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 Dimitrios Kapetanios, FEBG, PhD, Doctor, Department of Gastroenterology,
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Endoscopic advances in the management of non-variceal upper gastrointestinal bleeding: A review

Maliha Naseer, Karissa Lambert, Ahmed Hamed, Eslam Ali

ORCID number: Maliha Naseer (0000-0001-6891-1378); Karissa Lambert (0000-0002-0663-2549); Ahmed Hamed (0000-0001-7448-5715); Eslam Ali (0000-0002-3379-8683).

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Maliha Naseer, Eslam Ali, Division of Gastroenterology and Hepatology, Department of Internal Medicine, East Carolina University, Greenville, NC 27834, United States

Karissa Lambert, Ahmed Hamed, Department of Internal Medicine, East Carolina University, Greenville, NC 27834, United States

Corresponding author: Maliha Naseer, MD, Gastroenterology Fellow, Division of Gastroenterology and Hepatology, Department of Internal Medicine, East Carolina University, 521 Moye Blvd, Greenville, NC 27834, United States. naseerm18@ecu.edu

Abstract

Upper gastrointestinal bleeding is defined as the bleeding originating from the esophagus to the ligament of Treitz and further classified into variceal and non-variceal gastrointestinal bleeding. Non-variceal upper gastrointestinal bleeding remains a common clinical problem globally. It is associated with high mortality, morbidity, and cost of the health care system. Despite the continuous improvement of therapeutic endoscopy, the 30-d readmission rate secondary to rebleeding and associated mortality is an ongoing issue. Available Food and Drug Administration approved traditional or conventional therapeutic endoscopic modalities includes epinephrine injection, argon plasma coagulation, heater probe, and placement of through the scope clip, which can be used alone or in combination to decrease the risk of rebleeding. Recently, more attention has been paid to the novel advanced endoscopic devices for primary treatment of the bleeding lesion and as a secondary measure when conventional therapies fail to achieve hemostasis. This review highlights emerging endoscopic modalities used in the management of non-variceal upper gastrointestinal related bleeding such as over-the-scope clip, Coagrasper, hemostatic sprays, radiofrequency ablation, cryotherapy, endoscopic suturing devices, and endoscopic ultrasound-guided angiotherapy. In this review article, we will also discuss the technical aspects of the common procedures, outcomes in terms of safety and efficacy, and their advantages and limitations in the setting of non-variceal upper gastrointestinal bleeding.

Key words: Non-variceal upper gastrointestinal bleeding; Over the scope clip; Hemospray; Radiofrequency ablation; Endoscopic suturing device

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Core tip: In the last two decades, there has been drastic decline in the mortality and morbidity caused non-variceal upper gastrointestinal bleeding due to significant progress in the therapeutic endoscopy. The use of devices such as over the scope clips system, Coagrasper, hemospray and endoscopic suturing has tremendously evolved and expanded to achieve hemostasis as a primary method or when conventional therapeutic devices such as heater probe, hemoclips or epinephrine injection fails to control bleeding.

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INTRODUCTION

Gastrointestinal bleeding is a medical emergency that results in substantial morbidity, mortality, and health care cost^[1,2]. It can present as a massive life-threatening hemorrhage, or a slow chronic bleed. Upper gastrointestinal bleeding (UGIB) is defined as any gastrointestinal bleeding that originates above the ligament of Treitz^[3,4]. UGIB can be further classified as non-variceal UGIB (NVUGIB) and variceal UGIB (VUGIB). The common causes of NVUGIB are listed in [Table 1](#). The incidence and mortality associated with NVUGIB have been decreasing due to the advancements in the prevention and management of NVUGIB^[5-7]. Yet, it remains a common clinical problem with an annual incidence of about 90-108 per 100000 and mortality of 3% to 14%^[8,9].

The initial approach to the patient presenting with acute NVUGIB is highlighted in [Figure 1](#). Early endoscopic intervention within 24 h of presentation dramatically improves patient outcomes, and there was no difference observed compared to those who underwent endoscopic intervention < 12 h after presentation^[10,11]. When an endoscopic approach is performed, it is crucial to have a standardized method of diagnosing the cause of bleeding, evaluating the stigmata of recent hemorrhage (*i.e.*, active bleeding, a visible blood vessel, presence of clots, or red or black spots covering the ulcer lesion), and classifying gastric ulcers according to the Forrest classification^[12,13]. Endoscopy is important in revealing the etiology of NVUGIB.

The development and widespread use of endoscopy has been a major contributor to the reduced need for surgery and morbidity associated with NVUGIB^[14]. Endoscopic management is classified as injection, thermal, and mechanical methods. Amongst the traditional methods, injection of epinephrine is the most common and widely used modality because of its feasibility to perform and requires less coordination between endoscopist and assistant. However, epinephrine alone is less effective than combination with thermal or mechanical and other monotherapies such as clips, probes and electrocoagulation^[15,16]. According to the Cochrane review, combination treatment has been associated with significant reduced risk of rebleeding, surgery and mortality in peptic ulcers with active bleeding or high-risk stigmata such as adherent clot^[17]. Through the scope endoclips or hemoclips are found to be effective and safe hemostatic mechanical devices when applied precisely as mono or combine therapy. Clip grasp the vessel in the submucosa, seal the defect in the target blood vessel with or without approximation of the sides of the lesion. Furthermore, the tissue damage is minimal with clips and ulcer healing process is not hampered^[18,19]. Introduced in clinical practice in 1990s, over the years, clips are evolved in terms of functionality (such as precision, tensile strength, rotatability, overshoot and strength of closure), physical characteristics and cost^[20,21]. Recently published study by Wang *et al*^[22] compared the functionality of the five different types of hemostatic clips. According to the study findings, Resolution 360 (Boston Scientific, Marlborough, Mass) was the fastest rotating clip when operated by the physicians. Instinct (Cook Medical, Bloomington, Ind) was found more mechanically stronger and performed better for compression of thick, fibrous tissue and crated ulcers. Overshoot and whipping (defined as > 30° and > 1 half revolution respectively) tends to happen when clips are rotated multiply in same direction. For both overshoot and whip, the SureClip 16 mm performed well when compared with other types of through the scope clips^[22].

