Management of variceal bleeding
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Variceal hemorrhage complicates cirrhosis in as many as 50% of patients and results in considerable morbidity and mortality. This review covers all areas of importance in the prevention and treatment of this area, highlighting recent developments. Primary prophylaxis prevents first bleed, and pharmacotherapy with β-blockade is the most widely accepted option. In an acute variceal hemorrhage, initial resuscitation and multiple organ support are paramount and are recommended along with antibiotic prophylaxis and specific medical therapies that may be given empirically before emergency endoscopy to reduce bleeding. Endoscopic techniques usually arrest bleeding, but when they fail, salvage therapy in the form of balloon tamponade, then transjugular intrahepatic portosystemic shunts or surgery, may be appropriate. Secondary prophylaxis to prevent reblooding is often instituted in the ICU and is vital to prevent recurrence of this life-threatening complication. Curr Opin Crit Care 2002, 8:164–170 © 2002 Lippincott Williams & Wilkins, Inc.

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Abbreviations
EBL endoscopic band ligation
TIPS transjugular intrahepatic portosystemic shunt

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Variceal hemorrhage is a common cause of death in patients with cirrhosis resulting from portal hypertension. Portal hypertension and variceal bleeding may also be seen in patients without cirrhosis in conditions such as noncirrhotic portal hypertension and portal vein thrombosis. The increased blood flow through the portal system in cirrhosis [1], in addition to the architectural distortion within the liver that typifies the condition, results in portal hypertension. As a result, collateral circulation develops, shunting blood from the portal to the systemic circulation. These spontaneous shunts occur at the cardia through the intrinsic and extrinsic gastroesophageal veins, the anal canal, and the falciform ligament. These shunts enlarge with time and form varices.

The risk of bleeding from varices increases with disease severity and variceal size [2], but overall, bleeding from varices is reported in 20 to 50% of patients [3,4]. Mortality is also related to disease severity but overall is reported as high as 50% [3].

Recently there have been many key advances in the management of this common and devastating complication. This article reviews those in the areas of primary prophylaxis, management of the acute variceal bleed, and secondary prophylaxis for preventing further episodes of bleeding.

Definitions
Variceal bleeding is defined as bleeding from an esophageal or gastric varix at the time of endoscopy, or the presence of large esophageal varices with blood in the stomach and no other recognizable cause of bleeding. Acute bleeding is that which occurs up to 48 hours after the patient is admitted to any hospital with a bleed. Variceal rebleeding is defined as the occurrence of a new hematemesis or melena after a period of 24 hours or longer from a 24-hour time-point of stable vital signs and hemoglobin after an episode of acute variceal bleeding. Further bleeding within the initial 24 hours of therapy is defined as failure to control active bleeding.

Primary prophylaxis
Given the high rate of variceal bleeding in patients with cirrhosis and its high mortality, primary prophylaxis to prevent the first variceal bleed in these patients is common practice. If primary prophylaxis causes a reduction in the hepatic venous pressure gradient to less than 12 mm Hg or an absolute reduction of 20%, there is
a substantially decreased incidence of first variceal bleeding [5].

Nonselective β-blockade has been widely used in the prevention of the first variceal bleed in patients with cirrhosis who have varices on endoscopy. Meta-analyses indicate that β-blockade reduces the risk of variceal bleeding but has only a borderline effect on mortality [6].

Nitrates may also reduce portal pressure and have been studied alone and in combination with β-blockade. Recently they have been shown to be no more effective than placebo when used alone in patients intolerant of β-blockers [7•]. In addition, there is an increase in mortality in patients older than 50 years treated with nitrates [8]; therefore, they are not recommended as monotherapy to prevent variceal hemorrhage.

Whether patients should be treated with nitrates in combination with β-blockade has also been investigated recently. In a single-blinded study of 136 patients with well preserved liver function, there was a reduction in first variceal bleed in those taking both nadolol and isosorbide mononitrate compared with those taking nadolol alone, but there was no change in overall or liver-related mortality [9]. Considering the effect of nitrates alone upon mortality, it is important to note that this study was not powered to assess difference in mortality.

