Acute, nonvariceal upper gastrointestinal bleeding

Amir Klein[a,b] *and Ian M. Gralnek*[a,c]

Purpose of review
Acute, nonvariceal upper gastrointestinal bleeding (UGIB) is a common medical emergency encountered worldwide. Despite medical and technological advances, it remains associated with significant morbidity and mortality.

Recent findings
Rapid patient assessment and management are paramount. When indicated, upper endoscopy in patients presenting with acute UGIB is effective for both diagnosis of the bleeding site and provision of endoscopic hemostasis. Endoscopic hemostasis significantly reduces rebleeding rates, blood transfusion requirements, length of hospital stay, surgery, and mortality. Furthermore, early upper endoscopy, defined as being performed within 24 h of patient presentation, improves patient outcomes.

Summary
A structured approach to the patient with acute UGIB that includes early hemodynamic resuscitation and stabilization, preendoscopic risk stratification using validated instruments, pharmacologic and endoscopic intervention, and postendoscopy therapy is important to optimize patient outcome and assure efficient use of medical resources.

Keywords
endoscopic hemostasis, endotherapy, nonvariceal upper gastrointestinal hemorrhage, peptic ulcer bleeding

INTRODUCTION

Acute nonvariceal upper gastrointestinal bleeding (NVUGIB) remains a serious medical emergency with associated morbidity and mortality. Rapid assessment and management are paramount and should ideally be carried out by a multidisciplinary team trained in emergency medicine, gastroenterology, interventional radiology, and surgery.

The incidence of NVUGIB has been reported to range from 50 to 150 per 100 000 adults/year [1]. Despite a reduction in peptic ulcer-related complications with the widespread use of proton pump inhibitors (PPIs) and eradication of *Helicobacter pylori*, mortality from NVUGIB is still reported to range between 2 and 10% and rebleeding rates may reach 26% [2–4]. An increase in the proportion of elderly patients, increasing use of prescription and over-the-counter nonsteroidal anti-inflammatory drugs/low-dose acetylsalicylic acid (ASA)/antiplatelet agents, and acute onset of bleeding in hospitalized patients with multiple medical comorbidities may contribute to the observed high morbidity and mortality associated with this condition [4].

Peptic ulcer disease (PUD) accounts for the majority of NVUGIB (20–50%). Additional causes include gastroduodenal erosions (8–15%), erosive esophagitis (5–15%), Mallory–Weiss tear (8–15%), angioectasias/gastric antral vascular ectasias (5%), and upper gastrointestinal tumors (benign and malignant) (5%) [1,5]. Almost all of the published evidence on assessment and management of NVUGIB is derived from studies in PUD.

A structured approach that includes early hemodynamic resuscitation and stabilization, preendoscopic risk stratification, pharmacologic and endoscopic intervention, and postprocedure therapy is important to optimize patient outcome and assure efficient use of medical resources.

PREENDOSCOPIC ASSESSMENT AND MANAGEMENT

Establishing a diagnosis of NVUGIB can often be achieved with a proper history and physical

[a]Bruce and Ruth Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, [b]Department of Gastroenterology, Rambam Healthcare Campus, Haifa and [c]Department of Gastroenterology, Ha'Emek Medical Center, Afula, Israel

Correspondence to Ian M. Gralnek, MD, MSHS, FASGE, Bruce and Ruth Rappaport Faculty of Medicine, Chief, Department of Gastroenterology, Ha'Emek Medical Center, Afula 18101, Israel. E-mail: i_gralnek@rambam.health.gov.il

Curr Opin Crit Care 2015, 21:154–162
DOI:10.1097/MCC.0000000000000185

KEY POINTS

- Acute NVUGIB remains a serious medical emergency with associated morbidity and mortality.
- Preendoscopic risk stratification is important and helpful in guiding therapy.
- Endoscopic risk stratification of PUD predicts the risk of ongoing/recurrent bleeding, helps to predict patient outcome, and guides endoscopic hemostasis.
- Endoscopic hemostasis with thermal and mechanical therapy appears to have similar efficacy whereas injection of diluted epinephrine should be accompanied by a second hemostatic modality.
- Postendoscopic therapy should include acid suppression with high-dose PPI.

examination. Clinical clues to an upper gastrointestinal bleeding (UGIB) source include hematemesis and/or melena, nasogastric lavage demonstrating 'coffee grounds' or fresh blood, and a serum urea nitrogen to creatinine ratio greater than 30 [6▪▪]. It is, however, important to remember that up to 15% of patients with acute UGIB may present with hematochezia, thus a brisk variceal source of bleeding should always be considered, and there is no consensus supporting the routine use of nasogastric tube aspiration/lavage because it has not been shown to have diagnostic, prognostic, or therapeutic benefits in NVUGIB [6▪▪,7–9].