Table 1 Etiologies of non-variceal upper gastrointestinal bleeding

Etiologies of non-variceal upper gastrointestinal bleeding	
Ulcer/ inflammation	Peptic ulcer disease Erosive esophagitis, gastritis or duodenitis Anastomotic ulcers (post gastric bypass)
Vascular lesions	Gastric antral vascular ectasia Dieulafoy's lesion Angiodysplasia/ Arteriovenous malformation Aorto-enteric fistula
Congestive gastropathy	Portal hypertensive gastropathy
Malignant lesions	Gastrointestinal stromal tumors (GIST) Non-GIST (<i>e.g.</i> , Lipoma, schwannoma) Gastric and esophageal cancer Metastatic lesions in the upper GI tract
Post procedural	Endoscopic mucosal and submucosal dissection Post sphincterotomy
Others	Mallory Weis tear Cameron ulcers

GI: Gastrointestinal; GIST: Gastrointestinal stromal tumors.

Despite the continued improvements, traditional therapies sometimes lack effectiveness at primary control or prevention of rebleeding, which are reported to be as high as 10%-24%^[23-25]. Posterior duodenal wall ulcers or ulcers higher up the lesser curvature, actively bleeding lesions during endoscopy, ulcers larger than 2 cm in diameter, or with bleeding vessel > 2 mm are some of the major predictors of rebleeding^[26]. For the past decade, there is much interest in developing and studying endoscopic methods to effectively achieve hemostasis and overcome the limitation of the traditional endoscopic methods. Tables 2 and 3 summarize emerging endoscopic modalities for the management of NVUGIB and their pros and cons. In this article, we will review the advanced endoscopic modalities currently available for the management of NVUGIB.

EMERGING MECHANICAL TREATMENT OPTIONS FOR NVUGIB

Over the scope clips

It has been proved that mechanical hemostatic methods are more effective in achieving hemostasis than injections or thermal modalities alone. The Over-The-Scope Clip (OTSC, Ovesco Endoscopy GmbH, Tübingen, Germany) is a Food and Drug Administration approved novel endoscopic clipping device^[27]. The use of OTSC system was first reported in 2007 by Kirschniak *et al*^[28] for gastrointestinal tissue approximation. Since then, the device has been widely used to control gastrointestinal bleeding, particularly caused by large and fibrotic ulcers at anatomic locations that are difficult to treat with through-the-scope (TTS) clips or at risk of perforation^[29]. Other uses include the closure of perforation and fistula^[30].

The OTSC® System Set consists of an applicator cap with a mounted over the scope clip, thread, thread retriever, and a hand wheel for clip release. The clip is made up of a super elastic nitinol alloy, which is delivered by means of an applicator cap and released by tightening the thread with the hand wheel. OTSC caps are available in 3 diameters (11, 12, and 14 mm) and 2 working depths (3 and 6 mm). There are three versions of OTSC versions available currently (atraumatic, traumatic and more gastric wall closure clip)^[31]. Due to its unique design and elastic properties, the nitinol clip closes itself and secures the therapeutic effect by exerting constant circumferential compression force enough to stop bleeding from large size tissue defects and blood vessels^[32].

Over the scope clip system has been established to be safe and effective as a first line and in the rescue management of non-variceal gastrointestinal bleeding. The first case series comprises a total of 9 patients (7 patients with GI bleeding) and was first

