

CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Endoscopic Therapies for Non-Variceal Upper Gastrointestinal Bleeding: Expert Review



Daniel K. Mullady,¹ Andrew Y. Wang,² and Kevin A. Waschke³

¹Division of Gastroenterology, Washington University in St Louis School of Medicine, St Louis, Missouri; ²Division of Gastroenterology and Hepatology, University of Virginia, Charlottesville, Virginia; and ³Division of Gastroenterology, McGill University, Montreal, Quebec, Canada

DESCRIPTION: The purpose of this American Gastroenterological Association (AGA) Institute Clinical Practice Update is to review the available evidence and best practice advice statements regarding the use of endoscopic therapies in treating patients with non-variceal upper gastrointestinal bleeding. **METHODS:** This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Gastroenterology*. This review is framed around the 10 best practice advice points agreed upon by the authors, which reflect landmark and recent published articles in this field. This expert review also reflects the experiences of the authors who are gastroenterologists with extensive experience in managing and teaching others to treat patients with non-variceal upper gastrointestinal bleeding (NVUGIB). **BEST PRACTICE ADVICE 1:** Endoscopic therapy should achieve hemostasis in the majority of patients with NVUGIB. **BEST PRACTICE ADVICE 2:** Initial management of the patient with NVUGIB should focus on resuscitation, triage, and preparation for upper endoscopy. After stabilization, patients with NVUGIB should undergo endoscopy with endoscopic treatment of sites with active bleeding or high-risk stigmata for rebleeding. **BEST PRACTICE ADVICE 3:** Endoscopists should be familiar with the indications, efficacy, and limitations of currently available tools and techniques for endoscopic hemostasis, and be comfortable applying conventional thermal therapy and placing hemoclips. **BEST PRACTICE ADVICE 4:** Monopolar hemostatic forceps with low-voltage coagulation can be an effective alternative to other mechanical and thermal treatments for NVUGIB, particularly for ulcers in difficult locations or those with a rigid and fibrotic base. **BEST PRACTICE ADVICE 5:** Hemostasis using an over-the-scope clip should be considered in select patients with NVUGIB, in whom conventional electrosurgical coagulation and hemostatic clips are unsuccessful or predicted to be ineffective. **BEST PRACTICE ADVICE 6:** Hemostatic powders are a noncontact endoscopic option that may be considered in cases of massive bleeding with poor visualization, for salvage therapy, and for diffuse bleeding from malignancy. **BEST PRACTICE ADVICE 7:** Hemostatic powder should be preferentially used as a rescue therapy and not for primary hemostasis, except in cases of malignant bleeding or massive bleeding with inability to perform thermal therapy or hemoclip placement. **BEST PRACTICE ADVICE 8:** Endoscopists should understand the risk of bleeding from therapeutic endoscopic interventions (eg, endoluminal resection and endoscopic sphincterotomy) and be familiar with the endoscopic tools and techniques to treat intraprocedural bleeding and minimize the risk of delayed bleeding. **BEST**

PRACTICE ADVICE 9: In patients with endoscopically refractory NVUGIB, the etiology of bleeding (peptic ulcer disease, unknown source, post surgical); patient factors (hemodynamic instability, coagulopathy, multi-organ failure, surgical history); risk of rebleeding; and potential adverse events should be taken into consideration when deciding on a case-by-case basis between transcatheter arterial embolization and surgery. **BEST PRACTICE ADVICE 10:** Prophylactic transcatheter arterial embolization of high-risk ulcers after successful endoscopic therapy is not encouraged.

Keywords: Upper Gastrointestinal Tract Bleeding; Endoscopy; Hemostatic Powder; Hemospray; Hemostatic Forceps; Clips; Rebleeding.

Non-variceal upper gastrointestinal bleeding (NVUGIB) is a serious clinical problem with an incidence of approximately 61–78 cases per 100,000 persons in the United States in 2009–2012.¹ Mortality from NVUGIB is estimated to be between 2% and 10%.^{1,2}

Endoscopic evaluation and treatment for NVUGIB remains the clinical mainstay of care in patients who can be hemodynamically stabilized to undergo upper gastrointestinal endoscopy, typically by esophagogastroduodenoscopy. Numerous endoscopic devices have been developed over the past 30 years with demonstrated effectiveness in treating NVUGIB, including the use of hemoclips,³ over-the-scope clips,⁴ hemostatic forceps,⁵ and sprayed hemostatic powder.⁶ The purpose of this Clinical Practice Update is to review the key concepts, new devices, and therapeutic strategies in endoscopically combating this age-old clinical dilemma.

