New Techniques to Control Gastrointestinal Bleeding

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Abstract: For decades, the mainstay of endoscopic hemostasis for a wide variety of gastrointestinal bleeding etiologies was limited to a few tools and techniques, including epinephrine injection, thermal probes, and through-the-scope hemostatic clips. Several novel approaches have recently emerged to control acute gastrointestinal hemorrhage. The concepts behind these approaches are diverse, ranging from upgrading current techniques (eg, over-the-scope clips and endoscopic ultrasound–guided treatment of gastric varices) to developing new technologies (eg, hemostatic powders) and repurposing current tools (eg, Doppler endoscopic probe). This article presents an evidence-based review of the major advancements in endoscopic hemostasis techniques.

Current first-line endoscopic interventions for nonvariceal upper gastrointestinal bleeding (NVUGIB) include through-the-scope clips (TTSCs) and thermal probes, whereas portal hypertensive bleeding from esophageal or gastric varices has traditionally been treated with band ligation or cyanoacrylate (CYA) glue, respectively.[1,2] Although NVUGIBs may have declined due to the increased use of proton pump inhibitors,[3] underlying etiologies of and risk factors for gastrointestinal bleeding (GIB) have become more complex. For example, the rising incidence in combined antithrombotic use has increased morbidity from GIB,[4] particularly in elderly people,[5] and tumor-related GIBs, which exhibit unique physiology, are increasingly recognized with advances in oncologic therapies.[6] In addition, recurrent bleeding in high-risk peptic ulcer disease remains challenging,[7] and salvage therapy with surgery carries higher mortality and complications.[8] This article presents several advancements in endoscopic therapies for NVUGIBs and variceal GIBs.

Doppler Endoscopic Probe

The Doppler endoscopic probe (DEP) is a tool that is passed through the working channel of an endoscope and can be used to measure blood flow under a mucosal surface (Figure 1). The technology is not new, but recent studies have renewed interest in its utility. DEP was first used in 1982 for the treatment of ulcers, based on the concept that successful hemostasis hinges on elimination of blood

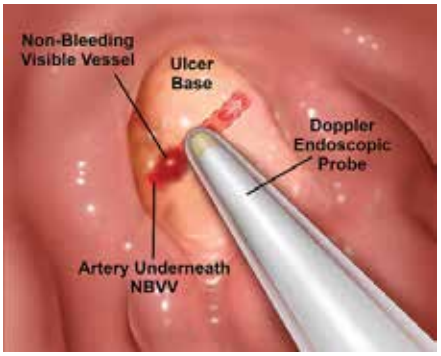

Figure 1. An illustrated depiction of the use of a Doppler endoscopic probe for ulcers. The probe is passed through the working channel of an endoscope and measures blood flow in the ulcer bed. Hemostasis with endoscopic therapies is achieved with successful ligation of the underlying artery, which may depend on the directionality of the underlying vessel. Doppler endoscopic probe can guide therapeutic endpoints by measuring flow before and after endoscopic therapy.

Adapted from Jensen D[63] with permission from the American Gastroenterological Association.

NBVV, nonbleeding visible vessel.

Table 1. Characterization of Blood Flow Based on Forrest Classification, Endoscopic Appearance, and Rate of Further Bleeding Without Endoscopic Therapy[62]

Forrest Classification	Endoscopic Appearance	Further Bleeding Without Endoscopic Therapy
Ia	Actively spurting bleed	55%
Ib	Actively oozing bleed	
IIa	Nonbleeding visible vessel	43%
IIb	Adherent clot	22%
IIc	Flat pigmented spot	10%
III	Clean based ulcer	5%

flow from the feeding culprit artery[9] and that persistent ulcer bed blood flow after endoscopic therapies correlates with incomplete treatment and increased likelihood to rebleed.[10] In addition, it has been suggested that grading ulcers based on Forrest classification has only modest interobserver agreement. An international panel of experts graded 100 consecutive video endoscopies of bleeding peptic ulcers and found that overall interobserver agreement was only fair (κ coefficient, 0.426).[11] Thus, DEP is also felt to be a more objective approach to risk assessment. Older prospective cohort studies and randomized trials have suggested that ulcers with positive flow on DEP have higher rebleeding rates, and DEP-directed therapy may lower rebleeding risk.[12-18] However, limitations include smaller sample size and heterogeneous interventions mostly consisting of epinephrine injection, which is inadequate as monotherapy.[19]

