradient below 12 mmHg, and to prevent recurrent bleeding. Therefore, the ideal way to adjust medical therapy would be to follow portal pressure as determined by the hepatic venous pressure gradient. The best time to measure portal pressure would be within the first month after a bleeding episode to determine which patients have severe portal hypertension and have the greatest risk of recurrent bleeding. More than a 20% reduction in portal pressure has been shown to significantly reduce the cumulative probability of recurrent bleeding from 28% to 4% in the first year and from 39% to 9% at 2 years [39]. Unfortunately, pressure measurements are expensive, invasive, and not readily available. Therefore, surrogate measures of portal pressure reduction commonly are used, such as a target

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**Fig. 1.** Suggested algorithm for managing acute variceal bleeding.
heart rate of 55 beats per minute or a 25% reduction in the heart rate from baseline. Not all patients, however, are protected from bleeding. Recent studies have shown that despite adequate beta-blocker therapy, there are a percentage of patients that still have hepatic venous pressure gradients above 12 mmHg, which puts them at continued risk for variceal hemorrhage [40].

Several trials have demonstrated the efficacy of a nonselective beta-blocker compared with placebo in decreasing the risk of recurrent bleeding and improving survival [41]. The addition of isorbide mononitrate (ISMN) to a beta-blocker regimen appears to further reduce the rate of rebleeding [42]. In addition, recent studies have shown that combination pharmacologic therapy may be superior to sclerotherapy and band ligation. Incidence of rebleeding was 25% over an 18-month period with combination medical therapy compared with 53% for sclerotherapy in Child-Pugh class A or B cirrhotics [43]. These same investigators compared combination therapy with band ligation and demonstrated a reduction in bleeding frequency from 49% to 33% [44]. The benefit of combined medical therapy, however, was realized mainly in patients who had Child-Pugh class A or B cirrhosis. More recent studies comparing combination pharmacologic therapy with band ligation revealed conflicting results. Lo and colleagues [45] observed that band ligation was superior to combination medical therapy. A study by Patch and colleagues [46] observed that both treatment modalities were equivalent. Most likely the differences in results lie in study methods. Combination therapy may be superior to endoscopic therapy. The adverse effects of pharmacologic therapy, especially with combination pharmacologic medical therapy, however, can limit compliance.

**Endoscopic therapy**

Even though sclerotherapy has been shown to be effective in reducing recurrent variceal hemorrhage and appears to be equivalent to beta-blocker therapy [47], band ligation appears to have similar efficacy in decreasing recurrent bleeding, but fewer complications and higher survival rates [48]. Therefore, for endoscopic therapy to prevent rebleeding, band ligation should be considered the procedure of choice. Combination band ligation with pharmacologic therapy may be the ideal treatment modality. So far, there have been two published trials comparing band ligation alone with band ligation plus pharmacologic therapy. In a study by Lo and colleagues comparing band ligation alone with band ligation plus nadolol and sucralfate, rebleeding was reduced from 47% to 23% with combination therapy [49]. A more recent study by Pena and colleagues comparing band ligation alone with band ligation plus nadolol, demonstrated that the rebleeding rate was reduced from 38% to 14% with the combination group [50]. In addition, postbanding ulcers are common, and significant bleeding from these ulcers occurs in 2% to 5% of cases. Varices rebleeding rates potentially can be reduced further by adding antiulcer therapy after endoscopic therapy. Shaheen and colleagues [51] performed a study to evaluate the efficacy of proton pump inhibitor in treating postbanding ulcers in the setting of elective endoscopic band ligation. This was a randomized,
double-blinded, placebo-controlled trial. After elective endoscopic band ligation, subjects received either intravenous pantoprazole 40 mg followed by 40 mg oral pantoprazole daily for 9 days (n = 22) or intravenous/oral placebo (n = 22). There was no difference in the number of postbanding ulcers among the groups. Ulcers in the control group, however, were twice as large as the pantoprazole group (82 mm² versus 37 mm², \( P < .01 \)). Two patients had postbanding ulcer bleeding; both were in the control group (\( P > .05 \)). Because proton pump inhibitors are tolerated well and simple to administer, their use in this setting appears reasonable.