Recently, meta-analyses comparing endoscopic band ligation (EBL) with placebo and β-blockade for primary prophylaxis have been published [10••]. Compared with placebo, EBL reduces relative risk of first bleed, bleeding-related mortality, and overall mortality. Comparison with β-blockade showed reduction in first bleed but no effect upon bleed-related or all-cause mortality. Because of the lack of mortality difference between β-blockade and EBL, it is suggested that prophylactic EBL be reserved for those who do not tolerate β-blockade, in whom it is preferred to nitrate therapy.

Management of acute variceal hemorrhage

Patients with acute variceal hemorrhage typically seek treatment for an acute clinical event with severe gastrointestinal hemorrhage manifesting as hematemesis with or without melena and commonly accompanied by hemodynamic instability and fall in hemoglobin. Mortality depends on severity of disease, most reliably assessed using the Child-Pugh score (Table 1) with those with Child-Pugh A having mortality of 5% within 1 year of variceal bleed, compared with 50% in those with Child-Pugh C cirrhosis [11].

Successful outcome relies on effective fluid resuscitation, maintenance of adequate perfusion pressure, monitoring of end-organ function, surveillance for the development of sepsis and multiple organ failure, and prompt diagnosis and achievement of hemostasis. Specific therapies are available to the attending physician in the treatment of these patients, but these therapies must not interfere with the multiorgan care these patients require. An algorithm for treatment of presumed variceal bleed is provided in Figure 1.

Fluid resuscitation should be aimed toward isovolumic resuscitation with appropriate fluids, because this procedure does not increase portal venous pressure and risk of bleeding [12]. Despite adequate volume resuscitation guided by invasive hemodynamic monitoring, hypotension often requires vasopressor support. Noradrenaline is standard in this regard, but the vasoconstrictor properties of terlipressin may be useful to reduce portal venous pressure and improve mean arterial pressure for an acute variceal bleed. Protection of the airway from aspiration in these patients is of paramount importance, particularly in the presence of altered conscious level, agitation, and preparation for endoscopy.

Infection is common after acute variceal hemorrhage and is associated with failure to control bleeding and the occurrence of rebleeding [13,14]. Indeed, infection may result in an increase in portal pressure, precipitating variceal bleeding [15]. A meta-analysis of studies of the use of prophylactic antibiotic in this setting suggests that antibiotic prophylaxis substantially increases the number of patients who remain free from infection and improves short-term survival in patients with cirrhosis admitted with variceal hemorrhage [16]. Infection should be sought particularly in the respiratory tract, and ascites and appropriate cultures should be sent for microbiologic analysis to guide therapy. However, the choice and dose of the empirical antibiotics should be based on the policy of the unit in which the patient is being treated, because there is no clear guidance on this issue in the available literature.

### Table 1. Child-Pugh score

<table>
<thead>
<tr>
<th>Score</th>
<th>Bilirubin/µmol/L</th>
<th>Albumin/g/L</th>
<th>INR</th>
<th>Ascites</th>
<th>Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;34</td>
<td>&gt;35</td>
<td>&lt;1.3</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>34–51</td>
<td>28–35</td>
<td>1.3–1.5</td>
<td>Mild</td>
<td>I/II</td>
</tr>
<tr>
<td>3</td>
<td>&gt;51</td>
<td>&lt;28</td>
<td>&gt;1.5</td>
<td>Moderate</td>
<td>III/IV</td>
</tr>
</tbody>
</table>

A score is given as shown for each column. The sum of the scores gives the Child-Pugh score. The categories are then decided as follows: Child-Pugh A, <6; Child-Pugh B, 7–9; Child-Pugh C, >10. INR, International Normalized Ratio.
### Specific therapies to arrest active bleeding

#### Pharmacotherapy

The advantages of pharmacotherapy are that it can be administered early and that it does not require technical expertise. Empirical therapy may be appropriate in patients with suspected variceal hemorrhage.

#### Vasopressin and its analogues

Although vasopressin reduces portal pressure, its use is limited by a notable side effect profile dominated by peripheral vasoconstriction, notably within the myocardial and mesenteric arterial supply. In addition, as a result of its short half-life, vasopressin must be given as an infusion. Combination with nitrates reduces these complications and improves the therapeutic effect [17].

