

*Medical Progress***GASTROESOPHAGEAL VARICEAL HEMORRHAGE**

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**G**ASTROESOPHAGEAL variceal hemorrhage, a major complication of portal hypertension resulting from cirrhosis, accounts for 10 to 30 percent of all cases of bleeding from the upper gastrointestinal tract.<sup>1</sup> Variceal hemorrhage occurs in 25 to 35 percent of patients with cirrhosis and accounts for 80 to 90 percent of bleeding episodes in these patients.<sup>2-4</sup> Variceal hemorrhage is associated with more substantial morbidity and mortality than other causes of gastrointestinal bleeding, as well as with higher hospital costs.<sup>5-7</sup> Up to 30 percent of initial bleeding episodes are fatal, and as many as 70 percent of survivors have recurrent bleeding after a first variceal hemorrhage.<sup>2,8</sup> Moreover, the one-year survival rate after variceal hemorrhage can be poor (32 to 80 percent).<sup>8,9</sup> Treatment of patients with gastroesophageal varices includes the prevention of the initial bleeding episode (primary prophylaxis), the control of active hemorrhage, and the prevention of recurrent bleeding after a first episode (secondary prophylaxis). Many new and exciting therapeutic options for variceal hemorrhage have become available during the past decade (Fig. 1).

**PATHOGENESIS OF GASTROESOPHAGEAL VARICES**

Chronic liver disease leading to cirrhosis is the most common cause of portal hypertension (increased portal venous pressure). Portal venous pressure is directly related to blood flow and resistance through the liver as described by Ohm's law —  $P=Q \times R$ , where P is the pressure along a vessel, Q is the flow, and R is the resistance to the flow. Although the pathogenesis of portal hypertension is complex, and a detailed discussion of this topic is beyond the scope of this re-

view, portal hypertension in most patients with cirrhosis results from increased intrahepatic resistance (at the presinusoidal, sinusoidal, and postsinusoidal locations) as well as increased flow through a hyperdynamic splanchnic system. Recent studies suggest that an imbalance between the potent vasoconstrictor endothelin-1 and the potent vasodilator nitric oxide may be important in the genesis of increased intrahepatic resistance, which is an early and critical component of most forms of portal hypertension.<sup>10-12</sup>

Varices are portosystemic collaterals formed after preexisting vascular channels have been dilated by portal hypertension. The distal 2 to 5 cm of the esophagus — the most common site of varices — contains superficial veins that lack support from surrounding tissues,<sup>13</sup> a feature consistent with the occurrence of prominent bleeding at this site. The dilatation of distal esophageal varices depends on a threshold pressure gradient. The most commonly used measurement of pressure is the hepatic venous pressure gradient, defined as the gradient between the wedged, or occluded, hepatic venous pressure and the free hepatic venous pressure (normal gradient, <5 mm Hg). At a hepatic venous pressure gradient of less than 12 mm Hg, varices do not form.<sup>14,15</sup> Varices do not invariably develop in patients with gradients of 12 mm Hg or more; thus, this pressure gradient is necessary but not sufficient.<sup>14,16</sup> Gastroesophageal varices are present in 40 to 60 percent of patients with cirrhosis; their presence and size are related to the underlying cause, duration, and severity of cirrhosis.<sup>17</sup>

**PREDICTION OF VARICEAL HEMORRHAGE**

Despite the high prevalence of varices in patients with cirrhosis, bleeding only occurs in about one third of patients.<sup>2,3</sup> Various factors may lead to variceal bleeding. Physical factors, including the elastic properties of the vessel and the intravariceal and intraluminal pressure, are important determinants of whether rupture will occur. However, the main determinant of bleeding is variceal-wall tension (T), which, according to Frank's modification of Laplace's law ( $T=[TP \times r] \times w^{-1}$ ), is a function of the transmural pressure (TP), the radius (r) of the vessel, and the thickness of the vessel wall (w).<sup>13</sup>

For optimal management, it is important to understand which patients are most likely to have bleeding. Clinical factors associated with an increased risk of a first variceal hemorrhage include continued alcohol use and poor liver function.<sup>2</sup> Endoscopic predictors of bleeding include large varices and endoscopic red signs (e.g., red wale markings) on the variceal

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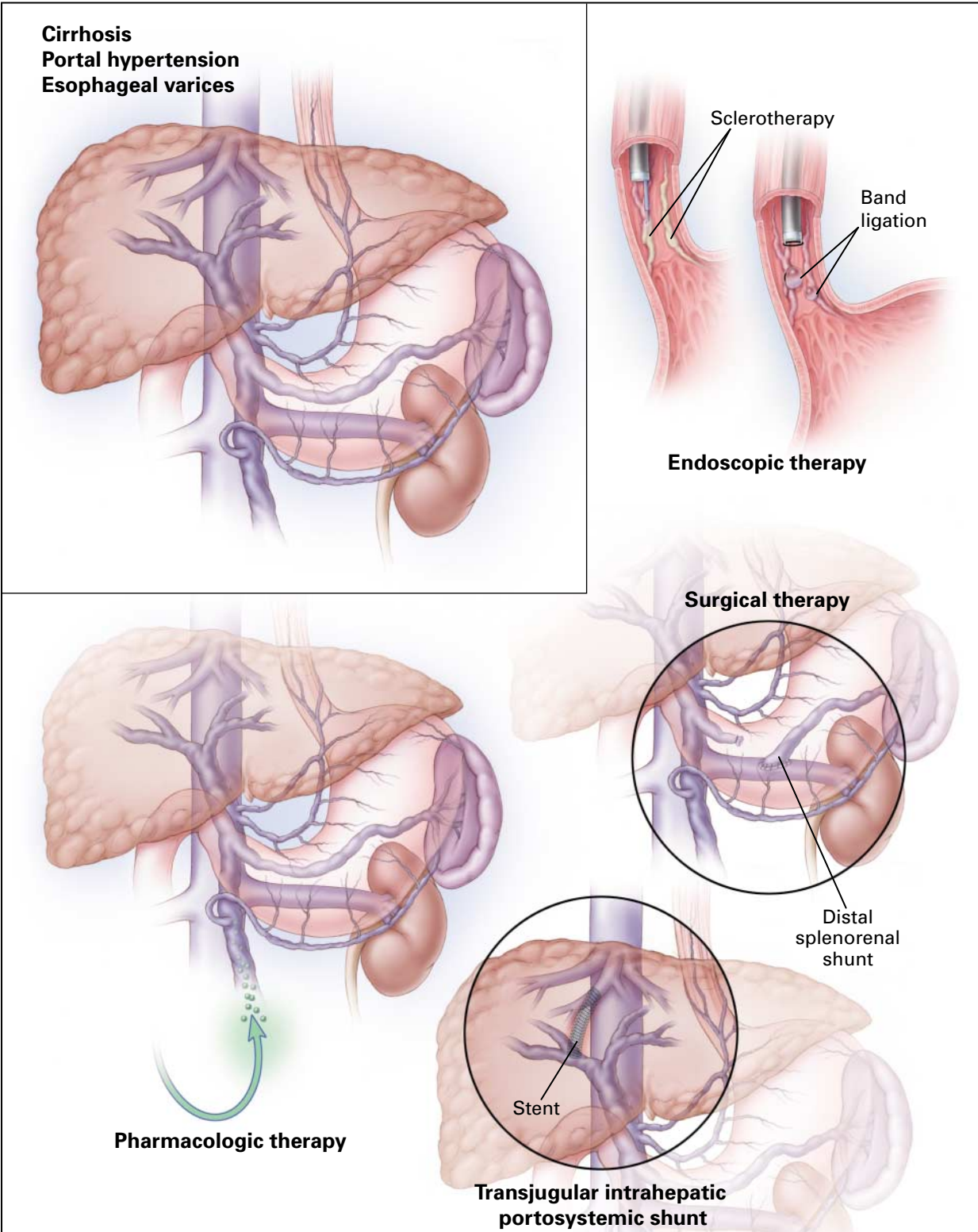


