Management of variceal bleeding in the 1990s

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■ **BACKGROUND** Variceal bleeding is a common and serious problem.

■ **OBJECTIVE** To review the current management of patients with variceal bleeding.

■ **SUMMARY** Therapeutic options now include pharmacologic reduction of portal hypertension, endoscopic obliteration of varices, placement of decompressive shunts (both surgical and percutaneous), and liver transplantation. Each of these options may be required in different settings. A nonselective beta blocker can prophylactically reduce the risk of an initial bleed. Acute variceal bleeding is best managed by endoscopic sclerosis. Selection of therapy to prevent recurrent bleeding should be based on a full evaluation of the risk of bleeding and of liver failure.

■ **CONCLUSIONS** Successful management requires a multidisciplinary team, full patient evaluation, and selection of appropriate therapy.

■ INDEX TERMS: ESOPHAGEAL AND GASTRIC VARICES; GASTROINTESTINAL HEMORRHAGE ■ CLEVE CLIN J MED 1993; 60:431–438

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VARICEAL BLEEDING is a common and serious problem: cirrhosis is the seventh leading cause of death in the United States, and variceal bleeding is one of the major causes of death in these patients.[1] The management of patients with variceal bleeding requires a multidisciplinary approach by a team that has all treatment options available. Patients develop portal hypertension and bleeding varices for many different reasons. Therefore, when varices are detected, a thorough evaluation is mandatory to define the etiology of the portal hypertension, and, when cirrhosis is the cause, to define the activity and severity of the disease and the prognosis. Selection of definitive therapy to prevent recurrent bleeding should be based on this evaluation.

Several new therapies for portal hypertension have been developed in the last decade. The repertoire of treatment options now includes drugs that reduce portal pressure,[2] endoscopic methods of variceal obliteration,[3] surgical[4,5] and percutaneous decompressive shunts placed under radiologic guidance,[6]

devascularization methods,[7] and liver transplantation.[8] Advances have occurred with all of these therapies, and there is a role for each in the management of different patients or at different times in the course of an individual patient's disease.

We shall review the current status of treatments for variceal bleeding, and present methods of evaluation and management.

RISKS OF VARICEAL BLEEDING

The prevalence of varices in patients with cirrhosis is about 60%, and 10% to 15% of patients with cirrhosis without varices will develop them each year. Approximately 30% of patients with varices that have never bled will eventually bleed from their varices. The mortality rate in acute variceal bleeding is 25% to 30%. In patients who have had variceal bleeding, approximately 70% will bleed again from their varices, one half of these in the first 6 weeks. These data from control limbs of prospective randomized trials[9,10] are an important basis for making management decisions.

MANAGEMENT METHODS

Pharmacotherapy

Portal hypertension can be treated by drugs administered either intravenously or orally.[11] As a general rule, pharmacotherapy can reduce the risk of bleeding by half.

Vasopressin constricts splanchnic inflow and thereby reduces portal pressure. Its short half-life of 10 to 20 minutes necessitates intravenous infusion, usually with an initial 20 units given over 20 minutes followed by 0.4 units per minute. Studies show that this regimen reduces acute variceal bleeding, but there is a high relapse rate when it is stopped.[11] The principal side effect is systemic vasoconstriction, and the cardiac effects of myocardial ischemia and bradycardia may limit its use.

Current standards of care call for concomitant infusion of nitroglycerin at 40 μg/min, titrated to maintain systolic blood pressure from 90 to 100 mm Hg. Nitroglycerin reduces the side effects of vasopressin and further reduces portal pressure. In controlled studies there has been a marginal benefit in control of bleeding with this combination compared with vasopressin alone. However, this has not been accompanied by an advantage in survival.[12,13]

Somatostatin has multiple effects, including inhibition of gastrointestinal hormones and reduction of splanchnic flow. It has been used for acute variceal bleeding, where its efficacy is similar to vasopressin's.[14] Its short half-life, measured in minutes, requires infusion, recommended at 250 μg/hour. Hemodynamic data are conflicting: some studies show no reduction in directly measured intravariceal pressure, while others show significant reduction in collateral (azygos) flow.[15] In a controlled study, somatostatin had significantly fewer side effects than vasopressin.[16] As with vasopressin, survival is not significantly improved in patients managed with somatostatin.

