

Grand Rounds

The Management of Variceal Bleeding: Past, Present and Future

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Abstract

The basic principles of managing variceal bleeding have changed little in the last fifty years. Fluid resuscitation, efforts to induce intra-variceal thrombosis, and treatments to reduce portal pressures remain the keys to successful therapy. However, the last decade has seen the introduction of new modalities which have improved treatment efficacy and safety. Octreotide and, at many institutions, terlipressin have supplanted intravenous vasopressin as acute pharmacologic therapy for variceal bleeding. Endoscopic management of variceal bleeding now includes endoscopic variceal ligation in addition to the widely practiced endoscopic sclerotherapy. Placement of transjugular intrahepatic portosystemic shunts has been proven to be a reliable means of emergently inducing a reduction in portal pressure and stopping variceal hemorrhage. In the out-patient setting, therapy with non-selective β -blockers, often coupled with oral nitrates, is increasingly accepted as a means of improving portal hypertension and reducing a patient's risk of first hemorrhage or recurrent variceal bleed.

This review focuses on the history and evolution of management strategies for variceal bleeding, discusses the physiologic basis for each type of therapy, summarizes current treatment approaches, and addresses recent developments in the field.

Key Words: Varices, variceal bleeding, gastrointestinal bleeding, portal hypertension, octreotide, sclerotherapy, endoscopic variceal ligation, TIPS, shunt surgery, review.

Physiology of Portal Hypertension

The formation of esophageal and gastric varices is a common sequela of portal hypertension. Portal hypertension is defined as elevated pressure within some portion of the portal venous system. Both portal hypertension and variceal bleeding have been associated with a wide variety of diseases, ranging from Budd-Chiari syndrome to malignant splenic vein thrombosis to cirrhosis. In patients with cirrhosis, increased splanchnic arterial blood flow and, accordingly, increased splanchnic venous inflow into the liver, play important contributing roles. Putative splanchnic vasodilators include: glucagon, vasoactive intestinal peptide, substance P, prostacyclin, bile acids, TNF- α and nitric oxide (1). Another contributing factor to the development of portal hypertension in cirrhosis is elevated resistance across the sinusoidal vascular bed of the liver. Factors which increase resistance to blood flow include: disruption of hepatic architecture and compression of hepatic venules by regenerating nodules; increased collagen deposition in the space of Disse; and increased intrahepatic levels of locally acting vasoconstricting chemicals. Amelioration of these factors in the cirrhotic patient can reduce portal pressure and stop or prevent variceal bleeding.

Varices form when portal hypertension causes dilation of portosystemic collateral vessels. Blood may be shunted from the portal circulation into the systemic circulation. In the case of esophageal and gastric varices, increased blood flow is noted in the azygos vein, on account of hepatofugal flow in the left gastric vein (or coronary vein) and short gastric veins (which collateralize with the splenic vein). Groszmann's group at Yale and others have shown that varices do not arise in mild portal hypertension. Once the hepatic venous pressure gradient (the difference in pressure between the portal vein and the hepatic vein) exceeds 12 mm Hg, varices may form in the esophagus and stomach (2, 3). Reduction of portal pressures below this threshold, whether it be by pharmacologic or by surgical means, virtually eliminates the patient's risk for variceal hemorrhage.

In the esophagus, varices first arise at the gastroesophageal junction. Local factors, including the amount of supporting esophageal tissue, may have an impact upon the diameter to which a superficial varix may dilate. Large varices, measured at more than 5 mm in diameter, have a greater predisposition to spontaneously rupture than small varices (4). This, presumably, is a result of the increase in wall tension which occurs when varices increase in size (5). It is now well appreciated that varices do not erode. Indeed, gastroesophageal reflux does not appear to play a role in inducing variceal hemorrhage. Rather, variceal bleeding appears to be an explosive event (6).

Epidemiology of Variceal Bleeding

Varices are identified in about 30% of patients with well-compensated cirrhosis and in 60% of patients with decompensated cirrhosis (7). Small varices are at low risk of hemorrhage. It is estimated that varices will increase in size from "small" to "large" at a rate of 10–20% per year (7, 8). Variceal bleeding occurs at a rate of 10–20% per year, when all patients with varices are considered (9–11), but rises to more than 20–30% per year in patients with large varices (4, 11). This statistic takes on added importance with the knowledge that bleeding from varices is the cause of more than one quarter of all deaths in patients with cirrhosis (12).

Initial variceal bleeding stops spontaneously in 60–70% of patients (13, 14). However, 17–42% of patients with early hemostasis will rebleed within 5–10 days of their initial hemorrhage (15, 16). Variceal bleeding and early rebleeding are associated with a high mortality rate, estimated at about 40% (see below). Exsanguinating hemorrhage itself is responsible for about 60% of deaths which occur within 6 weeks of the initial hemorrhage. Recurrent bleeding is responsible for about 40% of late deaths (13). Progressive liver failure and hepatorenal syndrome frequently complicate variceal bleeding and may result in death. These conditions are presumably precipitated by a state of decreased hepatic and renal blood flow. Thus, it is imperative that intravascular volume be maintained by aggressive resuscitation with fluid and blood products. However, care must be taken to avoid over-transfusion (above a hematocrit of 30%), as this may acutely worsen portal hypertension. Sepsis and, in patients with ascites, spontaneous bacterial peritonitis are frequently seen in the setting of variceal bleeding. Increasingly, there is interest in using selective intestinal decontamination (e.g., with norfloxacin 400 mg per nasogastric tube twice daily) in an effort to prevent serious infection in cirrhotic patients who develop gastrointestinal hemorrhage (17).