Figure 1. Therapies Used in the Management of Gastroesophageal Hemorrhage.

**TABLE 1.** CHILD–PUGH CLASSIFICATION OF THE SEVERITY OF CIRRHOSIS.\*

VARIABLE	SCORE		
	1 POINT	2 POINTS	3 POINTS
Encephalopathy	Absent	Mild to moderate	Severe to coma
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dl)†	<2	2–3	>3
Albumin (g/liter)	>3.5	2.8–3.5	<2.8
Prothrombin time (sec above normal)	1–4	4–6	>6

\*If the total score is 5 or 6, the cirrhosis is designated class A; if the score is 7 to 9, the cirrhosis is class B; if the score is 10 or higher, the cirrhosis is class C. The prognosis is directly related to the score. Adapted from Pugh et al.<sup>19</sup>

†To convert values for bilirubin to micromoles per liter, multiply by 17.1.

wall.<sup>2,18</sup> A combination of clinical and endoscopic findings including an advanced Child–Pugh class of cirrhosis (Table 1), large varices, and the presence of red wale markings correlate highly with the risk of a first bleeding episode in patients with cirrhosis.<sup>2</sup>

Hemodynamic measurement such as the hepatic venous pressure gradient, the intravariceal pressure, and the Doppler ultrasonographic measurement of portal pressure have been used in efforts to predict variceal bleeding. The hepatic venous pressure gradient provides a reliable measure of portal pressure in most patients with cirrhosis (but can underestimate portal pressure in patients with presinusoidal portal hypertension).<sup>20</sup> Furthermore, an increasing hepatic venous pressure gradient predicts an increased risk of bleeding, and the extent of the elevation of portal pressure is inversely related to the prognosis after hemorrhage.<sup>14,21,22</sup> In addition, changes in the hepatic venous pressure gradient after a pharmacologic intervention appear to predict the clinical response to therapy.<sup>23</sup> Unfortunately, although the measurement of the hepatic venous pressure gradient is a useful adjunct, the procedure is invasive and thus is not widely used in clinical practice.

#### PRIMARY PREVENTION OF BLEEDING FROM ESOPHAGEAL VARICES

Once esophageal varices have been identified in a patient with cirrhosis, the risk of a variceal hemorrhage is 25 to 35 percent.<sup>2,24–26</sup> Given the poor outcome associated with variceal bleeding, the identification of those at high risk and the prevention of a first bleeding episode are critical objectives. Screening endoscopy is generally recommended for patients with cirrhosis to determine whether large esophageal varices are present — although the cost effectiveness of this

approach is controversial. The use of clinical features, such as a low platelet count, may help physicians to predict which patients are likely to have large varices.<sup>27,28</sup> Therapy for primary prophylaxis against variceal bleeding has evolved considerably over the past decade and is summarized in Table 2 and Figure 2.

#### Pharmacologic Therapy

The general objective of pharmacologic therapy for variceal bleeding is to reduce portal pressure and, consequently, intravariceal pressure (Fig. 1). Indeed, the rationale for the use of pharmacologic therapy is similar for primary prophylaxis, acute bleeding, and secondary prophylaxis. Drugs that reduce the collateral portal venous flow (vasoconstrictors) or intrahepatic vascular resistance (vasodilators) have been used; these include beta-blockers, nitrates,  $\alpha_2$ -adrenergic blockers, spironolactone, pentoxifylline, and molsidomine.<sup>29–31</sup> Since varices are unlikely to bleed when the hepatic venous pressure gradient is less than 12 mm Hg, reduction of the gradient to this level is ideal. Substantial reductions in the hepatic venous pressure gradient (by more than 20 percent) are also clinically meaningful.<sup>23,32–34</sup>

Beta-blockers reduce splanchnic blood flow, portal pressure, and subsequently, gastroesophageal collateral blood flow.<sup>35,36</sup> Propranolol and nadolol, nonselective beta-blockers, are preferred because of their combined actions: blockade of  $\beta_1$ -adrenergic receptors causes splanchnic vasoconstriction by means of reflex activation of  $\alpha$ -adrenergic receptors, and blockade of  $\beta_2$ -adrenergic receptors results in splanchnic and peripheral vasoconstriction by eliminating  $\beta_2$ -receptor-mediated vasodilation.<sup>37</sup> Reducing the portal pressure by at least 20 percent or to a hepatic venous pressure gradient of less than 12 mm Hg is associated with significant protection against bleeding.<sup>33,34</sup> In the absence of a determination of the hepatic venous pressure gradient, the dose of beta-blockers is titrated on the basis of clinical measurements to achieve a resting heart rate of 55 beats per minute or a reduction of 25 percent from the base-line rate. In addition to their side effects, an important problem with beta-blockers is their variable effect on portal pressure and the consequent difficulty in predicting a clinical response. For example, although portal venous pressure is reduced in 60 to 70 percent of patients who receive propranolol, the reduction exceeds 20 percent in only 10 to 30 percent of patients.<sup>13,33,35</sup>

