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New Developments in Managing Variceal Bleeding



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Liver cirrhosis is the end stage of chronic liver disease, independent of etiology, and is characterized by accumulation of fibrotic tissue and conversion of the normal liver parenchyma into abnormal regenerative nodules. Complications include portal hypertension (PH) with gastroesophageal varices, ascites, hepatorenal syndrome, hepatic encephalopathy, bacteremia, and hypersplenism. The most life-threatening complication of liver cirrhosis is acute variceal bleeding (AVB) which is associated with increased mortality that, despite recent progress in management, is still around 20% at 6 weeks. Combined treatment with vasoactive drugs, prophylactic antibiotics, and endoscopic techniques is the recommended standard of care for patients with acute variceal bleeding. There are many promising new modalities including the combination of coil and glue injection for management of bleeding or nonbleeding gastric varices and hemostatic powder application, that requires minimal expertise, when performed early after admission of a cirrhotic patient with AVB and overt hematemesis acting as a bridge therapy till definitive endoscopic therapy can be performed in hemodynamically stable conditions and without acute bleeding.

Keywords: Portal Hypertension; Variceal Bleeding; Hemostatic Powder.

Portal hypertension is a clinical syndrome defined by pathologic increase of portal venous pressure gradient between the portal vein and inferior vena cava.[1] The hepatic venous pressure gradient (HVPG) accurately reflects the portal pressure gradient in most common causes of cirrhosis. HVPG measurement is the criterion standard method for assessing the presence of clinically significant portal hypertension (CSPH), which is defined as HVPG $\geq$ 10 mm Hg. Ascites and gastroesophageal varices are the most frequent manifestations of CSPH.[2]

The ability to assess liver stiffness, a physical property of liver tissue influenced by the amount of liver fibrosis content, has represented a major advance in this field. Liver stiffness by transient elastography (FibroScan, Echosens, France) can be considered the backbone of the noninvasive diagnosis of liver fibrosis and has proven very accurate for discriminating patients with and without CSPH, with a mean area under the receiver operating curve of 0.93.[3]

Three different risk stages have been proposed for compensated liver cirrhosis, based on 1-year mortality data: low-, intermediate-, and high-risk cirrhosis. Each category of risk is presented with the clinical features, HVPG value, main outcome to be prevented, and main pathophysiologic factor related to that category of risk. The 1-year mortality in these stages is $\leq$1%, 1%–20%, and $\geq$20%, respectively.[2,4]

Patients with a liver stiffness $<$ 20 kPa and a platelet count $>$ 150,000 have a very low risk of having varices requiring treatment and can avoid screening endoscopy.

Varices are present in 50% of patients with cirrhosis, and they form at a rate of 5%–15% per year. Variceal bleeding is the most serious complication; it occurs in one third of patients with varices and causes 70% of all upper gastrointestinal (GI) bleeding episodes in cirrhotic patients. Standardization of supportive care and new therapeutic options reduced bleeding-related mortality from about 50% to 15%–20% in the last 3 decades.[4]

Primary prophylaxis of variceal bleeding consists of one of two approaches: pharmacologic prophylaxis using nonselective beta blockers (NSBBs) or endoscopic prophylaxis using endoscopic variceal ligation (EVL). Both NSBB and EVL are superior to no treatment for the prevention of a first variceal hemorrhage in patients with medium- and large-sized varices and patients with small varices who have red signs.[4]

Propranolol and nadolol at a starting dosage of 20–40 mg/day are used in patients with good tolerability and no contraindication to beta blockers.[5,6]

Abbreviations used in this paper: **AVB, acute variceal bleeding; BRTO, balloon-occluded retrograde transvenous obliteration; CSPH, clinically significant portal hypertension; ES, endoscopic sclerotherapy; EVL, endoscopic variceal ligation; GI, gastrointestinal; HVPG, hepatic venous pressure gradient; NSBB, nonselective beta blocker; SEMS, self-expandable metallic stent.**

Most current article

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Carvedilol has been recommended at a dosage of 12.5 mg once daily for patients with Child–Turcotte–Pugh class A cirrhosis and 6.25 mg twice daily for patients with Child–Turcotte–Pugh class B or Child–Turcotte–Pugh class C cirrhosis.[4] Furthermore, the recent UK guidelines on the management of variceal haemorrhage[7] advise not exceeding 12.5 mg daily, because higher doses were not more effective in reduction of HVPG and were associated with more adverse effects.