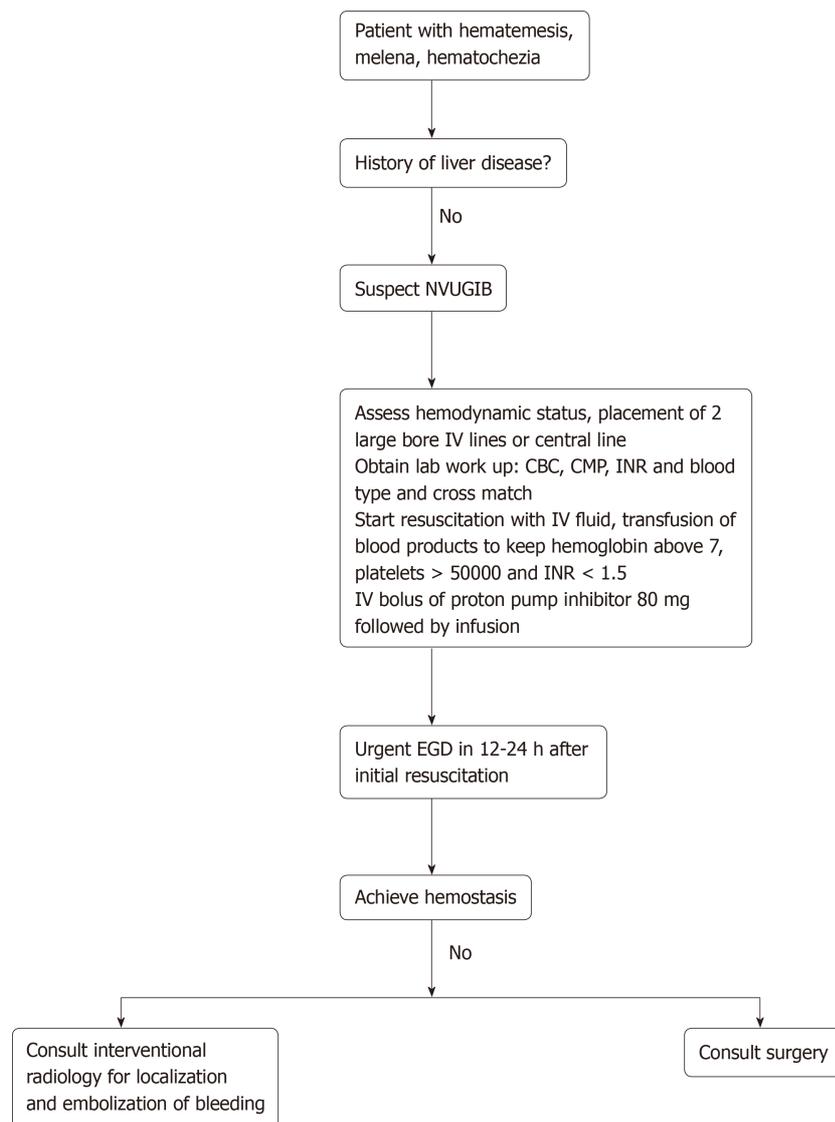


Figure 1 Initial evaluation and management of patient presented with suspected upper gastrointestinal bleeding. EGD: Esophagogastroduodenoscopy; CBC: Complete blood count; CMP: Comprehensive metabolic panel; INR: International normalized ratio; NVUGIB: Non-variceal upper gastrointestinal bleeding.

published in 2009 by Repici *et al*^[33] from Italy. It was followed by several other retrospective analyses of single and multi-center experience with OTSC to achieve hemostasis (Table 4)^[33-43]. Four retrospective studies with large sample sizes ($n = 67-93$) were published between 2016-2018. The primary outcomes of these studies were the technical success to control bleeding and rebleeding rates. Most of the studies reported success rates between 78% to 100% with the rebleeding risk of < 1%. However, rebleeding was seen approximately 26% patients in a retrospective analysis conducted by Brandler *et al*^[43]. In this study, the authors attributed high rebleeding rates and failure of OTSC to the history of coronary artery disease. Lamberts *et al*^[42] reported rebleeding rates of 26%. Their data suggest that first line endoscopic treatment of the ulcer with OTSC has higher success and low rebleeding rates as compared to its use as second-line treatment. Also, they found OTSC as the less preferable treatment for diffusely bleeding polypoid lesions and vascular malformations.

Only one prospective randomized control multicenter trial compared OTSC with standard treatment (TTS clips or thermal therapy plus injection with diluted adrenaline) of severe recurrent UGIB was published by Schmidt *et al*^[44]. According to the study, results demonstrated significant differences noted in the persistent bleeding rates between treatment (6.0%) and control group (42.4%) and rebleeding at 30 d. However, the rebleeding rates at day 7 were not significantly different between groups. A recently published study analyzed 1517 cases treated with OTSC in 30 published studies over a 9-year period. The overall success rate of OTSC to control

Table 2 Summary of emerging endoscopic modalities for the management of non-variceal upper gastrointestinal bleeding

Emerging endoscopic modalities	
Injection	Endoscopic ultrasound guided angiotherapy
Thermal therapies	Coagulation grasper, radiofrequency ablation, cryotherapy
Mechanical	Over the scope clip system, endoscopic suturing, flexible linear stapler (experimental)
Topical	Hemospray, endoclot, pure-Stat, ankaferd blood stopper, oxidized cellulose

hemorrhage was found to be 85% with the complication risk of about 1.7%. Procedural accidents for e.g. deviation of the over the scope clip system itself or deviation of the clip from fibrotic tissue, intraluminal stenosis, and perforation of the thin duodenal wall with the bear claw were a few of the reported complication in these studies^[45].

One of the major advantages of the OTSC system is it's simple to use and does not require special endoscopic skills to implant the clip^[46]. However, it is difficult to close hard, chronic, and severely fibrotic lesions with OTSC. Another limitation is the application of the clip in the emergency situations because after identifying the bleeding source, the scope must be removed to mount OTSC system on the scope (just like variceal band ligator) and reintroduced to deploy clips^[47].

Endoscopic suturing

An endoscopic suturing device to perform minimally invasive endoscopic interventions was first proposed by Kalloo *et al*^[48] more than a decade ago. Since its development, the endoscopic suturing device (Overstitch TM, Apollo Endosurgery, Austin, TX, United States) has continuously evolved and been established to be successfully used in a variety of endoscopic procedures including gastrointestinal fistula closure, perforations, leaks, endoscopic revision of gastro-jejunal bypass after bariatric surgery, and endoscopic submucosal dissection (ESD)^[49-51].

The endoscopic suturing device is introduced into the stomach through an over tube. The Overstitch system attaches proximally and distally to the double-channel endoscope, which is comprised of a cap-based suturing curved arm (to operate the tissue helix for atraumatic tissue manipulation), anchor exchange catheter (pass suture), and handle (to be mounted on the shaft of the endoscope to control suturing process). The suturing process begins at one of the edges of the ulcer using a curved needle. The curved needle then closes and grabbed by the anchor exchange and detached from the driver. The endoscope, with Overstitch, then moves proximally towards the other edge of the ulcer. This process repeats until the two edges of the ulcer are pulled together. Once the edges of the ulcer approximate each other, the 2 'O' polypropylene suture, placed by the cinching device, is tightened and secured^[52].