More recent studies led predominantly by Jensen and colleagues have expanded the application of DEP.[20-22] In a prospective cohort study of 163 patients with confirmed peptic ulcer disease bleeding, Jensen and colleagues used DEP to characterize blood flow based on Forrest classification (Table 1) and stigmata of recent hemorrhage (SRH), and after endoscopic intervention.[22] Ulcers were classified as either major SRH (spurting/pulsatile arterial bleeding, F-Ia; nonbleeding visible vessel, F-IIa; or adherent clot, F-IIb) or intermediate SRH (oozing from ulcer base, F-Ib; or flat spot, F-IIc). The authors found that 87.4% of major SRHs had positive flow on DEP compared with 42.3% of intermediate SRHs (P<.001).[22] Following endoscopic intervention, residual flow was detected in 27.4% of major SRHs vs 0% of intermediate SRHs (P<.005). Interestingly, when comparing blood flow on DEP of F-Ia to F-Ib lesions, significantly higher blood flow was detected at baseline (100% vs 46.7%, respectively; P=.0022) and after direct visual therapy (35.7% vs 0%, respectively; P=.02), and 30-day rebleeding rates were 28.6% vs 0%, respectively (P=.042).[22] These findings challenge the long-accepted combined categorization of F-Ia and F-Ib lesions by some experts as active bleeding and imply that there is a role for DEP in restratifying bleeding risk in future studies. In a study of similar design, the same authors applied these principles to clarify the natural history of diverticular bleeds, classifying again as major SRH (active bleeding, nonbleeding visible vessel, or adherent clot), minor SRH (flat spot), or no SRH.[21] They found that diverticula with major SRH after treatment had a 65.8% chance of rebleeding, with 44.7% of those patients requiring endoscopic, surgical, or radiologic intervention. These results further support a role for DEP in future studies of GIB.

In the largest randomized, single-blinded trial to date utilizing DEP-guided endoscopic intervention with modern hemostasis techniques, Jensen and colleagues randomized 148 patients with severe NVUGIBs (125 of which had peptic ulcer disease) to visual or DEP-guided endoscopic therapy.[20] The primary endpoint was 30-day rebleeding, with secondary outcomes of complications, death, blood transfusion, or need for surgery or angiography. Rebleeding by 30 days occurred in 26.4% of controls compared with 11.1% of patients in the DEP arm (P=.0214), with the odds ratio for rebleeding with

DEP being 0.35 (95% CI, 0.14-0.86).[20] DEP-guided therapy achieved a 15% absolute difference in rebleeding, amounting to a number needed to treat of 6.67. In addition, the authors noted that of the patients who rebled in the DEP group, 8 of 9 (89%) had faintly positive flow on DEP after interventions, further supporting the accuracy of DEP. There were no differences in secondary outcomes.

Recent studies on DEP have renewed interest in its application to GIBs, particularly lesions with SRH. In upper or lower gastrointestinal lesions, positive flow on DEP is present in a large majority of high-risk SRH, and it appears that failure to entirely obliterate the culprit feeding vessel can help explain rebleeding. Previously stratified rebleeding risk based on Forrest classification may need to be reevaluated, as DEP suggests that F-Ia and F-Ib lesions may have very different risks for rebleeding. When utilized to guide treatment endpoints using modern endoscopic hemostasis techniques, DEP can decrease rebleeding substantially. In addition, a recent cost-effectiveness analysis found that DEP-guided strategies in high-risk lesions are less costly and more effective.[23] However, the main limitation stems from generalizability, as DEP is largely available only at select major academic centers, requires specialized training, and has been adopted slowly despite having been present for over 3 decades.

