Endoscopic Hemostasis in Acute Esophageal Variceal Bleeding

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KEYWORDS
- Endoscopy • Hemostasis • Acute variceal bleeding • Portal hypertension

KEY POINTS
- Acute variceal bleeding (AVB) is a serious complication of patients with portal hypertension.
- Initial management includes appropriate volume replacement, transfusion of blood to keep hemoglobin levels around 7 to 8 g/dL, antibiotic prophylaxis, and endotracheal intubation in selected cases.
- Standard of care mandates early administration of vasoactive drug therapy followed by endoscopic band ligation (EBL) or injection endoscopic sclerotherapy (if EBL cannot be performed) within the first 12 hours of patient presentation.
- Patients who fail endoscopic hemostasis therapy may require the temporary placement of balloon tamponade or an esophageal stent; however, experience with esophageal stents is limited and use of balloon tamponade is associated with potentially lethal complications such as aspiration and perforation of the esophagus.
- Both modalities should be available for potential use and all patients surviving an episode of AVB should undergo secondary prophylaxis in order to prevent variceal rebleeding.

The development of portal hypertension in cirrhosis changes the natural course of patients with chronic liver disease because it has several consequences, including the development of gastroesophageal varices, variceal bleeding, ascites, hepatorenal syndrome, and hepatic encephalopathy. The initial appearance of varices in patients with compensated cirrhosis indicates a progression of the disease from a low-risk...
state to an intermediate state, but once bleeding occurs this indicates decompensation and an increased risk of death. Although mortalities caused by acute variceal bleeding (AVB) have declined from nearly 60% to 15% to 20% at 6 weeks in the past 3 to 4 decades, there is still a significant risk of recurrence and of morbidity and mortality. All patients surviving an AVB should therefore receive secondary prophylaxis. This article reviews the current management approach of patients with AVB with particular emphasis on endoscopic hemostatic techniques for bleeding varices.

NATURAL HISTORY AND DIAGNOSIS OF ACUTE VARICEAL BLEEDING

Patients with esophageal varices have an incidence of AVB that ranges from 4% to 15% per year depending on the severity of liver disease, variceal size, presence of red wale markings, and a hepatic venous pressure gradient (HVPG) value greater than 12 mm Hg. In most cases (80%), patients with cirrhosis and gastrointestinal bleeding have gastroesophageal varices as the cause of hemorrhage. Thus upper gastrointestinal bleeding in patients with cirrhosis must be presumed to be variceal in origin until proved otherwise. Although the clinical history is highly reliable in assuming the diagnosis of AVB, the gold standard for the diagnosis is upper endoscopy. Endoscopy can show active blood spurring or oozing from a varix (this can be present in 15% of patients) (Fig. 1), a white nipple or clot adherent to a varix, or the presence of varices without other potential sources of bleeding in the upper gastrointestinal tract. Although acute bleeding from varices may cease spontaneously in nearly half of patients, rebleeding rates are significantly high (30%–40%) if patients are not treated appropriately. The highest risk occurs within the 48 hours following the index bleed and most of the rebleeding episodes occur with the first 14 days. Initial endoscopic failure to control bleeding occurs most commonly in patients with Child class C cirrhosis, concomitant bacterial infection, portal vein thrombosis, active spurring of a varix, and an HVPG greater than 20 mm Hg.

Survival from an episode of AVB has improved greatly: from 42% in the 1980s to the current rates of 80% to 85%. This improvement has been caused by overall improvements in intensive care, volume repletion, pharmacologic and endoscopic therapy, implementation of transjugular intrahepatic portosystemic shunts (TIPS), and prophylaxis for bacterial infections. Current estimates of mortality from

![Endoscopic view of actively bleeding esophageal varix.](image)
uncontrolled bleeding are 4% to 8%.\textsuperscript{11} Approximately one-third of the deaths are a direct consequence of bleeding and the remainder are caused by liver failure, infections, and renal failure.\textsuperscript{20}

Recent studies stress the importance of identifying good prognostic markers in patients with episodes of acute bleeding. Although it is well known that HVPG greater than 20 mm Hg is associated with a high risk of 5-day treatment failure to control bleeding, obtaining this measurement is invasive and not available in all centers.\textsuperscript{14,15} However, easily obtainable clinical variables (Child-Pugh class C, systolic blood pressure <100 mm Hg at admission, and nonalcoholic causes of cirrhosis) are also associated with 5-day treatment failure to control bleeding,\textsuperscript{14} which means that the presence of any of these variables on admission helps clinicians to plan aggressive management and further therapies that may be needed if there is no good response to initial standard-of-care treatment.