The nonselective beta-adrenergic blockers propranolol and nadolol, given orally as long-term therapy, reduce portal hypertension. This effect is mediated through both a reduction in cardiac output and a direct splanchnic effect. The dose is adjusted to reduce the resting pulse by 20% or to 55 to 60 beats per minute. Reducing the hepatic venous pressure gradient to 12 mm Hg or less can prevent variceal bleeding.

Controlled trials have documented a prophylactic role for propranolol in reducing the incidence of initial variceal bleeding.[17] Randomized studies have also shown that the incidence of recurrent bleeding can be reduced from 70% to about 30% over the first year.[18] The principal side effect of beta blocker therapy is lethargy, which contributes to a noncompliance rate of about 20%.

The nitrates, serotonin antagonists, alpha-2 agonists, and calcium-channel blockers have also been shown in clinical trials to reduce the hepatic venous pressure gradient.[2] Side effects and marginal clinical responses have limited use of these agents. However, the pharmacotherapy of portal hypertension can be likened to the management of systemic arterial hypertension 30 years ago: it is only in its infancy, and further advances will be made.

Variceal obliteration

Endoscopic variceal sclerotherapy controls bleeding by creating either thrombosis (when sclerosants are injected directly into varices), or fibrosis (when sclerosants are injected around the varices).[2] An alternative is to place tight bands around the bases of the varices; thrombosis will occur and the varices will slough off.[19] In the past, rigid esophagoscopes were used, but virtually all sclerotherapy is now done with flexible endoscopes. A wide variety of sclerosing agents such as sodium morrhuate, sodium

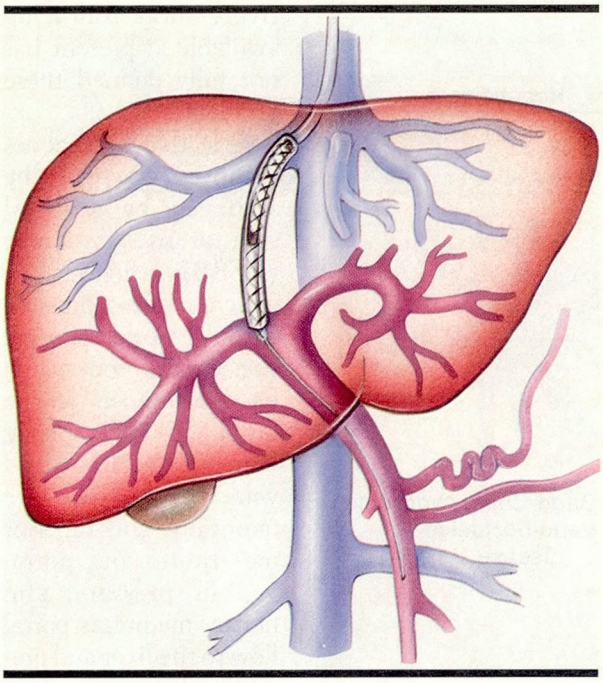

FIGURE 1. Transjugular intrahepatic portosystemic shunt (TIPS). A tract is made across liver parenchyma from a main hepatic vein to the portal vein. The tract is then dilated and stented.