Over-the-Scope Clips

Currently, first-line therapy for ulcer-related GIB includes thermal probes and TTSCs with or without submucosal epinephrine injection.[24] Despite recent improvement in the tensile strength, size, and rotatability of TTSCs, limitations to hemostasis during active hemorrhage include large and/or cratered fibrotic ulcers and challenging anatomic locations.[25] Over-the-scope clips (OTSCs) are larger-caliber clips composed of nitinol, a metal with shape-memory effect and high-grade elasticity allowing for high-pressure closure of larger mucosal areas, which captures deeper tissue layers and may improve hemostasis.[26] The OTSC system is contained in a cap, installed over the end of an endoscope, and deployed using a similar mechanism as rubber-band applicators. Currently, the 2 OTSCs on the market include the OTSC System (Ovesco Endoscopy AG) and Padlock Clip (US Endoscopy),[27] which are available in a variety of sizes and configurations depending on the applications. The former was first utilized in GIBs in 2007 in a case series of 11 patients with severe bleeding or perforation.[26]

In a review of all retrospective case series utilizing the OTSC System between 2010 and 2018, Kobara and colleagues found that aggregate successful hemostasis was achieved in 85% of cases of refractory bleeding (473/559).[28] Two recent high-quality studies specifically evaluate the role of an OTSC device in high-risk and recurrent lesions. In a retrospective analysis of a prospectively maintained cohort, Brandler and colleagues evaluated the efficacy of OTSCs as primary or rescue therapy after failed initial hemostasis in 67 patients with high-risk lesions defined as lesions situated in major arterial territories, a visible large artery greater than 2 mm in size (F-IIa), and/or excavated fibrotic ulcers with high-risk stigmata (F-Ia, F-IIa/b).[29] The cohort represented a high-risk group with a modified Blatchford score of 10.1±2.5 and Rockall score of 6.9±1.4. The majority of lesions were upper GIBs, and the rate of 30-day rebleeding was 28% (18/64). When accounting only for rebleeding from the prior OTSC site, the suggested true success rate was 81%, which is substantial compared to a failure rate of 40% for high-risk lesions treated with TTSCs, as suggested in a prior abstract by the same authors.[30]

In the STING (Endoscopic Treatment of Recurrent Upper GI Bleeding: OTSC [Over the Scope Clip] Versus Standard Therapy) study, a prospective, multicenter, randomized trial, Schmidt and colleagues randomized 66 patients with recurrent peptic ulcer bleeding to standard therapy (31 TTSCs, 2 thermal probes) vs OTSC, allowing crossover from standard therapy into the OTSC group for treatment failure.[31] Recurrent bleeding was defined as endoscopically confirmed rebleeding (spurting/oozing lesion, adherent clot, or nonbleeding visible vessel) in an ulcer previously treated successfully within 7 days. The primary composite endpoint included persistent bleeding or recurrent bleeding within 7 days, and occurred in 15.2% of the OTSC cohort vs 57.6% of the standard therapy cohort (P=.001; absolute difference, 42.4%; 95% CI, 21.6%-63.2%), with 100% success achieved in patients who failed standard therapy and crossed over to the OTSC group. Lastly, in a retrospective analysis of 118 patients with NVUGIBs treated with OTSC as first-line therapy, treatment with OTSC in high-risk patients based on Rockall score may confer a survival advantage when compared to the original 1993 to 1994 Rockall cohort, although the original Rockall study used older hemostasis techniques.[32]

As the OTSC is a relatively new device with multiple applications (such as fistula and perforation closures), its role in GIBs will continue to evolve. Current best evidence supports its use in high-risk and refractory bleeding that has failed prior endoscopy therapy (Figure 2). Despite nearly all trials being retrospective in nature, there is overall consistency and high success rates in these refractory lesions. STING was a well-designed study and is the only prospective, randomized trial to date, and it supports the use of OTSCs as rescue therapy.[31] An example of the evolving role of OTSCs includes a less orthodox case of successful hemostasis in a fibrotic esophageal variceal

