CURRENT CONCEPTS

Management of Varices and Variceal Hemorrhage in Cirrhosis

Guadalupe Garcia-Tsao, M.D., and Jaime Bosch, M.D.

Variceal hemorrhage is a lethal complication of cirrhosis, particularly in patients in whom clinical decompensation (i.e., ascites, encephalopathy, a previous episode of hemorrhage, or jaundice) has already developed. Practice guidelines for the management of varices and variceal hemorrhage in cirrhosis are mostly based on evidence in the literature that has been summarized and prioritized at consensus conferences. There are three main areas of management: primary prophylaxis to prevent a first episode of variceal hemorrhage, treatment of the acute bleeding episode, and secondary prophylaxis (prevention of recurrent variceal hemorrhage).

Natural History and Epidemiology

Gastroesophageal varices are present in almost half of patients with cirrhosis at the time of diagnosis, with the highest rate among patients with Child–Turcotte–Pugh (hereinafter called Child) class B or C disease (Table 1). Development and growth of gastroesophageal varices each occur at a rate of 7% per year. The 1-year rate of a first variceal hemorrhage is approximately 12% (5% for small varices and 15% for large varices). Besides variceal size, red wale marks on varices and advanced liver disease (Child class B or C) identify patients at a high risk for variceal hemorrhage. The 1-year rate of recurrent variceal hemorrhage is approximately 60%. The 6-week mortality with each episode of variceal hemorrhage is approximately 15 to 20%, ranging from 0% among patients with Child class A disease to approximately 30% among patients with Child class C disease.

Pathophysiology and Pathophysiological Bases of Therapy

Gastroesophageal varices are a direct consequence of portal hypertension that, in cirrhosis, results from both increased resistance to portal flow and increased portal venous blood inflow. Increased resistance is both structural (distortion of liver vascular architecture by fibrosis and regenerative nodules) and dynamic (increased hepatic vascular tone due to endothelial dysfunction and decreased nitric oxide bioavailability). When the portal-pressure gradient (the difference between portal-vein pressure and hepatic-vein pressure) increases above a certain threshold, collaterals develop at sites of communication between the portal and systemic circulations. This process is modulated by angiogenic factors. Concomitantly with the formation of portosystemic collaterals, portal venous blood inflow increases as a result of splanchnic vasodilatation and increased cardiac output. Increased portal flow maintains
and exacerbates portal hypertension. Gastro-esophageal varices are the most important collaterals, because as pressure and flow increase through them, they grow and eventually rupture (Fig. 1).

Available therapies for varices and variceal hemorrhage can be classified according to whether they act on the physiological mechanisms of portal hypertension.

**THERAPIES THAT REDUCE PORTAL PRESSURE**

Splanchnic vasoconstrictors such as vasopressin and somatostatin (and their analogues, octreotide and vapreotide) are administered parenterally and are therefore restricted to use in an acute care setting. Nonselective beta-adrenergic blockers affect portal flow by means of both $\beta_1$-blockade (reduction of cardiac output) and $\beta_2$-blockade (splanchnic vasoconstriction). Therefore, nonselective beta-blockers such as propranolol or nadolol are better than selective beta-blockers because of broader mechanisms of action. They are administered orally and are used in the long-term treatment of portal hypertension.

Drugs that increase the delivery of nitric oxide to the intrahepatic circulation, such as nitrates and simvastatin, and drugs that block adrenergic activity (e.g., prazosin and clonidine) or that block angiotensin (e.g., captopril, losartan, and irbesartan) act by inducing intrahepatic vasodilatation. Therefore, nonselective beta-blockers such as propranolol or nadolol are better than selective beta-blockers because of broader mechanisms of action. They are administered orally and are used in the long-term treatment of portal hypertension.