Surgical Shunt and Transjugular Intrahepatic Portosystemic Shunt Procedures
Portocaval or distal splenorenal shunts have been used in preventing recurrent variceal bleeding. A meta-analysis comparing distal splenorenal shunt with sclerotherapy found that shunt placement significantly reduced the rate of recurrent bleeding but also increased the incidence of encephalopathy and did not improve survival [52]. Rebleeding after surgical shunts typically is caused by shunt thrombosis, which occurs usually within the first year. It is unusual for surgical shunts to thrombose beyond 1 year. Similarly, with TIPS compared with endoscopic therapy the rebleeding rate was significantly lower with TIPS, 19% versus 47%, but the incidence of encephalopathy was higher with TIPS, 34% versus 19%, with no difference in survival [53]. Rosemurgy and colleagues compared TIPS with a surgically place H-graft shunt. This was a nonrandomized study of 132 patients. Rosemurgy and colleagues observed that the frequency of rebleeding was significantly less in the surgical group (3% versus 16%), and the patients who had TIPS required frequent interventions to maintain shunt patency. Thirty-day mortality rates, however, were higher in the surgical group, 43% versus 15% [54]. Therefore, surgical shunts should be used to prevent rebleeding in patients who do not tolerate or are not compliant with medical therapy and have relatively preserved liver function. TIPS should be reserved for patients who have poor liver function and who have failed medical therapy. Fig. 2 outlines a reasonable algorithm for preventing recurrent variceal hemorrhage.

BLEEDING FROM PORTAL HYPERTENSIVE GASTROPATHY
Portal hypertensive gastropathy (PHG) is the characteristic mosaic-like gastric mucosa with or without red spots; it is seen quite frequently in patients with both cirrhotic as well as noncirrhotic portal hypertension [55]. The histology of PHG is quite typical, and it reveals dilated capillaries and venules in the mucosa and submucosa without erosion, inflammation, or fibrin thrombi [56]. Although there are several published methods for grading portal gastropathy, the classification proposed by McCormack and colleagues appears to be the most widely used and reproducible [56]. According to this grading, PHG is classified into mild (fine pink speckles, superficial reddening, or mucosal mosaic pattern) or severe (discrete red spots or diffuse hemorrhagic lesions) categories.
Although the bleeding from PHG can be acute or chronic in nature, chronic bleeding presenting as iron deficiency anemia or occult blood in stool is far more frequent than acute bleeding [57–59]. In three recently published papers, the incidence of hemodynamically significant acute bleeding from PHG was less than 5% [57–59]. The specific treatment options for significant PHG include nonselective beta-blockers, endoscopic therapy, or TIPS or surgical shunts [55]. Nonselective beta-blockers have been shown to reduce the risk of bleeding in patients who have PHG [60–62]. In one study, compared with placebo, propranolol significantly reduced the risk of bleeding in patients who had severe PHG at 12 months (35% versus 62%) and 30 months (48% versus 93%) [62]. Endoscopic therapy in the form of coagulation (heater or bipolar probe or argon plasma coagulation) or injection sclerotherapy can be effective in patients who have acute bleeding caused by PHG. The role of endoscopic therapy for managing clinically significant chronic bleeding, however, is less clear. For these patients, it is not unreasonable to attempt endoscopic therapy with argon plasma coagulation, especially if such endoscopic expertise is available locally. TIPS can reduce the bleeding from severe PHG effectively, but it should be reserved for patients who are transfusion-dependent despite maximal medical and endoscopic therapy [63,64].

*Transjugular Intrahepatic Portosystemic Shunt*
Sometimes, patients who have portal hypertension present with bleeding from mucosal lesions resembling gastric antral vascular ectasia (GAVE) or watermelon stomach [59]. Although the pathogenesis of GAVE is not related to portal hypertension, its prevalence appears to be higher in patients who have cirrhosis and portal hypertension [59]. Although it usually is offered, the effectiveness of endoscopic laser therapy in portal hypertensive patients with GAVE is unclear. TIPS plays no significant role in the management of GAVE in patients who have cirrhosis and portal hypertension [63].

**BLEEDING FROM GaSTRIC VARICES**

Gastric varices are rare but important sources for bleeding in patients who have portal hypertension [65–67]. Gastric varices can be classified into gastro–esophageal varices (GOV) or isolated gastric varices (IGV) [68]. GOV are classified further into GOV 1 (in continuity with esophageal varices and extend 2 to 5 cm below the gastroesophageal junction) or GOV 2 (esophageal varices extending into the fundus). IGV can be located in the fundus (IGV 1) or body/antrum (IGV 2) (Fig. 4). Gastric varices located in the gastric fundus (either GOV 2 or IGV 1) carry a greater risk of bleeding than those located in other parts of the stomach [68].

Potential treatments for gastric variceal bleeding include endoscopic (cyanoacrylate or its derivatives or thrombin), radiological (TIPS or balloon-occluded retrograde transvenous obliteration), and surgical (gastric devascularization and splenectomy, surgical shunts, or liver transplantation) modalities [69–78].

Endoscopic therapy with N-butyl-2-cyanoacrylate (cyanoacrylate) is very effective in providing acute hemostasis and in reducing rebleeding in patients.