The effectiveness of beta-blockers for primary prophylaxis against variceal bleeding has been demonstrated in several controlled trials.<sup>38–40</sup> In addition, meta-analyses have revealed a 40 to 50 percent reduction in the risk of bleeding (from a 22 to 35 percent probability to a 17 to 22 percent probability; pooled odds ratio, 0.54) and a trend toward improved survival.<sup>24,26,41</sup> Furthermore, an analysis comparing propranolol with sclerotherapy and shunt surgery found

**TABLE 2.** SUMMARY OF THERAPY FOR ESOPHAGEAL VARICES.\*

PURPOSE OF THERAPY	FIRST-LINE THERAPY	COMMENTS	ALTERNATIVE THERAPY	COMMENTS
Primary prophylaxis†	Beta-blockers alone or in combination with isosorbide mononitrate‡	Nitrates alone are not recommended. In advanced (Child–Pugh class C) liver disease, optimal therapy is unclear (probably band ligation); transplantation should be considered for patients in this group.	Band ligation	Band ligation is indicated for patients with contraindications to or intolerance of medical therapy. The effectiveness of combined beta-blockers and band ligation is unknown. Neither TIPS nor sclerotherapy is recommended for primary prophylaxis.
Active variceal bleeding	Octreotide (or terlipressin) and endoscopic therapy§	Octreotide (or terlipressin) should be continued for a minimum of 24–48 hr. Band ligation may be superior to sclerotherapy.  Antibiotic prophylaxis should be considered, especially in patients with ascites.	Balloon tamponade  TIPS  Shunt surgery	Tamponade is indicated primarily as a temporizing measure.  TIPS is reserved for those with refractory or recurrent early bleeding. Surgery is reserved for those in whom TIPS is not feasible.
Secondary prophylaxis¶	Band ligation alone or in combination with beta-blockers with or without isosorbide mononitrate	The combination of band ligation and beta-blockers with or without isosorbide mononitrate is likely to be more effective than either alone. Patients with advanced liver disease often have an intolerance to beta-blockers.	TIPS  Shunt surgery	TIPS is best used as a bridge to transplantation in patients with advanced liver disease.  Shunt surgery should be reserved for selected patients with Child–Pugh class A and class B cirrhosis.

\*TIPS denotes transjugular intrahepatic portosystemic shunt.

†Variceal hemorrhage occurs in 25 to 30 percent of patients within two years after the documentation of varices.

‡Beta-blockers reduce the risk of variceal hemorrhage to 15 to 18 percent, and the combination of beta-blockers and isosorbide mononitrate reduces the risk to 8.5 to 10 percent. The beta-blocker propranolol is generally given as a long-acting preparation, and the dose is titrated to a maximum of 320 mg per day. The initial dose of the beta-blocker nadolol is 20 mg per day, and the dose is increased up to a maximum of 80 mg per day.

§Octreotide is usually given as an infusion of 25 to 50 µg per hour (with or without a bolus). The dosage of terlipressin is 2 mg every 4 hours for the first 24 hours, then 1 mg every 4 hours.

¶Bleeding recurs in approximately two thirds of patients within one year after the initial hemorrhage.

propranolol to be the only cost effective form of primary prophylaxis.<sup>42</sup>

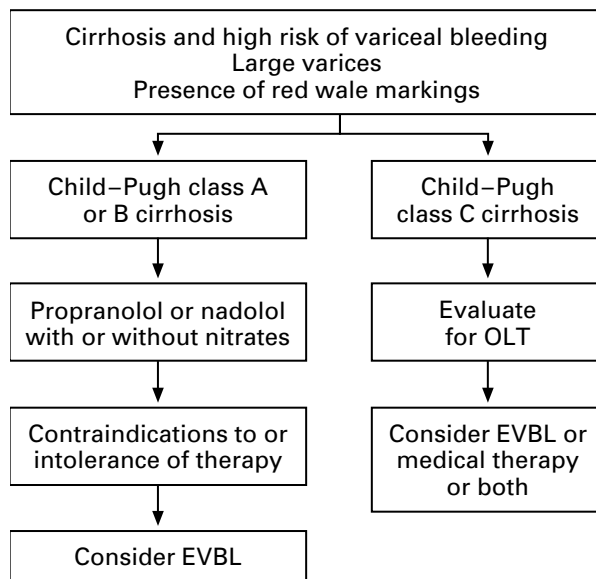
In addition to beta-blockers, a number of vasodilators have been investigated in patients with portal hypertension. Isosorbide mononitrate has received the greatest attention, in large part because of its long half-life (approximately five hours). The mechanism of action of nitrates is unclear — they may reduce intrahepatic resistance, reduce portal pressure by means of reflex splanchnic arterial vasoconstriction in response to vasodilatation in other vascular beds, or both.<sup>43,44</sup> Unfortunately, nitrates cannot currently be recommended as monotherapy (even for those with an intolerance of beta-blockers), because of their potential to accentuate the vasodilative hemodynamics typical of cirrhosis.<sup>45,46</sup> In one study, nitrates were associated with increased mortality in patients older than 50 years of age.<sup>46</sup>

The addition of isosorbide mononitrate to propranolol results in an enhanced reduction in portal pressure and may improve protection against variceal bleeding.<sup>47</sup> For example, in a randomized trial of mono-

therapy as compared with combination therapy, isosorbide mononitrate plus propranolol caused a reduction of more than 20 percent in the hepatic venous pressure gradient in 50 percent of patients, whereas propranolol alone caused such a reduction in only 10 percent of patients.<sup>47</sup> In addition, in patients with cirrhosis of Child–Pugh class A or B, isosorbide mononitrate (in doses of up to 20 mg twice daily) plus nadolol resulted in a reduction in the incidence of variceal bleeding that was more than 50 percent greater than the reduction achieved with nadolol monotherapy (an incidence of 12 percent vs. 29 percent) over a seven-year follow-up period.<sup>48</sup> Patients with advanced cirrhosis often cannot tolerate beta-blockers — let alone beta-blockers in combination with nitrates — and therefore the use of combination therapy in such patients remains controversial.

