

# Modern management of oesophageal varices

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## Abstract

**Haemorrhage from oesophageal varices is a life threatening emergency with a mortality rate in the order of 30%–50%. In the last three decades there have been many advances in the treatment and prevention of variceal bleeding. Over recent years the introduction of new pharmaceutical agents that reduce portal pressure, endoscopic variceal ligation, transjugular intrahepatic portosystemic shunt, and the availability of liver transplantation have further increased the therapeutic options available to the physician treating this disorder. This article reviews the literature regarding therapies available in the treatment of haemorrhage from oesophageal varices and provides guidelines to aid the physicians in clinical decision making.**

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Even in the year 2001 haemorrhage from oesophageal varices remains a major medical emergency with a high mortality rate. Over recent years, however, the introduction of new pharmaceutical agents that reduce portal pressure, endoscopic variceal ligation, transjugular intrahepatic portosystemic shunt (TIPS), and the availability of liver transplantation have further increased the therapeutic options in the treatment of oesophageal varices. The variety of treatment options has resulted in an explosion of literature dealing with oesophageal varices. Despite the increasing volume of clinical trials and laboratory research, therapeutic decision making concerning patients with variceal haemorrhage is often still difficult. Managing oesophageal varices at the start of the 21st century still poses considerable challenges to both the general internist and hepatologist.

## Pathophysiology of portal hypertension

The initiating factor in the development of portal hypertension is increased resistance to portal flow. In the Western world cirrhosis is the most common cause, and the major site of resistance to flow is the hepatic sinusoid (table 1). Stellate cells line the perisinusoidal space and are transformed into contractile myofibroblasts in response to liver injury. These cells play a central part in the development of hepatic fibrosis. Stellate cells regulate sinusoidal resistance and flow in response to vasoactive substances, especially endothelin<sup>1</sup> and nitric oxide.<sup>2</sup> Sinusoidal resistance exerts the “backward” component of portal hypertension. The “forward” component is the

Table 1 Causes of portal hypertension classified according to the site of increased vascular resistance (From: *Oxford Textbook of Medicine*)

Suprahepatic
Constrictive pericarditis
Right heart failure
Inferior vena cava thrombosis
Budd-Chiari syndrome
Veno-occlusive disease
Intrahepatic
Presinusoidal
Schistosomiasis
Primary biliary cirrhosis (early stage)
Sarcoid
Myeloproliferative diseases
Nodular regenerative hyperplasia
Sinusoidal
Cirrhosis
Chronic active hepatitis
Alcoholic hepatitis and fatty liver
Infrahepatic
Portal vein thrombosis
Splenic vein thrombosis
Increased hepatic blood flow
Hepatoportal arteriovenous fistula
Conditions associated with massive splenomegaly

increased splanchnic blood flow that accompanies the vasodilated circulation in cirrhosis. It has been demonstrated that the main site of low systemic vascular resistance is the splanchnic circulation.<sup>3</sup>

Haemodynamic studies have provided great insight into understanding the pathophysiology of portal hypertension and the development of oesophageal varices. It is difficult to directly measure the portal pressure gradient (the difference between portal pressure and inferior vena cava pressure) due to the inaccessibility of the portal vein to catheter placement. To overcome this obstacle an indirect measurement of portal pressure gradient can be obtained with the hepatic venous pressure gradient (HVPG). The HVPG reflects the difference between wedged and free hepatic venous pressure and closely reflects the portal pressure gradient in patients with cirrhotic portal hypertension. Normal HVPG is  $\leq 4$  mm Hg, it is not until the HVPG is above 10 mm Hg that oesophageal varices develop. However, not all patients with HVPG above this level have oesophageal varices. Once varices have developed they tend to steadily increase in size before they eventually rupture and bleed. There is little information regarding the rate of development of varices in patients with cirrhosis. In one large study approximately 8% of patients with cirrhosis developed varices per year.<sup>4</sup> In addition, in 10%–20% of patients with small varices they increase to large in the year after the first detection.<sup>5,6</sup> With this information a rational screening programme would involve second yearly endoscopy in patients without varices, and annual endoscopy in patients with small varices to detect patients at high risk of bleeding.