EVL is recommended for patients with medium or large varices who are intolerant of or have contraindications to beta blockers. Its effectiveness versus NSBB for primary prophylaxis has been widely studied. The overall data suggest that EVL is as effective as NSBB with somewhat less hemorrhage but no changes in overall mortality.[8]

EVL should be performed by expert endoscopists to avoid complications including banding-induced ulcerations and bleeding. Also, patients require routine endoscopic surveillance after EVL because of the probability of variceal recurrence. The frequency of endoscopic evaluation depends on multiple factors such as whether the patient has varices or not, size of varices, risk signs, and severity of liver disease. In general, patients require 2–4 sessions for eradication of varices. Combination therapies are not recommended.[7,9]

For patients with large gastric varices, BAVENO VI consensus did not recommend cyanoacrylate injection for primary prophylaxis of gastric variceal bleeding.[10] For the time being, patients with gastric varices should continue to receive NSBB for primary prophylaxis. There are no data supporting the use of transjugular intrahepatic portosystemic shunting (TIPS) or surgery for primary prophylaxis.[2]

Acute variceal bleeding (AVB) mortality differs whether it presents as an isolated complication of cirrhosis (20% 5-year mortality) or whether it presents in association with other complications (over 80% 5-year mortality). Rebleeding contributes to an important part of mortality that ranges between 15% and 25% at 6 weeks.[11]

Management of the Acute Variceal Bleeding Episode

Pharmacologic therapy should be started in all patients with advanced cirrhosis and upper.

GI bleeding known or at risk for having varices.[4,12]

Vasoactive drugs, selectively constricting the mesenteric arterioles and decreasing portal blood flow, are used as initial treatment of AVB before endoscopy. Many studies have shown that the early use of vasoactive drugs reduces the rate of active bleeding, making endoscopy easier to perform for diagnostic and therapeutic purposes.[13] These include vasopressin, somatostatin, and their analogs (terlipressin and octreotide, respectively). Improved hemostasis and reduced 7-day mortality, transfusion requirement, and duration of hospitalization have been confirmed in many studies.[14] The combination of vasoactive drugs with EVL was clearly shown to be superior to EVL alone for improvement of the 5-day success rate.[7,15]

Available evidence does not support a role of proton pump inhibitors for long-term prophylaxis of portal hypertension-related bleeding; however, the use of short-course proton pump inhibitor postendoscopic variceal ligation could reduce postbanding ligation ulcer size.[16]

The use of an intravenous prokinetic agent (e.g., erythromycin) should be considered during the pre-endoscopy patient management phase. Barkun et al[17] reported that an intravenous infusion of different prokinetic agents administered up to 2 hours before endoscopy in patients with acute upper GI bleeding improved endoscopic visualization and significantly decreased the need for repeat endoscopy.

Sedation use before diagnostic endoscopy is routine in North America and Australia but varies considerably among countries in Europe, Asia, and Africa.[18] Midazolam and propofol are both widely used for EVL. The role of general anesthesia with endotracheal intubation is still controversial and cannot be routinely recommended.[19]

Endoscopic sclerotherapy (ES) and EVL are the 2 available endoscopic methods for treating bleeding esophageal varices. ES consists in the injection of a sclerosing agent intravariceally or paravariceally. A variety of sclerosant solutions are used, the most common being ethanolamine oleate (5%), polidocanol (1%–2%), and cyanoacrylate, which proved equally effective for bleeding esophageal varices.[20] Emergency ES for bleeding esophageal varices was shown to be an effective procedure in expert hands[21]; however, it is no longer recommended as the first line of treatment because of high complication rate (systemic bacteremia being the most frequent).[22]

EVL is the standard care for management of AVB.[2] Actively bleeding varices or those with stigmata indicating recent bleeding (such as a fibrin plug or a “red wale” sign) should be primary targets even if they are not located at the gastroesophageal junction. The use of ligating devices may be difficult in patients with severe bleeding because of limited visibility caused by blood accumulating in the tip of the device.[23] It requires experience in therapeutic endoscopy.

