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REVIEW

Variceal Bleeding: Beyond Banding

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Abstract
Despite advances in the management of complications of portal hypertension, variceal bleeding continues to be associated with significant morbidity and mortality. While endoscopic variceal band ligation remains first line therapy for treating bleeding and high-risk non-bleeding esophageal varices, alternate therapies have been explored, particularly in cases of refractory bleeding. The therapies being explored include stent placement, hemostatic powder use, over-the-scope clips and others. For gastric variceal bleeding, endoscopic ultrasound-guided therapies have recently emerged as promising interventions for hemostasis. The aim of this article is to highlight these alternative therapies and their potential role in the management of gastric and esophageal variceal bleeding.

Keywords Variceal bleeding · Band ligation · Sclerotherapy · Esophageal stent · Coil therapy

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Introduction

Gastroesophageal varices are dilated submucosal veins that occur in the esophagus and/or stomach and can result in life-threatening gastrointestinal bleeding. Up to half of patients with cirrhosis will have underlying gastroesophageal varices with the presence of varices typically correlating with the severity of liver disease [1, 2]. While gastroesophageal varices may be asymptomatic, variceal hemorrhage is a feared complication and has been observed to occur at an annual rate of 5–15% [1, 3]. Common predictors of variceal bleeding include variceal size, decompensated cirrhosis, and evidence of high-risk stigmata such as platelet plugs or red wale signs [3]. Hepatic venous pressure gradient (HVPG), a surrogate indicator for portal hypertension, has been demonstrated to predict the risk of variceal bleeding, with higher pressure correlating with bleeding and increased mortality [4]. The mortality of variceal bleeding at 6 weeks after index bleed is 20% [5]. Recurrent variceal bleeding after index bleed is most common in the first 5 days after index bleed

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[6]. Rates of recurrent bleeding ranges between 30 and 40% at 6 weeks but decreases after 6 weeks [6].

Management of non-bleeding esophageal varices traditionally involves endoscopic variceal band ligation (EVBL) or medical management with beta-blockers. For actively bleeding esophageal varices, EVBL is the endoscopic treatment of choice. However, failure to control variceal bleeding can be as high as 20% [7, 8]. It therefore behooves the endoscopist to be familiar with non-banding endoscopic modalities as rescue maneuvers. Other non-banding endoscopic interventions include injection therapies, which entails the injection of sclerosants or glue to assist with variceal obliteration. Novel endoscopic therapies include esophageal stent placement for treatment of refractory bleeding and the use of hemostatic powder. Although not in formal guidelines, the use of hemostatic clips and argon plasma coagulation has also been described.

For cardiofundal gastric varices (Sarin Classification IGV-1 and IGV-2) and gastroesophageal varices type 2 (GOV-2), endoscopic injection of synthetic glues, thrombin, and sclerosants have been employed. More recently, endoscopic ultrasound (EUS) has been emerged as a powerful tool to assist with glue or sclerosant injection while assessing for real-time variceal blood flow [9]. Additionally, EUS-guided injection of hemostatic coils, with and without glue or sclerosants, has demonstrated high clinical and technical success rates [9].

This review will highlight endoscopic treatment modalities for the management of gastroesophageal varices, beyond EVBL. It is important to acknowledge that endoscopic therapies are local therapies that do not diminish portal flow or resistance. Therefore, many of the endoscopic therapies described herein are commonly used in conjunction with other portal hypertension altering therapies. This review will also discuss endoscopic options for gastric varices, including novel interventions beyond direct injection therapy of gastric varices with synthetic glues.

Esophageal Variceal Banding Ligation (EVBL)

Endoscopic variceal banding ligation (EVBL) is the initial choice of therapy for the treatment of bleeding esophageal varices and is recommended as a first line option for the treatment of medium to large varices that have not bled in patients with cirrhosis [1]. EVBL uses cap suction to capture a varix with the goal of placing a small rubber band at the base of the captured varix (Fig. 1). This results in partial or complete decompression of the variceal column and occlusion of the captured varix from thrombosis. The thrombosed varix eventually necroses and sloughs off, leaving a post-band scar.

While not the focus of this review, understanding the history of EVBL in the management of esophageal varices is instructive. EVBL was developed as an alternative to injection sclerotherapy, which despite being effective in hemostasis, carries risk of perforation, bleeding, mediastinitis, and other complications. The idea of a band ligation was first described by Swain et al. [10] but initially applied to endoscopic mucosal resection. Stiegmann developed the use of a bander for EVBL in the 1980s, which eventually led to the development of the single-shot Stiegmann-Goff band ligation device [11]. Subsequently, numerous studies revealed the effectiveness of band ligation for treating variceal bleeding including a landmark multicenter randomized controlled study in 1992 demonstrating the superiority of variceal band ligation over injection sclerotherapy for bleeding esophageal varices [12]. The band ligator continued to evolve with Saeed developing a multiband device now commonly known as the Saeed six shooter (Cook Medical, Winston Salem, NC) [13]. EVBL remains the cornerstone of esophageal variceal treatment, with numerous studies confirming its superiority when compared to endoscopic injection sclerotherapy [14–18]. The American Association for Study of Liver Diseases (AASLD) practice guidelines currently recommend non-selective beta-blockers, carvedilol, or EVBL for the prevention for index variceal bleed in patients with medium or large esophageal varices and EVBL for patients with acute variceal bleeding