Although approximately 90% of patients with cirrhosis will develop varices<sup>4,6</sup> bleeding

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**Box 1: Factors associated with high risk of first variceal haemorrhage**

- HVPG >12 mm Hg
- Red sign, red wale mark on varix
- Child class
- Continued alcohol abuse
- Varix size

occurs in only 25%–35% of patients.<sup>7 8</sup> Mortality from a first bleed is approximately 50%, the risk of recurrent bleeding is in the order of 70% with an associated inpatient mortality rate of 30%.<sup>4 9</sup> Most deaths occur after early rebleeding, which occurs in up to 50% of patients within the first week.<sup>7 10</sup> The risk of rebleeding and death remains elevated for the first six weeks after an initial bleed and then rapidly decreases.<sup>9</sup> The degree of hepatic decompensation (Child class) is the most important determinant of long term survival after a variceal haemorrhage.<sup>11 12</sup>

As not all patients with cirrhosis will develop varices and not all patients with varices will bleed it is essential to be able to predict patients at high risk of bleeding so as to best target preventative therapy (box 1). Patients with a HVPG of less than 12 mm Hg do not bleed from varices.<sup>13 14</sup> There is, however, no clear relationship between HVPG above 12 mm Hg and risk of bleeding. Variceal size is also a factor. Patients with large varices have a 20% to 30% annual incidence of bleeding compared with 10% to 15% in unselected patients with cirrhosis and varices.<sup>15 16</sup> This has been confirmed in a large prospective study.<sup>7</sup> Red sign and red wale marking on the variceal wall also indicate an increased risk of bleeding.<sup>7 17</sup> Additional risk factors include severity of liver disease and continued alcohol abuse.<sup>7 17</sup>

**Prevention of first bleed****β-BLOCKERS AS PRIMARY PREVENTION (BOX 2)**

Although a large number of drugs have been demonstrated to lower portal pressure, extensive clinical experience has only been gained with the use of non-selective β-blockers. Eighty mg of propranolol daily has been demonstrated to lower HVPG by 13%.<sup>18</sup> This reduction in HVPG has been demonstrated to continue during long term therapy.<sup>18</sup> The usefulness of β-blockers as primary prophylaxis has been investigated in a large number of randomised prospective trials.<sup>19–25</sup> The vast majority of these trials conclude that β-blockers lead to significantly fewer episodes of variceal haemorrhage in comparison with placebo. Yet only one study demonstrated a significant improvement in survival with β-blockers.<sup>19</sup> The benefit of β-blockers as primary prophylaxis becomes more pronounced when high risk patients are specifically included; namely HVPG >12 mm Hg and large varices.<sup>23</sup>

Several meta-analyses have addressed the effect of β-blockers as primary prophylaxis.<sup>16 26 27 28</sup> All have shown a significant reduction in the incidence of first variceal haemorrhage, but none have displayed a significant effect on survival. Failure to detect a

**Box 2: Role Of β-blockers in prevention of first bleed**

- Should definitely be used in all patients with “high risk” varices
- Reduce incidence of first bleed compared with placebo
- Treatment should be lifelong once initiated
- In those who experience side effects from β-blockers, nitrates should be used

survival advantage with β-blockers probably reflects a type II error; more patients need to be included in such studies to show an effect on mortality.

No mortality from treatment has been reported. It could be argued that β-blockers should be used as primary prevention in all patients with oesophageal varices. There is no doubt, however, that they are indicated in all patients who are at high risk of variceal haemorrhage (box 1), unless there is a specific contraindication. As there is evidence that stopping treatment may precipitate a bleed,<sup>29</sup> treatment once initiated, should be lifelong.

**SCLEROTHERAPY AS PRIMARY PREVENTION**

More than 20 trials have studied this issue enrolling in excess of 1000 patients.<sup>30</sup> The trial protocols were extremely heterogeneous, variceal size varied considerably, and only one required a HVPG of greater than 12 mm Hg. Sclerotherapy technique also varied, with a variety of sclerosants in different doses injected intravariceally or perivariceally or both. Although some early trials showed a reduction in bleeding in the sclerotherapy group more recent and larger trials have shown either no value or a deleterious effect of sclerotherapy.<sup>31</sup> Endoscopic sclerotherapy is therefore not indicated for the prevention of first variceal haemorrhage in cirrhotic patients.