Glypressin is an analogue of vasopressin with fewer side effects and longer half-life, allowing bolus administration. Terlipressin has recently been compared with endoscopic sclerotherapy in the treatment of acute variceal bleeding in the TEST study [18•]. This trial, with a large number of patients admitted with endoscopy-proven acute bleeding from esophageal varices, compared 6 days of terlipressin therapy with endoscopic sclerotherapy. Efficacy was similar for control of bleeding, transfusion requirements, and hospital stay and mortality. Side effects were higher in the endoscopic sclerotherapy group, suggesting that terlipressin may be an appropriate first-line therapy until definitive therapy can be initiated. Terlipressin has also been reported as effective as balloon tamponade when used in combination with nitroglycerin [19], which strengthens support for its use pending definitive treatment while avoiding the potential hazards of more invasive therapies.

#### Somatostatin and its analogues

It is postulated that somatostatin decreases portal blood flow, resulting in a sustained decrease in hepatic venous pressure gradient in acute variceal bleed during an infusion of this drug [20]. However, trial data are conflicting. Meta-analyses have shown better control of bleeding compared with vasopressin [21] but no clear advantage against placebo [22].

Octreotide is an analogue of somatostatin with a longer half-life; it also differs in its affinity for somatostatin receptors [23]. Detailed hemodynamic studies of the effect of octreotide upon portal pressure and ayzygous blood flow as a measure of collateral flow show that, as with somatostatin, there is a marked reduction in portal pressure and a decrease in ayzygous blood flow. However, the effects after bolus doses were transient. A prolonged infusion failed to increase the duration of these hemodynamic changes. Some conflicting data on the use of this therapy may be explained by the short-lived nature of the effect of octreotide on splanchnic and collateral hemodynamics [24]. Despite these conflicting data, a recent meta-analysis of trials of octreotide against other pharmacotherapy or placebo [25••] has demonstrated improved control of bleeding compared with vasopressin and terlipressin or placebo. It also had efficacy similar to immediate endoscopic sclerotherapy, with fewer major complications than terlipressin and vasopressin and a side effect profile comparable with the placebo and no intervention group. In addition, when used with endoscopic therapy, vapreotide, another somatostatin analogue, improves control of bleeding and survival compared with endoscopy alone [26]. Although previous conflicting data led some experts to conclude that there was no place for somatostatin and related analogues in this situation, the role of this drug now seems to be increasing.

#### Losartan

Original studies of captopril, a nonselective angiotensin-converting enzyme inhibitor, showed no effect upon hepatic venous pressure gradient but a considerable decrease in mean arterial pressure [27]. However, data with losartan, a selective angiotensin II receptor antagonist [28], showed a marked decrease in hepatic venous pressure gradient without notable arterial hypotension. However, more recent studies have been unable to confirm these results [29••,30•]. Irbesartan was shown to result in moderate decrease in portal pressure after 1 week of treatment, but at the expense of considerable arterial...
hypotension [29••]. Losartan is unlikely to add to the therapeutic armamentarium in the pharmacologic treatment of active variceal hemorrhage.

Endoscopic therapy
Endoscopic techniques rely upon the interruption of blood flow through the collateral system by either immediate occlusion (eg, EBL, tissue glue) or the induction of thrombosis (eg, endoscopic sclerotherapy).

Endoscopic sclerotherapy
Endoscopic sclerotherapy was the first endoscopic therapy described for this indication. It involves the intravariceal or paravariceal injection of sclerosant, resulting in obliteration of the varices through irritation and thrombosis. Assessment of the efficacy and safety of endoscopic sclerotherapy is marred by the variability of the technique (eg, choice of sclerosant, follow-up schedule, use of intravariceal or paravariceal injection, and competence of the operator).

Endoscopic band ligation
Meta-analysis shows that EBL is superior to endoscopic sclerotherapy in initial hemostasis, variceal obliteration, recurrent bleeding, mortality, and complications [31]. However, the use of the band ligation equipment can result in a decreased field of view of an already bloody field, making the procedure technically challenging.