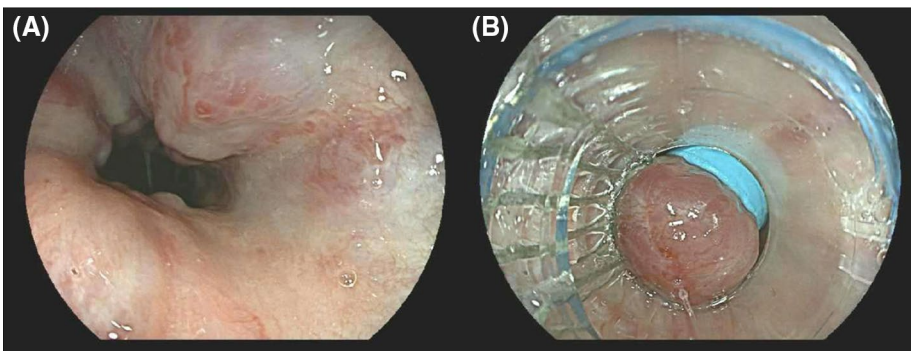

Fig. 1 Endoscopic variceal banding ligation (EVBL). (**A** esophageal varix; **B** banding ligation)

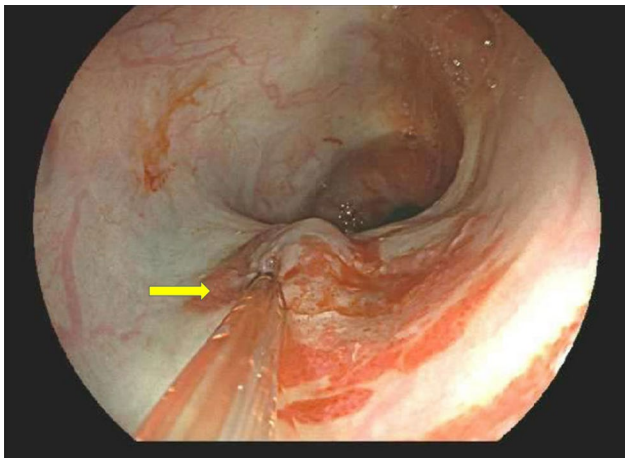

Fig. 2 Injection therapy (arrow denotes sclerotherapy needle entering varix)

[1]. The American Society for Gastrointestinal Endoscopy (ASGE) as well as the European Society of Gastrointestinal Endoscopy (ESGE) has also recommended EVBL in patients with acute variceal bleeding or those with stigmata of recent bleeding [19, 20].

Direct Variceal Injection Therapies

Endoscopic Injection Sclerotherapy

Endoscopic injection sclerotherapy involves the injection of a sclerosing agent directly into a varix with the goal of causing thrombosis with subsequent vascular obliteration [21] (Fig. 2). This treatment option was first introduced in 1939 by Crafoord and Frenckner, and, prior to the introduction of variceal band ligation, was the standard of care for management of bleeding esophageal varices in the USA [22, 23]. Despite its less frequent use in Western countries for treating esophageal variceal bleeding, injection sclerotherapy remains a treatment option that endoscopists may fall back to, particularly in cases where visualization for EVBL is inadequate or unsuccessful.

Several agents have been used for injection sclerotherapy. These include but are not limited to sodium tetradecyl sulfate, polidocanol (not approved for use in the USA), sodium morrhuate, ethanolamine oleate, and ethanol alcohol [23]. The agent of choice is determined by country of use, cost, and location of varices. In addition to variability in agent used, the technique by which a sclerosant is injected can vary as well. Intravariceal injections are performed with the aim of causing thrombosis of the varix but can be associated with more intraprocedural bleeding, while paravariceal injections are meant to tamponade the varix and ultimately cause endofibrosis. Most agents can be used with either technique; however, in a prospective RCT, intravariceal injection was associated with better control of active variceal bleeding and for variceal obliteration, but was associated with higher recurrence [24, 25]. However, ethanol alcohol and sodium tetradecyl sulfate have both been associated with increased adverse events when injected into the paravariceal area [23].

The adverse events profile of injection sclerotherapy partially explains its limited scale of use. A meta-analysis including 14 studies comparing EVBL to injection sclerotherapy found that sclerotherapy alone was associated with a higher rate of esophageal ulcers, perforations and strictures [24–26]. This conclusion, however, was limited by the fact that the sclerosing agents studied in the individual papers were not identified. Less common complications that have been reported include esophageal or gastric dysmotility, pneumonia, mediastinitis, and spontaneous bacterial peritonitis. In addition to the above, bacteremia has been described in up to 52% of patients undergoing injection sclerotherapy, leading to recommendations that immunocompromised patients (including those with cirrhosis), patients with mechanical prosthetic devices, vascular grafts or shunts, or ascites should receive prophylactic antibiotics prior to sclerotherapy [20, 27].