TABLE 1
Child Class

| Clinical and biochemical measurements | Points accorded | | |
|---|-----------------|---------------|---------------|
| | 1 | 2 | 3 |
| Encephalopathy | None | Stage 1 and 2 | Stage 3 and 4 |
| Ascites | Absent | Slight | Moderate |
| Bilirubin (mg/dL) | < 2 | 2–3 | > 3 |
| Albumin (g/dL) | > 3.5 | 2.8–3.5 | < 2.8 |
| Prothrombin time (seconds prolonged) | < 4 | 4–6 | > 6 |
| INR | < 1.7 | 1.7–2.3 | > 2.3 |
| Point modification for primary biliary cirrhosis or primary sclerosing cholangitis: | | | |
| Bilirubin (mg/dL): | < 4 | 4–10 | > 10 |
| Class A: 5–6 points | | | |
| Class B: 7–9 points | | | |
| Class C: 10–15 points. | | | |

Modified from Pugh RNH, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; 60:646–649 (19), and reproduced with the permission of the editors of the *British Journal of Surgery*.

It has long been known that both early and late mortality following variceal bleeding are closely tied to a patient's Child class at time of onset of bleeding (18–22). **Table 1**, derived from Pugh et al. (19), has been modified to include the international normalized ration (INR) readings for the prothrombin time. Patients with well-compensated liver disease receive a Child class A status. Patients who suffer from some degree of hepatic encephalopathy, ascites, jaundice or hepatic synthetic dysfunction, as marked by a depressed serum albumin or an elevated prothrombin time, have a Child class B or C status. Following variceal bleeding, 30-day mortality rates have been estimated at: less than 10% for Child class A, 30% for Child class B, and more than 45% for Child class C (20). For patients who survive the initial variceal bleed, the one-year mortality rate is estimated to be 50% when all patients with cirrhosis are considered (13). When segregated by severity of liver disease, one-year mortality rates are estimated at: 24% for Child class A, 48% for Child class B, and 65–89% for Child class C (20, 21).

Treatment to Reduce Intrahepatic Resistance

Since the 1940s, clinical investigators have recognized that reduction of portal pressure may abate active variceal bleeding and help prevent repeat bleeds. From a physiologic perspective, each treatment strategy has a primary mechanism of action: reduction of intrahepatic vascular resistance, reduction of portal venous inflow, or “non-physiologic” obliteration of esophageal varices. Both portocaval shunt surgery and its angiographic equivalent, the transjugular intrahepatic portosystemic shunt (TIPS), decrease portal pressure by bypassing the high-resistance sinusoidal bed of the cirrhotic liver (see below). Nitrates, administered either intravenously or orally, also help overcome sinusoidal resistance. Indeed, nitrates appear to relax the smooth muscle contraction of the myofibroblast cells (also known as stellate or Ito cells) which line the hepatic sinusoid. Furthermore, they appear to reduce portal-collateral resistance in other vascular beds. Nitrates are not effective as single agents in the control of acute variceal bleeding. However, they are often used in combination with other drugs. In the mid 1980s, it was demonstrated that nitroglycerin, administered intravenously at a rate of 50 µg/min, significantly improved the rate of control of variceal hemorrhage when added to a regimen of vasopressin (23). A decade later, many investigators showed that the addition of isosorbide-5-mononitrate to a regimen of propranolol or nadolol significantly improved portal hypertension (24) and increased the efficacy of oral β-blockers in preventing recurrent variceal bleeding (25, 26). Recently, nitrates were shown to be effective as single agents in the primary prophylaxis of variceal bleeding (27). The findings of this study require confirmation by additional investigations.

Treatment to Reduce Portal Venous Inflow

Over the last 40 years, and especially since the 1980s, it has been increasingly appreciated that a hyperdynamic circulation and increased portal venous inflow play major roles in the development of portal hypertension (1). Coincident with advances in understanding the basis for portal hypertension, there has been increased clinical investigation of pharmacologic strategies to reduce portal venous inflow.

“Posterior pituitary extract” was first administered to patients with bleeding esophageal varices in the 1950s and 1960s (28–30). Additional trials using arginine vasopressin, lysine vasopressin and the synthetic Pitressin were conducted from the mid-1970s to the late 1980s.

Vasopressin binds to the V_1 receptor of vascular smooth muscle cells and it induces vasoconstriction in the mesenteric arterial circulation. As a result, there is decreased portal venous inflow and a subsequent reduction in portal pressure. Disparate studies have demonstrated that acute variceal bleeding is controlled in 29–71% of cases treated with vasopressin alone, and in 45–73% of cases when vasopressin is combined with nitroglycerin. Most studies demonstrate the superiority of vasopressin over placebo, and the superiority of vasopressin plus nitroglycerin over vasopressin alone (7).

Typical vasopressin dosing is 0.4 units per minute intravenously, used in combination with nitroglycerin 50 μg per minute intravenously. Treatment with vasopressin and nitroglycerin is tapered once bleeding has stopped and the patient no longer has an ongoing need for blood transfusion. If bleeding does not cease, the vasopressin dose may be increased to as high as 1.0 units per minute. However, higher doses are associated with increased side effects, including myocardial and gastrointestinal ischemia. The incidence of these severe side effects is reduced by co-administration with nitroglycerin. The efficacy and safety of vasopressin are not improved by direct infusion into the superior mesenteric artery (31).