**LOCAL THERAPIES WITHOUT PORTAL PRESSURE—REDUCING EFFECTS**

Endoscopic procedures can be used to place elastic bands on variceal columns (variceal ligation) or to inject sclerosing agents (variceal sclerotherapy) or tissue adhesives (variceal obturation) into gastroesophageal varices. These techniques can achieve variceal obliteration (sometimes called “eradication”). However, gastroesophageal varices will eventually recur; therefore, close endoscopic surveillance and retreatment are necessary. Other shorter-term temporizing local measures include balloon tamponade and placement of expandable esophageal stents.
Risk Stratification for Patients with Portal Hypertension

One of the main issues confounding screening of and therapeutic studies involving patients with cirrhosis is a lack of proper risk stratification. At a minimum, patients should be stratified according to whether they have compensated or decompensated cirrhosis.25

In patients with compensated cirrhosis (i.e., those who do not have ascites, variceal hemorrhage, encephalopathy, or jaundice), risk stratification starts with an assessment for the presence of gastroesophageal varices. Patients with gastroesophageal varices have a higher rate of death and a greater risk of decompensation than those without gastroesophageal varices.26 The recommended method to determine the presence and size of gastroesophageal varices is esophagogastroduodenoscopy.1,2,27 Less invasive methods such as capsule endoscopy are being investigated and may be preferred by patients; however, their accuracy in evaluating the presence of varices, red wale marks, and variceal size is still suboptimal.27 Similarly, a ratio of platelet count (per cubic millimeter) to spleen size (the maximum bipolar di-
ameter in millimeters by ultrasonography) above 909 has a high negative predictive value (i.e., the patient is unlikely to have varices).28 However, this ratio requires further validation.29

In patients without varices and in those with variceal hemorrhage, measurement of portal pressure with the use of the hepatic venous pressure gradient (HVPG) is the best method to stratify risk. Portal hypertension is present when the HVPG is greater than 10 mm Hg, because in patients without varices, this pressure is the strongest predictor of the development of varices,5 clinical decompensation,30 and hepatocellular carcinoma.31 In patients with variceal hemorrhage, an HVPG of more than 20 mm Hg (measured within 24 hours after admission) is the best predictor of a poor outcome.32 In contrast, a reduction in the HVPG to less than 12 mm Hg or a reduction of more than 20% from the baseline value is associated with a decreased risk of variceal hemorrhage and improved survival.33,34

The HVPG is obtained by means of catheterization of a hepatic vein with a balloon catheter through a jugular or femoral vein. Although the procedure to obtain the HVPG is simple and safe (see the video, available with the full text of this article at NEJM.org), it is invasive and its use is not widespread in the United States. Standardization of the technique through the creation of multi-society guidelines, certification, and quality control is needed to help bring the HVPG into wider clinical use.3

Measurement of liver stiffness, a technique not yet widely available in the United States, is a non-invasive method that correlates reasonably well with the HVPG, particularly at HVPG values below 10 mm Hg.35 Therefore, it appears to be useful in identifying the presence of clinically significant portal hypertension. Notably, the presence of varices (or collaterals on imaging studies) indicates that clinically significant portal hypertension is present.

The Child class or its laboratory components (the levels of bilirubin and albumin and the international normalized ratio) correlate roughly with clinically significant portal hypertension26 and can be used to stratify risk in both compensated and decompensated cirrhosis.26 In patients with variceal hemorrhage, Child class C has been associated with an HVPG of more than 20 mm Hg and a poor outcome.41 The Model for End-Stage Liver Disease score, which is used for organ allocation in liver transplantation, has been shown to predict the development of decompensation in patients without varices39 and to predict 6-week mortality after variceal hemorrhage.37

### Prevention of Varices and a First Variceal Hemorrhage

Patients without gastroesophageal varices or with gastroesophageal varices that have never bled are at relatively low risk for bleeding and death, and therefore, therapies for these patients should be the least invasive. In patients without varices, treatment with nonselective beta-blockers is not recommended because they do not prevent the development of varices and are associated with side effects.5

In patients with low-risk, small varices (without red wale marks and in the absence of severe liver disease), nonselective beta-blockers may delay variceal growth and thereby prevent variceal hemorrhage.38 These agents are considered optional, given the limited existing evidence, the low-risk setting, and the alternative of periodic screening for variceal growth.