Injection Therapy with Cyanoacrylate

Cyanoacrylate (n-butyl-2 cyanoacrylate), a synthetic glue or adhesive that rapidly polymerizes when in contact with liquid, has been explored for the treatment of esophageal variceal bleeding. While cyanoacrylate carries a more established role in the endoscopic management of gastric variceal hemorrhage, it has also been studied in esophageal variceal bleeding. Several studies have compared cyanoacrylate injection with sclerotherapy [28]. For example, one study comparing injection sclerotherapy with 3% ethanolamine oleate to cyanoacrylate injection in the management of esophageal variceal bleeding in patients with Child Pugh class C cirrhosis reported a significantly lower re-bleeding and in hospital mortality rate in the patients treated with cyanoacrylate injection. There was also a lower rate of treatment failure requiring interventional radiologic (IR) intervention in the cyanoacrylate group [29]. A more recent study by Elsebaey et al. comparing 5% ethanolamine oleate to cyanoacrylate in the management of esophageal variceal bleeding found that control of bleeding was significantly higher in the cyanoacrylate group (98%) compared with the sclerotherapy group (84%) ($p=0.007$). Other outcomes evaluated included re-bleeding rate, complications, hospital stay, and 6-week mortality—all of which did not demonstrate any significant differences between both groups. Complications observed during the study included retrosternal pain,

dysphagia, fevers, and spontaneous bacterial peritonitis. Reassuringly, systemic embolic complications of cyanoacrylate were not observed in the study [30].

Cyanoacrylate injection has also been compared to EVBL for bleeding esophageal varices. Santos et al. performed a randomized trial comparing EVBL to cyanoacrylate injection in the treatment of medium/large esophageal varices in patients with Child–Pugh scores of 8 or greater. No difference was observed in the mean number of treatment sessions required until variceal eradication, mortality, or major complication rates (major complications defined as esophageal stenosis, esophageal ulcer bleeding, and cyanoacrylate embolization). They did, however, report a statistically significant higher rate of chest pain with dysphagia in the cyanoacrylate group [31]. More recently, Naga et al. performed a retrospective study evaluating the use of EVBL versus cyanoacrylate in the treatment of actively bleeding esophageal varices. Their study included a total of 401 patients. While both methods effectively achieved hemostasis in 92% and 97%, respectively, they found that re-bleeding occurred more frequently in the EVBL group ($p = 0.01$). Meanwhile, 6-week mortality and hospital length of stay were comparable in both groups [32].

It is important to note that while cyanoacrylate injection is a promising option for the management of esophageal varices, there remains some concern with its use, many of which have been demonstrated with its use in gastric variceal bleeding. Cyanoacrylate can be damaging to endoscopes, cause de-roofing of varices when needle is withdrawn and lead to systemic embolization. Complications of injecting acrylate polymers are discussed in the section on gastric variceal management. While cyanoacrylate has been mentioned and endorsed by AASLD in its guidelines on management of gastric varices, its role in the management of esophageal varices has not been endorsed. ESGE, British, and other international guidelines also do not comment on the use of cyanoacrylate for the management of esophageal variceal bleeding.

Hemostasis for Endoscopic Variceal Banding Ligation and/or Injection Sclerotherapy Failure

Balloon Tamponade

Historically, balloon tamponade has provided a means of rescue therapy and a bridge to more definitive therapy (e.g., transjugular intrahepatic portosystemic shunt (TIPS)) when conventional endoscopic options fail to control variceal bleeding. Balloon tamponade is effective in achieving hemostasis in esophageal variceal bleeding by applying lateral pressure to the esophageal wall which results in tamponade of the submucosal varices (Fig. 3a). Commercially available balloons include the Sengstaken–Blakemore tube, Minnesota tube, and Linton-Nachlas tube (Fig. 3b). While balloon tamponade can achieve bleeding control in up to 90% of cases, it is associated with severe complications such as aspiration pneumonia, esophageal ulceration, and rarely esophageal rupture [33–38]. Rates of re-bleeding can be as high as 50%. It is therefore recommended that these balloons do not remain in place for more than 24 h to avoid such complications [20, 38–40].

It is imperative that physicians caring for patients with variceal bleeding understand the role of balloon tamponade therapy and how to place these devices. Providers should familiarize themselves with the different types of balloons available at their institutions (Fig. 4). Balloon tamponade devices are usually placed at the bedside after airway protection is secured. The gastric balloon should be minimally inflated to ensure appropriate positioning (confirmed on X-Ray) below the diaphragm. Once confirmed, the gastric balloon can be inflated to its maximum manufacturer-suggested volume. While many may opt to keep the esophageal balloon deflated and allow for tamponade to occur using the gastric balloon alone, the esophageal balloon can be inflated (using target mmHg recommended by manufacturer) to provide additional hemostasis.