Triglycyl-lysine vasopressin, also known as terlipressin, was first used in clinical trials in the late 1970s. However, its use only became popular in the early 1990s. Although the parent drug has no vasoactive properties, it is converted to the vasoactive lysine vasopressin after its terminal glycine residue is cleaved off *in vivo*. This results in the “slow release” of a vasoactive chemical. Terlipressin’s theoretical advantages over vasopressin include: the convenience of bolus administration as opposed to continuous intravenous infusion; the drug’s decreased cardiotoxicity; and its ability to control up to 70% of variceal hemorrhages. However, there have been few clinical trials using terlipressin (32). This may be due, in part, to other drugs, somatostatin and octreotide, which have attracted considerably more clinical attention in the 1990s (33–39).

Octreotide is the synthetic octapeptide analog of somatostatin, a 14 amino acid hormone. Somatostatin has a half life of one minute, which necessitates administration via continuous infusion. Octreotide, with a half life of 10–22 minutes, is also administered by continuous infusion but, in some circumstances, is given subcutaneously. Although neither drug appears to have direct vasoconstrictive properties, both were recognized in the early 1980s to decrease splanchnic arterial blood flow, with a subsequent decrease in portal inflow. Their mechanism of action is believed to be due to inhibition of vasodilatory gastrointestinal peptides, including: glucagon, vasoactive intestinal peptide, calcitonin gene related peptide, and substance P (32). Although their effect on reducing portal pressure is variable, somatostatin and octreotide consistently reduce azygos blood flow (33). Intravenous administration of somatostatin (typically at doses of 250 $\mu\text{g}/\text{hr}$, after bolus administration of 250 μg) and octreotide (typically at doses of 50 $\mu\text{g}/\text{hr}$) have controlled variceal bleeding in 40–90% of cases (34–37). A number of studies have shown the efficacy of somatostatin (35, 37) and octreotide (36) to be equivalent to endoscopic sclerotherapy (ES). In general, treatment is continued for 2–5 days. Although bolus administration of octreotide has been shown to reduce cardiac output and increase pulmonary capillary wedge pressure in controlled settings, the clinical impact of this is unclear (38). Somatostatin and octreotide are associated with few other side effects. Their ease of

administration, their safety and their efficacy lead me to recommend the use of somatostatin or octreotide as soon as variceal bleeding is suspected. However, I am not yet prepared to recommend treatment with either drug as an alternative to emergent therapeutic endoscopy. An area for future exploration is the use of subcutaneous octreotide in the secondary prophylaxis of variceal bleeding. One preliminary study demonstrates that octreotide 100 μg administered subcutaneously every 8 hours increases the efficacy of ES in the prevention of variceal rebleeding (39) whereas a more recent work suggests this medication is ineffective (40). Other authors postulate that higher doses of octreotide, up to 500 μg administered subcutaneously every 8 hours, may be needed in order to maintain the plasma levels achieved by a 25 $\mu\text{g}/\text{h}$ intravenous infusion, an octreotide dose which has been successful at stopping variceal bleeding (41).

The ability of β -adrenergic blockers to decrease splanchnic blood flow has been known since the 1960s (42). Non-selective β -blockers like propranolol and nadolol are particularly effective in reducing portal pressures in cirrhotics. β_1 blockade reduces cardiac output. β_2 blockade produces a state of unopposed α -adrenergic stimulation, with resulting constriction of both the peripheral and splanchnic circulations. The subsequent reduction in portal venous inflow and portal pressure has a major clinical impact. Although β -blocker therapy does not play a role in the patient with acutely bleeding varices, a meta-analysis of heterogeneous studies comparing propranolol or nadolol to placebo showed a reduction in the relative risk of recurrent variceal bleeding (pooled odds ratio = 0.40, 95% confidence interval = 0.30–0.54) (7). Given the safety and low cost of β -blocker therapy, we routinely recommend it as secondary prophylaxis against variceal bleeding. The data is even more compelling vis-à-vis the use of β -blockers as primary prophylaxis. Meta-analysis demonstrates a significant decreased relative risk for initial variceal bleeding in patients with asymptomatic esophageal varices who are treated with a β -blocker (pooled odds ratio = 0.54, 95% confidence interval = 0.39–0.74). However, there was not a significant reduction in the mortality rate (pooled odds ratio = 0.75, 95% confidence interval = 0.57–1.06) (7). It has been estimated that 9–11 patients must be treated with β -blockers in order to prevent one bleeding event (11). However, the safety of treatment and the potential catastrophic nature of variceal bleeding argue strongly in favor of β -blocker primary prophylaxis.

Therapeutic Endoscopy: A “Non-Physiologic” Approach to Variceal Bleeding

The goal of therapeutic endoscopy is to stop acute variceal bleeding by creating an intravariceal thrombus. Repeated procedures may ultimately induce variceal obliteration. Two techniques are in common use: endoscopic sclerotherapy (ES) and endoscopic variceal ligation (EVL). Neither procedure produces a reduction in portal pressure. In fact, the successful obliteration of varices may actually increase portal pressures in some patients. Although portal hypertension is not ameliorated, both ES and EVL are highly effective in treating acute variceal bleeding and have acceptable complication rates.