Initial Management

Although endoscopy is a cornerstone in the management of NVUGIB, it should come after triage, medical management, and stabilization. The treating provider should consider patient-

Abbreviations used in this paper: AT, antithrombotic; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; MHF, monopolar hemostatic forceps; NVUGIB, non-variceal upper gastrointestinal bleeding; RCT, randomized controlled trial; TAE, transcatheter arterial embolization.

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related issues, including age, comorbid conditions, prior surgery, history of gastrointestinal bleeding, and medications (eg, antihypertensives, antithrombotics, nonsteroidal anti-inflammatory medications), which can contribute to the patient's clinical presentation and hemodynamic status and might predict bleeding that is difficult to control. Patients with NVUGIB may have variable presentations ranging from harmless, minor, self-limited bleeding that can be managed with an outpatient workup, to hypovolemic shock requiring transfer to the intensive care unit. The treating provider should be familiar with various scoring systems that have been developed to help triage patients with NVUGIB.⁷⁻¹⁰ These scoring systems are based on clinical parameters and endoscopic findings that predict mortality and rebleeding risk in patients with NVUGIB (Table 1).

After proper triage of the patient with suspected NVUGIB, the focus should be on medical management, including volume resuscitation with intravenous fluids and blood products via large bore catheters. Target hemoglobin is generally 9 g/dL in patients with significant cardiovascular disease and 7 g/dL for all others.¹¹⁻¹³ The consensus recommendation by an international group of experts was for blood transfusion for hemoglobin levels <8 g/dL with a higher threshold for those with cardiovascular disease.¹⁴

The need for reversal of antithrombotic (AT) medications (which for this article includes anticoagulant and antiplatelet agents) requires careful consideration of the risks of thromboembolic events, particularly in patients who present with active upper gastrointestinal tract bleeding.^{15,16} These decisions should be made by the gastroenterologist in consultation with intensivists, cardiologists, neurologists, and hematologists when appropriate to provide advice, including use of reversal agents, safe length of time to hold AT medications, and whether alternative shorter-acting agents (eg, heparin drip) should be used as bridge therapy.¹⁷ When there is doubt, it is usually better to err on the side of not reversing AT medication because a cardiopulmonary or neurologic thromboembolic event is usually far more devastating than ongoing NVUGIB, which can often be managed with supportive care in relatively stable patients.

Intravenous proton pump inhibitors should be administered to all patients with suspected NVUGIB because these have the effect of downgrading the stigma of recent hemorrhage on subsequent endoscopy, but should not delay endoscopic intervention.^{14,18} High-dose intravenous proton pump inhibitors should be continued post endoscopy because their use is associated with decreased risk of rebleeding.^{14,19} A single dose of

Table 1. Three Established and Commonly Used Risk Assessment Scores That Stratify Patients Into Lower- and Higher-Risk Groups for Poor Outcomes Related to Gastrointestinal Bleeding

Scoring system	Components	No. of points	Key concepts
Glasgow-Blatchford score	Systolic BP	1, 2, 3	Score ranges from 0–23
	BUN	2, 3, 4, 6	Calculated on admission
	Hemoglobin	1, 3, 6 (men); 1, 6 (women)	Patients with a score of 0 or 1 can be managed as an outpatient
	Tachycardia	1	Superior in predicting a combined end point of intervention and death
			Potentially leads to overadmission (ie, has low sensitivity)
	Melena	1	
	Syncope	2	
	Hepatic disease	2	
Rockall score	Cardiac failure	2	
	Age	0, 1, 2	Requires endoscopic evaluation to determine the full score
			Predicts risk of additional bleeding and death in hospitalized patients
	Signs of hemodynamic shock	0, 1, 2	
	Major comorbidities	0, 2, 3	
	Endoscopic diagnosis	0, 2	
AIMS-65	Stigmata of recent hemorrhage and/or presence of blood on endoscopy	0, 2	
	Albumin (<3 mg/dL)	0, 1	Easy to calculate
	INR (>1.5)	0, 1	Can be calculated pre-endoscopy
	Altered mental status	0, 1	Less sensitive for than Glasgow-Blatchford score and Rockall
	Systolic BP (<100 mm Hg)	0, 1	AIMS-65 score (% inpatient mortality):
	Age (>65 years)	0, 1	0 (0.3%), 1 (3.2%), 2 (5.3%), 3 (10.3%), 4 (16.5%), 5 (24.5%)

NOTE. These risk assessment scores cannot precisely identify individual high-risk patients who will die from gastrointestinal bleeding if they do not receive an intervention, but may have a clinical role in identifying patients who are at very low risk for mortality and may be amenable to outpatient medical care/endoscopy.¹
BP, blood pressure; BUN, blood urea nitrogen; GI, gastrointestinal; INR, international normalized ratio.