Endoscopic Hemostatic Powder

Endoscopic hemostatic powders have primarily been used for the treatment of non-variceal upper GI bleeding. Various studies have confirmed its safety and efficacy in achieving hemostasis in both upper and lower gastrointestinal bleeding [41–44]. Hemostatic powders absorb water when in contact with liquid mediums, such as blood, resulting in the formation of a mechanical barrier (Fig. 4). Commercially available hemostatic powders include Hemospray®, Endoclot® and Ankaferd® [45]. TC-325 (Hemospray; Cook Medical, Winston Salem, NC, USA) is a recently FDA-approved (2018), inert hemostatic powder indicated for the treatment of non-variceal upper GIB [46]. Several case reports and series have been published highlighting its potential role in the treatment of acute variceal bleeding, including both esophageal and gastric variceal bleeding [47–49]. In a randomized controlled trial by Ibrahim et al., patients with acute variceal bleeding who received hemostatic powder followed by early elective endoscopy had less need for emergency rescue endoscopy compared to patients only undergoing early elective endoscopy. This group was also found to have to improved 6-week survival rates [50]. The use of Hemospray for variceal bleeding currently remains off-label and is usually employed when standard endoscopic modalities for variceal hemostasis have failed. Temporary hemostasis with Hemospray may act as a temporizing measure or

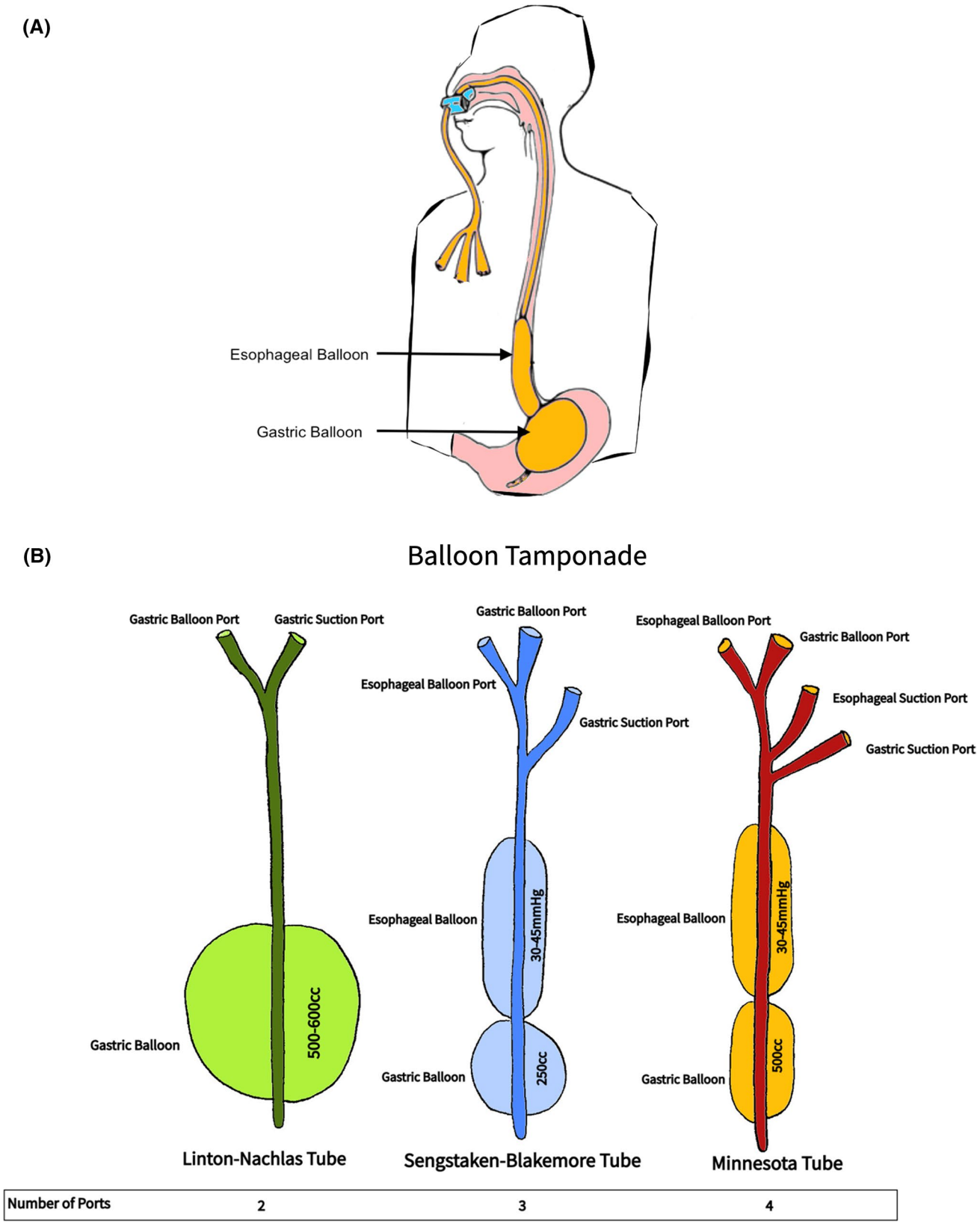

Fig. 3 **a** Balloon tamponade therapy. **b** Different types of balloon tamponade devices

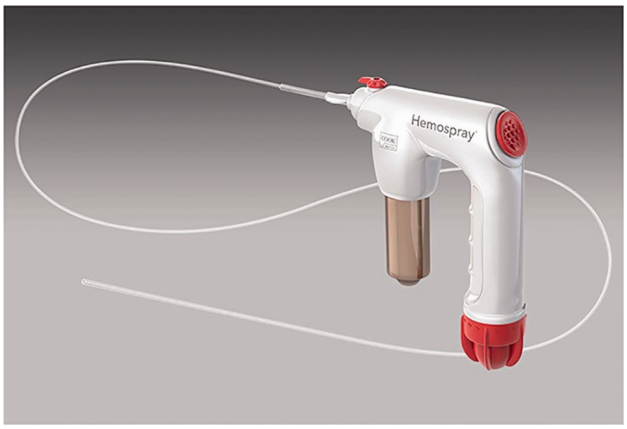

Fig. 4 Hemospray (cook medical)