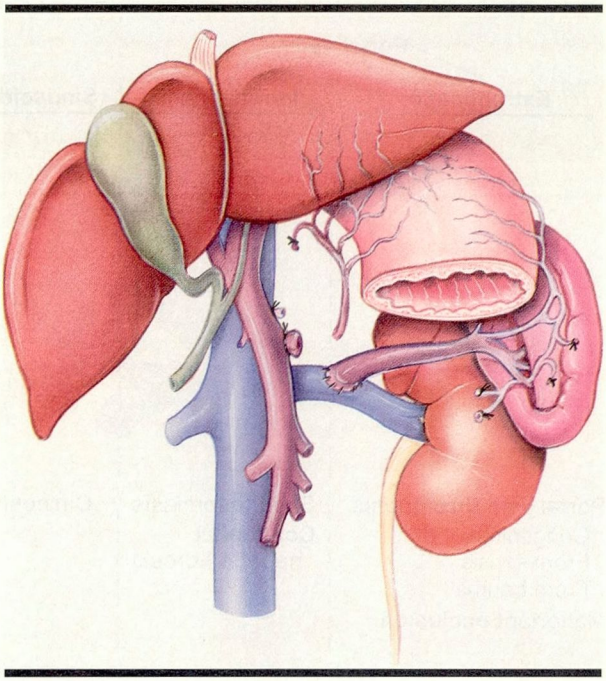

FIGURE 2. Distal splenorenal shunt (DSRS). The distal end of the splenic vein is anastomosed to the left renal vein. This type of shunt maintains portal flow to a cirrhotic liver, thereby preserving liver function.

tetradecyl sulfate, ethanolamine, and alcohol have been used, but no data have clearly indicated one to be superior to the others. Controversy exists over the relative merits of sclerotherapy and banding,[20] but both are "local" therapies that target varices directly, rather than addressing their pathophysiologic cause.

Sclerotherapy can control acute variceal bleeding in 85% to 90% of patients. It should be performed at the time of the initial diagnostic endoscopy, and is probably best accomplished by intravariceal injection.

The role of sclerotherapy in preventing recurrent variceal bleeding is less clear. Undoubtedly, recurrent bleeding can be prevented in some patients if repeated sclerotherapy can achieve obliteration of varices. Current recommendations are sclerotherapy of the varices on a weekly basis for 3 to 4 weeks and then every 3 to 4 weeks, completing the initial course within 2 to 3 months. However, because sclerotherapy does not correct the underlying problem, recurrence is the rule, and 50% to 60% of patients will have recurrent bleeding within 3 to 5 years. Sclerotherapy should be used to stabilize patients who are bleeding while they are undergoing a full evaluation. For some patients in whom varices are adequately obliterated or for whom there is no other good treatment option, sclerotherapy may be the treatment of choice.[21–23]

Decompressive shunts

Reducing the pressure in varices is the best method for preventing bleeding. This can be accomplished with decompressive shunts, which fall into three broad groups based on their hemodynamic effects. Shunts can totally decompress portal pressure and divert all portal flow,[24] partially decompress portal pressure while maintaining some portal flow,[25] or selectively decompress varices while maintaining portal and splanchnic pressure and portal flow to the liver.[5]

In the classic end-to-side portacaval shunt, the portal vein is divided at its bifurcation and anastomosed end-to-side to the inferior vena cava. This relieves splanchnic hypertension, but the sinusoids remain under high pressure with a concomitant risk of ascites. This operation is rarely indicated.

A variety of side-to-side portal systemic shunts anastomose the portal vein or one of its tributaries to