In ES, an irritant solution (e.g., sodium morrhuate, ethanolamine or polidocanol) or a dehydrating chemical (e.g., sodium tetradecyl sulfate) is injected into an esophageal varix or its adjacent supporting tissues. The goal is the acute induction of vascular spasm, with subsequent

development of intravariceal thrombosis, intimal thickening and perivenous fibrosis (43). ES, utilizing a rigid esophagoscope, was first reported by Crafoord and Frenckner in 1939 (44). Large esophageal varices were obliterated in a 16-year-old girl after a one-month course of quinine hydrochloride injections every other day. Two years later, Moersch (45) used repeated injections of sodium morrhuate to obliterate esophageal varices, with prevention of rebleeding in 6 of 11 patients under treatment. However, enthusiasm for ES waned as surgeons gained increasing experience with portocaval shunt surgery. A number of large series of patients undergoing successful ES, all employing rigid esophagoscopes, was reported in the 1970s (46–48). This, and the advent of flexible fiberoptic endoscopy in the mid-1970s, spurred interest in adapting this new technology for performance of ES. The first published report of ES utilizing a flexible fiberoptic endoscope appeared in 1979 (49). By the mid-1980s, it was recognized that ES could achieve early hemostasis in up to 95% of patients suffering from variceal bleeding. Controlled trials demonstrated that ES was consistently more effective than treatment with intravenous vasopressin (7). Accordingly, ES became the “gold standard” for the emergent treatment of bleeding esophageal varices.

Repeated application of ES or EVL, over a period of weeks to months, can obliterate varices and prevent rebleeding. When no attempt is made to obliterate varices, about 75% of patients eventually rebleed. When long-term ES is attempted, varices are obliterated in about 50% of patients (reported as a range of 27–85% by Laine and Cook) (50). Varices redevelop in 28–60% of patients following obliteration, with rebleeding in 4–44% of these cases (51, 52). These bleeds are usually less severe than the index hemorrhage. In most cases, rebleeding is controlled by reapplication of ES. Further episodes of bleeding are usually prevented by performance of additional ES (53) or by adding β -blockers and nitrates to the patient’s regimen. Patients who fail repeat ES and aggressive medical therapy will require TIPS or portocaval shunt surgery. It remains controversial as to whether successful obliteration of varices in patients following index variceal hemorrhage actually helps to improve long-term survival.

Esophageal sclerotherapy has a number of important problems. First, it usually takes 3–6 ES sessions to obliterate esophageal varices (50). ES is rarely successful in the emergent control of bleeding from large gastric varices. Furthermore, ES plays no role in treating the bleeding which may develop from portal hypertensive gastropathy. Finally, side effects and procedural complications are common, especially following treatment of the actively bleeding patient. The most common complications result from the development of post-sclerotherapy esophageal ulcers. Patients may experience chest pain or odynophagia in the early post-ES period. Bleeding from post-sclerotherapy ulcers is seen in 5–13% of patients (54). Encouragingly, bleeding is usually self-limited and stops without requiring endoscopic therapy or portal decompression. Post-sclerotherapy ulcers may also be complicated by esophageal dysmotility and esophageal stricturing, which are seen in 1.6–3% of patients. ES-induced strictures occasionally necessitate additional endoscopy to facilitate esophageal dilation (54). Sclerotherapy is known to worsen portal hypertensive gastropathy and increase the size of gastric varices seen at sites “upstream” from the level of variceal obstruction (55). Other important complications of ES include: esophageal perforation, estimated at an incidence of 0.5% per ES session; systemic infection; pleural effusion; aspiration pneumonia; adult respiratory distress syndrome; mediastinitis; and portal and mesenteric venous thrombosis (54). The mortality rate of ES, performed in the setting

of acute variceal bleeding, has been estimated at 1–2% (56). Elective ES in the non-bleeding patient is believed to be considerably safer.

Endoscopic variceal ligation (EVL) is a promising alternative to ES. The technique is derived from a hemorrhoid banding procedure which was first introduced in 1963. Stiegmann and Goff (57) reported the first clinical experience with EVL in 1988. Although band ligating devices have evolved over the last decade, the basic principles of the procedure remain unchanged. A standard endoscope is outfitted with a special ligating chamber at its tip. After insertion of the endoscope, a varix is identified by the endoscopist and the varix is suctioned into the ligating chamber. By pulling a trip wire, the endoscopist releases an elastic “O” ring around the neck of the varix, creating a “polyp” (57). This results in the coagulative necrosis of the ensnared polyp, with eventual sloughing. Varices in the adjacent submucosa subsequently thrombose. In addition, acute inflammation in the superficial mucosa leads to the formation of shallow ulcers. As ulcers heal, granulation tissue forms and helps to obliterate variceal channels, without damage to the underlying muscularis (58).

The original band ligating device could only deploy one “O” ring at a time. As a result, the endoscopist needed to pass an endoscopic overtube into the esophagus to facilitate band deployment, removal of the endoscope, reloading of a new band, and reinsertion of the endoscope. Although the original EVL procedure was associated with fewer post-procedure bleeds than ES, the procedure was cumbersome. Furthermore, overtube passage itself carried a risk of esophageal laceration and perforation. Multi-band ligating devices became available commercially in 1996. Because it became possible to load 6 or more bands onto the ligating chamber, only one passage of the endoscope was needed. Thus, the multiband ligator obviated the need for passing an overtube prior to starting EVL. Recent trials have shown that this development has increased the safety of the procedure and has increased its ease of application (59).

The first randomized trial comparing EVL with ES was reported in 1992 (60). In 1995, a total of 7 randomized trials underwent meta-analysis (50). Compared to ES, EVL significantly reduced the rebleeding rate (odds ratio = 0.52, 95% confidence interval = 0.37–0.74), the mortality rate (odds ratio = 0.67, 95% confidence interval = 0.46–0.98), and the death rate due to bleeding (odds ratio = 0.49, 95% confidence interval = 0.24–0.996). On average, it took 4 EVL sessions to obliterate varices, in contrast to 6 ES sessions. Furthermore, there were fewer treatment induced ulcers and fewer complications associated with EVL. Whereas 3.3% of ES procedures were accompanied by fatal complications, 1.0% of EVL procedures had fatal complications.