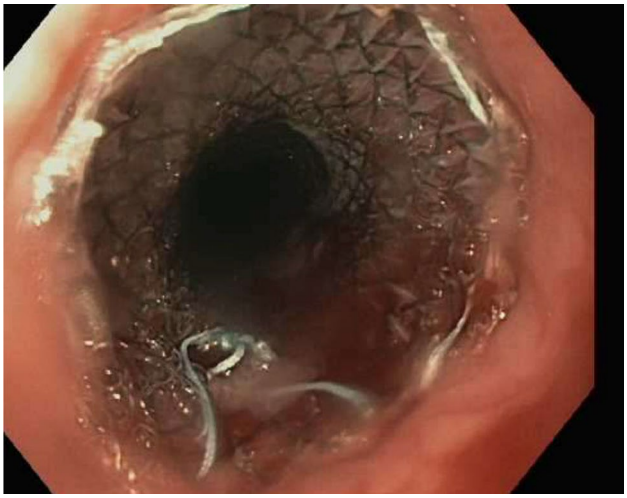

Fig. 5 Esophageal stent for esophageal variceal bleeding

bridge to definitive intervention. Further studies are required to evaluate the potential of hemostatic powders in variceal bleeding, particularly when standard endoscopic options are unsuccessful.

Endoscopic Stent Placement for Refractory Esophageal Bleeding

More recently, self-expanding metal stents (SEMS) have been used as bridging tamponade therapy in patients with esophageal varices refractory to standard endoscopic measures (Fig. 5). SEMS have a more favorable safety profile and can be left in place for up to 2 weeks, whereas a balloon should only be left in place for 24–48 h, after which the risk of developing esophageal ulcers increases [51]. SEMS for variceal bleeding can be placed through-the-scope or over a guidewire with endoscope assistance. Commonly used through-the-scope esophageal stents that can be deployed without fluoroscopic assistance include SX-Ella stent Danis (Ell-CS, Hradex Kralove, Czech Republic) and Taewoong Niti-S stent (Cook Medical). Other manufacturers have developed similar stents which are being used in clinical practice. These stents are advantageous in that they are placed endoscopically and can target the specific site of bleeding with low risk of perforation [52]. It is important to note that the SX-Ella stent Danis is the only stent developed for refractory variceal bleeding tamponade per manufacturer recommendations; however, while available in Europe and included in esophageal bleeding studies, it is not available in the USA. The use of currently available and approved through-the-scope stents in the USA such as Hanarostent (Olympus America, Center Valley PA), Agile (Boston Scientific, Marlborough MA), and Niti-S for refractory variceal bleeding is considered off-label use.

A study by Hubmann et al. examining esophageal stents for massive esophageal variceal bleeding in 20 patients revealed high technical success rate and immediate cessation of bleeding in all cases. All stents were removed after 2–14 days without any complications [53]. A multicenter study of 34 patients showed that SEMS controlled variceal bleeding in approximately 80% of patients but there was early re-bleeding within 6 weeks and mortality remained high [54]. In a randomized controlled trial by Angels et al. comparing balloon tamponade and covered SEMS placement in patients with refractory esophageal variceal bleeding, SEMS was associated with more frequent control of bleeding, lower transfusion requirements, and lower serious adverse events. There were no significant differences in 6-week survival (54% vs 40%; $p=0.46$) [55]. A meta-analysis by Babu et al. comparing SEMS to TIPS for refractory esophageal variceal bleeding showed SEMS to be associated with higher all-cause mortality, as well as lower immediate bleeding control rates and re-bleeding rates compared to TIPS. However, SEMS and TIPS were comparable in terms of adverse events (37% SEMS vs 41% TIPS), with stent migration being the most common AE in patients with SEMS placement, seen in more than one-third of patients (31.8%) [56]. A randomized controlled trial by Escorsell et al. comparing balloon tamponade to esophageal stent (SX-ELLA Danis, Ella-CS, Czech Republic) in patients with refractory variceal bleeding revealed that esophageal stent placement was associated with higher success of therapy (66% vs 20%, $p=0.025$) and control of bleeding (85% vs 47%, $p=0.037$), with lower blood transfusion requirements (2 units PRBC vs 6 units PRBC, $p=0.08$) and serious adverse events (15% vs 47%, $p=0.077$). While there were no differences in survival, the need for TIPS was more frequent in the balloon tamponade group [57].

While SEMS, hemostatic powder, and balloon tamponade devices are used as bridge to definitive therapy, the decision to choose one of these modalities over another depends on several factors, including physician expertise, resource availability, and extent of bleeding. Torrential large volume variceal bleeding may make Hemospray deployment limited as the catheter may become obstructed with blood preventing the release of Hemospray powder. Not all centers carry through-the-scope esophageal stents which have only more recently been introduced. Finally, balloon tamponade requires reasonable understanding of the device, appropriate placement and ability to trouble shoot the device. Head-to-head studies between these rescue therapies remain limited. Our recommendation when resources and expertise are available is to use esophageal stents for refractory bleeding over hemostatic powders or balloon tamponade. If stents are not available, balloon tamponade should be recommended before proceeding with IR-guided definitive interventions.