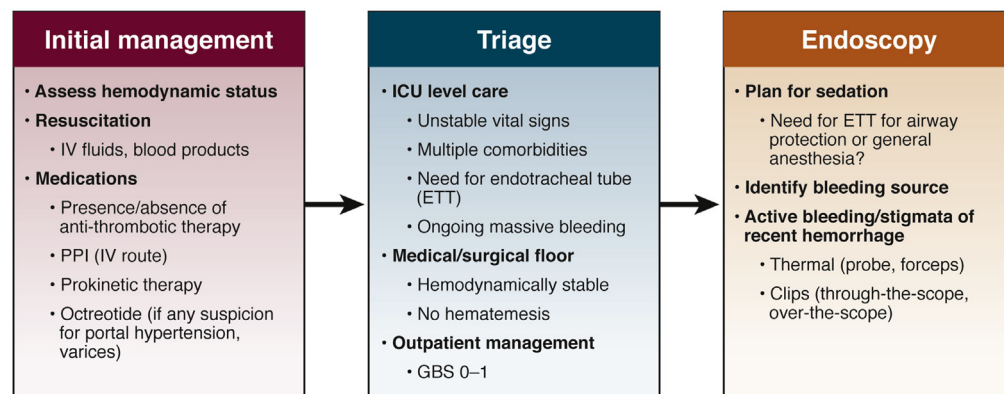


Figure 1. Approach to the initial management, clinical triage, and endoscopic decision making in treating patients with acute NVUGIB. ETT, endotracheal tube; GBS, Glasgow-Blatchford bleeding score; IV, intravenous; PPI, proton pump inhibitor.

erythromycin or metoclopramide may be given intravenously to selected patients before upper endoscopy to aid gastric emptying of clot to improve visualization, particularly of the gastric fundus, where clots tend to obscure complete visualization. Use of these prokinetics have been associated with reduced need for repeat endoscopy, with the published data favoring the use of erythromycin.²⁰ Both erythromycin and metoclopramide should be used cautiously in patients with prolonged QT intervals.^{20,21} Use of octreotide is not recommended in NVUGIB, but there should be a low threshold for its use if there is concern for underlying portal hypertension. Prophylactic antibiotics are not indicated in the setting of NVUGIB.

The use of nasogastric tubes in the evaluation and management of suspected NVUGIB is controversial, as their use does not impact clinical outcomes. Nasogastric lavage can assist in the removal of blood from the stomach and suggests the need for emergent endoscopy if there is return of continuous and copious bright red blood; however, a negative lavage should not delay endoscopy, particularly if other parameters are suggestive of active NVUGIB.¹⁴

Endoscopy Best Practices

After assessment, triage, resuscitation, and medical optimization, endoscopy should be performed to determine the source of bleeding, to assess rebleeding risk, and to treat lesions at high risk for rebleeding (Figure 1). Exactly when the endoscopy should be performed is a clinical judgment made by the gastroenterologist in consultation with the primary service. Understanding that the definitions of emergent, urgent, and elective endoscopy are somewhat variable, endoscopy should generally be performed within 12 hours for emergent cases, within 24 hours for urgent cases, and can wait more than 24 hours for elective cases.^{22,23} A common decision is deciding whether or not to wait until the next morning to perform endoscopy on a patient presenting after hours with suspected NVUGIB. Patients with suspected NVUGIB with persistent hemodynamic compromise after initial resuscitation and those with moderate- to large-volume hematemesis likely have persistent NVUGIB and should undergo emergent endoscopy. It should be noted, however, that patients undergoing emergent endoscopy may have worse outcomes, possibly due to inadequate resuscitation.^{22,23} Patients who are hemodynamically stable, do not have ongoing hematemesis, and have melena only can generally be deferred to the following morning.

A recently published trial included patients who presented with acute upper gastrointestinal tract bleeding and were at high risk for further bleeding or death (Glasgow-Blatchford score ≥ 12). Patients were randomized to urgent (within 6 hours) or early (the next morning and within 24 hours) endoscopy after gastroenterology consultation, which occurred on average 7–8 hours after presentation. This study included patients with variceal hemorrhage and excluded, among others, patients in hypotensive shock or whose condition did not stabilize after initial resuscitation. This pivotal trial demonstrated that urgent endoscopy was not associated with lower 30-day mortality than endoscopy performed the next morning or between 6 and 24 hours after consultation.²⁴ In general, patients with suspected NVUGIB and a Glasgow-Blatchford score of 0–1 may be discharged from the emergency department for timely outpatient management.^{25,26}