After the initial target, additional banding can be performed and is started in the most distal part of the esophagus at the gastroesophageal junction. Bands are applied in a spiral pattern up the esophagus until 28 cm from incisors on all major columns of varices (Supplementary Video 1). For the next procedures, a 1-week ligation interval is often recommended.[24] The decision regarding ligation intervals may be individualized based on physician and patient preferences and local logistics and resources.

EVL combined with a vasoactive drug is considered the standard care for AVB, and it is currently recommended by BAVENO VI.[2] Combining EVL and ES has no advantage.[25] Other techniques such as APC, microwave cautery, and clipping play no role, may be dangerous, and must be avoided.[26,27]

Gastric varices are present in up to 20% of patients with portal hypertension; 65% of these patients bleed within 2 years.[28]

Cyanoacrylate injection is the globally accepted primary intervention for bleeding gastric varices and is highly satisfactory in controlling bleeding.[29] It has proven to be more effective and safer than band ligation and sclerotherapy in this subset of patients and has been considered as standard therapy in Europe, the Middle East, and Asia for more than 25 years.[30]

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In our daily practice, we use always a mixture of *N*-butyl-2-cyanoacrylate and lipiodol for bleeding gastric varices using a dedicated 21-gauge needle with the purpose of obliterating the bleeding gastric varices and those at risk to bleed (Supplementary Video 2).[31]

Novel Endoscopic Modalities for Variceal Bleeding

Self-Expandable Metallic Stents (SEMSs)

Dedicated fully covered SEMS (ELLA Danis, Hradec Kralove, Czech Republic) may provide a useful alternative in those cases for which balloon tamponade is considered.[32] In a recent meta-analysis included 13 studies, mainly case series, ranging from 2 to 34 patients (134 patients total) with refractory bleeding from esophageal varices, a SEMS was successfully placed in 95% of patients, achieving hemostasis within 24 hours in 96%.[33] Overall, the pooled estimate rates for failure to control bleeding during follow-up was 0.18.

The major adverse events include rebleeding after 48 hours, ulceration, rebleeding after removal (16%), and stent migration (28%). Hence, retrieval of the stent is recommended within 7 days to avoid development of pressure-induced ulceration of the esophageal wall.[33]

This technique finds a niche of application mainly for patients with esophageal (and not gastric) bleeding varices for whom hemostasis cannot be controlled by pharmacologic or drug therapy. In this high-risk group of patients, SEMS could be considered as a bridge to transjugular intrahepatic portosystemic stent shunting or liver transplantation.

Hemostatic Powder

Recently, hemostatic powders have been added to the endoscopic armamentarium to treat GI bleeding. There are three hemostatic powders currently available for endoscopic usage: hemostatic agent TC-325 (Hemospray; Cook Medical, Bloomington, IN), EndoClot polysaccharide hemostatic system (EndoClot Plus, Santa Clara, CA), and Ankaferd Bloodstopper (Ankaferd Health Products Ltd, Istanbul, Turkey). All three powders, when they have contact with moisture, form a stable mechanical barrier that covers the bleeding site, inducing hemostasis. Only the first one has been investigated in AVB management.

Hemostatic powder (Hemospray) is delivered endoscopically through a dedicated delivery system. It acts as a mechanical barrier when put in contact with moisture (e.g., blood or tissue) in the GI tract: the powder becomes cohesive and adhesive, forming a mechanical barrier that adheres to and covers the bleeding site, achieving very rapid hemostasis.[34] After approximately 24 hours, the adherent layer subsequently sloughs off into the lumen from the mucosal wall and is eliminated from the GI tract.[35]

This technique requires minimal experience in therapeutic endoscopy, a feature that might help solve the problems of delay between admission and definitive endoscopic therapy due to a lack of available expertise. This hemostatic powder is currently licensed for endoscopic hemostasis of nonvariceal upper GI bleeding,[35] including high-risk patients receiving anticoagulant or antithrombotic therapy,[36] those with tumor-related bleeding, and those with lower GI bleeding.[37] In severe peptic ulcer bleeding, it is often considered as a (temporary) salvage therapy.[38]