In patients with small varices that are associated with a high risk of hemorrhage (varices with red wale marks or varices in a patient with Child class B or C disease), nonselective beta-blockers are recommended.

In patients with medium or large varices, either nonselective beta-blockers or endoscopic variceal ligation can be used, since a meta-analysis of high-quality, randomized, controlled trials has shown equivalent efficacy and no differences in survival.39 The advantages of nonselective beta-blockers are that their cost is low, expertise is not required for their use, and they may prevent other complications, such as bleeding from portal hypertensive gastropathy, ascites, and spontaneous bacterial peritonitis because they reduce portal pressure.33,40,41 The disadvantages of these agents include relatively common contraindications and side effects (fatigue and shortness of breath) that preclude treatment or require discontinuation in 15 to 20% of patients. The advantages of endoscopic variceal ligation are that it can be performed at the time of screening endoscopy and that its side effects are less frequent. However, specific expertise is necessary, and there is potential for lethal hemorrhage from postprocedure ulcers.17 Some centers perform endoscopic variceal liga-

A video showing HVPG measurement is available at NEJM.org
tion in most patients, whereas other centers prefer to use nonselective beta-blockers initially, switching to endoscopic variceal ligation in patients with intolerance or contraindications to nonselective beta-blockers; the latter is a rational approach. The schedule, doses, goals, and follow-up of therapies for primary prophylaxis are shown in Table 2 (see Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Carvedilol at low doses (6.25 to 12.5 mg per day) was compared with endoscopic variceal ligation in a recent randomized, controlled trial. Carvedilol was associated with lower rates of first variceal hemorrhage (10% vs. 23%) and had an acceptable side-effect profile, unlike endoscopic variceal ligation, for which compliance was low and the rate of first hemorrhage was at the upper end of the range of rates in previous studies. Whether carvedilol is more effective or better tolerated than nonselective beta-blockers remains to be determined.

### Table 2. Primary Prophylaxis against Variceal Hemorrhage.*

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<td>Starting dose of 20 mg given orally twice a day</td>
<td>Increase to maximally tolerated dose or until heart rate is approximately 55 beats/min</td>
<td>Indefinite</td>
<td>Ensure heart-rate goals met at each clinic visit; no need for follow-up endoscopy</td>
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<td>Nadolol</td>
<td>Starting dose of 40 mg given orally once a day</td>
<td>Increase to maximally tolerated dose or until heart rate is approximately 55 beats/min</td>
<td>Indefinite</td>
<td>Ensure heart-rate goals met at each clinic visit; no need for follow-up endoscopy</td>
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<tr>
<td>Endoscopic variceal ligation</td>
<td>Every 2–4 weeks</td>
<td>Obliterate varices</td>
<td>Until variceal obliteration achieved (usually 2–4 sessions)</td>
<td>Perform first surveillance endoscopy 1–3 mo after obliteration, then every 6–12 mo indefinitely</td>
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* Therapies that should not be used as prophylaxis include nitrate alone, endoscopic variceal sclerotherapy, shunt therapy (either transjugular intrahepatic portosystemic shunt or surgical shunt), nonselective beta-blockers plus endoscopic variceal ligation, and nonselective beta-blockers plus nitrates.
† Only one of the three regimens should be used.

The rate of death from acute variceal hemorrhage has been decreasing over the past two decades, probably as a result of improved general management (with prophylactic antibiotics) and more effective therapies (endoscopic variceal ligation and vasoactive drugs). Although therapy is not currently targeted at specific risk groups, recent data suggest that in patients at high risk (Child class C or an HVPG of >20 mm Hg), the approach should be more aggressive.