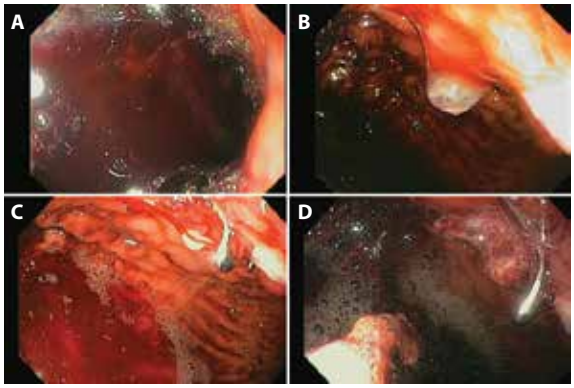

Figure 2. The use of an over-the-scope clip (OTSC) for a large visible vessel. A 51-year-old man with a Roux-en-Y hepaticojejunostomy with loop gastrojejunostomy due to complications of a prior cholecystectomy developed hematemesis and hemorrhagic shock. An upper endoscopy revealed large amounts of blood clots (**A**), which were cleared after extensive snare-assisted suctioning to reveal a pulsatile 7- to 8-mm visible vessel along the lesser curvature (**B**). An OTSC was successfully deployed (**C**), but the vessel continued to ooze. Sustained hemostasis was achieved after combination with bipolar cautery (**D**).

bleed failing band ligation.[33] The primary drawback is that the OTSC is technically more demanding and requires some degree of specialized training, which limits its availability at this time. Given the high prevalence and annual health care costs of GIBs, the cost-effectiveness of OTSCs remains to be determined.

Hemostatic Powders

Hemostatic powders are highly absorptive mineral powders that form a mechanical barrier and activate the clotting cascade upon contact with water.[34] First utilized in the military for combat-related hemorrhages,[35] hemostatic powders were adapted to GIBs in 2011 in a proof-of-concept study in F-Ia/b lesions.[36] Hemostatic powder significantly shortens clotting time and forms a barrier that sloughs off by 48 hours, sometimes as early as 24 hours.[34] The hemostatic powder TC-325 (Hemospray, Cook Medical) is the most widely used formulation; other commercially available products include EndoClot (EndoClot Plus) and Ankaferd Blood Stopper (Ankaferd Health Products Ltd).[37]

Only recently introduced, hemostatic powders are most often used in NVUGIBs, with the majority of data coming from case series and retrospective analyses. The GRAPHE registry is the largest multicenter, prospectively maintained database to date on TC-325 use in upper GIB.[38] In a retrospective analysis of 202 patients in this prospective cohort, Haddara and colleagues found that the immediate hemostasis rate was 96.5%, with recurrence rates of upper GIB on days 8 and 30 of 26.7% and 33.5%, respectively.[38] Etiologies of upper GIB were heterogeneous, with ulcer in 37.1% of patients, tumor in 30.2%, and postendoscopic therapy in 17.3%. TC-325 was used as salvage therapy in 53.5% of cases. The authors noted the favorable safety profile and ease of use, with no reported adverse events; 87.1% of endoscopists rated TC-325 as either easy or very easy to use. Although TC-325 is the most commonly used hemostatic powder, a retrospective study of 154 patients predominantly with upper GIBs of heterogeneous etiologies found no difference in hemostasis rates between TC-325 and EndoClot.[39] Hemostasis at 72 hours was achieved in 81% of patients and rebleeding occurred in 27%, which is consistent with findings from the GRAPHE registry.[39] There are little data to guide the comparison of TC-325 to current standard first-line endoscopic therapies. Baracat and colleagues conducted a pilot, randomized, controlled trial of TC-325 vs a TTSC (Resolution Clip, Boston Scientific), in which 39 patients with endoscopically confirmed active NVUGIBs were randomized 1:1.[40] Initial hemostasis was achieved in 100% of TC-325 patients and in 90% of TTSC patients (P=.487). All patients underwent a second-look endoscopy, with 5 patients in the TC-325 group requiring repeat application vs 0 in the TTSC group. Rebleeding occurred in 27.8% of the TC-325 arm and in 15.8% of the TTSC arm (P=.572).[40] The etiologies were also heterogeneous, with 45% attributed to ulcers. Although this small study is the only trial to date comparing TC-325 to another modality, its results are consistent with prior studies in that TC-325 carries a very high initial hemostasis rate, but the effect is not durable and may not be the best initial choice for therapy.