Other Endoscopic Interventions

Hemostatic Clip Placement

Endoscopic hemostatic clips have primarily been used for the treatment of non-variceal upper and lower gastrointestinal bleeding such as ulcers and Dieulafoy lesions. While no standardized treatment recommendation is available, hemostatic clips can be used in patients with bleeding from post ligation esophageal ulcers [58]. However, the use of clips for the management of variceal bleeding is less established without robust literature to support its use. The use of clips for the treatment of variceal bleeding was first described by Miyoshi et al. in 1990. From there, few case reports have demonstrated the potential use of clips for variceal bleeding hemostasis. Yol et al. [59] conducted a prospective study comparing endoscopic clipping to band ligation in bleeding esophageal varices. Their study revealed endoscopic clipping had similar eradication rates as endoscopic banding, with clipping having significantly lower number of sessions to achieve eradication. Re-bleeding rates were similar between both groups [59]. Urita et al. [60] demonstrated the combined use of endoscopic clipping with intravariceal and paravariceal injection sclerotherapy in 51 patients. This combination therapy was deemed effective in 45 patients (88%).

Additionally, cap-mounted clips such as over-the-scope clips (OTSC, Ovesco Endoscopy, Tubingen, Germany), while used mostly for non-variceal bleeding and closure of gastrointestinal defects [61, 62], have also been investigated in the management of variceal bleeding. Many of the studies have been limited to isolated case reports or case series [63–65]. One study included 5 patients with acute variceal bleeding from small varices treated with over-the-scope clip after failure of EVL. Bleeding halted in all patients without adverse events at 30 days. However, two patients developed solid food dysphagia at 3 months requiring clip removal [66]. A more recent study of 21 patients with variceal bleeding treated with over-the-scope clip revealed an immediate hemostasis rate of 100%. However, 3 patients had recurrent bleeding within 7 days. No adverse events were observed [67].

Further studies will need to evaluate the full potential of through-the-scope and cap-mounted clips for variceal bleeding, particularly as to how they compare to more traditional methods of variceal hemostasis.

Argon Plasma Coagulation

Argon plasma coagulation (APC) is a non-contact thermal method of hemostasis that has proven efficacy in endoscopic management of various gastrointestinal diseases. Its application is commonly employed in the management of residual polyps, non-variceal bleeding and angiodysplasia. Several studies have investigated the role of APC in the management of esophageal variceal bleeding. A randomized controlled trial of 60 patients with esophageal varices evaluated the role of EVBL plus APC to EVBL alone. The hypothesis was that APC may provide additive benefit by promoting mucosal fibrosis. The authors revealed that the cumulative recurrence rate of varices was significantly lower in the combined group than the EVBL group. While the incidence of complications was similar between both groups, there was a high incidence of fevers in the combined group [68]. Increased issues with swallowing were noted in some studies with combination therapy. A similar study in 2017 including 40 patients in a randomized controlled trial revealed that APC after esophageal variceal banding ligation resulted in less recurrent esophageal varices and need for re-banding when compared to EVBL alone [69]. While several prospective single arm and comparative randomized studies on EVBL plus APC have replicated this data with similar results, demonstrating safety and efficacy of this combination therapy, there still remains a paucity of data on this combination modality with additional well-designed studies required before its use in common clinical practice [70–72].

APC has also been combined with injection sclerotherapy (IS) in the management of esophageal varices. Deguchi et al. [73] revealed in a single-center case–control study that the 1-year and 2-year recurrence rate of varices was significantly lower in the IS + APC group than the IS group alone without the presence of APC related adverse events. A similar study of APC + IS using 1% polidocanol resulted in significantly reduced recurrence of esophageal varices [74]. An interesting study by Takayuki et al. demonstrated that IS and APC resulted in esophageal variceal eradication in all 48 patients

included. However, the authors revealed that HVPG did not change post-combination therapy confirming the absence of portal pressure effect using this technique. The presence of submucosal vessels in the cardia ≥ 12 mm^2 was the only significant factor for variceal recurrence on post treatment EUS surveillance [75]. Finally, a single-center study comparing EVBL, IS, EVBL + APC, and EVBL + IS in 200 patients revealed that EVBL + APC resulted in rapid eradication of varices with low recurrence rate and minimal adverse events. The authors acknowledged this combination therapy was limited by availability in endoscopy centers and its associated costs [71].

While these non-traditional modalities for variceal hemostasis are enticing, they are still not commonly used in clinical practice in the USA. We recommend endoscopists continue standard of care with esophageal band ligation or injection therapies and to reserve APC or hemostatic clip placements for patients with high risk of bleeding despite traditional methods of hemostasis.