Recent trials into the use of variceal ligation in the prevention of the first episode of variceal bleeding are just being completed. In one study of patients with large varices, ligation therapy significantly reduced the incidence of variceal haemorrhage compared with propranolol. In this study, however, approximately half the patients had non-cirrhotic portal hypertension and no difference in mortality was demonstrated.<sup>32</sup> A second study used no treatment in the control group and reported a significant reduction in prevention of bleeding and death with variceal ligation. The preliminary results concerning the use of variceal ligation as primary prevention appear promising. The results of further trials confirming these results are still needed.

**OTHER MEASURES AS PRIMARY PREVENTION (BOX 3)**

Nitrates may be as effective as β-blockers for primary prophylaxis and offer an alternative to patients who are intolerant of β-blockers. Isosorbide mononitrate has been compared to propranolol in one study.<sup>33</sup> There was a slight

**Box 3: Role of other measures in prevention of first bleed**

- No indication for prophylactic sclerotherapy
- Newer evidence suggests that variceal ligation may be more effective and safer
- Nitrates can be used in patients in whom  $\beta$ -blockers are contraindicated

surplus of haemorrhagic events with the nitrate group; the majority of patients, however, remained without haemorrhage.

There have been several studies examining the combination of  $\beta$ -blockers and nitrates in reducing portal pressure gradient. This combination of therapy appears more effective in reducing pressure than  $\beta$ -blockers alone. There are very few studies which examine the role of this combination as primary prevention. One study which enrolled only well compensated cirrhotics revealed significantly less variceal bleeding in the combination group compared with  $\beta$ -blockers alone, but no effect on mortality.<sup>34</sup> Recently results from a seven year follow up of this study have been published and report findings results to the original; namely a reduction in variceal bleeding but no difference in mortality.<sup>35</sup> Currently there is too little clinical evidence to make strong recommendations about the use of  $\beta$ -blockers in addition to nitrates as primary prevention.

Four studies have demonstrated that shunt surgery is very effective in preventing variceal bleeding,<sup>36-39</sup> however, this was at the cost of an increased incidence of encephalopathy and reduced survival.

The role of TIPS in the prevention of first variceal haemorrhage, surprisingly, has not been examined. TIPS is unlikely, however, to play an important part in the primary prevention of variceal haemorrhage due to the high

incidence of encephalopathy that complicates this procedure.

**Treatment of acute variceal haemorrhage (box 4)**

GENERAL MANAGEMENT

In managing patients with acute variceal haemorrhage the involvement of experienced medical staff from the outset is essential. Large bore intravenous access is necessary to allow rapid transfusion if required. Initial fluid resuscitation should be titrated to restore the systolic blood pressure to 80 or 90 mm Hg, further fluid requirements should aim to maintain haemoglobin at 100 g/l and urine output above 30 ml/hour. Overly aggressive fluid replacement should be avoided as overfilling may increase portal pressure leading to rebleeding.

Pulmonary aspiration of blood or gastric secretions is common due to the combination of encephalopathy and impaired consciousness due to shock. In patients with significantly reduced conscious state early endotracheal intubation is mandatory.

Bacterial infection complicates variceal haemorrhage in cirrhosis in up to 66% of patients.<sup>40-42</sup> A recent meta-analysis has demonstrated that short term prophylactic antibiotics significantly reduces the incidence of infection and increases short term survival.<sup>43</sup> Prophylactic antibiotics therefore, should be routinely used in all patients for seven days after admission for variceal haemorrhage.

ENDOSCOPIC MANAGEMENT

Urgent endoscopy plays a crucial role in the management of all patients with variceal bleeding. It allows confirmation as to the cause of bleeding in addition to allowing specific therapy to be initiated. It is a point worth emphasising that variceal haemorrhage is not the only cause of upper gastrointestinal bleeding in cirrhotic patients. The incidence of pep-