Patients who have Child class A or B disease or who have an HVPG of less than 20 mm Hg have a low or intermediate risk and should receive standard therapy — specifically, the combination of a safe vasoconstrictor (terlipressin, somatostatin, or analogues such as octreotide or vapreotide, administered from the time of admission and maintained for 2 to 5 days) and endoscopic therapy (preferably endoscopic variceal ligation, performed at diagnostic endoscopy <12 hours after admission), together with short-term prophylactic antibiotics (either norfloxacin or ceftriaxone). The only vasoconstrictor currently available in the United States is octreotide. In other countries, the choice of vasoconstrictor depends on availability and cost. Antibiotic prophylaxis with ceftriaxone is recommended in patients with severe liver disease, particularly if they are receiving quinolone prophylaxis, whereas others can receive oral norfloxacin or intravenous ciprofloxacin (Table 3).

Placement of a transjugular intrahepatic portosystemic shunt is currently considered a salvage therapy for the 10 to 20% of patients in whom standard medical therapy fails (Fig. 2 in the Supplementary Appendix). However, two randomized, controlled trials have shown that early placement of such a shunt (within 24 to 48 hours after admission) was associated with significant improvement in survival among high-risk patients (i.e., patients with an HVPG >20 mm Hg or with Child class C disease with a score between 10 and 13 points [Table 1]). Therefore, early place-
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<td>Vasoconstrictor</td>
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<tr>
<td>Octreotide</td>
<td>Intravenous 50-μg bolus, followed by infusion of 50 μg/hr</td>
<td>2–5 days</td>
<td>Bolus can be repeated in first hr if variceal hemorrhage uncontrolled; if rebleeding occurs during therapy, consider TIPS</td>
<td>Available in the United States</td>
</tr>
<tr>
<td>Terlipressin</td>
<td>2 mg given intravenously every 4 hr for first 48 hr, followed by 1 mg given intravenously every 4 hr</td>
<td>2–5 days</td>
<td>If rebleeding occurs during therapy, consider TIPS</td>
<td>Not available in the United States</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Intravenous 250-μg bolus, followed by infusion of 250–500 μg/hr</td>
<td>2–5 days</td>
<td>Bolus can be repeated in first hr if variceal hemorrhage uncontrolled; if rebleeding occurs during therapy, consider TIPS</td>
<td>Not available in the United States</td>
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<tr>
<td>Vapreotide†</td>
<td>Intravenous 50-μg bolus, followed by infusion of 50 μg/hr</td>
<td>2–5 days</td>
<td>If rebleeding occurs during therapy, consider TIPS</td>
<td>Not available in the United States</td>
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<tr>
<td>Antibiotic</td>
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<tr>
<td>Ceftriaxone</td>
<td>Intravenous ceftriaxone at a dose of 1 g once a day</td>
<td>5–7 days or until discharge</td>
<td>No long-term antibiotics unless spontaneous bacterial peritonitis develops</td>
<td>Used in patients with advanced liver disease, high probability of quinolone resistance, or both</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>400 mg given orally twice a day</td>
<td>5–7 days or until discharge</td>
<td>No long-term antibiotics unless spontaneous bacterial peritonitis develops</td>
<td>Used in patients with low probability of quinolone-resistant organisms</td>
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<tr>
<td>Endoscopic therapy</td>
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<tr>
<td>Endoscopic variceal ligation</td>
<td>Once, at time of diagnostic esophagogastroduodenoscopy</td>
<td>Until variceal obliteration achieved</td>
<td>If rebleeding occurs during therapy, consider TIPS</td>
<td>Requires endoscopist with special expertise</td>
</tr>
<tr>
<td>Endoscopic variceal sclerotherapy</td>
<td>Once, at time of diagnostic esophagogastroduodenoscopy</td>
<td>Only at diagnostic endoscopy</td>
<td>Continue with endoscopic variceal ligation until obliteration achieved</td>
<td>Used when endoscopic variceal ligation not possible; requires endoscopist with special expertise</td>
</tr>
</tbody>
</table>

* Only one vasoconstrictor plus one antibiotic plus endoscopic therapy should be used. Therapies that should not be used for first-line management of acute esophageal variceal hemorrhage are endoscopic variceal obliteration (which is indicated in fundal gastric hemorrhage but not in esophageal variceal hemorrhage) and recombinant factor VIIa. NA denotes not applicable, and TIPS transjugular intrahepatic portosystemic shunt.