**INITIAL MANAGEMENT**

The most important initial step in providing adequate care for patients with AVB consists of (1) providing optimal hemodynamic management with cautious correction of hypovolemia, (2) preventing complications, and (3) stopping the hemorrhage. An established protocol that takes into account adequate volume resuscitation, airway management, prophylactic antibiotics, administration of vasoconstrictors, and therapeutic endoscopy should be followed in all cases of AVB.

A decision to secure the airway before endoscopy should be considered carefully in patients with hepatic encephalopathy and those actively vomiting blood because of the high risk of pulmonary aspiration. Although there are scarce data on this practice and some investigators claim intubation is not safe, others have shown benefits in improving patient outcome.\textsuperscript{21,22} Volume resuscitation with plasma expanders should be instituted in order to keep systolic blood pressure at 100 mm Hg. This measure ensures adequate tissue perfusion with avoidance of hemodynamic shock; hemodynamic shock can cause renal failure, which is associated with an increased risk of death.\textsuperscript{20,23} In contrast, overtransfusion should be avoided because it may induce rebound increases in portal pressure and variceal rebleeding.\textsuperscript{24,25} Blood transfusions should aim for a hemoglobin (Hb) level of 7 g/dL, except in patients with active ongoing bleeding or with ischemic heart disease.\textsuperscript{23} A recent study that compared a restrictive transfusion policy that administered blood products if Hb levels decreased to less than 7 g/dL with a liberal policy (transfusion if Hb <9 g/dL) showed that the probability of survival was significantly higher in patients with cirrhosis and Child-Pugh class A or B disease who were assigned to the restrictive policy group. Moreover, within the first 5 days, the portal-pressure gradient increased significantly in patients in the liberal strategy group but not in patients assigned to the restrictive strategy group.\textsuperscript{25}

There are no evidence-based data to support the routine use of platelet transfusion or fresh frozen plasma administration. Current consensus and expert opinion suggest that, in patients with platelet counts less than 50,000 per µL and/or with an International Normalized Ratio greater than 1.5, it is prudent, weighing the risks and benefits, to consider transfusion of platelets and/or fresh frozen plasma before the procedure.\textsuperscript{26} Bacterial infections are a poor prognostic indicator in AVB.\textsuperscript{12} The most common infections are spontaneous bacterial peritonitis, urinary tract infections, and pneumonia. Prophylactic antibiotics in patients with AVB reduce the risk of rebleeding and mortality,\textsuperscript{27–29} thus all patients on admission should receive them. Norfloxacin 400 mg by mouth twice daily for 7 days may be given; however, patients with hypovolemic shock, ascites, malnutrition, encephalopathy, or bilirubin greater than 3 mg/dL should receive
intravenous ceftriaxone (1 g/d) because it is more effective than oral norfloxacin in the prophylaxis of bacterial infections in patients with cirrhosis and AVB.29

Prompt initiation of vasoactive drugs and timing of endoscopy should be planned from the time the patient arrives at the hospital. This promptness facilitates establishing a diagnosis and performing therapy. Emergency endoscopy should be performed within the first 12 hours after admission.23,30 If patients are actively vomiting blood, it should be performed once the patient has been hemodynamically stabilized in a monitored unit. Recent data indicate that the early placement of TIPS (within 72 hours) for patients with AVB with Child B actively bleeding or Child C cirrhosis (<13 points) is associated with a significant reduction in rebleeding and mortality and thus should be considered in such cases.31

SPECIFIC TREATMENT

Vasoconstrictors

In suspected variceal bleeding, vasoactive drugs (which reduce portal pressure and decrease variceal blood flow) need to be given as soon as possible and before upper endoscopy. This advice is supported by randomized controlled trials (RCTs) and meta-analyses showing that the use of vasoactive drugs achieves hemostasis and reduces the rate of active bleeding, making endoscopy easier to perform for diagnostic and therapeutic purposes.32–36 In addition, these drugs reduce rebleeding and all-cause mortality among patients with cirrhosis and AVB.36 Two types of drugs are used: vasopressin and its analogues (terlipressin) and somatostatin and its analogues (octreotide/vapreotide) (Table 1).