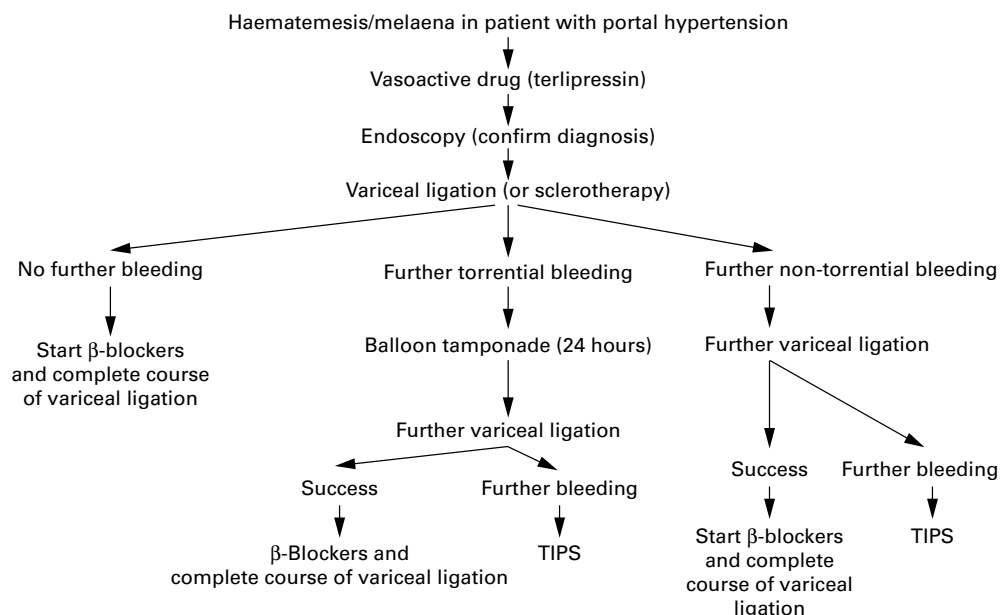


Figure 1 Suggested practice protocol for the management of bleeding oesophageal varices. In all patients with bleeding from oesophageal varices liver transplantation should be considered.

#### Box 4: Treatment of acute variceal haemorrhage

- Titrated fluid resuscitation to a systolic blood pressure of 80–90 mm Hg only
- Endotracheal intubation in patients with grade III–IV encephalopathy to protect airway
- Prophylactic antibiotics increases short term survival in cirrhotic patients with acute variceal haemorrhage
- Terlipressin, somatostatin, and octreotide control bleeding in approximately 80%–90%
- Variceal ligation appears to be equally as effective as sclerotherapy in controlling acute variceal haemorrhage
- Balloon tamponade has a high complication rate, its use should be restricted to patients with massive bleeding not controlled by initial therapy
- TIPS is the treatment of choice in patients unresponsive to endoscopic management

tic ulceration is increased in cirrhosis,<sup>44</sup> bleeding may be directly from portal hypertensive gastropathy and gastric or duodenal varices may be also bleed. These different pathologies require alternative therapies than would be routinely employed in haemorrhage from oesophageal varices.

Sclerotherapy is still widely used as first choice in endoscopic treatment because it controls haemorrhage in 80%–90% of cases.<sup>45</sup> Minor complications such as pain, fever, and transient dysphagia are common. In addition, mucosal ulceration develops in up to 80% of patients<sup>43</sup> and may cause rebleeding in 20% of patients.<sup>46–47</sup> Differences in the site of injection (intravariceal or perivariceal or both), type, or volume of sclerosant do not appear to appreciably influence the efficacy of the treatment.

Variceal ligation appears to be as equally effective as sclerotherapy in controlling acute variceal haemorrhage.<sup>48–52</sup> The choice between the two procedures primarily depends on operator experience, although variceal ligation is associated with fewer side effects.

#### PHARMACOLOGICAL MANAGEMENT

A number of drugs have been used in the treatment of acute variceal bleeding in an attempt to induce haemostasis while endoscopic therapy is arranged, in addition to reducing the risk of early rebleeding.

Vasopressin is the oldest of these drugs and was first introduced into clinical practice in the 1950s. Vasopressin induces splanchnic vasoconstriction and thereby reduces portal pressure. Side effects with the use of this drug are unfortunately common. In particular vasopressin induces systemic vasoconstriction, reducing cardiac output and myocardial blood flow, potentially resulting in myocardial ischaemia, myocardial infarction, arrhythmias, and cerebrovascular accidents. For these reasons vasopressin should not be routinely used in

acute variceal haemorrhage as there are far safer drugs available.