Hemospray was reported to be useful in emergency management of AVB as an added treatment modality to the medical management before definitive endotherapy, with no major adverse events or device-related mortalities.[39]

There is theoretical risk of gas embolization due to high-pressure gas delivery of the hemostatic agent to the bleeding site; however, the risk of embolization in this group of patients is most probably low because of the fact that the technique is a noncontact application with delivery pressure less than 15 mm Hg, that is, most often inferior to intravariceal pressure.[40] However, use of hemostatic powder in variceal bleeding is off label, and it should be used only within research protocols with institutional review board approvals.

The timing of endoscopic hemostasis in AVB has been a topic of intense recent discussion. The current recommendations for management of AVB combine vasoactive drugs at admission with endoscopic therapy within 12 hours plus prophylactic antibiotics, although the availability of an on-call, experienced GI endoscopist proficient in endoscopic hemostasis is not always easy in most centers, a limitation that raised the need for a bridging maneuver until more definitive endoscopic therapy could be provided.[40]

We recently performed a randomized controlled trial in which 86 patients with AVB were randomized to receive medical therapy plus classical endotherapy within 12–24 hours of admission or medical treatment plus hemostatic powder application within 2 hours of admission (Supplementary Video 3) followed by classical endotherapy within 12–24 hours. This novel policy consisting of early application of a hemostatic powder in addition to standard pharmacotherapy and endotherapy significantly reduced clinical rebleeding within 24 hours compared with standard pharmacotherapy plus endotherapy alone and had an impact on early and 30-day survival,[41] suggesting a role for this powder as a bridge therapy.

Also, hemostatic powder application had been studied on a small scale for such difficult bleeding situations as postbanding ligation ulcer[42]; however, to date the only validated option in this situation is a high dose of proton pump inhibitors and injection of cyanoacrylate underneath the ulcer.[43]

Transjugular Intrahepatic Portosystemic Shunting

TIPS involves the creation of a low-resistance channel between the hepatic vein and the intrahepatic portion of the portal vein (usually the right branch) using angiographic techniques. The tract is kept patent by deployment of a dedicated expandable metal stent across it, thereby allowing blood to return to the systemic circulation. Positioning of TIPS as a rescue treatment has been challenged in recent studies, which recommend TIPS as the initial treatment of choice in high-risk patients, which improves their prognosis.[44]

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TIPS with covered stents is the rescue therapy of choice if combined pharmacologic and endoscopic treatment have failed. Rebleeding during the first 5 days may be managed by a second attempt at endoscopic therapy, and if severe, polytetrafluoroethylene-covered TIPS is likely the best option.[45]

Randomized controlled trials have shown that, compared with standard therapy, early TIPS (placed within 72 hours of admission) is associated with significantly lower treatment failure and mortality rates in carefully selected high-risk patients with Child-Pugh class B liver cirrhosis and active bleeding during endoscopy or patients with Child-Pugh class C liver cirrhosis. Furthermore, any patient who experiences rebleeding should be considered for TIPS placement.[4] Even if clinical evidence exists for selected patients that TIPS is the treatment of choice after initial failure of endotherapy,[46] its availability within the recommended time frame (48–72 hours) remains a matter of concern in many places.

Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)

From the interventional radiologist's perspective, the main tools available for the management of gastric varices are TIPS and BRTO.

BRTO is an interventional radiologic technique that involves occluding blood flow by inflation of a balloon catheter within a draining vessel, followed by instillation of a sclerosant proximal to the site of balloon occlusion.[47]

BRTO requires the presence of a spontaneous shunt into which a balloon catheter is retrogradely introduced. Ethanolamine oleate has been used most commonly in Asia as a sclerosant.[48]

However, reported complications include renal dysfunction, pulmonary edema, cardiogenic edema, and anaphylaxis.