The method of sedation (endoscopist-directed or requiring anesthesia support) and whether airway protection is necessary are important considerations before endoscopy. Patients with suspected ongoing or massive NVUGIB, active hematemesis, or suspected retained gastric contents should undergo endotracheal intubation to decrease the risk of aspiration.²⁷ The choice of endoscope is largely at the discretion of the endoscopist. Therapeutic upper endoscopes have a larger working channel that accommodate 10F accessories and also enable improved suction of retained gastric contents and blood clots and may be preferred in situations of severe bleeding.²⁷

Upper endoscopy in the patient with suspected NVUGIB should be performed methodically. The esophagus should be examined carefully for pathology such as varices and Mallory-Weiss tears. Careful examination of the esophagus should be done on the initial scope insertion because retching during the procedure can cause a Mallory-Weiss tear and create a diagnostic and treatment dilemma. If there is a large clot in the stomach, it is not advised to spend time clearing the clot unless a source is not found distally. There are various ways to manipulate clots and improve visualization of the fundus, including repositioning the patient (eg, reverse Trendelenburg or supine/right lateral decubitus), preprocedural prokinetics, using “clot busting” tubing/6-mm channel endoscopes (that provide increased suction power), and extraction/foreign-body retrieval nets. If no bleeding source is found and retained clot prevents full examination of the stomach, endoscopy should be

repeated after allowing time for gastric emptying to complete the examination of the stomach, with the timing dependent on patient stability and the degree of bleeding.

The etiology of bleeding frequently dictates endoscopic therapy. Broadly speaking, definitive endoscopic therapy can be categorized as mechanical (eg, clips) or thermal (eg, heater probes, bipolar/multipolar catheters, hemostatic forceps). Within each group, there are multiple available endoscopic tools and techniques for the management of NVUGIB.^{28,29} Diluted epinephrine (1:10,000 dilution, which is equivalent to 100 µg/mL) can be injected at or near the bleeding site to attain initial hemostasis by inducing vasospasm, but this is only a temporizing measure that allows for improved visualization to target definitive therapy. Epinephrine monotherapy should be avoided, given the high risk for rebleeding.^{30–32} If epinephrine injection is used, a second endoscopic-hemostasis modality should be employed;^{27,32} however, dual therapy with epinephrine and another endoscopic therapy has no advantage over properly applied thermal or mechanical monotherapy.³⁰ In subgroup analyses from meta-analyses, there was no difference between hemoclips and thermal treatment in terms of peptic ulcer rebleeding rates^{30–32}; data showing superiority of one modality over the other are largely lacking.

As there is no definitively superior modality for endoscopic hemostasis, use of through-the-scope hemoclips vs thermal therapy for active NVUGIB or for treatment of stigmata of recent hemorrhage is largely at the discretion of the endoscopist. In terms of active peptic ulcer bleeding and stigmata of recent hemorrhage (using the Forrest classification), the endoscopist should consider the location of the bleeding, as certain locations (eg, posterior wall of duodenum, lesser curvature of the stomach) and certain ulcer characteristics (eg fibrosis, large ulceration, size of visible vessel) can make clip placement more challenging and less effective than thermal therapy. In many situations, a low-profile distal attachment cap on a forward-viewing endoscope can facilitate visualization and therapy.³³ Similarly, a duodenoscope might be required for lesions in the posterior duodenal bulb and second portion of the duodenum.

Endoscopically identified lesions at increased risk for persistent bleeding or rebleeding, such as Forrest Ia (spurting), Ib (oozing), and IIa (nonbleeding visible vessel) ulcers should receive endoscopic-hemostasis therapy. Peptic ulcers with an adherent clot should be treated by endoscopic clot removal to evaluate for high-risk stigmata that might require endotherapy.²⁷

When applying contact thermal therapy, the endoscopist should use, when possible a 10F probe. Generator settings of 25–30 J per pulse, for 4–5 pulses, for a total of 100–150 J, should be used with a heater probe, and 15–20 W are recommended for bipolar/multipolar probes. Forceful contact using the probe should be applied for an extended period (at least 8 seconds), with the tip of the scope as close as possible to the treatment site to ensure complete obliteration of the culprit vessel.^{28,34–36} Failure to obliterate the culprit vessel may cause bleeding during treatment or increase the risk for rebleeding. Excellent visualization is paramount to successful hemostasis, and endoscopes that possess a dedicated water jet should be used to treat NVUGIB.