It now appears that EVL is the endoscopic procedure of choice for treating bleeding esophageal varices. However, the performance of EVL may be technically difficult in an esophagus awash in blood. ES is appropriate in this setting. At follow-up endoscopy sessions, it becomes increasingly difficult to ligate residual, partially-treated varices. A combination of EVL for large varices and ES for small varices may be warranted.

For decades, investigators have been intrigued by the challenge of preventing variceal

hemorrhage in cirrhotic patients with asymptomatic varices, whether it be by surgical or endoscopic means. Although a few trials have supported the performance of prophylactic ES, the data remain inconclusive (61). The relative safety of EVL is leading endoscopists to reinvestigate the question of prophylactic endoscopic treatment. One recent abstract addressed the issue by randomizing 80 patients with varices to prophylactic EVL and 76 patients with varices to no treatment. Over a median follow-up period of 32 months, variceal bleeding occurred in 8.7% of treated patients and 36.8% of control patients ($p < 0.05$). Furthermore, the treated patients experienced a survival advantage as well, with 18.7% of the treated patients and 40.7% of the untreated patients dying during the study ($p < 0.05$). This abstract raises the possibility that prophylactic EVL may be incorporated into the management of patients with asymptomatic varices (62).

A number of alternative endoscopic approaches are being explored in treating variceal bleeding. They offer the hope that endoscopy may be refined so that bleeding gastric varices may be treated endoscopically. One approach uses sclerotherapy technique to inject the tissue adhesive N-butyl-2-cyanoacrylate in an attempt to occlude the lumen of bleeding varices. Studies employing cyanoacrylate injection for treatment of large varices, with simultaneous traditional sclerotherapy for treatment of small varices, have been associated with rebleeding rates of 10% or less. However, the technique is somewhat cumbersome and it has not yet been approved by the Food and Drug Administration for use in the United States (63).

Other techniques use the endoscope to deploy detachable clips (64) and detachable snares (65) in an effort to entrap esophageal varices and induce thrombosis. A recent report describes the successful obliteration of gastric varices in 10 patients by use of a detachable endoscopic snare (66). These devices are deserving of additional investigation.

Medical and Endoscopic Management of the Patient with Acute Variceal Bleeding

The keystone of therapy for variceal bleeding remains aggressive resuscitation with blood products. Since the early 1980s, many gastroenterologists have recommended that emergent endoscopy be performed at the earliest possible moment in order to confirm the clinical suspicion of variceal bleeding and to rule out other causes of upper gastrointestinal bleeding. Indeed, up to 50% of gastrointestinal bleeds in patients with cirrhosis are said to arise from sources other than varices. Emergent endoscopy also offers an opportunity to perform ES or EVL if varices are at the bleeding site, or cautery or epinephrine injections if there is bleeding from another site. Thus, emergent performance of endoscopy remains a tenet of the management of upper gastrointestinal bleeding.

The medical therapy of acute variceal bleeding remains controversial. In the past, concern over the potential side effects of vasopressin led many gastroenterologists to hold the use of this drug in reserve, unless the patient was experiencing massive variceal bleeding or unless bleeding was incompletely controlled by ES. In contrast, the safety profiles of somatostatin and octreotide permit clinicians to institute drug therapy in the emergency room, as soon as the diagnosis of variceal bleeding is suspected. I do not recommend either somatostatin or octreotide as monotherapy for acute variceal bleeding. In practice, I administer octreotide intravenously at 50 $\mu\text{g/hr}$ for up to 5 days following a moderate or massive hemorrhage, even if

there is initial endoscopic control of bleeding. This approach is supported by a recent study in which cirrhotic patients with upper gastrointestinal bleeding were randomized to intravenous somatostatin or placebo prior to undergoing emergency therapeutic endoscopy. Patients receiving both somatostatin and ES for bleeding esophageal varices required transfusion with fewer blood products than patients treated with placebo prior to ES. Furthermore, patients receiving combination therapy had a reduced requirement for rescue therapy with repeat ES, balloon tamponade or TIPS (67).

Ongoing treatment with octreotide is warranted if bleeding is incompletely controlled by initial therapeutic endoscopy. I tend towards repeating ES or EVL if there is incomplete control of bleeding or in the event of rebleeding. Treatment with a non-selective β -blocker is initiated once bleeding is well controlled and octreotide is withdrawn. In general, treatment is started with nadolol 40 mg once daily. Attempts are made to increase the dose until there is a 25% reduction in heart rate from baseline. Co-treatment with isosorbide-5-mononitrate may be offered as well.

The proper timing of follow-up endoscopy after control of initial variceal hemorrhage remains controversial. In the past, follow-up sclerotherapy was often performed 48–72 hours after initial ES. It is now recognized that re-treatment of varices at this stage may increase the risk for complications (68). Many institutions, including our own, perform follow-up therapeutic endoscopy every 1–2 weeks after the initial procedure in an effort to obliterate varices. Once varices are obliterated, patients are re-endoscoped after 3 months, and then every 6 months to assure that varices do not recur. Recurrent varices may be re-treated using either EVL or ES.

Many studies have demonstrated that a combination of β -blockers and ES is more successful at preventing variceal rebleeding than either β -blockers alone or ES alone (7). These conclusions can presumably be extended to β -blockers used in combination with EVL for secondary prophylaxis of variceal bleeding. In our practice, patients remain under treatment with β -blockers at least until the time that varices have been obliterated. The utility of β -blocker and nitrate therapy after successful obliteration of varices remains unknown.