Endoscopic suturing is found to be a promising modality in the management of NVUGIB in several case reports and case series due to its excellent ability to close large mucosal defects after conventional methods fail to achieve hemostasis. Recently, Agarwal *et al*^[53], published a case series of 10 patients and demonstrated the endoscopic suturing device was used successfully to control bleeding related to large recurrent peptic ulcers. Mean suturing time was reported to be 13.4 ± 5.6 (range 3.5-20) min. No early or delayed procedural related complications were reported^[53].

The endoscopic suturing device has several advantages over OTSC and hemospray (HS). Although these devices have high success rates in controlling NVUGIB, the endoscopic suturing device is technically more feasible and efficacious for larger, deep, and fibrotic ulcers. However, bleeding from small, shallow, and non-fibrotic ulcers can be more efficiently controlled with OTSC placement^[54]. HS, on the other hand, can be utilized as the temporizing measure to control bleeding, as published data suggested that its rebleeding rate is up to 29% to 38%^[55]. Limitations of the endoscopic suturing device include the need for a double channel endoscope and expert endoscopic skills. The use of endoscopic suturing should be avoided if there is a suspicion of malignant ulcer^[56].

Endoscopic band ligation

Endoscopic band ligation (EBL) was initially developed for esophageal and hemorrhoidal ligation; however, it can be also used in the management of upper gastrointestinal vascular lesions, such as nodular gastric antral vascular ectasia (GAVE)^[57]. Studies have demonstrated that EBL may be superior to argon plasma coagulation and endoscopic thermal therapy regarding the reduction of treatment sessions, control of bleeding and need for transfusion, proving to be a promising

Table 3 Summary of the pros and cons of new emerging endoscopic treatment modalities for non-variceal gastrointestinal bleeding

Emerging endoscopic treatment	Pros	Cons
Over the scope clips	<ol style="list-style-type: none"> 1 Simple to use 2 Special endoscopic skills are not required to implant the clip 3 Effective for the ulcers larger than 2 cm in diameter, or with bleeding vessel > 2 mm 	<ol style="list-style-type: none"> 1 Difficult to close hard, chronic, and severely fibrotic lesions with OTSC 2 Time consuming especially in the emergency situations (after identifying the bleeding source, the scope must be removed to mount OTSC system on the scope and reintroduce to deploy clips)
Endoscopic suturing	<ol style="list-style-type: none"> 1 Technically more feasible and efficacious for larger, deep, and fibrotic ulcers 	<ol style="list-style-type: none"> 1 Double channel endoscope and expert endoscopic skills are required to operate endoscopic suturing device
Endoscopic band ligation (EVL)	<ol style="list-style-type: none"> 1 Associated with the reduction of treatment sessions, control of bleeding and need for transfusion 2 EVL is safe, technically straightforward, and highly effective in this patient with complete eradication of GAVE 	<ol style="list-style-type: none"> 1 Few cases of Hyperplastic gastric polyps
Coagrasper	<ol style="list-style-type: none"> 1 One of the safest and most efficacious hemostasis modalities due to large surface area of the forceps and anti-slip jaw design provides mechanical tamponade effect to the surrounding tissue 2 The risk of perforation is extremely low because coagrasper works at a lower voltage as compared to other thermal treatments coagulates tissues without any carbonization and does not extend to deeper tissue 3 The forceps can be used to treat multiple bleeding sites proving to be cost-effective 	<ol style="list-style-type: none"> 1 Coagulation may be incomplete because of electrical leakage if the lesion submerged in water or lesion with large tissue volume or surface area 2 Because the devices used for soft coagulation, including disposable hemostatic forceps, are relatively expensive, the method may be appropriate only for centers that perform ESD frequently 3 Few cases of aspiration pneumonia reported
Radiofrequency ablation	<ol style="list-style-type: none"> 1 Feasible and safe in ablating GAVE lesions 2 Able to deliver high energy captive coagulation of superficial mucosa including blood vessels 3 Wider surface area coverage of mucosa owing to the various electrode sizes 4 Contact technique with uniform zone of energy distribution and penetration such that deeper ectatic submucosal vascular channels are coagulated 	<ol style="list-style-type: none"> 1 Endoscopic skills are required to perform RFA 2 Exact apposition of the gastric antral mucosa with electrode is required to allow effective delivery of the electric energy which means the endoscope may have to be removed, the electrode rotated, and reintroduced multiple times. The newer through-the-scope internally rotatable ablating catheter may sidestep this disadvantage but has smaller surface area
Endoscopic ultrasound guided angiotherapy	<ol style="list-style-type: none"> 1 EUS-guided therapy of nonvariceal bleeding has been shown to be feasible and safe for peptic ulcer disease, Dieulafoy's lesions, bleeding tumors, and pseudoaneurysms due to the ability to directly visualize and target the bleeding vessel with a specific therapy and subsequently confirm hemostasis with real-time Doppler ultrasound are significant advantages of EUS-guided therapy 	<ol style="list-style-type: none"> 1 Endoscopic skills are required to perform endoscopic ultrasound 2 EUS guided angiotherapy more resource intensive than other routine hemostasis endoscopic procedures
Topical therapies, <i>i.e.</i> , Hemospray and Endoclot	<ol style="list-style-type: none"> 1 Easy to use, safe and effective. Cost effective. Can be used for malignant GI hemorrhage 	<ol style="list-style-type: none"> 1 Theoretically possible side effects of Hemospray include embolization, intestinal obstruction, and allergic reaction to the powder 2 If hemostasis fails, there is the disadvantage that the powder attached to the mucous membrane may limit the use of other hemostatic modalities 3 Hemospray works only on active bleeding

EVL: Endoscopic band ligation; GAVE: Gastric antral vascular ectasia; EUS: Endoscopic ultrasound; GI: Gastrointestinal; RFA: Radiofrequency ablation; ESD: Endoscopic submucosal dissection; OTSC: Over-The-Scope Clip.

efficacious alternative modality^[58,59]. However, further prospective studies are warranted with larger sample sizes, longer follow-up interval, and examination of cost-effectiveness and procedural time.