Cyanoacrylate injection
Gastric varices are located deeper in the submucosa, and standard techniques are not successful at achieving hemostasis. Cyanoacrylate tissue glue has been used to control gastric variceal bleeding [32]. This method had now been compared in a randomized controlled trial with EBL for treatment of acutely bleeding gastric varices and their subsequent ablation [33•]. The researchers demonstrated superior initial hemostasis and rebleeding rates in patients treated with cyanoacrylate, and decreased transfusion requirements and mortality in the same group. Complications in the form of treatment-induced ulceration were also lower in the cyanoacrylate group. Therefore, cyanoacrylate injection remains the treatment of choice for bleeding gastric varices.

A recent report in small numbers of patients with decompensated liver disease and severe esophageal variceal hemorrhage suggests that tissue glue injection rather than sclerosant may result in improved initial hemostasis, reduced rebleeding and survival [34]. However, this method requires further study and comparison with EBL and other therapies before it is universally adopted.

Balloon tamponade
The placement of a Sengstaken Blakemore tube (Mallinckrodt Medical, Athlone, Ireland) or similar tamponade device is effective at controlling bleeding in as many as 90% of patients, but 50% will rebleed when the balloon is deflated. In most cases, effective tamponade is achieved by inflation of the gastric balloon only. However, this modality of treatment is associated with serious complications, including esophageal ulceration and even perforation and pulmonary aspiration. It remains a life-saving therapy in the face of massive, uncontrolled variceal hemorrhage.

Transjugular intrahepatic portosystemic shunt
As many as 15% of patients with variceal bleeding, especially those with bleeding gastric varices, will prove refractory to the therapies discussed here. In such cases, creating of an artificial shunt between systemic and portal circulation allows diversion of blood from the collateral circulation to the systemic circulation. These shunts can be placed either intrahepatically, using radiologically-guided access (transjugular intrahepatic portosystemic shunt [TIPS]), or surgically. Recent publications comment on the use of both of these modalities of decompressing the portal system as emergency salvage therapy in patients who do not respond to other treatments.

Two recent descriptive studies comment on the use of TIPS as a salvage procedure in patients with decompensated cirrhosis in which hemorrhage was not controlled by pharmacotherapy and endoscopic therapy [35••,36]. Both studies describe control of bleeding in more than 90% of patients with severe liver disease and actuarial survival of 51% and 71%, respectively. Both groups recommend TIPS as a rescue therapy in these patients with cirrhosis and refractory variceal bleeding. Survival rates are higher in those with severe liver disease—mortality as high as 60% at 40 days has been reported in a similar patient population [35••]—than in previously published studies.

Surgery
Despite reduction in surgical shunts as a rescue therapy for variceal hemorrhage in recent years, two studies now suggest that a role may still exist for such procedures. A retrospective analysis of patients treated with TIPS or surgical shunt reports that, in refractory bleeding in well compensated patients, surgical shunts can result in excellent survival (86%) and a reduction in rebleeding [37]. This study was not randomized, and direct comparisons between treatments were not possible, but the results do point to the acceptability of surgical shunts in patients with preserved synthetic function. A randomized, controlled trial of the two modalities is expected and will answer questions about efficacy and cost of these modalities in patients with preserved liver function.

In addition to surgical shunting, esophageal transection with or without esophageal devascularization may control bleeding, but mortality remains above 80% [38]. Liver transplantation remains a rare method of treating variceal bleeding, and there are no trials. However, when an or-
gan becomes available and the patient is stable, transplantation offers the chance to normalize portal pressure rapidly and to control bleeding.

**Treatment after control of active bleeding**

Patients who survive their index variceal bleed have a risk of rebleeding as high as 80% at 2 years [39]. Because risk of bleeding is related to the severity of underlying liver disease, improvement in liver function may result in a decrease in risk of rebleeding. Such conditions should be sought and treated when possible (eg, alcohol abstinence, steroid therapy in autoimmune liver disease). In addition, in those without contraindications, referral for assessment for liver transplantation may be appropriate, depending on the patient. Secondary prevention reduces the risk of rebleeding. Several secondary prevention strategies have been evaluated.