† Recommendations for vapreotide are based on findings from a single study.47
ment of a transjugular intrahepatic portosystemic shunt could be considered in these patients and, although this deserves further investigation, the decision to use this approach as salvage therapy in this high-risk population should be made sooner rather than later. In these patients, the use of recombinant factor VII has been found to be of little value.12

Gastric varices are present in 20% of patients with cirrhosis, either in isolation or in combination with esophageal varices. Bleeding from fundal varices is more severe and is associated with a higher rate of death than bleeding from gastroesophageal varices.50

Endoscopic variceal obturation with the use of tissue adhesives such as N-butyl-2-cyanoacrylate is more effective than endoscopic variceal ligation in controlling initial hemorrhage and preventing rebleeding from gastric varices.51,52 A transjugular intrahepatic portosystemic shunt is also effective in patients with bleeding fundal varices. In a recent randomized, controlled trial in which endoscopic variceal obturation was used to control acute hemorrhage in all patients (with a 93% success rate), a transjugular intrahepatic portosystemic shunt was more effective than endoscopic variceal obturation in preventing recurrent hemorrhage.53

Even though fundal varices were the source of bleeding in less than half the patients included in these studies and vasoactive drugs have not been investigated, data suggest that endoscopic variceal obturation is the best endoscopic technique to control acute hemorrhage and the transjugular intrahepatic portosystemic shunt is more effective than variceal obturation in preventing recurrent hemorrhage. Among tissue adhesives, N-butyl-2-cyanoacrylate is not available in the United States, and although the off-label use of another adhesive, 2-octyl cyanoacrylate, has been reported,54 endoscopic variceal obturation requires careful attention to technique and is not free of serious complications. If an endoscopist with the requisite expertise is unavailable, placement of a transjugular intrahepatic portosystemic shunt should be considered first-line therapy when bleeding is not controlled by vasoactive drugs.

Currently, treatment recommendations apply to all patients with variceal hemorrhage. Patients with Child class A disease have a good response to current therapies, with a minimal risk of death (0 to 5%). Whether pharmacologic therapy alone would suffice in these patients deserves further examination. Strategies are being investigated that may improve survival in patients with Child class C disease, but new strategies should be investigated for those at intermediate risk (Child class B).

**Prevention of Recurrent Variceal Hemorrhage**

Given the high recurrence rate, patients who survive an acute variceal hemorrhage should receive therapy to prevent recurrence before they are discharged from the hospital. Combination pharmacologic therapy (nonselective beta-blockers plus nitrates) or combination endoscopic variceal ligation plus drug therapy are warranted because of the high risk of recurrence, even though the side effects will be greater than those with single-agent therapy (recommended for primary prophylaxis).

These two strategies were compared in a randomized, controlled trial that showed a significantly lower rate of variceal rebleeding with a combination of endoscopic variceal ligation and drug therapy (nonselective beta-blockers plus nitrates) than with drug therapy alone. However, the rate of hemorrhage from all sources was not significantly different because of bleeding from esophageal ulcers induced by endoscopic variceal ligation.55

A meta-analysis showed that rates of rebleeding (from all sources and from varices) are lower with a combination of endoscopic therapy plus drug therapy than with either therapy alone, but without differences in survival.56 Therefore, current guidelines recommend the combined use of endoscopic variceal ligation and nonselective beta-blockers for the prevention of recurrent variceal hemorrhage, even in patients who have had a recurrent hemorrhage despite treatment with nonselective beta-blockers or endoscopic variceal ligation for primary prophylaxis. In patients who are not candidates for endoscopic variceal ligation, the strategy would be to maximize portal-pressure reduction by combining nonselective beta-blockers plus nitrates.

Patients who have rebleeding despite combined treatment with endoscopic variceal ligation and drugs at the recommended doses and schedule (Table 4) should undergo percutaneous placement of a transjugular intrahepatic portosystemic shunt...
or surgical creation of a shunt; the two shunts are equally effective (Fig. 3 in the Supplementary Appendix).