Management of the Patient with Refractory Variceal Bleeding

About 10% of patients who suffer from esophageal variceal bleeding experience massive, continuous or recurrent bleeding which is refractory to optimal medical and endoscopic management. In practice, I attempt to perform repeat ES or EVL before declaring that a recurrent bleeding event is refractory. Other reasons for declaring that a variceal bleed is refractory include: bleeding from gastric varices (although some gastric varices may be amenable to endoscopic therapy); and two or more recurrent bleeds over the course of weeks to months in spite of aggressive endoscopic and β -blocker treatment. Patients with refractory variceal hemorrhage often require urgent or emergent decompression of the portal venous system (Fig. 1).

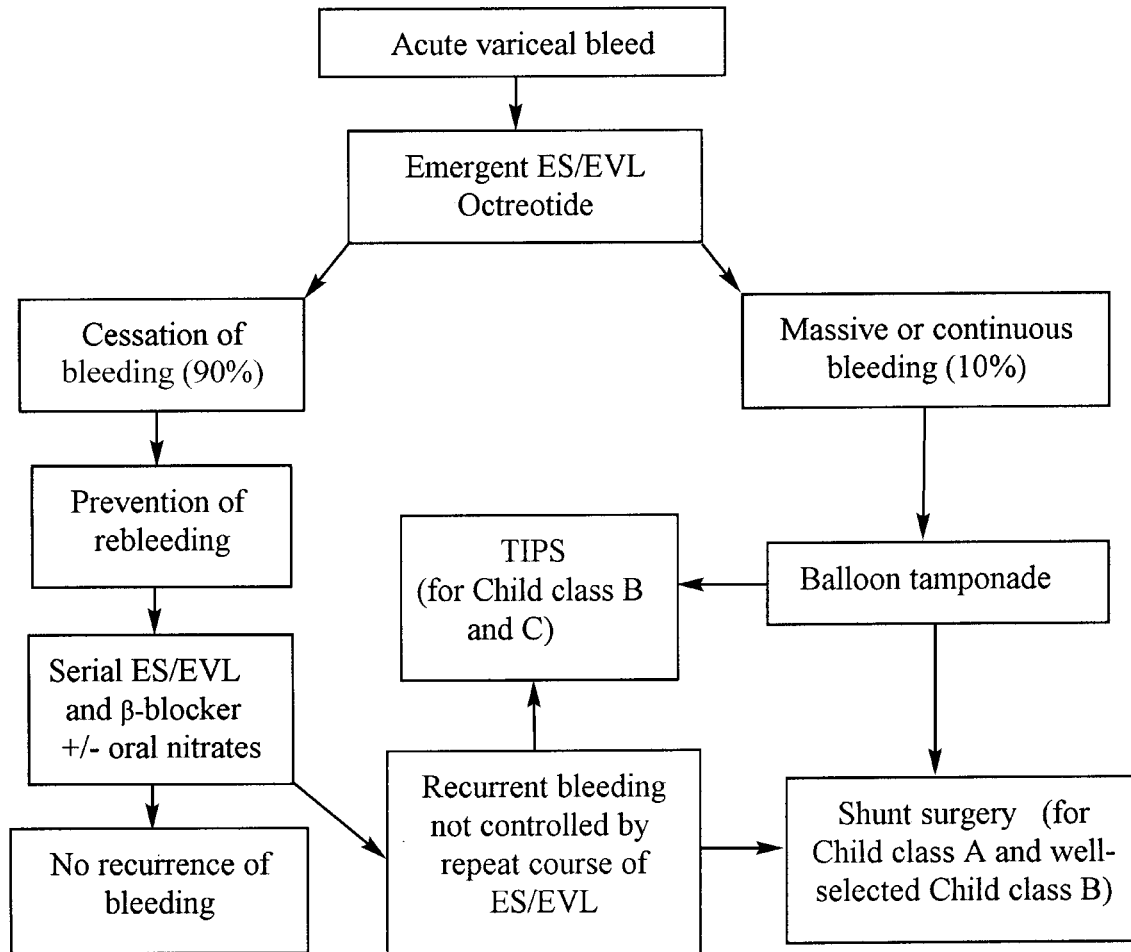


Fig. 1. Suggested Management of Acute Variceal Bleeding.

Patients who suffer from massive or continuous bleeding are particularly challenging to manage. Many such patients require balloon tamponade in order to stabilize them prior to performing lifesaving shunt surgery or TIPS. The Sengstaken-Blakemore tube (Davol Inc., Cranston, RI) was first introduced in 1950 (69). This device and its subsequent variations, the Minnesota tube and Linton-Nachlas tube, are passed per nares or per os in an intubated patient. Correct positioning of the tube is documented by chest and abdominal X-ray. The gastric balloon is then inflated with about 300 cc air, and gentle traction, usually about 0.5 kg using a pulley system, is applied. Sengstaken-Blakemore and Minnesota tubes are also equipped with an esophageal balloon which can permit balloon tamponade directly to bleeding esophageal varices. However, gastric balloon insufflation and traction alone is often sufficient for short-term control of either gastric or esophageal variceal bleeding. Balloon tamponade induces initial hemostasis in 40–90% cases of bleeding esophageal varices (7). However, fatal complications arise in 6–20% of cases (7). They include: necrosis of the gastroesophageal wall, rupture of the esophagus,

and aspiration pneumonia. In spite of these problems, balloon tamponade should be employed as a temporizing measure when patients with massive hemorrhage fail emergent endoscopic and medical therapies.

Portocaval shunts provide rapid, effective portal decompression and are highly successful at halting variceal bleeding. Concerns over procedural mortality and postoperative complications limit their utility in the primary treatment of acute variceal bleeding. However, 50 years after its introduction, shunt surgery, as well as its modern counterpart, TIPS, remain the mainstays of therapy for refractory variceal bleeding (**Table 2**).