#### Endoscopic Therapy

During the past 20 years, endoscopic therapies have assumed a prominent role in the treatment of esophageal varices. Endoscopic sclerotherapy, most often



**Figure 2.** Suggested Algorithm for Primary Prophylaxis of Variceal Bleeding in Patients with Cirrhosis.

EVBL denotes endoscopic variceal band ligation, and OLT orthotopic liver transplantation.

with ethanol, morrhuate sodium, polidocanol, or sodium tetradecyl sulfate, has been used extensively, and endoscopic variceal band ligation, recently facilitated by the use of multiband ligating devices, has been implemented over the course of the past decade. Each of these treatments effectively eradicates esophageal varices (Fig. 1). Recently, ligation has become favored in most settings because it is as effective as sclerotherapy in eradicating varices and leads to fewer complications. Most trials have shown no advantage of sclerotherapy in primary prophylaxis.<sup>49</sup> Furthermore, one large randomized, controlled study was halted prematurely because of increased mortality after sclerotherapy.<sup>25</sup>

A recent trial comparing propranolol with endoscopic variceal ligation for the primary prevention of variceal bleeding revealed that the actuarial rate of bleeding was 43 percent with propranolol and 15 percent with ligation.<sup>50</sup> However, the results of this study have been questioned because the rate of bleeding in the propranolol group was higher than expected. Nonetheless, ligation is an acceptable option for patients at high risk of variceal bleeding who have an intolerance of or contraindications to medical therapy. Ongoing studies will further classify its role in primary prophylaxis, including its possible use as an adjunct to pharmacologic therapy.

#### MANAGEMENT OF ACUTE VARICEAL HEMORRHAGE

Variceal hemorrhage is typically an acute clinical event characterized by severe gastrointestinal hemor-

rhage presenting as hematemesis, with or without melena or hematochezia. Hemodynamic instability (tachycardia, hypotension, or both) is common. A successful outcome, as in all cases of gastrointestinal hemorrhage, hinges on prompt resuscitation, hemodynamic support, and correction of hemostatic dysfunction, preferably in an intensive care unit.

After the stabilization of hemodynamics, the physician should focus on the differential diagnosis. Although variceal bleeding is common in patients with cirrhosis who have acute upper gastrointestinal hemorrhage, other causes of bleeding, such as ulcer disease, must be considered. Empirical pharmacologic therapy is indicated in situations in which variceal hemorrhage is likely (Fig. 3).<sup>51,52</sup> Subsequently, esophagogastroduodenoscopy facilitates an accurate diagnosis and endoscopic therapy. Physicians should consider using endotracheal intubation as a precaution against aspiration before they perform endoscopy in patients with massive bleeding, severe agitation, or altered mental status. Systemic antibiotics (e.g., third-generation cephalosporins) should be considered — especially for patients with ascites — because they decrease the risk of bacterial infection and reduce mortality.<sup>53,54</sup>

Gastric variceal hemorrhage is characterized by massive bleeding that is often more severe than esophageal variceal hemorrhage. Because of the higher likelihood that gastric varices are caused by splenic venous thrombosis, this diagnosis must be considered in patients without cirrhosis. The management of gastric varices differs from that of esophageal varices in that gastric variceal bleeding and recurrent bleeding are usually much more difficult to control, especially endoscopically.

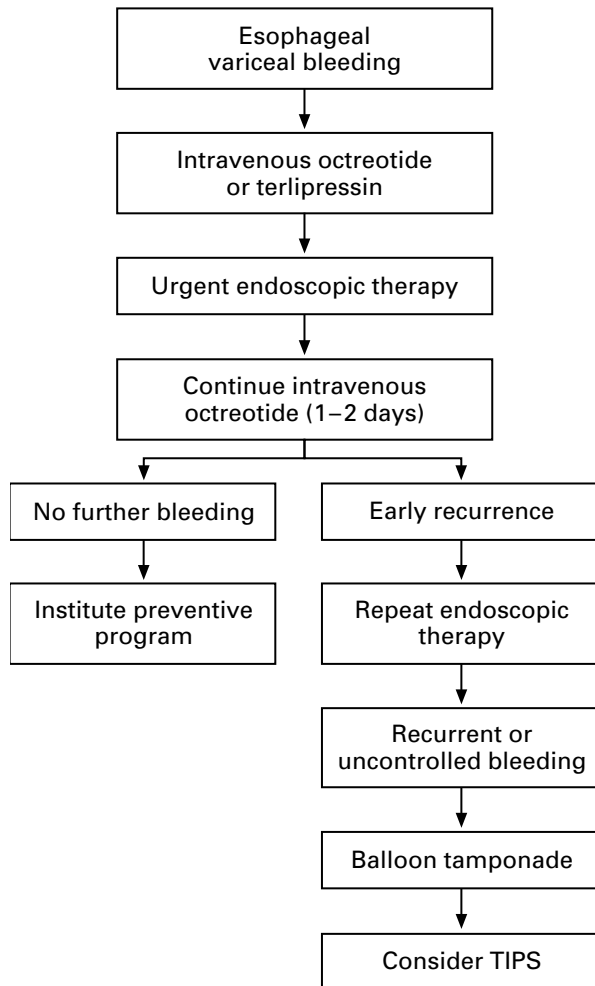
There are several treatment options for patients with acute variceal hemorrhage. The optimal treatment varies and depends on multiple clinical factors (Fig. 3).

#### Pharmacologic Therapy

A critical advantage of pharmacologic therapies for acute hemorrhage is that they can be administered early and do not require special technical expertise. Pharmacologic therapy has thus evolved into an attractive first-line approach in patients with probable variceal hemorrhage.