EMERGING THERMAL TREATMENT OPTIONS FOR NVUGIB

Coagrasper

Coagrasper (Olympus Corp., Tokyo, Japan) or hemostatic forceps is a combination of

Table 4 Efficacy and safety of over the scope clips in the management of non-variceal upper gastrointestinal bleeding (2009-2018)

Authors and year of publication	Study design	Study participants	Sample size	Duration	Outcomes of the study	Success rate
Repici <i>et al</i> ^[33] , 2009	Retrospective	Mean age, 70 yr, gender (M/F): 5/2	7	Unknown	Success rates with the first endoscopic therapy	Success rates with the first endoscopic therapy
Kirschniak <i>et al</i> ^[34] , 2011	Retrospective	Mean age, 68 yr, gender (M/F): 18/9	27	2006-2010	1 Success rates with the first endoscopic therapy 2 Rebleeding episodes	Primary hemostasis was achieved in all cases (100%) Rebleeding was observed in 2 cases
Albert <i>et al</i> ^[35] , 2011	Retrospective	Mean age, 62 yr, gender (M/F): 5/2	7	Unknown	1 Success rates with the first endoscopic therapy 2 Rebleeding episodes	Primary success rate was observed in 100%
Skinner <i>et al</i> ^[36] , 2014	Retrospective	Mean age, 59 yr, gender (M/F): 8/5	12	2012-2013	1 Success rates with the first endoscopic therapy 2 Rebleeding episodes	Hemostasis was achieved in all patients. Rebleeding occurred in two patients 1 d and 7 d after OTSC placement
Nishiyama <i>et al</i> ^[37] , 2013	Retrospective	Mean age, 77 yr, gender (M/F): 5/4	9	2011-2012	Success rates with the first endoscopic therapy	Primary success rate was observed in 77.8%
Manta <i>et al</i> ^[39] , 2013	Retrospective	Mean age, 64 yr, gender (M/F): 14/16	30	2011-2012	1 Success rates with the first endoscopic therapy 2 Rebleeding episodes	Primary hemostasis was achieved in 29 of 30 cases (97%) Rebleeding was observed in two cases (one duodenal bulb and one gastric ulcer)
Manno <i>et al</i> ^[38] , 2016	Retrospective	Mean age, 69 yr, gender (M/F): 33/7	40	2013-2014	1 Success rates with the first endoscopic therapy 2 Rebleeding episodes	Technical success and primary haemostasis were achieved in all patients (100%). No re-bleeding need for surgical or radiological embolization treatment or other complications were observed during the follow-up period of 30 d
Richter-Schrag <i>et al</i> ^[40] , 2016	Retrospective	Mean age, 72 yr, gender (M/F): 58/35	93	2012-2016	1 Success rates with the first endoscopic therapy 2 Rebleeding episodes	Primary hemostasis and clinical success of bleeding lesions (without rebleeding) was achieved in 88/100 (88%) and 78/100 (78%), respectively
Wedi <i>et al</i> ^[41] , 2016	Retrospective	Mean age, 71 yr, gender (M/F): 50/34	84	2009-2012	Success rates with the first endoscopic therapy	Success rate 35/41 (85.36%)

Lamberts <i>et al</i> ^[42] , 2017	Retrospective	Mean age, 71.7 yr, gender (M/F): 55/20	75	February 2011 and June 2014	1 Success rates with the first endoscopic therapy 2 Rebleeding episodes	Application of the OTSC resulted in immediate hemostasis (primary success rate) in all 75 patients. However, in 34.7% a rebleeding episode was noted that could be treated by further endoscopic interventions. Only 3 patients had to be sent to the operating room because of failure of endoscopic therapy. In the rebleeding group the use of antiplatelet therapies was higher (73.1% vs 48.9%)
Brandler <i>et al</i> ^[43] , 2018	Retrospective	Mean age, 71 yr, gender (M/F): 38/29	67	2011-2015	OTSC safety and efficacy in GI bleeding	OTSC success rate of 81.3%
Schmidt <i>et al</i> ^[44] , 2018	Prospective, randomized, controlled multicenter trial	Mean age: 77 yr, gender (M/F): 37/29	67	March 2013 to September 2016	1 Persistent bleeding despite endoscopic therapy according to the protocol or 2 Recurrent bleeding within 7 d after initial successful endoscopic therapy	Persistent bleeding after per-protocol hemostasis was observed in 14 patients (42.4%) in the standard therapy group and 2 patients (6.0%) in the OTSC group ($P < 0.001$) Recurrent bleeding within 7 d occurred in 5 patients (16.1%) in the standard therapy group vs 3 patients (9.1%) in the OTSC group ($P = 0.468$)

GI: Gastrointestinal; OTSC: Over-The-Scope Clip.

a thermal and mechanical hemostasis device that delivers targeted monopolar coagulation at the precise site of bleeding^[60]. It was initially developed to prevent and treat gastrointestinal bleeding associated with minimally invasive endoscopic procedures, such as EMRs, ESD, and resection of small gastric tumors^[61]. Three sizes of the coagrasper are available with different jaw widths to allow effective hemostasis.