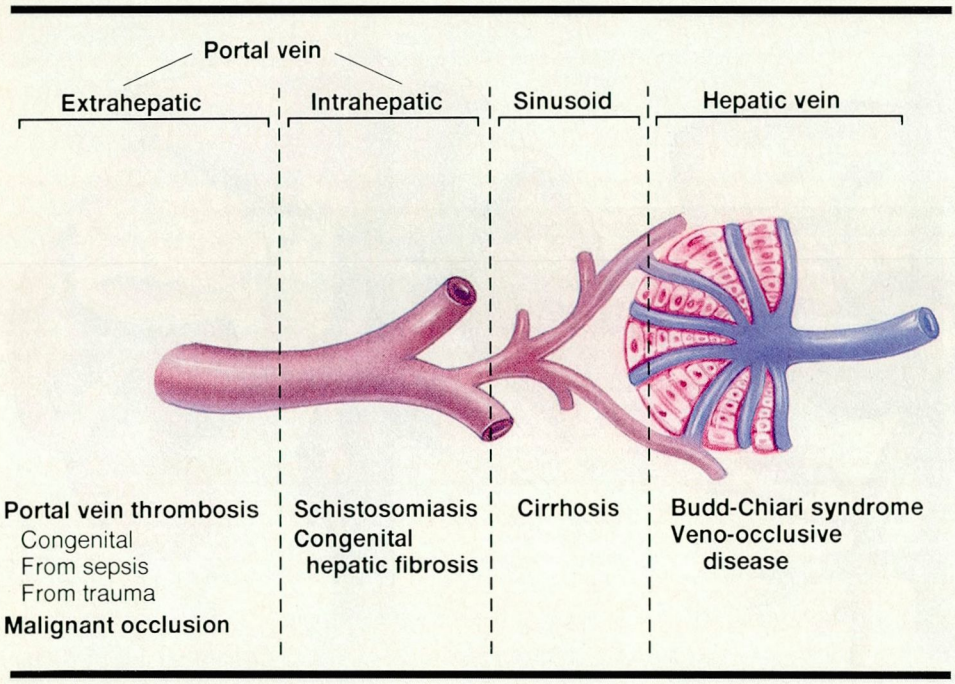

FIGURE 3. Schematic representation of the causes of portal hypertension. Accurate diagnosis is important as this affects prognosis.

the vena cava or one of its tributaries. When these shunts exceed 10 to 12 mm in diameter they are "total" shunts, diverting all portal flow away from the liver. They are hemodynamically different from end-to-side portacaval shunts in that the portal vein acts as an outflow from the obstructed sinusoids; hence, they will alleviate ascites. They control bleeding well, but impart a high risk of liver failure.[26]

Shunts of 8 mm in diameter reduce the portal pressure to approximately 12 mm Hg. These achieve partial shunting: 80% of patients maintain some portal flow to the liver.[25]

The recently introduced transjugular intrahepatic portosystemic shunt (TIPS) is a percutaneous option for achieving side-to-side shunting (*Figure 1*). The ability to place a decompressive shunt without an operation in some patients is a major advance. Under radiologic guidance, a tract is made through the liver from a major hepatic vein to the portal vein. This is dilated, and a metallic stent is placed to keep the tract open. The hemodynamic effect of this shunt is again related to its diameter: total diversion of portal flow occurs when the diameter is greater than 10 mm, whereas an 8-mm shunt achieves partial diversion. Stenosis and occlusion are concerns with these shunts, but the relatively short follow-up available at present has not fully defined these problems.[27–29]

Selective variceal decompression can be achieved by a distal splenorenal shunt (DSRS) (*Figure 2*), which reduces pressure within gastroesophageal varices and the spleen by anastomosis of the distal end of the splenic vein to the left renal vein.[5] This procedure maintains the superior mesenteric and portal venous pressure, and hence, maintains portal flow to the liver and preserves liver function. This selective action is well maintained in patients with nonalcoholic cirrhosis, but approximately 50% of patients with alcoholic disease lose portal flow over time after this procedure.[31] The distal splenorenal shunt has become the most widely used shunt for the control of variceal bleeding[30] because it controls bleeding well and maintains liver function in appropriately selected patients.

Surgical devascularization

Surgical devascularization involves splenectomy, gastric and esophageal devascularization, and esophageal transection. Excellent results have been achieved by Sugiura[32] in Japan, who popularized the procedure, but significant recurrent bleeding has been reported in North American series.[33] More recent data from Mexico have shown good results with extensive devascularization.[34] The major advantage of this operative approach is that it maintains portal flow and liver function.