Vasopressin reduces splanchnic blood flow and portal pressure. Because of its short half-life, vasopressin must be given by continuous intravenous infusion. Its use is limited because it may cause systemic vasoconstriction and severe vascular complications such as myocardial and mesenteric ischemia and infarction.<sup>55</sup> The addition of nitroglycerine to vasopressin results in improved therapeutic efficacy and a reduction in the vascular side effects.<sup>56,57</sup>

Terlipressin is a synthetic vasopressin analogue with fewer side effects and a longer half-life than vasopressin and thus can be used in bolus form. This advan-



**Figure 3.** Suggested Management of Acute Variceal Hemorrhage.

TIPS denotes transjugular intrahepatic portosystemic shunt.

tage has led to its successful use for suspected variceal bleeding.<sup>51</sup> Although terlipressin appears to be at least as effective as vasopressin, somatostatin, or endoscopic therapy, it is currently not available in the United States.<sup>58,59</sup>

Somatostatin, a naturally occurring peptide, and its synthetic analogues, octreotide and vapreotide, stop variceal hemorrhage in up to 80 percent of patients and are generally considered to be equivalent to vasopressin, terlipressin, and endoscopic therapy for the control of acute variceal bleeding.<sup>59-61</sup> The mechanism of action of somatostatin and octreotide is unclear, but they may work by preventing postprandial hyperemia (blood in the gut stimulates splanchnic blood flow) or by reducing portal pressure through effects on vasoactive peptides (i.e., substance P or glucagon). Both somatostatin and octreotide, given intravenously, have few side effects (which include mild

hyperglycemia and abdominal cramping). Because of their excellent safety profile and the absence of systemic circulatory effects, somatostatin, octreotide, and vapreotide can be used without special monitoring.

An important new approach to treatment has been the use of pharmacologic agents such as octreotide in combination with endoscopic therapy. The addition of octreotide (or vapreotide) to endoscopic sclerotherapy or ligation for a period of five days resulted in improved control of bleeding and reduced transfusion requirements,<sup>62,63</sup> particularly within the first 24 to 48 hours.

#### Endoscopic Therapy

Endoscopic therapy has revolutionized the care of patients with cirrhosis who have acute variceal hemorrhage. Indeed, current endoscopic therapies are capable of stopping bleeding in nearly 90 percent of patients.

Endoscopic sclerotherapy stops bleeding in 80 to 90 percent of patients with acute variceal hemorrhage.<sup>7,64-66</sup> The advantages of sclerotherapy include its ability to establish definitive control of bleeding under direct endoscopic guidance, its wide availability, its ease of use, and its low cost. Its drawbacks include a small, albeit important, risk of local complications, including perforation, ulceration, and stricture.

Randomized trials of patients with acute variceal bleeding have shown that endoscopic variceal band ligation is essentially equivalent to sclerotherapy in achieving initial hemostasis.<sup>67-69</sup> The complications associated with ligation are fewer and include superficial ulcerations and, rarely, the formation of strictures.<sup>67,69</sup> One drawback of ligation in cases of acute bleeding is that the use of a band ligating device can make visualization of the (bloody) endoscopic field difficult.

Because gastric varices are located deeper in the submucosa than esophageal varices, sclerotherapy and ligation are usually ineffective in controlling acute bleeding from gastric varices and may be hazardous. *N*-butyl-2-cyanoacrylate (tissue glue) has been shown to be effective for bleeding gastric varices,<sup>70</sup> but no data are available from a randomized trial. In addition, endoscopic ligation with a detachable mini-snare has been shown, in small, uncontrolled trials, to be effective for bleeding gastric varices.<sup>71</sup>

#### Balloon Tamponade

Balloon tamponade applies direct pressure to the bleeding varix with an inflatable balloon fitted on a specialized nasogastric tube (e.g., Minnesota tube). Only experienced physicians should use this technique. Properly applied balloon tamponade successfully achieves hemostasis in the majority of cases.<sup>72</sup> Unfortunately, recurrent bleeding after the decompression of the balloon is common, and thus, tamponade should be used as a rescue procedure and a bridge to more definitive therapy in cases of uncontrolled hemorrhage.

### Transjugular Intrahepatic Portosystemic Shunt

Treatment with a transjugular intrahepatic portosystemic shunt consists of the vascular placement of an expandable metal stent across a tract created between a hepatic vein and a major intrahepatic branch of the portal system (Fig. 1). Transjugular shunting leads to hemodynamic changes similar to those that result from the placement of a partially decompressive side-to-side portacaval shunt. Although transjugular intrahepatic portosystemic shunts are associated with substantially lower morbidity and mortality than surgical shunts, immediate complications (such as bleeding and infection) can occur.

A major advantage of transjugular shunting for the 5 to 10 percent of patients with refractory acute variceal bleeding, including those with gastric variceal bleeding, is that if it can be successfully performed, it almost invariably stops the bleeding.<sup>73,74</sup> However, patients who have advanced liver disease and multi-organ failure at the time of shunting have a 30-day mortality that approaches 100 percent.<sup>73,75</sup>

### Surgical Therapy

Surgical shunting should be considered in cases of continued hemorrhage or recurrent early rebleeding that cannot be controlled by endoscopic or pharmacologic means — and when transjugular shunting is not available or technically feasible. Surgical options include portosystemic shunting or esophageal staple transection with or without esophagogastric devascularization.<sup>77,78</sup> Regardless of the choice of surgical technique, morbidity is high in patients with advanced liver disease, and the 30-day mortality associated with emergency surgery approaches 80 percent in such patients.<sup>73</sup>

### PREVENTION OF RECURRENT VARICEAL BLEEDING

Variceal hemorrhage recurs in approximately two thirds of patients, most commonly within the first six weeks after the initial episode.<sup>8,77,78</sup> Clinical predictors of early recurrence include the severity of the initial hemorrhage (i.e., the development of hypotension or a substantial transfusion requirement), the degree of liver decompensation, and the presence of encephalopathy and impaired renal function.<sup>79</sup> Endoscopic features predictive of early recurrence include active bleeding at the time of the initial endoscopy, stigmata of recent bleeding, and large varices.<sup>16,79</sup> In addition, the severity of portal hypertension, measured by the hepatic venous pressure gradient, correlates closely with the risk of recurrent bleeding as well as with the actuarial survival rate after an initial variceal hemorrhage (implying that the measurement of the hepatic venous pressure gradient could be useful for the triage of high-risk patients).<sup>22,80</sup>

Given the risk of recurrent hemorrhage and its associated morbidity and mortality, secondary prophylaxis should be instituted after the initial episode (Fig. 1, 4, and 5).