Given the ease of use and wide area of effect of TC-325, several studies suggest a role for the powder in diffuse lesions (Figure 3) as salvage therapy, or as an adjunct to current standard therapies. In a prospective cohort study of TC-325 in 50 patients with active lower GIBs (73% from polypectomy), initial hemostasis was reported in 98% (n=49) of patients, with rebleeding noted in only 10% (n=5). TC-325 was utilized as salvage therapy in 32.7% of patients and as adjunct therapy in 42.3%.[41] Cahyadi and colleagues reported their single-center experience of TC-325 in 52 patients with diffuse or refractory lesions defined as bleeding not amenable to or failing standard therapies.[42] All patients received TC-325, as monotherapy (44%) or as salvage therapy (56%), with an immediate hemostasis rate of 98%. However, rebleeding rates on days 3 and 7 were 43% and 49%, respectively, which may have been due to the presence of diffuse

lesions. Specifically, tumor-related bleeding is difficult to treat with current endoscopic tools due to friable tissue and diffuse oozing. The use of TC-325 in bleeding tumors may be a promising temporizing therapy prior to embolization, surgery, or radiotherapy, as first suggested by a case series noting a trend toward lower rebleeding rates.[43] In a multicenter, retrospective study of 99 patients with active gastrointestinal tumor–related bleeding, Pittayanon and colleagues assessed the efficacy of TC-325 and predictors of survival.[44] Immediate hemostasis was achieved in 97.7% of patients, with rebleeding occurring in 32% in total; however, 38% of patients did not receive definitive nonendoscopic therapy. On multivariable analysis, a significant prognosticator of 6-month survival was receiving definitive treatment (ie, surgery, chemotherapy, radiotherapy, or embolization; *P*=.002; hazard ratio, 0.24; 95% CI, 0.09-0.59), which implies the importance of TC-325 as a bridge to definitive therapy.[44]

Lastly, TC-325 has been used as an adjunct agent to standard therapy. In a retrospective analysis of 20 patients with F-Ia and F-Ib ulcers, TC-325 was used with a TTSC or thermal probe in 60% of patients or epinephrine in 40%; initial hemostasis was achieved in 95% of patients, with 7-day rebleeding occurring in 16%.[45] However, the strongest evidence for TC-325 as an adjunct agent appears to be for variceal bleeding, first successfully trialed in 2013 by Ibrahim and colleagues for acute variceal and postbanding ulcer bleeding.[46,47] Ibrahim and colleagues recently reported a randomized, clinical trial of early application of TC-325 to confirmed variceal bleeds, with a primary combined endpoint of endoscopic and clinical hemostasis.[48] Eighty-six patients were randomized 1:1 to early TC-325 (within 2 hours) plus usual care vs usual care alone (banding within 12-24 hours). The primary endpoint was achieved in 88% of patients in the TC-325 group and in 63% of controls (*P*=.0057), with day 5 treatment failure occurring in 12% of the TC-325 group and in 38% of controls (*P*=.006). The 6-week mortality rate was 7% in the TC-325 group vs 30% in controls (*P*=.006), although the study was not powered to detect mortality.[48] The detection of a 6-week mortality difference raises the question of whether earlier definitive therapy should be attempted in all variceal hemorrhages. Furthermore, a recent study proposed that TC-325 as an adjunct to standard therapy is cost-effective, which argues that its use should be considered as early definitive therapy.[49]