Liver transplantation

Liver failure is the most common cause of death in patients with cirrhosis and portal hypertension in whom variceal bleeding has been controlled. A question should be asked at the initial evaluation of a patient with variceal bleeding: Will this patient

now, or at some time in the future, need liver transplantation? The answer to this question affects other treatment decisions.

Replacement of a cirrhotic liver not only relieves portal hypertension, but also restores functional liver mass. However, rejection is an ever-present risk, and immunosuppressive therapy carries a significant morbidity. Correct patient selection and optimal timing are key considerations in using this treatment.[35,36] Liver failure, not variceal bleeding, is the indication for transplantation.

PATIENT EVALUATION

Bleeding from esophageal varices is a sentinel event that mandates a full evaluation. This evaluation should define the etiology of the portal hypertension, the bleeding risk, and, in the case of patients with cirrhosis, the etiology, severity, and activity of the liver disease. The causes of portal hypertension are summarized in *Figure 3*. In the United States, the vast majority of patients with portal hypertension have cirrhosis as its cause; hence, the evaluation and management decisions focus on the liver disease. However, it is important to look for other causes; this can be done with angiography and liver biopsy.

Table 1 summarizes the evaluation of patients with cirrhosis. This workup should be completed within 3 to 4 days after stabilization of the acute bleeding. A full discussion of this evaluation is beyond the scope of this review, but the reader is referred to references 36–38. The hepatologist and the surgeon should discuss the objective data to make long-term management decisions.

MANAGEMENT STRATEGIES

Management of gastroesophageal varices can be considered in terms of time frames: prophylactic treatment of varices that have never bled, control of acute variceal bleeding, and prevention of recurrent variceal bleeding.

Prophylactic treatment

At the present time, beta blockade with either propranolol or nadolol is the only treatment that has been shown, in controlled trials, to be indicated before the initial bleeding episode. Beta blockade reduces the risk of an initial bleeding episode, from 30% without treatment to between 15% and 20%

TABLE 1
EVALUATION OF PATIENTS WITH VARICEAL BLEEDING

Observations to determine the risk of bleeding
Endoscopy
Angiography
Hepatic venous pressure gradient
Anatomy
Observations to determine the risk of liver failure
Clinical
Jaundice, ascites, encephalopathy
Laboratory
Bilirubin and albumin levels, prothrombin time
Liver enzyme levels
Hepatitis serologic tests
Specific disease markers
Quantitative tests

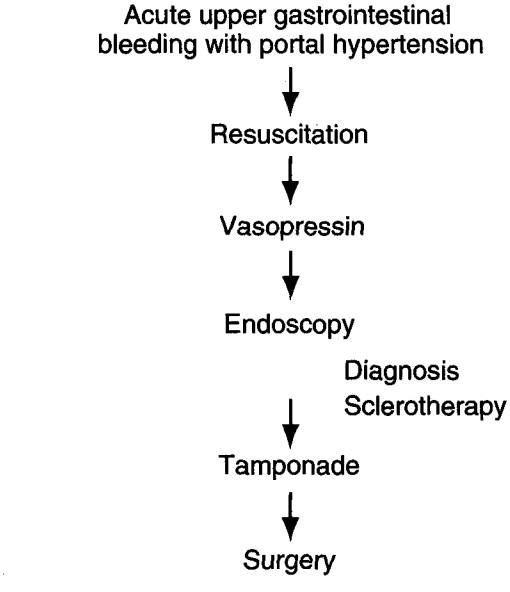

FIGURE 4. Algorithm for management of acute variceal bleeding.

with it. However, it has not been shown uniformly to reduce mortality.[12,18]

Sclerotherapy and shunt surgery are not advised for prophylaxis of the initial bleeding episode. There are conflicting data for both therapies, but the weight of evidence indicates that the risks exceed the benefit.