After achievement of hemostasis, use of a through-the-scope Doppler probe can be considered, as data suggest presence of Doppler signal after hemostasis is a risk factor for rebleeding. A single-blind randomized controlled trial (RCT) demonstrated a significantly decreased rate of rebleeding within 30 days of endoscopic hemostasis in patients randomized to post-treatment Doppler assessment compared with controls.³⁷

Hemostatic Forceps and Concepts in Electrosurgical Energy

Monopolar hemostatic forceps (MHF) were initially used for the treatment of bleeding during endoscopic submucosal dissection (ESD) using low-voltage current.³⁸ The MHF have relatively small, flat, rotatable jaws (Coagrasper, Olympus America, Center Valley, PA) that can be used to grasp and coagulate exposed submucosal vessels in order to treat active bleeding and prevent delayed bleeding from ESD. Using the low-voltage, soft coagulation mode (80W, effect 4) produced by the ERBE VIO series of the electrosurgical generators limits peak voltage thereby minimizing depth of penetration and tissue effect. A variety of studies have examined the use of MHF soft coagulation in peptic ulcer bleeding, including a recent randomized trial of 112 patients that demonstrated their effectiveness compared with the use of hemostatic clips for Forrest Ia, Ib, and IIa gastric or duodenal ulcers.⁵ The initial hemostasis success rate was 98% in the MHF soft coagulation group and 80% in the hemoclip group ($P = .004$).⁵ Of note, in peptic ulcer bleeding studies, the technique differs from ESD, as the MHF are applied to a bleeding point closed (without first opening the atraumatic jaws to grasp the bleeding vessel), followed by applying soft coagulation (80W, effect 4, 1–2 seconds), and then retracting the forceps and retreating as needed. A particular advantage of the MHF stems from the ease and flexibility of targeting with the forceps. The smaller-sized forceps can be used in difficult locations, particularly when clip application is deemed difficult due to location or a rigid fibrotic base. Unlike certain thermal probes units, which apply a fixed current for a defined time, the application of current is also controlled by the endoscopist and the electrosurgical generator, making retreatment more controlled, with less tissue injury. A potential downside to the use of MHF soft coagulation occurs when there is limited coagulation effect at the bleeding point. Treating in the presence of a large blood clot would potentially dissipate the coagulation effect, preventing hemostasis from occurring. Another situation where the limited tissue effect is potentially suboptimal is when a large area of tissue needs to be treated and repeated applications could be required.

As the hemostatic forceps (typically available in ESD centers) are relatively costly, some endoscopists use a snare tip to apply soft coagulation for hemostasis, and others have tried to apply noncontact thermal methods (such as argon plasma coagulation) to conduct and/or provide heat through already applied hemostatic clips. Another less costly alternative is to use closed, hot biopsy forceps that usually cost a fraction of the cost of MHF. However, these uses of thermal energy delivery to treat peptic ulcer bleeding have not been formally studied. Switching

generator settings to a forced coagulation mode (available on several commercially available electrosurgical generators), for example, could be used to overcome pools of liquid or blood between the forceps and bleeding point; however, the endoscopist could potentially treat a larger area than desired and have less ability to limit the depth of tissue injury. Endoscopists should monitor the coagulum being created and be aware of the potential for deep tissue injury, perforation, or delayed bleeding whenever electrosurgical energy is applied. Until their effectiveness is formally studied, these latter techniques should be employed only by endoscopists very familiar with their use in advanced endoscopic procedures and who possess a good understanding of electrosurgical current settings.

Over-the-Scope Clips

In selected patients with peptic ulcer bleeding or other causes of NVUGIB, over-the-scope clips can be an effective treatment option. There are currently 2 clips (OTSC; Ovesco Endoscopy, Cary, NC) and (Padlock clip; Steris Endoscopy, Mentor, OH) with different designs and deployment mechanisms. There have been no head-to-head comparisons of these clips or head-to-head trials of over-the-scope clips to through-the-scope clips or thermal therapy. Most of the reported experience with over-the-scope clips in NVUGIB has been with peptic ulcer bleeding. There are several scenarios in which over-the-scope clips may be utilized in NVUGIB, including rescue treatment, rebleeding, and initial treatment.

In the setting of persistent bleeding despite conventional methods of hemostasis, data from small case series suggest that over-the-scope clips are an effective rescue modality.^{39–42} A recent RCT demonstrated that over-the-scope clips were more effective than standard therapy in patients with recurrent peptic ulcer bleeding.⁴ There are also nonrandomized data suggesting that over-the-scope clips may be superior to standard treatment in initial treatment of peptic ulcer bleeding compared with historical rebleeding rates.^{43–46} Before suggesting a paradigm shift to over-the-scope clips, large RCTs are needed that demonstrate considerable benefit. However, there may be situations in which over-the-scope clips should be considered as first-line treatment—namely, large, fibrotic ulcer beds with a large visible vessel that may not be amenable to through-the-scope hemoclip fixation or when thermal therapy is predicted to be ineffective.