Coagrasper has several advantages over conventional heater probe thermal coagulation and hemoclips. Due to these unique properties, it is one of the safest and most efficacious hemostasis modalities^[62]. The large surface area of the forceps and anti-slip jaw design provides mechanical tamponade effect to the surrounding tissue making it a highly efficacious hemostasis method. In addition, the risk of perforation is extremely low because coagrasper works at a lower voltage as compared to other thermal treatments coagulates tissues without any carbonization and does not extend to deeper tissue. The forceps can be used to treat multiple bleeding sites proving to be cost-effective^[63].

A recent randomized prospective trial by Toka B and co-authors compared the efficacy of hemostatic forceps ($n = 56$) with hemoclip ($n = 56$) for NVUGIB^[64]. The study reported an initial success rate in more than 98% of patients treated with coagrasper as compared to 80% in the hemoclip group. Rebleeding rates were lower in coagrasper group without adverse events. The shorter length of hospitalization and duration of endoscopic procedure in patients treated with coagrasper were reported. Another randomized controlled trial comparing efficacy of soft mode coagulation and heater probe thermocoagulation for peptic ulcer bleeding was published in 2015^[65]. Significant differences were observed in achieving primary hemostasis in treatments groups with coagrasper (96%) and heater probe (67%). No reports of rebleeding and adverse events were observed in the coagrasper group. In contrast, perforation occurred in 2 patients treated with a heater probe, which were managed conservatively.

Radiofrequency ablation

Radiofrequency ablation (RFA) was primarily used for the treatment of Barrett's esophagus; however, it is an emerging endoscopic treatment for GAVE^[66]. RFA can be performed by either using focal catheter (Barrx™ HALO⁹⁰ and HALO^{ULTRA}) or Barrx TTS RFA catheter.

In a prospective open-label single center study, Raza and colleagues demonstrated 100% technical success with the HALO system and 67% clinical success in 9 patients after an 11-mo follow-up interval^[67]. Further studies confirmed similar results of technical and clinical success with improved post-procedural hemoglobin without major adverse events observed^[67,68]. Despite the promising results, the studies do not present a randomized design and have a short follow-up interval. A multicenter open-label retrospective case series demonstrated a significant increase in hemoglobin post-procedural with the HALO system, as well as a reduction of blood transfusions needed in 24 patients^[68]. There are limited studies examining the use of RFA in other gastrointestinal related bleeds.

Cryotherapy

Cryotherapy has been proposed as a useful hemostasis modality by inducing cell necrosis through localized freezing of the large surface area of tissue^[69]. Cho and colleagues demonstrated 50% of patients achieving complete response, while the other half achieved a partial response of GAVE related bleeding^[70]. There was a reduction of blood transfusions required post-procedural, and an increase in hemoglobin was observed. There were no immediate complications observed. However, this was a small single-study pilot study with a short follow-up period. The number of treatment sessions and the type of cryogen need to be determined.

Endoscopic laser coagulation

Endoscopic laser coagulation is another non-contact modality thermal method of hemostasis. An Nd: YAG laser is applied through the channel of an endoscope with the tip positioned 5 to 10 mm from the ulcer and the beam directed at the site of bleeding. Although ND: YAG laser therapy has been shown to be effective, it is not routinely used in the management of NVUGIB^[55]. This is due to the technical constraints of the technique, the large size of laser delivery unit, requirement of special electrical and water supplies, and least cost-effective as compared to other modalities^[71].

EMERGING TOPICAL TREATMENT OPTIONS FOR NVUGIB

Hemospray

Hemostatic spray (Cook Medical, Winston-Salem, NC, United States), also known as HS or TC-325, is an absorptive inorganic powder that coalesces and adheres to the bleeding site forming a mechanical barrier^[72]. It is not absorbed or metabolized by the gastrointestinal tract, limiting systemic toxicity, and sloughs off once hemostasis is achieved allowing for re-application if necessary^[72]. HS does not require direct contact with the bleeding vessel and can, therefore, cover a larger surface area. In addition, it may promote platelet aggregation, activate the clotting cascade, as well as promote tissue formation^[72]. HS has been evaluated as a monotherapy modality, such as in the management of a bulbar ulcer related bleed, as well as with other conventional therapy and as a rescue therapy^[73]. In addition, it has been studied in malignancy related bleeding and use after therapeutic endoscopic interventions (Table 5).

Several case series described the effect of HS on malignancy related bleeding. Chen *et al*^[55] described 100% (5/5) of patients attaining immediate hemostasis with one recurrence of bleeding in a patient with severe metastatic disease complicated by disseminated intravascular coagulation^[55,73]. As studied by Leblanc *et al*^[72], 100% (5/5) of patients achieved immediate hemostasis (absent bleeding > 5 min after application) with one of two patients (esophageal tumor and stent placement) considered a treatment failure (not achieving immediate hemostasis or with recurrent bleeding despite 2 separate applications)^[72]. Furthermore, Arena *et al*^[74] demonstrated 93% achieving immediate hemostasis with a rebleeding rate (drop in hemoglobin > 2 g/dL) of 20%. Lastly, in a retrospective study, immediate hemostasis was achieved in 97.7% patients with recurrent bleeding of 15% (classified as early, < 3 d) and 17% (classified as delayed, > 3 d)^[75]. No adverse events or procedural complications were observed in either study. Although bleeding may recur, HS appears to be effective for NVUGIB related to malignancies. The rate of recurrent bleeding and mortality have also been studied.