The need for frequent revision of a transjugular intrahepatic portosystemic shunt, reported in a randomized, controlled trial, appears to have been overcome with the current use of coated stents, which have a significantly lower occlusion rate.

The choice between a transjugular intrahepatic portosystemic shunt and surgery will therefore depend on local expertise and the patient's preference.

The rate of recurrent variceal hemorrhage is lowest (approximately 10%) among patients in whom the HVPG decreases to less than 12 mm Hg or is reduced by more than 20% from the baseline value. 35 Perhaps the most rational approach to the prevention of recurrent hemorrhage would be to choose therapies on the basis of the HVPG response; however, the issue will remain unresolved until randomized, controlled trials show that HVPG-guided therapy is superior to the current empirical treatment.

Other than the HVPG response, therapeutic approaches in patients who have recovered from variceal hemorrhage are not targeted at specific risk groups. Given that the severity of liver disease has been consistently shown to be a good predictor of recurrent hemorrhage and death, the Child classification could also be a good way to stratify patients according to risk. Although the prevalence of portal hypertensive gastropathy is higher among patients with Child class A disease than among patients with Child class B or C disease, or on the transplantation list. It is recommended for patients who are not candidates for ligation.

Table 4. First-Line Prevention of Recurrent Variceal Hemorrhage.*

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<td>Start at 20 mg orally twice a day</td>
<td>Increase to maximally tolerated dose or until heart rate is approximately 55 beats/min</td>
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<td>Nadolol</td>
<td>Start at 40 mg orally once a day</td>
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<td>Isosorbide mononitrate in association with a beta-blocker (either propranolol or nadolol)†</td>
<td>10 mg given orally every night, with stepwise increase to a maximum of 20 mg twice a day</td>
<td>Increase to maximally tolerated dose with maintenance of blood pressure at &gt;95 mm Hg</td>
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55,56 It appears to have been overcome with the current use of coated stents, which have a significantly lower occlusion rate. The choice between a transjugular intrahepatic portosystemic shunt and surgery will therefore depend on local expertise and the patient's preference.

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<td>First surveillance endoscopy 1–3 mo after obliteration, then every 6–12 mo indefinitely</td>
</tr>
<tr>
<td>Isosorbide mononitrate in association with a beta-blocker (either propranolol or nadolol)†</td>
<td>10 mg given orally every night, with stepwise increase to a maximum of 20 mg twice a day</td>
<td>Increase to maximally tolerated dose with maintenance of blood pressure at &gt;95 mm Hg</td>
<td>Indefinite</td>
<td>Ensure compliance with medication regimen at each visit; no need for follow-up endoscopy</td>
</tr>
</tbody>
</table>

* Only one beta-blocker plus ligation should be used. Therapies that should not be used for first-line prevention of recurrent variceal hemorrhage are nonselective beta-blockers alone, endoscopic variceal sclerotherapy, endoscopic variceal ligation alone, and endoscopic variceal ligation plus endoscopic variceal sclerotherapy.† This therapy is being studied. It is recommended for patients who are not candidates for ligation.

55,56
among those who have not,60,61 the clinical course is the same. The most common presentation, occurring mainly in patients with severe portal hypertension, is chronic, slow hemorrhage resulting in anemia. The initial management consists of iron supplementation and use of nonselective beta-blockers; this therapy has been shown in a randomized, controlled trial to be effective in preventing recurrent hemorrhage.40 If hemorrhage continues and the patient requires frequent transfusions, shunt therapy (either a transjugular intrahepatic portosystemic shunt or shunt surgery) should be considered.

ASSOCIATED PORTAL-VEIN THROMBOSIS

The development of portal-vein thrombosis is an important event in the natural history of advanced cirrhosis.62 It is associated with worsening liver function, ascites, and variceal hemorrhage. The incidence of portal-vein thrombosis is approximately 16% per year in patients with advanced liver disease. Treatment for portal-vein thrombosis in these patients (e.g., with anticoagulation, thrombolysis, or placement of a transjugular intrahepatic portosystemic shunt) is currently determined on a case-by-case basis.63

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