A recent meta-analysis of a total of 1016 patients from 24 studies showed that the technical success rate for BRTO was 96.4%, the clinical success (defined as no recurrence or rebleeding of gastric varices, or complete obliteration of varices on subsequent imaging) rate was 97.3%, and the esophageal variceal recurrence rate was 33.3%.[48]

Endoscopic Ultrasonography (EUS)–Guided Angiotherapy

In the last few years, EUS-guided vascular access and injection emerged as a new option to achieve hemostasis. EUS provides real-time, high-quality images of both the GI wall and major arterial and venous vessels like the confluence, splenic artery, and hepatic artery that can be accessed and obliterated.[49]

This technique may allow a rescue EUS-guided therapy via injection of cyanoacrylate or insertion of coils.

The safety and efficacy of the EUS-guided sclerotherapy were shown in a randomized controlled trial that compared endoscopic sclerotherapy with EUS-guided sclerotherapy in which 50 cirrhotic patients were randomized to undergo either endoscopic sclerotherapy or EUS-guided sclerotherapy. EUS-guided sclerotherapy was at least as effective as endoscopic sclerotherapy, with a lower recurrence rate.[50]

EUS has a higher sensitivity to detect gastric varices because even in situations with active bleeding or clots in the stomach, EUS visualization is not impaired, enabling a safer and faster therapeutic hemostatic procedure. Romero-Castro et al[51] compared cyanoacrylate injection with coil deployment and showed a similar efficacy but fewer adverse events in the coil group (9%) compared with the cyanoacrylate injection group (58%). It must be noticed, however, that 9 of the 11 complications observed in the cyanoacrylate group were asymptomatic glue micro-embolisms observed in the lungs on computerized tomography scan.

As an alternative approach to glue injection, coils usable for intravascular embolization treatments via EUS fine needle aspiration have become commercially available. Hence, combining coil and cyanoacrylate (Supplementary Video 4) is a hybrid approach that may offer the advantages of both techniques. When used in conjunction with cyanoacrylate injection, coils may favor immediate polymerization of the glue and reduce the risk of embolization. The synthetic fibers ("wool coils") covering the coils function as a scaffold to retain cyanoacrylate within the varix and may decrease the amount of glue injection needed to achieve obliteration.[52]

A recent series was published regarding combining cyanoacrylate and coil for the treatment of gastric fundal varices with more than 150 patients. Technical success was 99%; the mean number of inserted coils was 1.4, and the mean amount of cyanoacrylate injected was 2 mL. To our knowledge, there are no data analyzing the cost of using coils for hemostatic EUS-guided procedures.[53]

Limitations of coils include the relative technical difficulty of deploying multiple coils within the varix lumen and the cost when multiple coils are required for varix obliteration.

Conclusions

The management of variceal bleeding combining appropriate medical support, pharmacologic therapy, and endoscopic treatment is well established. TIPS has become a new modality that should be offered, if possible, early after a first episode of bleeding in patients with severe liver diseases. Other new modalities might find their place in the future armamentarium to improve the outcomes of these patients. In the case of failure to control bleeding from esophageal varices, temporary stent placement may offer a bridge to TIPS or liver transplantation.

Gastric varices are usually considered more difficult to manage, and glue injection is associated with potential risks. EUS-guided coil application, used alone, offers a possible alternative with a lower risk and is particularly useful in areas where variceal obliteration with cyanoacrylate is not approved. The combination of coils and glue might offer a lower-risk alternative at a reasonable cost. Finally, in the case of relapsing bleeding due to gastric varices and TIPS contraindication, BRTO could find a niche of application.

The powder application by endoscopy is a simple technique that does not require expertise in endotherapy; it

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could be proposed with few logistical hurdles early after clinical presentation, offering a possibility for early hemostasis that could potentially improve outcomes and lead to elective therapy in stable conditions. Its role as a rescue therapy for failure of elective therapy or early relapse of bleeding after EBL should not be neglected.

All of these modalities may influence different parts of variceal management. Some have not yet found their place in the currently accepted recommendations for treatment, but it is highly probable that their roles will soon be better defined in improving overall outcomes for these patients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.02.023.

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Conflicts of interest
The authors disclose no conflicts.

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