HS use in post-procedural related bleeds has also been studied. Leblanc and

Table 5 Efficacy and safety of hemospray in the management of non-variceal upper gastrointestinal bleeding (2013-2018)

Study	Type of study	Sample size	Bleeding source	Modality	Outcomes	Results
Leblanc <i>et al</i> ^[72] , 2013	Case series, single arm (July 2011-March 2012)	17 patients	Procedural (12/17) and malignancy related bleeding (5/17)	Monotherapy or rescue therapy	Immediate hemostasis, recurrent bleeding and mortality at 7 and 30 d, and related adverse events	Immediate hemostasis achieved in 100% patient in both groups; 2 patients with recurrent bleeding with 1 of 2 with treatment failure. No adverse events. No related complications
Sakai <i>et al</i> ^[73] , 2016	Case report	1 patient	Ulcer related bleeding	Monotherapy	Immediate hemostasis	Immediate hemostasis achieved. No recurrent bleeding. No adverse events
Chen <i>et al</i> ^[55] , 2015	Retrospective single center study; (July 2011-July 2013)	60 patients	21 for nonmalignant nonvariceal upper gastrointestinal bleeding, 19 for malignant upper gastrointestinal bleeding, 11 for lower gastrointestinal bleeding, and 16 for intra-procedural bleeding	Monotherapy	Immediate hemostasis and early rebleeding (≤ 72 h)	Immediate hemostasis achieved in 66 cases including upper and lower (98.5%), with 6 cases (9.5%) of early rebleeding
Arena <i>et al</i> ^[74] , 2017	Retrospective cohort study; (January 2014-December 2015)	A total of 15 patients, 8 males, mean age 74 yr \pm 7.7	Malignancy related bleeding	Monotherapy	Immediate hemostasis, bleeding recurrence, adverse events, clinical outcome at 1 and 6 mo	Immediate hemostasis achieved in 93% (14/15). 3 (21%) patients with recurrent bleeding. 12/14 (80%) with good clinical outcome at 30 d and 50% (6/12) at 6 mo. No related adverse events
Pittayanon <i>et al</i> ^[75] , 2018	Retrospective study; (2011-2016)	99 patients (70.5% were male, age 65 \pm 14 yr)	Malignancy related bleeding	Monotherapy and adjuvant therapy	Immediate hemostasis, early (≤ 3 d) and late (> 3 d) recurrent bleeding	Immediate hemostasis was 97.7%, with recurrent bleeding in 15% (early) and 17% (delayed). Six-month survival was 53.4%
Baracat <i>et al</i> ^[76] , 2017	Case report	1 patient	Post-sphincterotomy bleeding	Rescue therapy	Hemostasis	Immediate hemostasis achieved
González <i>et al</i> ^[77] , 2016	Case report	1 patient	Post-sclerotherapy bleeding	Monotherapy	Hemostasis	Immediate hemostasis achieved
Sung <i>et al</i> ^[78] , 2011	Prospective single-arm	20 patients (18 men, 2 women; mean age 60.2 yr)	Peptic ulcer bleeding (Forrest score Ia or Ib)	Monotherapy	Immediate hemostasis (max of 2 applications allowed), bleeding recurrence post-operatively, after 72 h endoscopically, and after 30 d <i>via</i> phone; mortality, need for surgery, and complications	Immediate hemostasis in 95% (19/20) of patients; (1/20) with a pseudoaneurysm requiring arterial embolization. Bleeding recurred in 2 patients ≤ 72 h (hemoglobin drop); neither had active bleeding at the 72-h endoscopy. No mortality, adverse events, or procedural-related complications at 30-d

Sinha <i>et al</i> ^[79] , 2016	Retrospective single center	20 patients (median age of 75 yr; 50% men)	Peptic ulcer related bleeding (forrest 1a and 1b)	Adjuvant therapy to adrenaline, or to adrenaline with clips or a thermal device	Immediate hemostasis, 7 and 30-d rebleeding; all-cause and GI-related 30-d mortality	Initial hemostasis was attained in 95% with an overall rebleeding rate (RBR) at 7 d of 16%. No difference between the 7 and 30-d RBR. Hemospray + adrenaline = 100% initial hemostasis and 25% 7-d RBR. Hemospray as third agent = 92% initial hemostasis and 9% RBR. All-cause mortality was 15% with 1 GI-related death (3%)
Haddara <i>et al</i> ^[80] , 2016	Prospective registry; (published 2016)	202 patients	Ulcer related bleeding in 75 patients, malignancy related bleed in 61 patients, procedural related bleed in 35 patients, and other in 31 patients	Monotherapy or rescue therapy	Feasibility, efficacy, re-bleeding rate at day 8 and 30	Application of hemospray was found to be very easy or easy in 31.7% and 55.4%, respectively. Immediate hemostasis achieved in 96.5%. Re-bleeding rate at day 8 and 30 were 26.7% and 33.5%, respectively
Yau <i>et al</i> ^[81] , 2014	Retrospective (February 2012-July 2013)	19 patients (mean age 67.6 yr)	Peptic ulcers in 12 (63.2%) patients, Dieulafoy lesions in 2 (10.5%), mucosal erosion in 1 (5.3%), angiodysplastic lesion in 1 (5.3%), ampullectomy site in 1 (5.3%), polypectomy site in 1 (5.3%), and an unidentified lesion in 1 (5.3%)	Monotherapy, adjuvant therapy, and rescue therapy	Immediate hemostasis, recurrent bleeding at 7- and 30 d, mortality at 7 and 30 d (related to GIB), and adverse events (related to Hemospray)	Hemostasis in 14 of 15 (93.3%) patients; Rebleeding within 7 d in 7/18 (38.9%) patients. Potential adverse events in 2 (10.5%) patients (visceral perforation and splenic infarct). Mortality in 5 (26.3%) patients with 1 with hemoperitoneum
Smith <i>et al</i> ^[82] , 2014	Multicenter registry (June 2011-September 2011)	63 patients (44 men; median age 65)	30 patients with ulcer related bleeding	Monotherapy or rescue therapy	Immediate hemostasis	47/55 (85%) patients in monotherapy group achieved immediate hemostasis
Sulz <i>et al</i> ^[83] , 2014	Case series; (published in 2014)	16 patients	NVUGIB, unidentified	Monotherapy or rescue therapy	Immediate hemostasis	Immediate hemostasis of 93.75% (15/16)