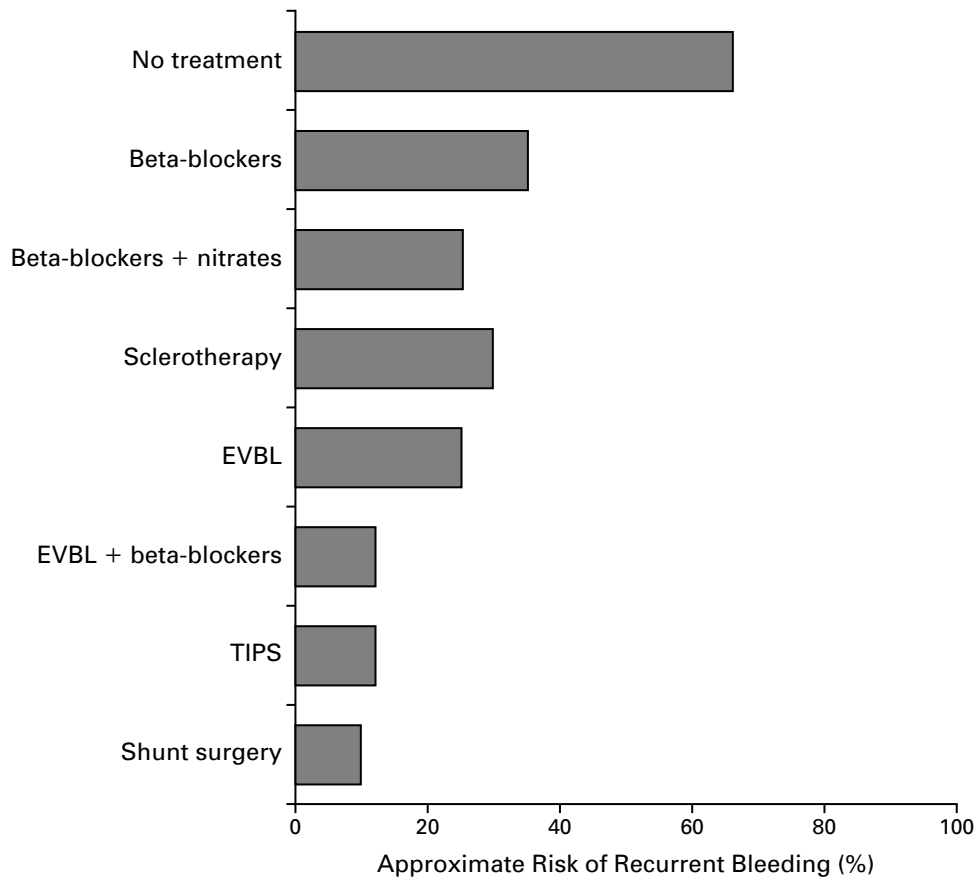
However, there are some types of cases for which management is controversial and not standardized. For example, secondary prophylaxis with surgical shunts may be more effective than medical or endoscopic therapy in patients with Child–Pugh class A or B cirrhosis with preserved synthetic function. The effectiveness of shunts notwithstanding, their use is critically dependent on the local availability of surgical expertise.

### Pharmacologic Therapy

Reducing the portal pressure by more than 20 percent from the base-line value pharmacologically results in a reduction in the cumulative probability of recurrent bleeding from 28 percent at one year, 39 percent at two years, and 66 percent at three years to 4 percent, 9 percent, and 9 percent, respectively.<sup>33</sup> Although adjusting medical therapy on the basis of a measurement of portal pressure would be ideal, the means to determine the hepatic venous pressure gradient may not be readily available; thus, therapy must be adjusted with the use of empirical clinical variables.

A number of pharmacologic agents that reduce portal pressure have been proposed for use in secondary prophylaxis,<sup>29-31</sup> but the only ones for which there is sufficient evidence of efficacy are beta-blockers. Several randomized, placebo-controlled trials, including a meta-analysis, have demonstrated that nonselective beta-blockers decrease the risk of recurrent bleeding and prolong survival.<sup>81-84</sup> An important consideration regarding beta-blockers, however, is their side effects, which often limit their usefulness in patients with cirrhosis.

The addition of isosorbide mononitrate to beta-blockers appears to enhance the protective effect of beta-blockers alone for the prevention of recurrent variceal bleeding<sup>85</sup> but offers no survival advantage and reduces the tolerability of therapy. The combination of beta-blockers and isosorbide mononitrate has been compared with endoscopic sclerotherapy in a randomized trial in patients with Child–Pugh class A or B cirrhosis.<sup>34</sup> Over a mean follow-up period of 18 months, nadolol plus isosorbide mononitrate was found to be superior to sclerotherapy for the prevention of recurrent bleeding (incidence of recurrent bleeding, 25 percent vs. 53 percent). Furthermore, there was a trend toward improved survival in the medical-therapy group, but the difference was not statistically significant. In addition, the combination of beta-blockers and isosorbide mononitrate has recently been compared with endoscopic variceal band ligation in a randomized trial including patients with Child–Pugh class A, B, or C cirrhosis.<sup>86</sup> The frequency of recurrent bleeding was 49 percent in the ligation group as compared with 33 percent in the medication group for all patients ( $P=0.04$ ), but after stratification according to Child–Pugh class, pharmacologic therapy



**Figure 4.** Relative Effectiveness of Available Therapies for the Prevention of Recurrent Variceal Bleeding. The estimates shown are based on the cumulative data available in the literature (recurrent bleeding at one year). EVBL denotes endoscopic variceal band ligation, and TIPS transjugular intrahepatic portosystemic shunt.

was found to be effective largely in patients with Child–Pugh class A or B disease. Notably, in patients who had a hemodynamic response to therapy (defined as a reduction in the hepatic venous pressure gradient to less than 12 mm Hg or by more than 20 percent of the base-line value), the risk of recurrent bleeding and of death was significantly reduced.