Gastric Variceal Bleeding

Gastric varices (GV) account for 15–20% of all variceal bleeding [76]. While less frequently encountered than esophageal varices, GV are associated with more severe bleeding and rates of re-bleeding [77]. GV occur as a consequence of portal hypertension from cirrhosis, but are also not infrequently encountered in patients without cirrhosis, such as in those with splenic vein thrombosis [78, 79]. The most commonly used classification system is the Sarin Classification, which characterized gastric varices into isolated gastric varices (IGV1 and IGV2) and gastroesophageal varices (GOV1 and GOV2) [80]. GOV-1 are extension of gastroesophageal varices along the lesser curvature of the stomach and are the most commonly encountered gastric varices, where IGV-1 are associated with the highest risk of bleeding [81–83]. A recent AGA practice update on gastric varices recommended an alternative nomenclature based on GV location within the stomach and divide these into: cardiofundal GV, lesser curvature GV, and distal GV [84].

It is important to note that fewer well-established guidelines exist on gastric varices and its management and that many recommendations are based on expert opinion and consensus recommendations and are deduced from robust guidelines on management of esophageal varices such as those available from the American Society for Gastrointestinal Endoscopy and American Society for the Study of Liver Disease [4, 20, 85].

Management of gastric varices encompasses primary and secondary prophylaxis measures for bleeding, in addition to primary hemostatic measures for acute variceal bleeding. Options for primary hemostasis including medical management, interventional radiology (IR)-guided therapies such as balloon retrograde transvenous obliteration (BRTO) and transjugular intrahepatic portosystemic shunts (TIPS) and endoscopic therapies. This section will focus on traditional and novel endoscopic therapies for the management of acute gastric variceal bleeding. It is important for the endoscopists to note that GOV1, which represent extension of EV into the gastric cardia/lesser curvature, are managed in similar fashion to esophageal varices, including EVBL and injection sclerotherapy. Therefore, when endoscopist management of varices is mentioned here, this refers to management of non-GOV-1 gastric varices (i.e., cardiofundal GV).

Endoscopic management of gastric varices has historically involved the injection of synthetic glues and thrombosis-inducing agents using a needle injector and standard forward viewing endoscope. Agents that have been used for injection include procoagulants such as thrombin and tissue adhesives such as acrylate polymers (with and without lipiodol which delays polymerization). The use of direct thrombin injection for bleeding GV has been met with high bleeding cessation rates, but re-bleeding and the need for re-intervention is not uncommonly encountered [86–89]. Numerous single arm and comparative studies have been published on direct injection of acrylate polymers for the management of bleeding gastric varices, revealing high technical and clinical success rates in achieving hemostasis [90–95]. However, injection of acrylate polymers into gastric varices is associated with complications including variceal re-bleeding and systemic embolization ($< 1\%$, but associated with significant morbidity and mortality) [96–99]. Cases of systemic embolization have been reported in the lungs, spleen, and brain.

More recently, endoscopic ultrasound (EUS) has been introduced as a novel diagnostic and therapeutic tool for the management of gastric varices. EUS with Doppler flow provides real-time information on hemostasis while also allowing for direct, targeted injection therapy. EUS-guided cyanoacrylate injection has been shown to be associated with high clinical and technical success rates [100–102]. A study by Bick et al. [103] revealed that EUS cyanoacrylate injection was superior to direct injection therapy as it resulted in less frequent re-bleeding despite lower volume of glue injected. Current practices to ensure safe injection of acrylate polymers include mixing it with lipiodol to prevent early polymerization as seen in the recent literature and rapid withdrawal of needle after glue injection to prevent de-roofing of injected varices and re-bleeding. Despite these practices, injection of glue continues to result in complications and adverse events.

EUS-guided coil embolization, with or without concurrent glue injection, has emerged as an effective method for GV hemostasis, while potentially reducing the risk associated with direct glue injection. It is thought that coils, in addition to inducing hemostasis, may act as a scaffold to

prevent glue embolization. The combination of coils and glue injected under EUS guidance has been associated with high clinical and technical success rates, and low rates of re-bleeding and intervention [104–106]. Non-cyanoacrylate alternatives that have been concomitantly injected with coils under EUS guidance include absorbable gelatin sponge (Gelfoam) and thrombin [107, 108]. EUS-guided coil injection therapy has demonstrated significant efficacy in the treatment of bleeding gastric varices. A recent meta-analysis revealed that for patients undergoing EUS-guided therapies, EUS combination therapy with coil and cyanoacrylate injection was superior to EUS monotherapy with coil or cyanoacrylate alone [109] Specifically, EUS-guided cyanoacrylate and coil embolization resulted in a better technical and clinical success compared to cyanoacrylate alone (100% vs. 97%; $p < 0.001$ and 98% vs. 96%; $p < 0.001$) and coil embolization alone (99% vs. 97%; $p < 0.001$ and 96% vs. 90%; $p < 0.001$). Combination therapy also resulted in lower adverse event rates compared to cyanoacrylate alone (10% vs. 21%; $p < 0.001$) and comparable rates to coil embolization alone (10% vs. 3%; $p = 0.057$) [109].