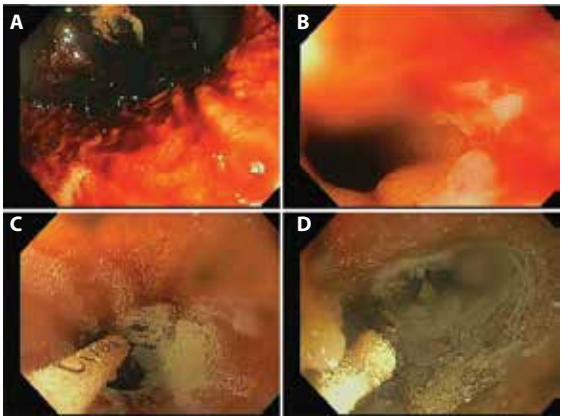

Figure 3. Hemostatic powder for diffuse lesions. A 55-year-old man was hospitalized for a myocardial infarction requiring drug-eluting stent placement complicated by cardiogenic shock, resulting in renal and respiratory failure. He developed bloody nasogastric tube output with a 3-point decline in hemoglobin in the setting of dual antiplatelet therapy. An upper endoscopy revealed large amounts of blood clot obscuring the gastric fundus (**A**) and diffusely and actively oozing severe esophagitis (**B**). Due to the diffuse nature of bleeding and coagulopathy, a hemostatic powder was circumferentially applied (**C**), and successful hemostasis was achieved (**D**).

Endoscopic Ultrasound–Guided Treatment of Gastric Fundal Varices

Gastric varices are present in approximately 20% of patients with cirrhosis and are classified according to the Sarin classification as gastroesophageal varices extending along the lesser curvature (GOV1s), gastric fundal varices (GFVs; GOV2s or isolated gastric varices [IGV] 1s), or ectopic varices (IGV2s).[50] Compared to esophageal varices, gastric varices bleed less often but more severely.[50] GFVs are portosystemic shunts with gastrophrenic drainage that open gastrocaval and gastrorenal shunts, producing a low-pressure but high-flow system.[51] Thus, GOV1s are typically treated as esophageal varices with band ligation, but the recommended endoscopic treatment for GFVs is CYA glue embolization, as postbanding ulcers eroding into GFVs can result in catastrophic hemorrhage.[2] Two randomized trials comparing glue to banding in gastric varices have demonstrated significantly lower rebleeding rates.[52,53] However, direct visual endoscopic gluing has several limitations and complications that can be circumvented through newer techniques using endoscopic ultrasound (EUS). First, direct visualization is often obscured during massive GFV hemorrhage, making safe and effective gluing impossible. EUS allows not only for the direct visualization of GFVs, but also for the targeting of perforating veins that feed the varix and for confirmation of obliteration via lack of flow on Doppler.[54] Second, visualization under EUS combined with embolization coils decreases the amount of glue used. Lastly, complications of glue embolization are theoretically

decreased by the nature of less glue used and coils acting as a scaffold to prevent embolization.[54] Of note, the incidence of glue emboli is ill-defined due to heterogeneous definitions and lack of high-quality studies. One retrospective study of 753 cases of GFV gluing found the incidence of glue emboli to be 0.7%, but emboli were defined based on symptoms.[55] However, a retrospective analysis of a prospectively maintained cohort of patients receiving EUS-guided glue vs coiling screened all patients for emboli using computed tomography imaging, and found the incidence of asymptomatic glue emboli to be 47% (9/19).[56]

EUS-guided treatment of GFVs deploys glue and/or embolization coils under ultrasound guidance. The 2 CYA glue formulations most often utilized are N-butyl-2-CYA (Histoacryl, B. Braun) and 2-octyl-CYA (Dermabond, J&J Medical).[57] N-butyl-2-CYA has a shorter polymerization time and is thus mixed with lipiodol, an oily radiopaque agent, in ratios of 1:1 to 1:2 when used as glue monotherapy. When combined with coil embolization, 2-octyl-CYA is the preferred agent, as the longer polymerization time allows the glue to be injected without lipiodol and to polymerize onto the coils.[58] Embolization coils 10 to 20 mm in diameter and 7 to 14 cm in length are chosen depending on the size of the GFV, and are deployed first followed by 2-octyl-CYA injection. The glue and/or coils may remain in place or can be extruded as a cast into the gastrointestinal lumen in approximately 3 months.[57]