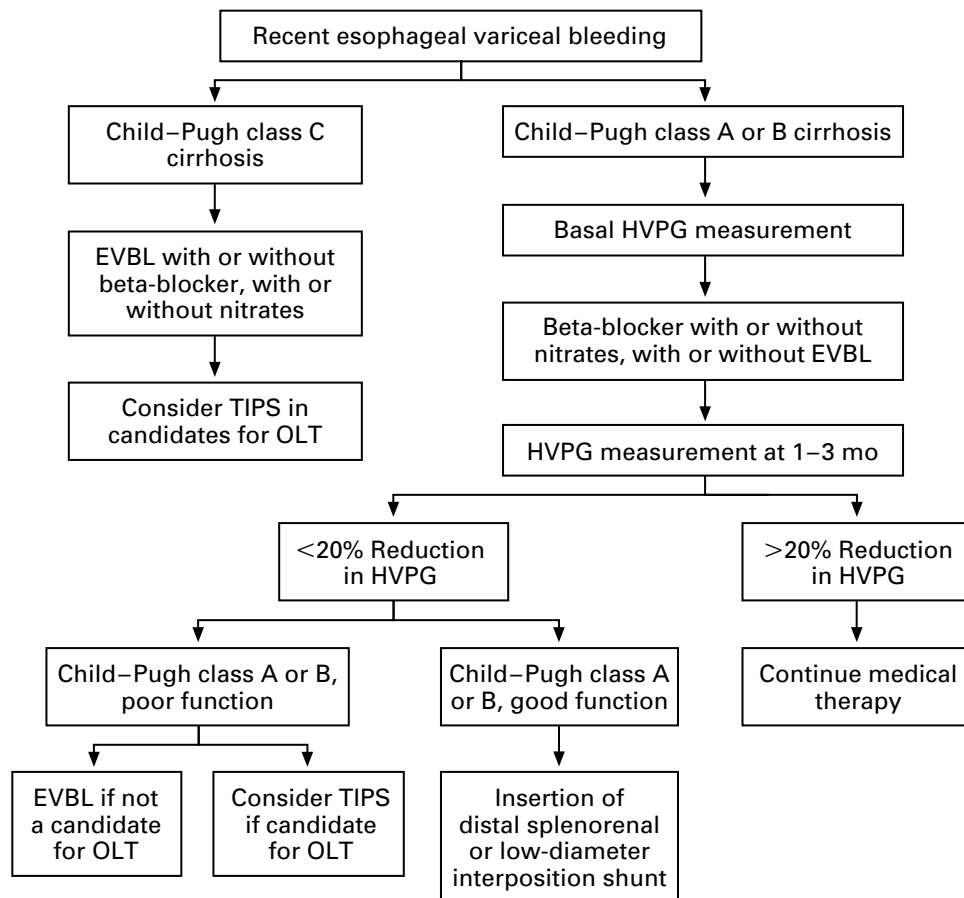
#### Endoscopic Therapy

Endoscopic therapy has been established during the past decade as a cornerstone of treatment for the prevention of recurrent esophageal variceal hemorrhage. Gastric varices, however, cannot be treated effectively by endoscopic sclerotherapy or ligation. Patients with recurrent gastric variceal hemorrhages are best treated by *N*-butyl-2-cyanoacrylate injection<sup>70</sup> or by nonendoscopic means.

Sclerotherapy reduces the risk of recurrent esophageal variceal bleeding from approximately 65 percent

to between 30 and 35 percent at one year,<sup>67,87</sup> but it does not appear to reduce overall mortality. Sclerotherapy is performed every 10 to 14 days until the varices are eradicated, which usually takes five or six sessions. A meta-analysis of nine trials found sclerotherapy and beta-blockers to be equivalent with respect to the risk of recurrent bleeding and the rate of survival.<sup>88</sup> Moreover, combination pharmacotherapy (beta-blockers plus isosorbide mononitrate) is superior to sclerotherapy alone in patients with Child–Pugh class A or B cirrhosis.<sup>34</sup>

Endoscopic variceal band ligation is highly effective in obliterating varices. Ligation is associated with a lower risk of recurrent bleeding than is sclerotherapy (approximately 25 vs. 30 percent at one year), fewer complications, lower overall cost, and higher rates of survival.<sup>67,69,87,89</sup> Therefore, ligation should be considered standard therapy for secondary prophylaxis. As with sclerotherapy, ligation is performed every 10



**Figure 5.** Suggested Algorithm for the Prevention of Recurrent Variceal Bleeding.

In patients with Child-Pugh class C cirrhosis, pharmacologic therapy is often associated with intolerable side effects. The determination of the hepatic venous pressure gradient (HVPG) may be helpful in assessing the response to pharmacologic therapy and the risk of recurrent bleeding. If varices are not eradicated by endoscopic variceal band ligation (EVBL) and the patient cannot tolerate beta-blockade, consider a transjugular intrahepatic portosystemic shunt (TIPS). In patients with Child-Pugh class A or B cirrhosis, the determination of the HVPG is preferred if it is available. If it is not available, beta-blockade with assessment of hemodynamic variables is recommended. Further management depends on the severity of the liver disease, the patient's compliance with treatment, the clinical response, and the medical expertise available locally. OLT denotes orthotopic liver transplantation.

to 14 days until the varices have been eradicated, which typically requires three or four sessions.

Approaches that combine methods, usually including an endoscopic treatment and a pharmacologic treatment, are attractive given the pathophysiology of gastroesophageal variceal hemorrhage and may be more effective than either form of therapy alone. Combined sclerotherapy and beta-blockers led to a lower incidence of recurrent bleeding than beta-blockers alone (but provided no survival benefit).<sup>90,91</sup> In addition, the combination of ligation and nadolol was significantly more effective than ligation alone in preventing recurrences.<sup>92</sup> Although the addition of sclerotherapy to ligation may theoretically offer greater

protection against recurrent bleeding, this combination does not appear to be advantageous.<sup>93,94</sup> Nonetheless, certain combination approaches that target more than one pathophysiologic factor are likely to become popular.