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**Fig. 3.** Severe portal hypertensive gastropathy. Gastric body and antrum reveal discrete red spots intermingled with diffuse hemorrhagic lesions.
who have bleeding gastric varices [69–72]. Peripheral embolization (to lungs, brain, or viscera) is a rare but important complication of cyanoacrylate therapy. Although this form of therapy is used widely in Europe and Asia, cyanoacrylate is not commercially available and seldom is used in the United States [69].

Studies have shown that TIPS is effective in providing acute hemostasis and in reducing rebleeding in patients with gastric variceal bleeding [73,74]. In some patients, however, TIPS may not be effective because of insufficient anterograde portal venous blood flow caused by extensive collaterals. In these patients, selective embolization of the collaterals may improve the effectiveness of TIPS by enhancing the anterograde flow.

Balloon-occluded retrograde transvenous obliteration (B-RTO) is a newly developed technique performed by the interventional radiologists to treat gastric fundal varices associated with spontaneous gastro–renal shunts [75]. This procedure employs ethanolamine oleate to obliterate fundal varices, feeding vessels and the gastro–renal shunt. Several Japanese studies have shown that this form of therapy is effective in selected patients with gastric variceal bleeding who also have gastro–renal shunts [75,76]. More recently, Shiba and colleagues reported that balloon-occluded injection sclerotherapy is safe and effective for treating high-risk gastric varices; the procedure can be performed even in patients without gastro–renal shunts [79].

As there are relatively few randomized controlled trials investigating the relative efficacy of various treatment modalities, the management of gastric variceal bleeding is controversial and geographically variable. At most institutions in the United States, TIPS usually is considered as the first line of therapy for patients with gastric variceal bleeding.
Although some studies have advocated prophylactic endoscopic therapy for high-risk gastric varices [79,80], primary prophylaxis against gastric variceal bleeding has not been investigated adequately. Until more data become available showing the safety and efficacy of prophylactic endoscopic therapy, it is the authors’ opinion that patients with high-risk gastric varices who have never bled before should be treated with maximal doses of nonselective beta-blockers.

**PREVENTING THE FIRST VARICEAL BLEEDING (PRIMARY PROPHYLAXIS)**

As each episode of variceal bleeding carries significant risk of morbidity and mortality, it is essential that primary prophylaxis should be considered in every patient who has suspected or proven cirrhosis. It has been recommended that all patients with cirrhosis (either suspected or diagnosed) should undergo diagnostic upper endoscopy. Those who are found to have high-risk gastro–esophageal varices should receive treatment to prevent the first variceal bleed [81–83]. Patients who have large gastro–esophageal varices (irrespective of Child-Pugh score or presence of red signs) and those with small varices bearing red signs are at risk for rupture and thus should be offered prophylactic therapy (Fig. 5).

Recent studies have identified that certain nonendoscopic variables can predict the presence of varices (or large varices). These variables include thrombocytopenia, splenomegaly, portal vein diameter by ultrasonography, or Child’s C cirrhosis [84]. Based on the presence or absence of these variables, some investigators have developed models to predict the presence of varices or large varices [85]. These models are promising but lack optimal precision. Until validated prediction models with clinically acceptable precision are available, endoscopic screening is the best practice to detect and risk stratify gastro–esophageal varices [83].

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**Fig. 5.** Large esophageal varices in the distal esophagus.
Therapeutic options for primary prophylaxis include nonselective beta-blockers and prophylactic endoscopic banding (Fig. 6). Nonselective beta-blockers (propranolol or Nadolol) significantly reduce the risk of first variceal bleeding and remain the treatment of choice for patients with high-risk varices [85]. When beta-blockers are given for the primary prophylaxis, the dosage should be titrated to a heart rate of 55 beats per minute. Many patients, however, may not tolerate beta-blockers because of adverse effects (asthenia, sexual dysfunction, or hypotension) requiring their discontinuation [85]. The monitoring of hepatic venous pressure gradient can identify precisely those who will benefit the most from pharmacotherapy. Its utility, however, has not been tested in clinical trials [86,87]. If nonselective beta-blockers are provided for primary prophylaxis, their administration should be continued indefinitely, as their discontinuation can lead to significantly increased risk of bleeding [88]. Studies have shown that isosorbide mononitrate as monotherapy is not effective in preventing the first variceal bleed, and thus it should not be used for primary prophylaxis [83].