Terlipressin (Glypressin) is a synthetic analogue of vasopressin, with a prolonged half life of 3–4 hours. This enables the drug to be given as bolus intravenous injections. Terlipressin controls bleeding in 80% of cases and is the only pharmacological agent that has been shown to reduce mortality from variceal bleeding.<sup>53</sup> Terlipressin is superior to vasopressin (with or without nitroglycerine) in controlling bleeding.<sup>54–56</sup> In addition side effects are less common.<sup>57</sup>

Somatostatin has similar efficacy in controlling bleeding as terlipressin.<sup>58</sup> As it has a short half life (2–3 min) it needs to be given by infusion. Studies comparing somatostatin with terlipressin reveal similar efficacy in controlling bleeding, and significantly fewer side effects than with the use of terlipressin.<sup>59</sup>

Octreotide is a synthetic longer acting analogue of somatostatin. Octreotide is a much newer drug and thus has been less extensively investigated. Control of bleeding appears to be similar to that seen with terlipressin and somatostatin.<sup>60</sup>

Pharmacological therapy has an established role in the management of the acute variceal haemorrhage. Several drugs including terlipressin, vasopressin plus nitroglycerine, somatostatin, and octreotide have been shown to be effective. The decision regarding the best pharmacological therapy has currently not been resolved, but vasopressin is best avoided due to the high incidence of side effects.

#### BALLOON TAMPONADE

Balloon tamponade is aimed at obtaining temporary haemostasis by direct compression of varices at the oesophagogastric junction. Efficacy in controlling bleeding is highly variable, ranging from 40%–90%.<sup>61–63</sup> Rebleeding occurs in 50% of patients within 24 hours of balloon deflation.<sup>63</sup> Placement of the balloon is associated with an unacceptable death rate of 6%–20% due primarily to oesophageal perforation and pulmonary aspiration.<sup>61–64</sup> Due to the high incidence of complications associated with balloon placement it is prudent for the patient to be intubated and sedated before balloon insertion to minimise potential risks. Inflation of the gastric balloon followed by continual gentle pressure on the apparatus is usually adequate to control bleeding from oesophageal varices. After 24 hours the balloon should be deflated due to the risk of mucosal ulceration. It is rarely necessary to inflate the oesophageal balloon. Due to its high complication rate there is no indication for the routine use of balloon tamponade in the first line management of acute bleeding. Its use should be restricted to patients with massive bleeding not controlled by initial therapy while definitive treatment is arranged.

#### TIPS

This radiological intervention creates an intrahepatic shunt by placing a stent connecting the hepatic and portal veins. TIPS is now widely used as rescue therapy in patients unresponsive



**Box 5: prevention of rebleeding**

- $\beta$ -Blockers indicated in all patients after variceal bleed
- Overall  $\beta$ -blockers reduce the risk of rebleeding by about 40% and mortality by 20%
- Reduced incidence of rebleeding and death if  $\beta$ -blockers combined with endoscopic eradication of varices
- Variceal ligation requires fewer sessions to obliterate varices and results in fewer complications compared with sclerotherapy
- Sclerotherapy may be necessary after successful ligation therapy to eradicate small residual varices and prevent recurrence of varices

to endoscopic management and is the accepted procedure of choice in this situation. Failure of endoscopic therapy has been defined as "further variceal bleeding after two endoscopic treatments during a single hospital admission for an acute bleeding episode".<sup>65</sup> Used in this situation TIPS leads to immediate cessation of bleeding in 73%–96% of cases.<sup>66–69</sup>

**Prevention of rebleeding (box 5)**

## PHARMACOLOGICAL AGENTS

$\beta$ -Blockers are the most widely used pharmacological agent in the prevention of rebleeding. Numerous trials and three meta-analyses have confirmed the efficacy of  $\beta$ -blockers over placebo.<sup>70–79</sup> Overall  $\beta$ -blockers reduce the risk of rebleeding by about 40% and mortality by 20%.<sup>27</sup>

## ENDOSCOPIC MANAGEMENT

The benefits of sclerotherapy in preventing rebleeding have been clearly illustrated by a series of well designed randomised controlled trials. Initial trials compared sclerotherapy with no treatment<sup>77–80</sup> and meta-analysis revealed a significant reduction in rebleeding and improved survival in the groups treated with sclerotherapy.<sup>30</sup> Subsequent trials have compared sclerotherapy plus  $\beta$ -blockers with  $\beta$ -blockers alone. These trials reported a reduced incidence of rebleeding and death in the combined treatment groups.<sup>81–82</sup> Pooled results from these two trials reveal the reduction in rebleeding and death to be statistically significant.<sup>30</sup>