Hemostatic Powder

Topical hemostatic agents are a noncontact modality that can be used to treat NVUGIB. The main advantage of these agents is related to their mode of action and technique of deployment. Unlike other endoscopic hemostatic modalities, topical hemostatic powders can be diffusely deployed from a catheter without having to be positioned en face and do not require advanced endoscopic training or skills. Much of the initial clinical experience with these agents occurred in countries outside of the United States. Initially, hemostatic powder was used only in cases of NVUGIB due to concern of embolization risk, but a recent study in patients

with variceal bleeding demonstrated clinical effectiveness without adverse events.⁴⁷ Although patients in hemostatic powder studies have experienced adverse events, they were unlikely to be due to the sprayed powder.⁴⁸

Although there are a few hemostatic agents available worldwide, the commercially available product in North America is TC-325 (Hemospray, Cook Medical, Bloomington, IN). This agent is propelled through a delivery catheter on to a bleeding lesion using a carbon dioxide canister. Upon contact with moisture, the endoscopic powder aggregates, creating a mechanical barrier upon the mucosa.⁴⁹ This makes it particularly useful in situations where bleeding is diffuse, cannot be localized, or if visualization is poor due to bleeding (Figure 2). In most instances, hemostatic powder should be preferentially used as a rescue therapy and not for primary hemostasis, except in cases of malignant bleeding or massive bleeding with inability to perform thermal therapy or hemoclip placement.

When using this type of hemostatic powder and delivery system, the endoscopist should make an effort to prevent the delivery catheter from becoming blocked. Both 7F and 10F catheters are available for different-sized accessory channels (such as those found in diagnostic vs therapeutic endoscopes). Care must be taken when using duodenoscope elevators or when in retroflexed positions to avoid kinking the delivery catheter. Additional steps must also be taken to avoid moisture coming into contact with the catheter, such as keeping the catheter tip out of contact with pools of fluid or blood, as this will prematurely activate the powder within the catheter and prevent deployment. Keeping the accessory channel free of moisture by preflushing with air (using a 60-mL syringe) and detaching suction tubing temporarily before inserting the delivery catheter to avoid inadvertent suctioning are steps that may minimize unintended activation of the powder within the delivery catheter. Once in position near the bleeding site, the spray is typically deployed from a distance of 1–2 cm away in short controlled bursts. Once delivery begins, the endoscopist should take care to avoid accidental powder spray on the lens. Overapplication can lead to a diffuse spray effect, potentially limiting subsequent mucosal assessment. Subsequent washing at the lesion site is not recommended, as this can wash away the powder. If multiple treatment modalities are planned, it is ideal to plan the timing and sequence of modalities due to the effect of powder deployment on endoscopic visibility.

Retrospective studies demonstrated the powder remains present less than 24 hours,⁵⁰ hence monotherapy with TC-325 is not recommended in ulcers with high-risk stigmata for rebleeding. In these situations, hemostatic powder should be used as a temporary measure to stop bleeding, followed by another treatment modality either at the index procedure or during a second-look endoscopy.¹⁴ However, 2 pilot RCTs^{6,51} and a noncontrolled registry study⁵² have suggested a potential role for TC-325/Hemospray as monotherapy in patients with upper gastrointestinal tract bleeding, raising the need for an appropriately powered clinical trial. Hemostatic powder may be particularly useful in centers where advanced endoscopic expertise is not always available and temporizing methods are needed before more definitive therapy or transfer to a specialized center.