The role of endoscopic ligation as a primary prophylactic measure has been investigated in the recent years. In comparison to no therapy, in patients with moderate-to-large esophageal varices, prophylactic endoscopic banding leads to a significant reduction in the incidence of first variceal bleeding and improves survival [89] (Table 1). Prophylactic banding has been compared with nonselective beta-blockers in several randomized controlled studies, and two meta-analyses that aggregated the results of these studies were published [89,90] (Table 2). Prophylactic banding is more effective than beta-blockers in preventing the first variceal bleeding in patients with moderate-to-large esophageal varices,

![Fig. 6. Suggested algorithm for preventing first variceal bleeding.](image-url)
but it offers no survival advantage over nonselective beta-blockers \[82,89,90\] (Table 2). The long-term benefits of prophylactic banding are unclear, as most studies had modest duration of follow-up. Furthermore, the effects of prophylactic banding as compared with beta-blockers on the cost-effectiveness and quality of life have not been addressed adequately. Until more studies addressing these issues are available, prophylactic endoscopic banding should be offered to patients with moderate-to-large varices who are intolerant to or have contraindications for nonselective beta-blocker therapy \[82\].

Two recent studies have evaluated if nonselective beta-blockers can modify the natural history of portal hypertension in patients with small varices or no portal hypertension \[91,92\]. In one study, 161 cirrhotic patients who have small esophageal varices who have never bled before were randomized to receive nadolol (n = 83) or placebo (n = 78) and were followed for a mean duration of 36 months \[91\]. Compared with placebo, patients receiving nadolol had significantly lower development of large varices and lower incidence of bleeding \[91\]. In another multi-center study, 213 patients who had cirrhosis with portal hypertension (defined as hepatic vein pressure gradient greater than 5 mmHG) but no esophageal varices were randomized to receive timolol or placebo \[92\]. In this study, timolol therapy had no effect on the development of varices, variceal hemorrhage, ascites, or death. The findings of these two studies suggest

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<th>Outcomes</th>
<th>Relative risk (CI)</th>
<th>Relative risk reduction</th>
<th>NNT (CI)</th>
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<tr>
<td>First esophageal variceal bleed</td>
<td>0.36 (0.26–0.50)</td>
<td>64%</td>
<td>4 (3–6)</td>
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<td>Bleed-related mortality</td>
<td>0.20 (0.11–0.39)</td>
<td>80%</td>
<td>7 (5–11)</td>
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<tr>
<td>All-cause mortality</td>
<td>0.55 (0.43–0.71)</td>
<td>45%</td>
<td>5 (4–9)</td>
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<thead>
<tr>
<th>Outcome</th>
<th>Relative risk (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>First esophageal variceal bleed</td>
<td>0.56 (0.36–0.87)</td>
<td>10</td>
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<tr>
<td>Bleed-related mortality</td>
<td>0.84 (0.44–1.61)</td>
<td>-</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.03 (0.78–1.36)</td>
<td>-</td>
</tr>
<tr>
<td>Severe adverse events</td>
<td>0.36 (0.16–0.72)</td>
<td>9</td>
</tr>
</tbody>
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that primary prophylaxis with nonselective beta blockers can be provided to cirrhotics with small esophageal varices but not to those with no varices [91,92]. Several cost-effectiveness analyses have found that a strategy of universal beta-blocker therapy to all cirrhotics without subjecting them to upper endoscopy is more cost-effective than other strategies of providing primary prophylaxis [93–95]. The only clinical trial that tested the strategy of universal beta-blocker therapy, however, did not find it to be effective [96]. Until more data become available, the authors do not recommend the strategy of universal beta-blockers (without investigating their varices status), as it would subject a large number of cirrhotics without gastroesophageal varices (approximately 50%) to an indefinite therapy with unpleasant adverse effects. Indeed, the recently concluded Baveno IV consensus workshop recommended that it is not indicated to treat patients who have cirrhosis with beta-blockers without prior assessment of the presence of esophageal varices [83].

**SUMMARY**

Variceal bleeding is one of the dreaded complications of portal hypertension. Patients who have suspected or proven cirrhosis should undergo diagnostic upper endoscopy to detect medium and large gastro–esophageal varices. Patients with medium and large gastro–esophageal varices should be treated with nonselective beta-blockers (propranolol or nadolol), and these agents should be titrated to a heart rate of 55 beats per minute or adverse effects. If there are contraindications to or if patients are intolerant to beta-blockers, it is appropriate to consider prophylactic banding therapy for individuals with medium-to-large esophageal varices. When patients who have cirrhosis present with GI bleeding, they should be resuscitated and receive octreotide or other vasoactive agents. Endoscopy should be performed promptly to diagnose the source of bleeding and to provide endoscopic therapy (preferably banding). The currently available treatment for acute variceal bleeding provides hemostasis in most patients. These patients, however, are at significant risk for rebleeding unless secondary prophylaxis is provided. Although various pharmacological, endoscopic, radiological, and surgical options are available, combined pharmacological and endoscopic therapy is the most common form of secondary prophylaxis. TIPS is a radiologically placed portasystemic shunt, and if placed in suitable patients, it can provide effective treatment for patients with variceal bleeding that is refractory to medical and endoscopic therapy.

**References**