TABLE 2
History of the management of acute variceal bleeding.

| 1950 | 1980 | 1997 |
|---------------------|---|--|
| Fluid resuscitation | Fluid resuscitation Endoscopy • Sclerotherapy | Fluid resuscitation Endoscopy • Sclerotherapy • Variceal ligation (EVL) |
| | IV medications • Vasopressin | IV medications • Vasopressin, terlipressin • Somatostatin, octreotide |
| Balloon tamponade | Balloon tamponade | Balloon tamponade TIPS |
| Portocaval shunt | Portocaval shunt | Portocaval shunt Liver transplantation |

Whipple (70), Blakemore (71), and others at Presbyterian Hospital in New York were instrumental in the development of the end-to-side portocaval shunt in 1945. It was recognized early on that many patients developed post-operative liver failure or hepatic encephalopathy. This was presumably due to the diversion of blood and nutritional substrates from patients' already compromised livers. In response to this observation, side-to-side portocaval shunt surgery was introduced a few years later. The mesocaval shunt, developed during the 1950s and 1960s, represented a variation on a theme, by interposing a Dacron graft between a large mesenteric vein and the inferior vena cava. These newer procedures decreased the incidence of post-operative liver failure and hepatic encephalopathy by partially maintaining blood flow to the liver.

Portocaval shunt surgery is highly effective in the initial treatment of bleeding. Only 9–22% of patients experience late episodes of rebleeding (7). This figure should be appreciated in the context of a 23–55% rebleeding rate for patients treated with sclerotherapy (72). Non-emergent portocaval shunt surgery carries with it a 7–13% operative mortality rate (73).

However, operative mortality jumps to more than 50% when portocaval shunt surgery is performed emergently, especially in the patient with Child class C status (72). The most optimistic and controversial results are reported by Orloff et al. (74). They studied 43 patients who underwent surgery following variceal bleeding. Emergency portocaval shunt surgery was performed in 21 patients within 8 hours of presentation with variceal bleeding. Elective portocaval shunt surgery was performed in 22 patients who were initially stabilized by use of vasopressin and esophageal balloon tamponade. Of the patients who underwent emergent surgery, all 10 patients with Child class A or B status survived their initial hospitalization, with a 90% one-year survival rate. Seven of 11 patients with Child class C status (64%) survived initial hospitalization. Only one of these survivors died during the first year of follow-up. Survival data were significantly better for patients who underwent emergent shunt surgery than for patients who underwent elective surgery (74). Other investigators have not been able to duplicate these results (75).

Distal splenorenal shunt surgery (76) attempts to selectively decompress gastroesophageal varices by diverting splenic venous outflow into the renal vein. Splanchnic venous return to the liver is maintained. Its theoretic advantage over portocaval shunts is a decreased incidence of post-operative hepatic encephalopathy and liver failure. The surgery requires considerable technical expertise and is not appropriate in either obese patients or in the emergent setting. However, when performed in an appropriately selected patient, it is highly effective. On average, 17% of patients will suffer rebleeding, with as low as a 3% rebleeding rate described by Henderson et al. (77). There is a 9–13% operative mortality rate (73, 77).

Shunt surgery should be considered when emergent portal decompression is required in a relatively well-compensated cirrhotic patient (patients with Child class A status and well-selected patients with Child class B status). The choice of shunt operation depends upon the clinical setting and the expertise of the operator. The advent of TIPS provides us with an additional option in patients with advanced Child class B and C cirrhosis.

Work by Rosch (78), Colapinto (79), Palmaz (80) and colleagues in the 1970s and 1980s laid the groundwork for the first successful creation of TIPS in humans in 1989 (81). TIPS is physiologically equivalent to a side-to-side portocaval shunt. However, it represents a dramatic departure from portocaval shunt surgery. The procedure can be performed in the interventional radiology suite in 1–2 hours, often without the need for general anesthesia. TIPS are created by introducing a catheter into the right hepatic vein, typically using an approach through the right jugular vein. A needle is deployed within the catheter. It is briskly inserted into the liver parenchyma until it is positioned in the right portal vein. A guide wire is inserted into the portal vein, the needle is removed, and a tract through the hepatic parenchyma is created by balloon dilation. An expandable metal stent is introduced into the newly created tract between the hepatic and portal veins. The stent is balloon dilated, forming a conduit which shunts blood from the hypertensive portal vein into the hepatic vein. The result is a rapid and sustained decrease in portal pressure. Refractory variceal bleeding is particularly amenable to therapy with TIPS (82, 83). The procedure has also been used electively in order to reduce portal pressures in patients suffering from massive ascites (84, 85). However, this indication is not universally accepted (82).

TIPS procedures fail to create a shunt in up to 10% of cases. In an effort to improve the efficacy and safety of the procedure, an alternative transmesenteric-transfemoral method (tmTIPS) is used at Westchester Medical Center. With the patient under general anesthesia, a stone retrieval basket is introduced via a femoral vein approach, and positioned and opened in the hepatic vein. A mini-laparotomy is performed and a blunt directional cannula is introduced via a mesenteric approach into the selected branch of the portal vein. Under fluoroscopic guidance, a 20 gauge needle is inserted through the cannula. The hepatic parenchymal puncture is performed, the needle is grasped by the retrieval basket in the hepatic vein, and a guide wire is introduced. Control of both the mesenteric and femoral ends of the guide wire facilitates deployment of the intrahepatic stent (86). Although the transmesenteric-transfemoral technique necessitates general anesthesia and mini-laparotomy, operative complications have been minimal and there have been no direct procedure-related deaths in more than 130 cases (G Rozenblit, personal communication). The tmTIPS procedure decreases the risk of extracapsular puncture during needle insertion through hepatic parenchyma, reduces fluoroscopy time, facilitates careful positioning of the intrahepatic stent, and is associated with a 100% technical success rate, even in the setting of portal vein thrombosis (86).