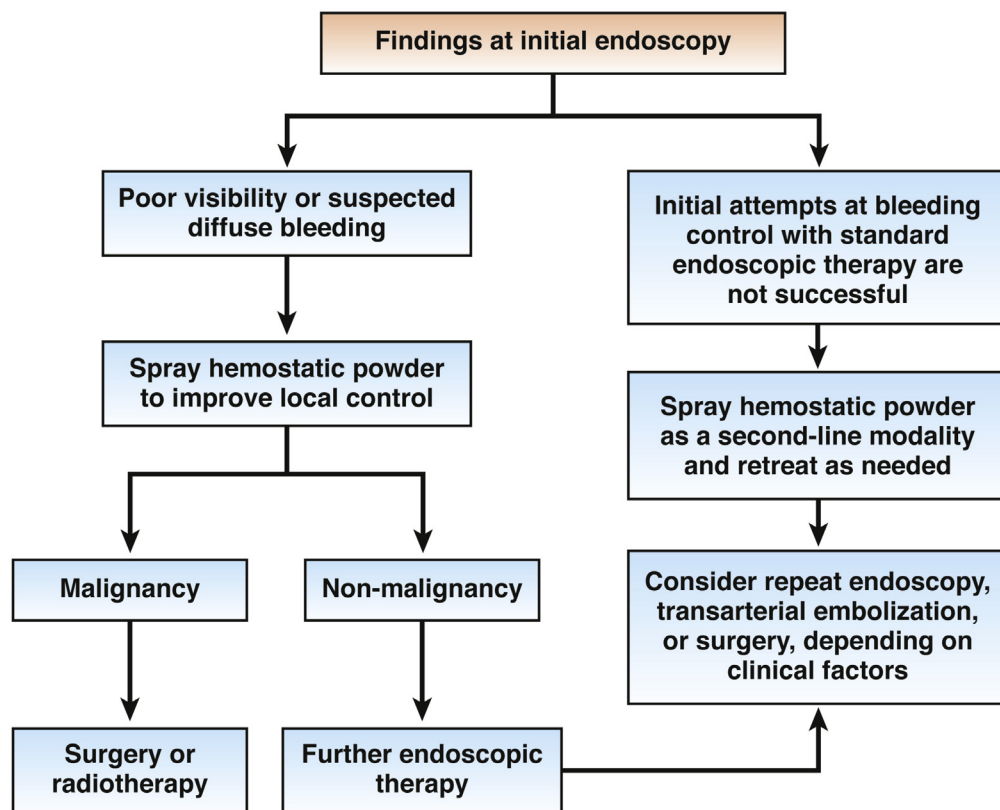


Figure 2. Flow diagram incorporating hemostatic powder therapy as an option for the management of acute NVUGIB.

Diffuse tumor bleeding is a challenging clinical problem that is often not responsive to conventional endoscopic therapy. A pilot RCT⁵¹ did show that hemostatic powder may be useful in such situations, optimally as a bridge to radiotherapy or surgery.

According to the US Food and Drug Administration, on February 4, 2020 Cook Medical recalled their Hemospray Endoscopic Hemostat (hemostatic powder) device due to “Complaints that the handle and/or activation knob on Hemospray devices have cracked or broken when the device is activated. In some cases, this has caused the carbon dioxide cartridge to exit the handle.”⁵³ This was in conjunction with a voluntary global recall initiated by the company in January 2020 for the same reason. Cook Medical has addressed this issue. On June 10, 2020 the US Food and Drug Administration issued 510(k) premarket approval (K200972) for Hemospray. At the time this Clinical Practice Update went to print, Hemospray is available again in the US and Canadian markets and in many other countries worldwide.

Hemostatic Considerations in Advanced Endoscopy Settings

There are certain endoscopic interventions that are associated with an increased risk for inducing bleeding.¹⁵ These include endoscopic mucosal resection (EMR), ESD, and endoscopic sphincterotomy. Bleeding can be immediate/intraprocedural or delayed/postprocedural. Endoscopists who perform these procedures should be comfortable managing bleeding and have tools readily available in the event of

intraprocedural bleeding. Procedure-related bleeding is treated in the same manner as other types of NVUGIB, but with special considerations. For example, thermal therapy, particularly with hemostatic forceps, for bleeding during EMR or ESD may be preferable to treatment with hemoclips because the latter may interfere with completing the resection. For post-sphincterotomy bleeding, biliary stents may be used to tamponade a bleeding site. Clips and thermal therapy can also be used to treat post-sphincterotomy bleeding; however, the endoscopist needs to be aware of the potential difficulty in clip placement through a duodenoscope and the possibility of pancreatitis with thermal therapy or errant clip placement. Therefore, when clips or thermal coagulation are used in post-sphincterotomy bleeding, a low threshold for placing a prophylactic pancreatic duct stent should exist. Endoscopists should be prepared to perform an endoscopic retrograde cholangiopancreatography, if needed, for all delayed post-sphincterotomy bleeds, as biliary and/or pancreatic duct stenting may be required.

Postprocedural bleeding prophylaxis is an important issue that the endoscopist should address. This is particularly important in patients who require reinstitution of AT therapy. Although there is recent evidence that clip closure of right-sided colonic EMR sites might decrease the risk of post-polypectomy bleeding,⁵⁴ there is no similar high-level evidence for upper gastrointestinal interventions. For bleeding prophylaxis of upper gastrointestinal EMR or ESD sites, options include use of MHF to treat visible vessels or closure of the defect with clips or endosuturing. There are no comparative trials to guide practice, but consideration should be

given to closing sites, when amenable, in patients who require immediate resumption of AT medications. There are no data with regard to prophylaxis of post-sphincterotomy bleeding; however, in patients who require immediate resumption of AT medication, a fully covered metallic biliary stent may be used.

Interventions for Recurrent or Refractory Bleeding

In patients who rebleed after endoscopic therapy, a second attempt at endoscopic hemostasis is typically advised. In patients treated initially with thermal therapy who rebleed, additional thermal therapy might be possible, or mechanical therapy with a clip could be applied. Hemospray should also be considered as rescue therapy. In difficult situations, a second opinion from a colleague or assistance from a more experienced endoscopist are important considerations.