Acute variceal bleeding

The algorithm in *Figure 4* outlines the management of acute variceal bleeding. The goals are to

TABLE 2
CHILD-PUGH CLASSIFICATION OF THE SEVERITY OF LIVER DISEASE*

	1 Point	2 Points	3 Points
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Increase in prothrombin time (s)	1-3	4-6	>6
Ascites	None	Slight	Moderate
Encephalopathy grade†	None	1-2	3-4

*Grades: A, 5 to 6 points; B, 7 to 9 points; C, 10 to 15 points. Modified from reference 39
†According to the system of Trey et al (Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exhange blood transfusion. N Engl J Med 1966; 274:473–481)

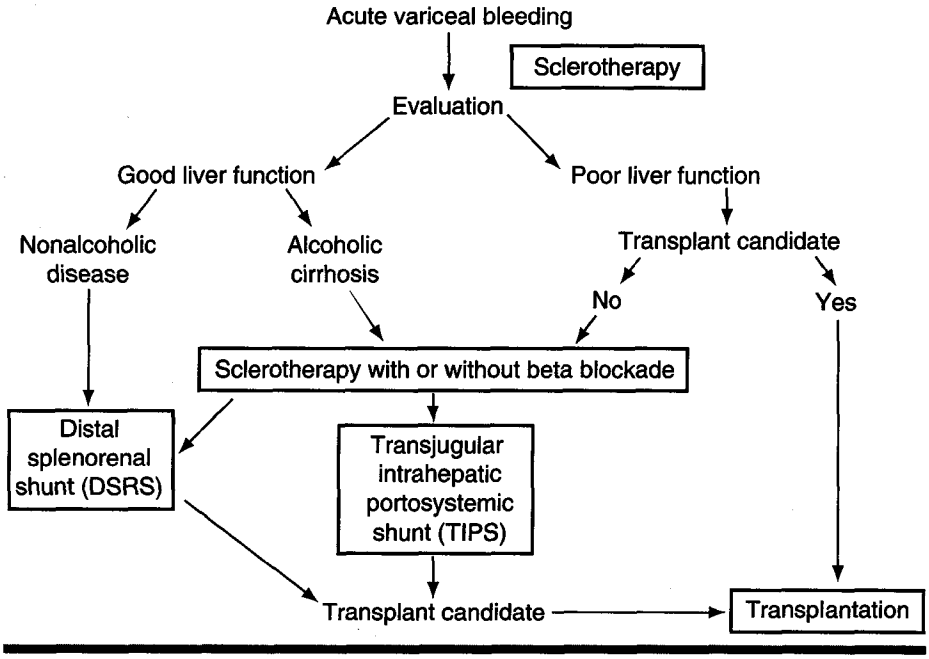

FIGURE 5. Algorithm for management of recurrent variceal bleeding.

achieve hemodynamic stability, perform endoscopy without delay (the procedure should be both diagnostic and therapeutic), and stabilize the patient to allow full evaluation.

Resuscitation of the patient with variceal bleeding differs from resuscitation of other patients with major gastrointestinal bleeding in that plasma volume expansion with crystalloid solutions should be limited if possible. Intravenous infusions containing free sodium will exacerbate ascites, and it is preferable to use blood, fresh-frozen plasma, and 5% albumin, as appropriate. If bleeding is massive at the time of presentation and portal hypertension is suspected, intravenous vasopressin may be useful in stabilizing the patient. However, vasopressin should not be used if bleeding has stopped, or if the patient is hemodynamically stable.

Upper gastrointestinal endoscopy should be done as soon as the patient is stable. Identification of a bleeding varix, or the presence of a platelet plug on a varix, is confirmatory evidence of variceal bleeding. However, in many patients these obvious signs may be absent, and it is important to exclude other gastroduodenal sources of bleeding. Gastric varices and portal hypertensive gastropathy are important to recognize because they may require a different management strategy than for esophageal varices. A final caution: interpretation of endoscopic findings at the time of the acute bleeding episode must take into account the blood volume status and concomitant administration of vasopressin.