**Medical therapy**

Through reduction in portal blood flow, β-blockers prevent recurrent variceal hemorrhage [40]. Meta-analyses have confirmed their benefit, and they are widely endorsed for this use [41]. The addition of nitrate therapy to β-blockers used as prevention of variceal hemorrhage may improve efficacy in prevention of recurrent variceal bleeding, especially in those younger than 50 years, but it did not affect survival over a 2-year follow-up period [42].

Six weeks after a variceal bleed treated successfully with endoscopy, losartan, in contrast to propranolol, failed to reduce portal pressure and substantially decreased arterial blood pressure [30•]. The investigators concluded that losartan is not an alternative to propranolol in prevention of variceal bleeding.

**Endoscopy**

Recently, EBL has been directly compared with the combination of β-blockade, propranolol, and isosorbide mononitrate. Treatment began 5 days after successful endoscopic treatment of a variceal bleeding episode. At a median follow-up of 21 months, medical therapy was more effective than EBL at preventing recurrent bleeding and was associated with a lower complication rate [43••]. However, the success of EBL in preventing the recurrence of varices and variceal rebleeding is improved by its combination with β-blockade and sucralfate [44]. This combination of treatments results in reduced transfusion requirements, reduced recurrence of varices after initial eradication, and even a trend toward survival.

**Transjugular intrahepatic portosystemic shunt or surgical shunt**

Transjugular intrahepatic portosystemic shunt has been compared with both EBL and endoscopic sclerotherapy in recently published studies for prevention of variceal rebleeding after the control of index bleed. Compared with EBL in a randomized trial involving patients with poor synthetic function (Child-Pugh score 7–12) (Table 1), TIPS resulted in a decrease in variceal rebleeding but not in mortality at 2 years. The rate of encephalopathy was not increased in the patients treated with TIPS, and the number of days in hospital was the same in both groups during the 2-year follow-up period [45••]. In another study of similar size, the rebleeding rate and mortality were not different between those treated with TIPS and those treated with sclerotherapy. However, the number of further hospitalizations was higher in the TIPS group, and there was a 71% incidence of shunt dysfunction over a 3-year follow-up period, suggesting the possibility of higher cost with no outcome benefit [46•].

In 20 patients with compensated cirrhosis, comparison between TIPS and surgical shunt placed 48 hours after last bleeding episode demonstrated that TIPS resulted in higher rebleeding rate and transfusion requirements, repeat hospitalization, shunt revision, and cost [47•]. Surgical shunts may be more durable and cost-effective in those with well compensated cirrhosis. For this reason, they may be preferred over TIPS in well compensated patients.

**Conclusions**

Variceal hemorrhage remains a devastating complication of portal hypertension, often associated with a poor outcome. Therapies are rapidly evolving. Primary and secondary prophylaxes are important in preventing the problem in those at risk. However, in the acute setting, prompt resuscitation and multiorgan intensive care set the scene for the use a wide range of pharmacologic, endoscopic, and surgical therapies with which the intensive care physician should be familiar.

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•• Of outstanding interest


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therapy alone with 72 patients after variceal hemorrhage in each group. The trial
reports reduced rebleeding in the medically treated patients, with fewer complica-
tions but no difference in mortality over a period of 21 months.

combined treatment with nadolol and isosorbide mononitrate to prevent re-
A well conducted, randomized trial of endoscopic ligation alone versus medical
therapy alone with 72 patients after variceal hemorrhage in each group. The trial
reports reduced rebleeding in the medically treated patients, with fewer complica-
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hepatic portosystemic shunt (TIPS) versus endoscopic variceal ligation in the
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A randomized study of TIPS versus band ligation in the secondary prophylaxis of
variceal bleeding, demonstrating reduced bleeding with TIPS but no increase in
encephalopathy despite advanced disease. Survival was the same and days in the hospital were similar during the follow-up period in two groups.


A randomized trial comparing TIPS with sclerotherapy in secondary prophylaxis after variceal bleed demonstrates similar rebleeding and mortality but increased rehospitalization in TIPS group as a result of shunt dysfunction. This finding casts doubt on the role of TIPS in secondary prophylaxis.


A retrospective, case-control study in patients with compensated cirrhosis, demonstrating better effectiveness and durability for surgical shunt than TIPS in this patient group, emphasizing the potential role for this often overlooked treatment option.