Endoscopists wanting to pursue EUS-guided coil therapy should familiarize themselves with the length and diameters available for embolization coils. Common coil diameters include 0.035″ (advanced through 19G FNA needle) and 0.018″ (advanced though 22G FNA needle). These coils are preloaded onto the FNA needle with the use of a stylet. Patients are positioned in left lateral decubitus and sedation is performed with general endotracheal anesthesia. It is recommended to instill 300–400 cc of sterile water into the stomach to improve visualization of peri-gastric and intra mural varices. After the target varices are identified endosonographically, the needle is advanced into the varix and the stylet is advanced until the coil can be seen filling the variceal nest, under endosonographic and fluoroscopic guidance. This technique is repeated until the varix is sufficiently packed with coils and Doppler flow is seen to significantly reduce or halt (Fig. 6a–d) Next, in the absence of runoff shunts, glue or absorbable gelatin sponge (mixed with contrast) can be injected using the same FNA needle. If ongoing runoff of shunts is present, concurrent glue or gelatin sponge should not be injected to avoid the risk of systemic embolization and its complications.

It is important to note that while EUS has assisted in more targeted and novel hemostasis for bleeding gastric varices, this modality is associated with limitations including its availability in select centers with therapeutic EUS expertise, little knowledge about the optimal number and length of coils used and the relative contribution of coils or glue as adjunctive therapy. We recommend that endoscopists well versed in EUS with resources available for coiling pursue EUS-guided coil therapy, with or without adjunctive glue or absorbable gelatin sponge injection, particularly when IR-guided therapies are not available. In centers without resources or EUS capabilities or expertise, endoscopists should continue with direct cyanoacrylate injection, while monitoring patients closely for re-bleeding and systemic embolization.

Future Directions

All of the endoscopic therapies presented in this review are strategies focused on achieving hemostasis at the bleeding site—i.e., the varix. An intriguing concept is endoscopic

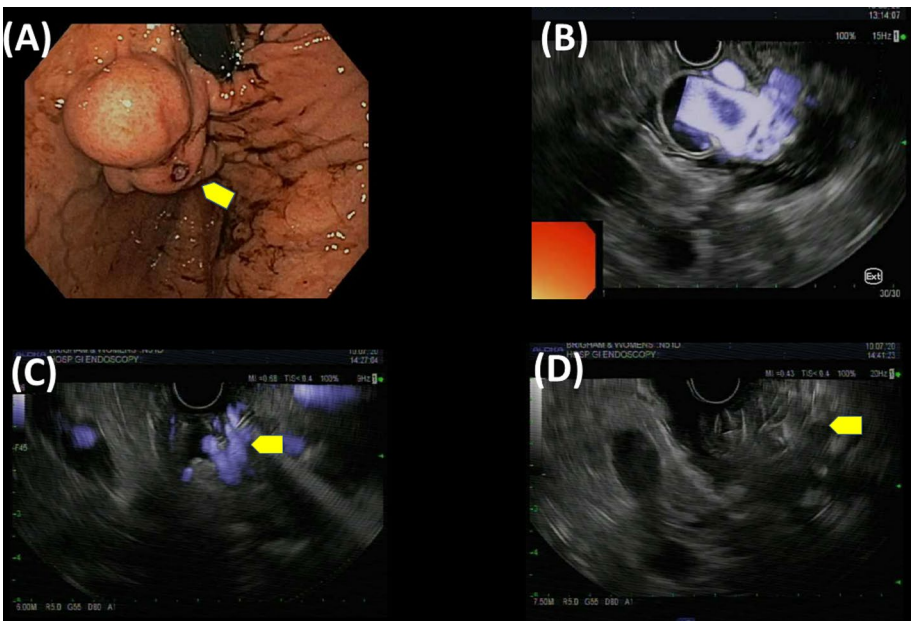

Fig. 6 EUS-guided coil injection of bleeding gastric varices. [**a** isolated gastric varix with ulcer (arrow); **b** gastric varix under EUS-Doppler interrogation; **c** EUS-guided needle insertion (arrow); **d** coils injected into gastric varix (arrow)]

creation of a portosystemic shunt, similar to TIPS, to reduce the underlying portal hypertension causing bleeding gastroesophageal varices. EUS-guided intrahepatic portosystemic shunt (EUS-IPS) was first described by Buscaglia et al. in an animal model in 2009 [110]. In 2011, Binmoeller et al. [111] described the use of EUS-IPS using a lumen-apposing metal stent (LAMS) in a porcine model. Schulman et al. [112] performed a similar preclinical study with simultaneous direct portal pressure measurement. In 2018, Poincloux et al. [113] reported successful EUS-IPS in 19 of 21 pigs [ref]. In this study, four stents were dysfunctional (2 thrombosed and 2 were poorly positioned). Further device and procedural refinements would be required prior to commencement of clinical studies.

Key Messages

- Endoscopic variceal band ligation remains first line therapy for bleeding esophageal varices.
- Injection sclerotherapy with sclerosants or cyanoacrylate can still be used in cases of refractory bleeding after band ligation.
- Limited data exists on argon plasma coagulation, through-the-scope and over-the-scope clips and hemostatic powders, but these therapies can be used as adjunctive therapy or in cases of refractory bleeding.
- Esophageal stents have largely replaced balloon tamponade devices at centers with expertise for a refractory bleeding and as a bridge to definitive therapy.
- Endoscopic ultrasound can be used as a diagnostic and therapeutic tool for the management of gastric varices. EUS with Doppler provides real-time information on variceal blood flow while also allowing for direct, targeted injection therapy.
- EUS-guided therapies for gastric varices, particularly coil injection therapy, have shown the promising results and should replace direct endoscopic glue injection therapy when expertise is available.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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