Endoscopy

Endoscopy is one of the cornerstones of AVB management because it confirms the diagnosis and allows therapy during the same session. Endoscopic therapies for varices are designed to reduce variceal wall tension by obliteration of the varix. The 2 endoscopic methods available for AVB are endoscopic sclerotherapy (EST) and endoscopic band ligation (EBL) (Fig. 2). Endoscopic therapy should be used in conjunction with vasoconstrictors. This strategy is strongly supported by several trials and guidelines showing that the efficacy of both emergency EST and EBL is significantly improved when they are associated with pharmacologic treatment.23,37–40

Endoscopic sclerotherapy

For AVB, this technique consists of the injection of a sclerosing agent into the variceal lumen (intravariceal injection); this causes thrombosis of the varix and inflammation of the surrounding mucosa that with time creates a scar over the esophageal wall. EST is performed with an injection catheter (needle tip, 23 or 25 gauge) and the sclerosant solution. The most common sclerosants are ethanolamine oleate (5%), polidocanol

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<td>Terlipressin</td>
<td>IV bolus 2 mg every 4 h for 24–48 h then 1 mg every 4 h</td>
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<td>Somatostatin</td>
<td>IV bolus 250 μg followed by infusion of 250–500 μg/h</td>
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<tr>
<td>Octreotide</td>
<td>IV bolus of 50–100 μg followed by infusion of 50 μg/h</td>
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<td>Vapreotide</td>
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Abbreviation: IV, intravenous.
(1%–2%), or sodium morrhuate (5%). The first injection of 1 to 2 mL of the sclerosant should be placed immediately below (distal to) the bleeding site. Afterward, the remaining varices are injected with 1 to 2 mL adjacent to the bleeding varix. The main objective is to target the lower esophagus near the gastroesophageal (GE) junction. In most cases, up to 15 mL of a sclerosant solution are required. The advantages of using EST for AVB are mainly related to the technique being user friendly because the injection catheter fits through the working channel of a diagnostic gastroscope and does not require a second oral intubation. In addition, there is rapid formation of a thrombus. Drawbacks include a variety of local and systemic side effects, including substernal chest pain, fever, dysphagia, and pleural effusion.

**Endoscopic band ligation**

This technique consists of placing elastic bands on the varices in order to occlude the varix and cause thrombosis and the subsequent necrosis of the mucosa. The bands fall off in 5 to 8 days leaving a superficial mucosal ulceration that heals and eventually scars. Clinical trials and a meta-analysis have shown that EBL is better than EST for all major outcomes, including initial control of bleeding (primary hemostasis), recurrent bleeding, side effects, time to variceal obliteration, and survival.

There are several multiband devices available for EBL; the most common are the Saeed Multiple Ligator (Wilson-Cook Medical, Inc) and the Speedband (Microvasive, Boston Scientific Corporation). They have between 4 and 10 preloaded bands, but in most cases the ligators with 6 or 7 bands are used. All work on the same principle, which is placement of elastic bands on the varix after it is sucked into a clear plastic cylinder attached to the tip of the endoscope. After the diagnostic endoscopy is
performed and the variceal bleeding site is identified, the endoscope is withdrawn and
the ligation device is loaded. After reintubation with the ligation device placed on the
endoscope, the varix (usually in the distal third of the esophagus) is identified and the
tip is pointed toward it and continuous suction applied so that it fills the cap. Once
inside the cap has a red-out sign, the band can be deployed (Figs. 3 and 4). After
the varix is ligated, the endoscope should not be advanced, to avoid dislodgement
of the bands, which is why banding should always commence in the most distal
portion of the esophagus near the GE junction. Bands are applied in a spiral pattern
progressing the esophagus up (proximally) until all major columns of varices of the
lower third of the esophagus (usually no more than 10 cm above the GE junction)
are banded. If there is active bleeding and there is a limited view, the bands should
be placed at the GE junction. This method reduces ongoing bleeding and further
bands can be fired afterward until active bleeding ceases.

Complications of EBL include transient dysphagia and chest pain, which are com-
mon and respond well to analgesics as well as an oral suspension of antacids. Patients
should commence liquids for the first 12 hours and then progress to soft foods.
Shallow ulcers at the site of bands are common but rarely bleed. The use of a proton
pump inhibitor per os decreases the size of ulcers but does not prevent them from
bleeding.\textsuperscript{51} Severe but rare complications, such as massive bleeding from ulcers
or rarely from variceal rupture, esophageal perforation, esophageal strictures, and
altered esophageal motility, may occur with EBL.\textsuperscript{52}