There are many published trials comparing variceal ligation with sclerotherapy for the prevention of recurrent variceal bleeding.<sup>49–51–83–84</sup> A meta-analysis of these studies concludes that treatment with variceal ligation is associated with a reduced risk of rebleeding and an overall improved survival compared with sclerotherapy.<sup>48</sup> Variceal ligation requires fewer sessions to obliterate varices and results in fewer complications compared with sclerotherapy. Follow up from these studies however has been short, generally less than 12 months. More recent evidence suggests that there is a high rate of recurrence of varices in patients treated solely with ligation therapy compared with sclerotherapy.<sup>85</sup> Ligation therapy followed by

sclerotherapy to obliterate small residual varices appears most effective in preventing recurrence of varices and minimising complications.<sup>86</sup>

The conclusions to draw from these endoscopic data are that variceal ligation is superior to sclerotherapy in eradication of varices, due primarily to its lower incidence of side effects. Following successful ligation therapy preliminary evidence suggests that sclerotherapy may be necessary to complete the eradication of small remaining or recurrent varices.

## TIPS

Recently TIPS has been compared with sclerotherapy and ligation therapy in the prevention of rebleeding in a number of randomised controlled trials.<sup>87–89</sup> These trials have varied in design with different endoscopic measures employed, and only three have used  $\beta$ -blockers with the endoscopic therapy. No trials have compared TIPS with  $\beta$ -blockers and ligation therapy. Generally the studies have shown reduced rebleeding in the TIPS group, but higher rates of encephalopathy and only one has shown a survival advantage in the TIPS group.<sup>89</sup> From these data TIPS cannot currently be recommended for the routine prevention of rebleeding.

## SURGERY

Early studies comparing portacaval shunt to non-specific treatment reported greatly reduced rebleeding in the shunt group but significantly higher rates of encephalopathy.<sup>90–92</sup> Distal splenorenal shunts have also been compared to portacaval shunts but no significant difference in rebleeding was reported in any trial.<sup>93–94</sup> Shunt surgery has been compared with sclerotherapy in a meta-analysis and found reduced rates of rebleeding but higher rates of encephalopathy in the shunt group.<sup>95</sup> Over recent years surgical shunts have received renewed interest due primarily to their effectiveness in preventing rebleeding. Data on surgical shunts performed in recent years indicate better outcomes than earlier reported series. This is primarily due to patient selection, with the majority of procedures performed in Child class A and B patients.<sup>96–98</sup> Although more recent results of surgical shunts are encouraging, it is premature to suggest that shunt surgery should be recommended in any patient for the indication of prevention of rebleeding. Its present indication lies as rescue therapy in patients in whom TIPS cannot be performed due to portal vein thrombosis or in whom an attempt at TIPS has failed due to technical difficulty.

## LIVER TRANSPLANTATION

Liver transplantation is the definitive treatment for patients with advanced liver disease who have bled and should be considered in all such patients. TIPS, unlike surgical shunts, does not seem to compromise subsequent transplant surgery and has been used as bridging therapy to liver transplantation in patients who have bled.<sup>99</sup>

## Conclusions

The management of haemorrhage from oesophageal varices has undergone enormous change over recent years. This is due to a combination of the development and implementation of new techniques and pharmaceuticals, in addition to a vast volume of data from randomised trials dealing with management issues in this condition. This has allowed us to make an increasing number of management decisions based on evidence rather than gut feeling.

$\beta$ -Blockers have demonstrated efficacy as primary prophylaxis in the prevention of variceal haemorrhage in cirrhotic patients with oesophageal varices. Prophylactic endoscopic therapy, TIPS, or shunt surgery cannot be recommended on current evidence. Treatment of acute variceal bleeding should be aimed at arresting haemorrhage in addition to preventing early rebleeding and thus reducing mortality. Vasoactive drugs control bleeding in up to 90% of patients. Emergency endoscopic therapy stops bleeding in 90% of patients. Endoscopic variceal ligation appears equally effective to sclerotherapy and results in less side effects. TIPS is the procedure of choice in patients who fail endoscopic therapy. Both  $\beta$ -blockers and endoscopic therapy reduce the risk of rebleeding and death. Shunt surgery and TIPS virtually abolish the risk of rebleeding but do so at the cost of precipitating or exacerbating encephalopathy. Liver transplantation should be considered in all patients with advanced liver disease who have bled.

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