NVUGIB: Non-variceal upper gastrointestinal bleeding; GI: Gastrointestinal; GIB: Gastrointestinal bleeding; RBR: Rebleeding rate.

colleagues studied its efficacy after endoscopic intervention (5 patients after esophageal endoscopic mucosal resection, 4 after duodenal endoscopic mucosal resection, 2 after ampullary resection, and 1 after biliary sphincterotomy)^[72]. Immediate hemostasis was achieved in 100% of patients whether used initially alone or as rescue therapy (after epinephrine injection and hemostatic clip placement)^[72]. Further proving that HS is an appropriate and efficacious post-procedural hemostatic modality, two case reports highlighted immediate hemostasis achieved in post-sphincterotomy and post-sclerotherapy related bleeding^[76,77].

HS can be used as adjunct and rescue therapy^[78-81]. Per Sinha, it was used as an adjunct therapy to adrenaline in 40% of patients. Hemostasis was achieved in 95% of patients with an overall rebleeding rate of 16% at 7 d suggesting it should be considered as an adjunct therapy. Per Yau, HS was used as rescue therapy in 84.2% of patients with an overall hemostasis rate of 93.3%, however with a rebleeding rate of 38.9%^[81]. Anticoagulant and antiplatelet use, coagulopathy, and thrombocytopenia likely contributed to the significant rebleeding rate^[81].

To provide additional data on the efficacy of HS, there is a multicenter registry, by Smith and colleagues, which includes 63 patients^[82]. Immediate hemostasis is defined

as the absence of bleeding at the completion of the procedure, while rebleeding was defined as clinical manifestations of gastrointestinal bleeding and a reduction in hemoglobin by 2 g/dL. 10 of the 63 patients were treated for post-procedural bleeding. As a monotherapy use, 85% (47/55) achieved immediate hemostasis, while 100% achieved immediate hemostasis with HS used as adjunct therapy^[82]. The efficacy of HS, whether as monotherapy, adjunct therapy, or rescue therapy, appears promising in the management of NVUGIB^[83]. However, further, larger prospective studies are warranted to confirm.

Endoclot

Endoclot is an absorbable polysaccharide powder that has been proposed as a useful hemostatic agent. It has been shown to have similar rates of immediate hemostasis achieved and rebleeding compared to standard conventional therapy^[84]. Examining endoclot as a primary monotherapy, Kim *et al*^[85] studied its use in 12 patients with malignancy-related bleeding. 11 of the 12 patients had advanced gastric cancer. Immediate hemostasis was achieved, regardless of the tumor location and size, or previous use of antiplatelet medications, in all patients with a rebleeding rate in 2 patients (16%) at three and five days after treatment. There were no procedural related adverse events, nor all-cause mortality at 30 d after the procedure^[85]. Although the sample size was small and limited to Forrest 1b classification of bleeding, as well as the type of malignancy-related bleed, it appeared to be an efficacious modality.

To further evaluate its efficacy as a rescue therapy, Beg *et al*^[86] studied the use of endoclot in 21 patients with various gastrointestinal bleeding lesions. Immediate hemostasis was achieved in all patients. The 30-d rebleeding rate was 4.8% and the mortality rate was 19.0%, however, without a statistically significant difference compared to the dual or triple endoscopic therapy group ($P = 0.51$ and $P = 0.31$, respectively). Only one death was attributed to the UGI bleed in a patient with a malignant related bleed and significant comorbidities^[86].

EMERGING INJECTION TREATMENT OPTION FOR NVUGIB

Endoscopic ultrasound guided angiotherapy

Endoscopic ultrasound (EUS)-guided angiotherapy with doppler monitoring of the vascular response is a promising modality for the management of bleeding lesions that are inaccessible or refractory to standard endoscopic and interventional radiologic techniques^[87]. EUS can detect vascular lesions in the gastrointestinal tract that are not visually apparent at endoscopy and target lesions for fine-needle injection of therapeutic agents^[88]. Despite most reports on EUS-guided angiotherapy pertain to varices, the technique has also been described for the management of NVUGIB lesions. Although the feasibility and apparent safety of EUS-guided angiotherapy has been demonstrated, the use of EUS as an interventional tool in the managing NVUGIB has remained limited to a few centers worldwide. This is because of the lack of endosonographer training expertise and limited availability of EUS in the acute care setting.

CONCLUSION

In conclusion, NVUGIB continues to be a persistent challenge despite advancements in the both pharmacologic and endoscopic techniques. Several new modalities, as well as, modifications to traditional therapeutic modalities have clearly shown promise in improving outcomes whether used as monotherapy, adjuvant therapy, or rescue therapy for the management of NVUGIB. Due to the numerous NVUGIB etiologies, the indications, efficacy, and safety of the emerging endoscopic techniques continue to be defined. Additional studies are warranted to further define the role of these modalities into the treatment algorithm of NVUGIB and to determine the optimal treatment modality for specific NVUGIB pathology.

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