Both EST and EBL have been shown to be highly effective in the control of AVB, with
an immediate efficacy of between 80% and 90%.\textsuperscript{53} Two well-performed RCTs specif-
ically comparing EBL and EST in AVB\textsuperscript{54,55} have clearly shown that treatment with
EBL along with vasoconstrictors is associated with greater efficacy and safety, and
improved mortality, compared with EST and vasoconstrictors. In addition, in another
8 trials these 2 modalities were also compared in AVB and in the prevention of rebled-
ing. A meta-analysis of the 10 trials shows that EBL is better than EST in the initial con-
trol of bleeding, and is associated with fewer adverse events and improved mortality.\textsuperscript{56}
In addition, EST, but not EBL, may induce a sustained increase in portal pressure after
the procedure.\textsuperscript{57} Therefore, EBL should be the endoscopic therapy of choice in AVB.
Although we prefer EBL to EST for an episode of AVB, in the setting of active hemor-
rhage or torrential bleeding EBL is sometimes difficult to perform because of a lack of
visibility. Therefore, both techniques are reasonable options in the setting of AVB.

Fig. 3. Endoscopic view of large varices with red spots (left) and endoscopic view of a
successfully placed band on a varix (right).
Other Methods

Sengstaken-Blakemore tubes and esophageal stents
Balloon tamponade of the esophagus may be required in patients with uncontrolled bleeding or in patients with such massive and profuse bleeding in whom an upper endoscopy cannot safely be performed. Pneumatic compression of the fundus and the distal esophagus stops bleeding in approximately 85% of cases. The problem is that recurrence after balloon deflation, which must occur within 48 hours of placement, is high (50%) and major complications, including aspiration pneumonia and esophageal perforation, may occur in up to 30% of patients. Given the high success rates of current endoscopic and pharmacologic therapies, balloon tamponade is uncommonly performed. A recently introduced, fully covered, self-expandable metallic stent (Ella-Danis, Czech Republic) for AVB may be useful in cases for which balloon tamponade is considered (Fig. 5). The stent may be placed blindly or over a guidewire previously passed to the stomach. The stent has a distal balloon that is inflated with a syringe to ensure proper location in the gastric cardia and distal esophagus so no fluoroscopy is needed. The stent can be left in place for up to 7 to 10 days and can be retrieved by endoscopy with a hook system. Although there are limited data for its use, a multicenter RCT (published in abstract form) comparing esophageal stenting with balloon tamponade in 28 patients with AVB refractory to medical and endoscopic treatment and/or with massive bleeding precluding endoscopy has shown esophageal stents to be more effective and safer than balloon tamponade for the temporary control of AVB.

Cyanoacrylate glue and Hemospray
Although endoscopic injection of cyanoacrylate glue is mainly used for patients who bleed from gastric varices, its use has also been proposed for patients with AVB. There are 2 small studies that indicate that injection of cyanoacrylate glue (1 mL per injection) is safe and effective for patients with AVB. However rebleeding rates are higher compared with EBL. In one study, there were no technical difficulties in performing secondary prophylaxis with EBL. Other hemostasis methods seem promising as hemostatic techniques for patients with variceal bleeding. Three small
case series indicate that Hemospray (hemostatic powder), which is used for nonvariceal gastrointestinal bleeding, is effective in controlling bleeding from portal gastropathy and gastric varices, but there are no data in patients with acute esophageal variceal hemorrhage. These emerging hemostasis modalities therefore may be useful for those patients in whom EBL or EST fails to achieve primary hemostasis at index endoscopy, but additional comparative data are needed.

**Failures**

Approximately 10% to 15% of patients do not respond to the current first-line therapies. In such cases, if the patient is stable, a second therapeutic endoscopy may be performed. However, if this is unsuccessful or there is massive bleeding, the patient should be considered for TIPS because it is considered the rescue therapy of choice. This topic is beyond the scope of this article and is discussed elsewhere.

**SUMMARY**

AVB is a serious complication of patients with portal hypertension. Initial management includes appropriate volume replacement, transfusion of blood to keep Hb levels around 7 to 8 g/dL, antibiotic prophylaxis, and endotracheal intubation in selected cases. Standard of care mandates starting vasoactive drug therapy early followed by EBL or injection EST (if EBL cannot be performed) within the first 12 hours of patient presentation. Pharmacologic agents may be administered for up to 5 days. Patients who fail endoscopic hemostasis therapy may require the temporary placement of balloon tamponade or an esophageal stent. However, experience with esophageal stents is limited and the use of balloon tamponade is associated with potentially lethal complications such as aspiration and perforation of the esophagus. Therefore, both modalities should be available for potential use. All patients surviving an episode of AVB should undergo secondary prophylaxis in order to prevent variceal rebleeding.
REFERENCES


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The timing of endoscopy, and endoscopic technique are key in managing these patients. This article reviews the current endoscopic hemostatic strategies for patients with AVB.

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