#### Transjugular Intrahepatic Portosystemic Shunt

Transjugular shunting is more effective than endoscopic therapy for the prevention of recurrent variceal bleeding.<sup>95-97</sup> The cumulative risk of recurrence after transjugular shunting is 8 to 18 percent at one year.<sup>95-97</sup> The tradeoff, however, is an increased incidence of clinically significant hepatic encephalopathy, since new or worsened encephalopathy occurs in at least 25 per-

cent of patients after shunting.<sup>98,99</sup> In addition, the use of a transjugular shunt offers no survival benefit over endoscopic therapy, and patients with advanced liver disease may have poor outcomes after shunting.<sup>75,100,101</sup> Consequently, transjugular shunting should be used with caution in patients with advanced liver disease; we believe that this method is best used as a bridge to transplantation.

Stenosis and dysfunction of the shunt after transjugular shunting represent an important complication; the reported rates are 31 percent at one year and 47 percent at two years.<sup>102,103</sup> Doppler ultrasonographic examination is routinely performed at some centers to evaluate the patency of the shunt, but it has extremely low sensitivity and specificity.<sup>104</sup> Balloon dilation or replacement of the occluded stent is often required. In aggregate, hepatic encephalopathy and stenosis of the shunt result in substantial affiliated costs. Indeed, an analysis comparing the cost of transjugular shunting with that of sclerotherapy found no difference in the cumulative cost despite the lower incidence of recurrent bleeding with shunting.<sup>105</sup>

**Surgical Therapy**

Decompressive surgical shunts, including nonselective and selective shunts (Fig. 1), are preferred for patients who are noncompliant with medical or endoscopic therapy and for those who are not candidates for liver transplantation. Although nonselective shunts are effective in eradicating varices and preventing recurrent bleeding, they are associated with important operative and postoperative complications. Selective

shunts are slightly less effective in achieving portal decompression but typically preserve liver function more effectively than nonselective shunts and do not adversely affect the potential for future liver transplantation. Elective surgical therapy is largely reserved for patients with Child–Pugh class A or B cirrhosis. Assuming that appropriate surgical expertise is available, the choice of surgical therapy should be individualized and must take into account the severity of the liver disease, the patient’s compliance, and the likelihood of progressive liver dysfunction.

Commonly used shunts include the distal spleno-renal shunt and the low-diameter (mesocaval or portacaval) interposition shunt. Rates of recurrent bleeding range from 10 to 20 percent, with the highest risk occurring during the first month after surgery.<sup>106,107</sup> Devascularization procedures (i.e., esophageal transection and devascularization) are usually considered in patients who cannot receive shunts because of splanchnic venous thrombosis and should be performed only by experienced surgeons.

**COST EFFECTIVENESS OF AVAILABLE THERAPIES**

Data on the cost of variceal bleeding and the cost effectiveness of commonly used therapies are limited.<sup>5,105,108-110</sup> The cost of treatment for an episode of variceal bleeding has been estimated at \$10,000 to \$35,000.<sup>5,111</sup> The cost effectiveness of the diagnostic methods used to guide therapy remains largely unknown. For example, the determination of the hepatic venous pressure gradient, which may accurately pre-

**TABLE 3.** EFFICACY AND COST OF TREATMENTS FOR THE PREVENTION OF RECURRENT VARICEAL BLEEDING IN PATIENTS WITH CIRRHOSIS.\*

TREATMENT	CHARACTERISTICS OF SUITABLE PATIENTS	RISK OF BLEEDING AT 12 MO†	COST AT 12 MO‡	COMMENTS
		%	\$	
Medical therapy (nadolol or propranolol and isosorbide mononitrate)	Child–Pugh class A or B cirrhosis Reduction of ≥20% in HVPG with medication High degree of compliance	4–25	3,000–3,700	Includes cost of HVPG determination at base line and at 1–2 mo of therapy
Endoscopic variceal band ligation	Child–Pugh class A–C cirrhosis Compliance with repeated medical therapy	20–30	8,500–9,500	Estimate based on a mean of 4 sessions until varices are obliterated followed by diagnostic esophagoscopy at 3 and 12 mo
Transjugular intrahepatic portosystemic shunt	Current or future candidates for liver transplantation	8–15	12,000–15,000	Includes cost of Doppler ultrasonography of shunt every 3 mo to monitor for stenosis or occlusion
Distal spleno-renal shunt or low-diameter (mesocaval or portocaval) interposition shunt	Child–Pugh class A or B Good liver function	5–10	25,000–40,000	Includes preoperative venous phase arteriography and measurement of liver volume

\*HVPG denotes hepatic venous pressure gradient.

†The risk of bleeding varies with the severity of the liver disease.

‡Costs represent the hospital charges, where applicable. The cost of care for bleeding episodes is not included.

dict the pharmacologic response to therapy,<sup>23</sup> is an attractive, although invasive, adjunct in the treatment of patients with variceal bleeding, but its cost effectiveness is unknown. Finally, although screening endoscopy is recommended for the detection of large varices, it has not been demonstrated to be cost effective.

When choosing a specific treatment plan, the clinician must take into consideration the direct costs as well as the efficacy of various therapies and the morbidity associated with them. The physician should tailor the treatment plan to the patient's clinical condition while taking into account the possibility that the patient's liver disease may progress and thus necessitate transplantation. Furthermore, when calculating the cost effectiveness of various methods of treatment, clinicians should factor in the cost of failed therapy (e.g., recurrent bleeding and revision of the shunt, especially for transjugular intrahepatic portosystemic shunts, since this form of shunt is associated with a high incidence of stenosis) and that of treatment-related complications (e.g., encephalopathy and esophageal stricture).<sup>110</sup> Common methods of treatment used for primary and secondary prophylaxis and for acute bleeding in patients with variceal hemorrhage are listed in Table 3.

### CONCLUSIONS

Gastroesophageal variceal hemorrhage is a common and devastating complication of portal hypertension and is a leading cause of disability and death in patients with cirrhosis. Because outcomes are poor once variceal bleeding has occurred, primary prophylaxis is indicated. Although the role of endoscopic variceal band ligation in primary prophylaxis is not established, treatment with beta-blockers is well accepted. The treatment of acute variceal hemorrhage is aimed at volume restoration and ensuring hemostasis with pharmacologic agents, endoscopic techniques (ligation or sclerotherapy), or both. Because there is a high risk of recurrence after an initial hemorrhage, preventive strategies are required and should be tailored to the patient's clinical condition, surgical risk, and prognosis. As with the treatment of acute hemorrhage, treatment with a combination of methods is likely to gain in popularity.

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