Sclerotherapy can control acute variceal bleeding in 90% of patients, but the risk of recurrent bleeding is high.[21] The choice of other therapy must be individualized based on either the failure to control the acute bleeding or on the nature of the recurrent bleeding. Balloon tamponade is required in only about 5% of patients; placement should follow a strict protocol. Emergency surgery is rarely required. Continued major bleeding, particularly in a higher-risk patient, and early recurrent bleeding in a high-risk patient can now be managed with a transjugular intrahepatic portosystemic shunt. Early recurrent bleeding in a low-risk patient should be managed with a distal splenorenal shunt.

Prevention of recurrent variceal bleeding

Upper gastrointestinal bleeding that is definitely or probably due to portal hypertension mandates full evaluation. A scheme for evaluating and managing patients to prevent recurrent bleeding is given in *Table 1* and *Figure 5*. The major points of emphasis are that all patients require full evaluation, availability of all treatment options is required to provide optimal care for all patients, and the treatment choice for an individual patient is based on the cause of the portal hypertension and the liver disease, as well as the liver function.

Evaluation must include assessment of the risks of recurrent bleeding and liver failure. Endoscopy can identify varices at high risk for recurrent bleeding based on size, tortuosity, and color. Angiography should be a component of this evaluation, and it should include measurement of the hepatic venous pressure gradient as well as venous phase superior mesenteric and splenic arteriography to define structure. While Doppler ultrasonography is adequate to assess portal vein patency and direction of flow in most patients, angiography is required to measure the hepatic venous pressure gradient and to visualize the splenic vein and variceal inflow vessels. In fact, angiography should be the standard of practice for evaluating variceal bleeding, especially if any shunt option is being considered.

Liver failure risk, based on liver function, is primarily assessed using the clinical and laboratory parameters given in *Table 1*. The Child-Pugh classification of the severity of liver disease is based on these data (*Table 2*).[39] Further information on hepatic reserve can be obtained from quantitative tests; galactose elimination capacity has proved useful in clinical practice.[36]

The indication for liver transplantation is end-stage liver disease, not variceal bleeding. Patients with poor liver function should undergo a transplantation evaluation, because transplantation is the best treatment choice for such patients, if they are suitable candidates.[35,36] If the patient is not a suitable candidate for transplantation and has poor liver function, the prognosis is very poor. Pharmacotherapy, endoscopic sclerotherapy, and transjugular intrahepatic portosystemic shunting can reduce the risk of recurrent bleeding while the patient undergoes treatment of reversible conditions that are obstacles to transplantation, such as alcoholism. In the patient who may become a candidate for transplantation in the future but does not need one at present, any other operations performed should avoid the hilus of the liver.

In patients with good liver function, the data support primary use of a distal splenorenal shunt if they have nonalcoholic disease, or even if they have stable alcoholic disease, provided they are abstinent. With appropriate patient selection, distal splenorenal shunts can achieve survival rates of 91% at 1 year and 77% at 3 years.[36] Sclerotherapy or beta blockade, or both, should be primary therapies in patients with alcoholic cirrhosis in whom there is active or uncertain disease.[40] Transjugular intrahepatic portosystemic shunting is currently a popular treatment option,[27–29] but its role is unproven, and significant complications including bleeding, infection, and shunt stenosis or thrombosis are being reported. Longer follow-up and more data are required to establish the role of this procedure.

With all treatment options, continued management of the underlying liver disease is important. The following questions should be addressed: Is the disease reversible? Is the underlying liver disease stable? Is this patient approaching the need for transplantation? The emphasis of management is treatment of the whole patient, and not solely treatment of the varices.

SUMMARY

Variceal bleeding is a significant event that requires a multidisciplinary approach for evaluation and management. Acute bleeding is best managed by endoscopic sclerotherapy. Full evaluation should follow stabilization of the patient and should emphasize characterizing the liver disease; this will determine the course of treatment. Definitive management to prevent recurrent bleeding requires the use of pharmacologic, endoscopic, radiologic, and surgical methods.

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