Intimal hyperplasia within the hepatic vein, pseudointimal hyperplasia within the TIPS stent, thrombosis, and stent “shortening” will cause one half of TIPS to stenose or even occlude within 1–2 years of initial placement (87, 88). Portal hypertension redevelops in these cases, placing patients at risk for recurrent variceal bleeding or the redevelopment of ascites. Most cases of severe stenosis or occlusion can be detected if patients are enrolled in a program of surveillance Doppler ultrasonography, usually scheduled every 3 months after TIPS placement. Some authors recommend routine venography to follow TIPS patency. In the vast majority of cases of TIPS stenosis, repeat angiographic intervention can successfully reestablish patency. However, at the present time, TIPS cannot be considered to be a long-term solution for the treatment of portal hypertension.

Although TIPS has not been compared to portocaval shunt surgery in a clinical trial, its procedural complication rate of about 10%, mortality rate of 1–2%, the new onset or worsening of hepatic encephalopathy in 10–30% of patients (82), and a long-term rebleeding rate of 13–22% (88–90) compare favorably with portocaval shunts. However, the low risk of surgical shunt failure and the well-known propensity of TIPS stents to stenose or occlude lead me to favor portocaval shunt surgery in the well compensated cirrhotic patient with refractory bleeding. Distal splenorenal shunt surgery is the operation of choice in patients with Child class A status. Side-to-side portocaval or mesocaval shunt surgery may be performed instead in the emergent setting or if technical factors are likely to interfere with the creation of a distal splenorenal shunt. However, a majority of patients with refractory variceal bleeding have Child class B and C status. TIPS is the treatment of choice for these patients, recognizing that patients will require life-long ultrasonographic and angiographic surveillance.

It remains unclear if TIPS should be employed after a patient’s initial variceal bleed in an effort to reduce the risk of rebleeding and improve long-term survival. As an example, two simultaneously published studies reached different conclusions after randomizing patients to receive either multiple sclerotherapy sessions or TIPS, following control of patients’ index

variceal hemorrhages by ES. Cello et al. (89) reported that 13% of patients undergoing TIPS and 48% of patients undergoing ES rebled from varices ($p = 0.012$). A trend toward improved survival was noted in the TIPS group. Sanyal et al. (90) reported that 22% of patients undergoing TIPS and 21% of patients undergoing ES rebled from varices ($p = \text{NS}$). Also, patients in the TIPS group had a higher mortality rate than patients in the sclerotherapy group. In my opinion, it remains premature to recommend TIPS for patients who have not received an adequate trial of ES or EVL, with or without co-therapy with β -blockers and nitrates.

A number of other surgical interventions have been performed in patients with acute variceal bleeding. Esophageal transection and reanastomosis by an EEA stapler, occasionally combined with devascularization of the proximal stomach, is frequently employed in the United Kingdom and Japan (91–94). Liver transplantation has also been used successfully to salvage patients with active, uncontrollable variceal bleeding (95). However, patient instability prior to liver transplantation increases the chance for intra-operative bleeding and post-operative infection, thus jeopardizing the overall success of transplant. Given the critical shortage of donor organs, emergent transplant should only be offered to patients if: a) there is no suspicion for underlying infection, and b) variceal bleeding continues in spite of attempts at TIPS or shunt surgery. Because a history of variceal bleeding increases a patient's chance of early morbidity and mortality, it should be factored into any decision with respect to timing of liver transplantation.

What Is the Future?

The use of multi-band ligating devices will grow in popularity over the next few years. The devices' technical ease of operation, and their favorable complication rate, make EVL the endoscopic treatment of choice in the patient with acute variceal bleeding. However, gastroenterologists will still need to be well versed in the performance of ES, as small esophageal varices might not be amenable to treatment with EVL. Widespread availability of EVL will result in the more aggressive use of this modality as secondary prophylaxis against variceal bleeding. We can also anticipate a resurgence of clinical interest in exploring EVL as primary prophylaxis against variceal bleeding. Although previous primary prophylaxis trials studying portocaval shunt surgery and ES did not conclusively demonstrate a survival advantage for patients treated with either modality, the low side effect profile of EVL may tip the balance in favor of prophylactic therapy in well-specified subsets of patients. Individuals with well-compensated liver disease and large varices would appear to be particularly appropriate subjects to study. Additional clinical experience with detachable endoscopic clips and snares and with injectable tissue adhesives may make their use popular in the endoscopic therapy of gastric varices. This may save some patients with gastric varices from otherwise obligatory portal decompression.

Primary and secondary prophylactic therapies with β -blockers and nitrates are likely to gain increasing acceptance over the next few years. We hope to see trials that explore novel drugs which target specific mediators of splanchnic vasodilation.

Work is ongoing to improve the long term patency of TIPS shunts by using covered stents (96). Other groups are attempting to determine the optimal diameter of the TIPS stent at

time of initial deployment so that the risk of post-TIPS hepatic encephalopathy and liver dysfunction can be reduced.

Finally, clinicians look forward to the day that we can unlock the secrets of hepatic fibrogenesis. Medical therapy might then be able to forestall the development of hepatic fibrosis and cirrhosis in patients with liver disease. With such an advance, we might then substantially reduce the incidence of life-threatening complications of portal hypertension.

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