EUS-guided treatment of GFVs was first reported in 2007 in a case series of 5 patients who received CYA-lipiodol injections targeted toward perforating veins, theoretically minimizing the amount of glue used and risk for glue emboli.[59] The mean CYA glue volume was 1.6 mL per treatment. In a retrospective study of 104 patients comparing EUS vs direct visual injection of CYA glue into active bleeding or high-risk GFVs, EUS guidance utilized less glue (2.0±0.8 mL vs 3.3±1.3 mL; *P*<.001) and achieved fewer rebleeding events (8.8% vs 23.7%; *P*=.045). This supported the concept that targeting perforating veins is more effective and uses less CYA glue. Coil embolization using EUS was introduced in 2008 by Levy and colleagues in a successful case report with obliteration of IGV2s[60] and was later applied to 4 patients with GFVs in a case series by Romero-Castro and colleagues.[61] The primary advantage of coils over glue is thought to be avoidance of glue emboli. In a retrospective analysis of a prospective database, Romero-Castro and colleagues compared coils vs CYA glue in nonbleeding GFVs in 11 and 19 patients, respectively, both under EUS guidance.[56] GFV obliteration rates were similar (91% with coil vs 95% with CYA glue), but coils required fewer sessions. All patients received a computed tomography scan to monitor for emboli, which revealed asymptomatic glue emboli in 47% (9/19) of the CYA glue group. The total adverse event rate was 9% for coil (1/11) vs 58% for CYA glue (11/19; *P*=.01). In addition to demonstrating the efficacy of coil embolization, the authors suggested that coil embolization was safer and required fewer treatments compared to CYA glue, as both methods were deployed under EUS guidance.

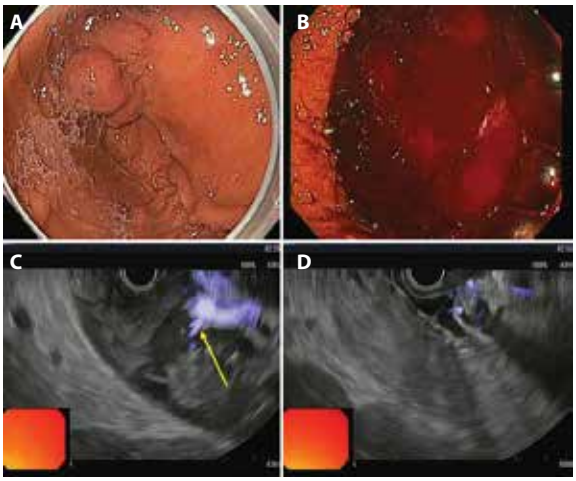

Figure 4. EUS-guided treatment of gastric fundal varices. A 65-year-old man with alcoholic cirrhosis was admitted for an upper gastrointestinal bleed and, on initial esophagogastroduodenoscopy, was found to have a GOV2 with nipple sign (**A**). Two days later, the patient developed a massive hemorrhage with blood obscuring direct endoscopic visualization of the gastric fundus (**B**), but EUS revealed an actively bleeding gastric varix (**C**). Hemostasis was achieved with EUS-guided cyanoacrylate embolization with confirmed obliteration of the gastric varix (**D**).

EUS, endoscopic ultrasound; GOV2, gastroesophageal varix.

Binmoeller and colleagues combined the efficacy of glue and coil embolization in a pilot study in 30 patients with GFVs, 16 of which had active or recent hemorrhage.[54] Coils were deployed first followed by 2-octyl-CYA, with the concept that coils function as a scaffold that reduces the amount of glue used and number of glue emboli. The average amount of CYA glue used was 1.4 mL per varix. The authors reported a 100% hemostasis rate in acute bleeding, with 96% of patients requiring only 1 session for GFV obliteration. No complications were reported. Bhat and colleagues reported their 6-year experience of EUS-guided combined glue and coil embolization in 152 patients with GFVs, with active or recent bleeding in 112 patients and follow-up in 125 patients.[58] They reported a 100% hemostasis rate in active bleeding (n=7), 99.3% technical success rate, and GFV obliteration confirmed by EUS in 93% of follow-ups with 79% of patients requiring only a single procedure.[58] Complication rates