However, despite the increasing availability of different effective endoscopic modalities, a subset of patients with NVUGIB will still develop rebleeding despite high-quality endoscopic interventions. The exact point at which an endoscopist will determine that repeat endoscopic intervention has a low chance of technical and clinical success is a complex decision that will depend on local expertise and resources; familiarity with advanced endoscopic techniques; and clinical predictors, such as type of disease, severity, and location. Second-look endoscopy should not be performed routinely, but it does have a role in cases where rebleeding risk is high, despite initial endoscopic success or if the index procedure does not adequately control bleeding. Prior endoscopic therapy can be suboptimal due to ulcer characteristics, such as size, location, or presence of fibrosis; the use of epinephrine-injection monotherapy or single use of a hemostatic powder for a high-risk lesion; or if thermal or mechanical therapy alone or in combination was performed but did not adequately control bleeding for technical reasons (eg, inadequate coagulation or insufficient tissue grasped by a hemostatic clip).

The main options in cases of endoscopic failure with rebleeding or refractory bleeding are transcatheter arterial embolization (TAE) and surgery. In earlier studies, a variety of surgical options were used, with TAE reserved for poor surgical candidates. With high technical and clinical success rates, TAE has been shown to be equally effective, with trends toward lower 30-day mortality rates compared with surgical intervention.⁵⁵⁻⁵⁷ TAE has become increasingly available, with the advantage of being able to be used in patients who are unfit for surgery, even in the setting of coagulopathy. Studies of TAE have shown fewer complications than surgery, albeit with higher rebleeding rates.⁵⁷ Embolization is most effective when active extravasation can be demonstrated, or if a site can be endoscopically prelocalized (either anatomically or by using a hemoclip) before empiric embolization. Studies of embolization show that multiple or large duodenal ulcers, gastritis, coagulopathy, or multi-organ failure are believed to contribute to clinical failures.⁵⁸ The choice of embolic agent should also be taken into account by the performing interventional radiologist, as the multiple agents that exist have different properties that influence rebleeding rate, risk of

recanalization, and subsequent ischemic complications. An important point is that prophylactic TAE of high-risk ulcers after successful endoscopic therapy is not recommended.^{1,59}

As patients with rebleeding and refractory bleeding are typically complex, with multiple comorbidities, often receiving anticoagulants, or with severe coagulopathies (such as seen in hematologic malignancies), the choice among repeat endoscopy, surgery, and TAE must be decided on a case-by-case basis. Weighing the risks and benefits of each intervention will depend on the expected rates of clinical success, risk of rebleeding, potential adverse events, and after taking into account local expertise and resource availability. For optimal clinical outcomes in refractory bleeding, a multidisciplinary approach is required involving gastrointestinal endoscopists, intensivists, surgeons, interventional radiologists, and in some cases hematologists and/or oncologists.

Summary

Recent advances in endoscopic devices and techniques now enable endoscopists to treat NVUGIB lesions more effectively and with a variety of often complementary methods. With this expanded endoscopic armamentarium, endoscopic therapy should achieve hemostasis in the majority of patients with NVUGIB. Hemostatic forceps, over-the-scope clips, and sprayed hemostatic powders are newer and relatively expensive endoscopic devices that have established roles in treating NVUGIB, and may be particularly useful in difficult-to-treat or recurrent bleeding lesions. Despite the increased costs of newer devices or multimodal therapy, effective hemostasis to prevent rebleeding and the need for hospital readmission is likely to be a dominant cost-saving strategy. Practicing endoscopists should be comfortable applying conventional thermal therapy and placing hemoclips, and they should familiarize themselves with newer techniques to manage NVUGIB, which can occur from a variety of etiologies ranging from peptic ulcer disease to adverse events after therapeutic endoscopy. In situations where thermal or mechanical therapies are not successful at achieving hemostasis, sprayed hemostatic powder is a valuable rescue therapy; and it might also enable endoscopists with limited training or backup to temporize severely bleeding lesions to allow time for transfer to a specialized referral center. Finally, multidisciplinary consultation and an assessment of endoscopic, radiographic, and surgical expertise should inform the selection of therapy in refractory NVUGIB.

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Correspondence

Address correspondence to: Andrew Y. Wang, MD, AGAF, FASGE, FASGE, Division of Gastroenterology and Hepatology, University of Virginia, Box 800708, Charlottesville, Virginia 22908. e-mail: ayw7d@virginia.edu; fax: 434-244-7590.

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Conflicts of interest

Daniel Mullady discloses the following: consultant, Boston Scientific; consultant, ConMed; Hemospray Advisory Board, Cook Medical. The remaining authors disclose no conflicts.