Table 2. Summary of Techniques With Their Therapeutic Applications, Advantages, Disadvantages, and Level of Evidence

Technique	Therapeutic Application(s)	Advantages	Disadvantages	Level of Evidence
Doppler endoscopic probe	• Doppler-guided therapeutic endpoints for high-risk lesions and ulcers • Diverticular hemorrhage	• Decreased rates of rebleeding • Doppler-guided endpoints as immediate, intraprocedure feedback	• Requires specialized training • Limited availability outside of major academic medical centers	• Randomized, single-blinded, clinical trial • Prospective cohort studies
Over-the-scope clips	• High-risk lesions • Rescue therapy for refractory bleeding • Large, cratered, and/or fibrotic ulcers	• Significantly higher tensile force • Significantly larger size	• Requires some degree of training and experience • Somewhat limited visualization and maneuverability	• One multicenter randomized trial • Most studies are retrospective analyses
Hemostatic powders	• Tumor-related bleeding • Bridge to definitive therapy • Diffuse or refractory bleeding • Adjunct/bridge therapy for variceal bleed	• ≥95% initial hemostasis rate • Minimal training required; ease of use	• High rebleeding rates (30%-40%) • Short therapeutic duration (24-48 hours)	• Largely retrospective analyses • Single randomized, controlled trial for adjunct therapy in variceal bleeding
EUS-guided variceal embolization	• Gastric fundal varices bleeding (GOV2s, IGV1s)	• Preserved visualization via Doppler during massive hemorrhage • High hemostasis rates during acute bleed • Decreased amounts of glue used, especially when combined with coil embolization • Decreased number of sessions required for variceal eradication	• Requires specialized training in EUS • Limited availability outside of major academic medical centers • Glue emboli still occur • Risk of damaging endoscopes	• All studies are retrospective analyses

EUS, endoscopic ultrasound; GOV2s, gastroesophageal varices; IGV1s, isolated gastric varices.

were low and included minor bleeding due to glue cast extrusion (3%; n=4) and clinically significant pulmonary embolism (1%; n=1), although patients were not actively screened for glue emboli. Despite its retrospective nature, this report is the largest and most comprehensive to date, demonstrating the high technical and clinical efficacy and safety of EUS-guided glue and coil embolization. A successful case of EUS-guided glue embolization at our institution is described in Figure 4. Limitations to EUS-guided interventions include operator dependence and availability that may be limited to tertiary care centers.

Summary

While TTSC, thermal probe, and band ligation will likely remain the first-line endoscopic treatments for the majority of GIBs, recent advancements in hemostasis techniques provide effective solutions for several unique situations (Table 2). DEP is not a new technology, but its recent resurgence has questioned the accuracy of risk stratification via the Forrest classification, which could partly be explained by its modest interobserver agreement. When used to guide endoscopic treatment endpoints in high-risk lesions, DEP can increase the rate of complete obliteration of culprit feeding vessels. OTSCs have shown promise in treating high-risk or refractory lesions, such as large ulcers that are fibrotic or cratered. Numerous retrospective studies and a single well-designed randomized trial have demonstrated high success rates in hemostasis using the OTSC as first-line or salvage therapy for NVUGIB. Hemostatic powders carry the widest area of effect, are safe and easy to use, and demonstrate remarkable consistency in high initial hemostasis rates across currently available studies (approximately 95%). However, their rebleeding rates are also consistently high at 25% to 30%. Thus, hemostatic powders are probably

best deployed for diffusely oozing lesions such as tumor-related bleeding, as a salvage or adjunct agent, or as bridge to definitive therapy. Lastly, EUS-guided coil and glue embolization carries several key advantages over visually directed gluing for GFVs. When massive GFV hemorrhage obscures visualization, EUS allows the endoscopist to locate GFVs and target perforating veins that feed the varix, with variceal obliteration confirmed by Doppler. Precise targeting with EUS decreases the amount of glue used, and using EUS-guided glue combination with coils can lower the rate of glue emboli.

The authors have no relevant conflicts of interest to disclose.

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