Hemodynamic resuscitation

Initial fluid resuscitation and hemodynamic stabilization is essential and recommended by evidence-based guidelines [7,8]. Blood transfusions should be considered in patients with a hemoglobin level below 70 g/l. Hearnshaw *et al.* [10] conducted a prospective cohort study on the outcomes of patients who received blood transfusions within 12 h of presentation. Early transfusions were associated with higher rates of rebleeding [odds ratio (OR) 2.26, adjusted for Rockall score and initial hemoglobin level] and higher 30-day mortality (albeit not significantly when controlled for Rockall score and initial hemoglobin level). Villanueva *et al.* [6▪▪] randomized 921 patients with UGIB (peptic ulcer bleeding 48%) to either a restrictive (transfuse at a hemoglobin level of $\leq$70 g/l) or liberal (transfuse at a hemoglobin level of $\leq$90 g/l) transfusion strategy. Patients who received the restrictive blood transfusion strategy had significantly lower mortality at 45 days [95 versus 91%; hazard ratio 0.55; 95% confidence interval (CI) 0.33–0.92], less rebleeding (10 versus 16%; hazard ratio 0.68; 95% CI 0.47–0.98), and fewer overall adverse events. However, in the subset of patients with NVUGIB, significantly improved outcomes were limited to the reduced need for surgery and only statistical trends suggesting less rebleeding and improved survival were demonstrated.

It is important to note that these blood transfusion thresholds may not apply to patients with significant comorbidities (i.e., acute coronary syndrome, symptomatic peripheral ischemia, stroke, or transient ischemic attack). Such patients may benefit from a liberal transfusion policy in an attempt to avoid exacerbations induced by significant gastrointestinal blood loss.

Evidence-based recommendations regarding platelet transfusion are lacking. Platelet counts greater than 50 000 are generally considered safe. Reversal of anticoagulation should be attempted but should not delay endoscopy [7]. Endoscopic hemostasis can be successfully achieved even with an international normalized ratio of up to 2.5 [7]. An international normalized ratio higher than 1.5 is associated with death (most likely due to the overall medical condition of the patient and the presence of significant comorbidities) but not rebleeding [11]. New oral anticoagulants are associated with an increased risk of gastrointestinal bleeding [12▪▪]. With the ever-increasing dissemination of new oral anticoagulants, gastrointestinal bleeding associated with these agents will become increasingly important to gastroenterologists.

Risk stratification

Stratification of patients into high and low-risk groups based on clinical, laboratory, and endoscopic findings is recommended and allows for identification of high-risk individuals who may benefit from earlier interventions and closer monitoring and low-risk individuals who may be safely discharged following endoscopy [13▪].

The two most commonly used risk stratification scores include the Glasgow–Blatchford score and the Rockall score [1,14] (Figs 1 and 2). The Glasgow–Blatchford score relies solely on preendoscopic parameters to predict the need for interventions, rebleeding, and death whereas the Rockall score uses preendoscopic and endoscopic findings to predict rebleeding and mortality. Patients with a Glasgow–Blatchford score of 0–3 or a complete Rockall score of 2 or less can be considered for outpatient management [15▪,16]. Schiefer *et al.* [17] reviewed 478 patients with acute UGIB in two centers in the Netherlands. One hundred and four patients had a Glasgow–Blatchford score of 2 or less. When this

Glasgow–Blatchford score			
Blood urea (mmol/l)		Systolic blood pressure (mmHg)	
≥6.5 <8.0	2	100–109	1
≥8.0 <10.0	3	90–99	2
≥10.0 <25.0	4	<90	3
≥25	6	Pulse >100 (per min)	1
Hemoglobin (g/dl) for men		Presentation with melena	1
≥12.0 <13.0	1	Presentation with syncope	2
≥10.0 <12.0	3	Hepatic disease	2
<10.0	6	Cardiac failure	2
Hemoglobin (g/dl) for women			
≥10.0 <12.0	1		
<10.0	6		

- Score of 0–3 may be managed as outpatients

FIGURE 1. Glasgow–Blatchford score. The modified Glasgow–Blatchford score includes only the quantitative variables and appears to have similar accuracy in predicting clinical outcomes. Reproduced with permission from [14].

cutoff was used, only two patients required endoscopic intervention and there were no deaths. Cheng *et al.* [18] evaluated a modified Glasgow–Blatchford score which used only the quantitative parameters included in the Glasgow–Blatchford score (pulse, systolic blood pressure, blood urea nitrogen, hemoglobin). In their study, the modified score was compared with the full score and the Rockall score in predicting clinical outcomes of patients with NVUGIB. The modified score as well as the full score performed better than the Rockall score. More recently, Tammaro *et al.* [19▪] evaluated and validated a simplified clinical risk score (*T* score) in 472 patients who presented to 30 endoscopy units in Italy. Patients were stratified based on a composite score of their general condition, pulse, systolic blood pressure, and hemoglobin levels. Patients were also stratified using the Glasgow–Blatchford score. The *T* score

Rockall score for risk of rebleeding and death in patients with NVUGIB				
Score	0	1	1	3
Age	<60	60–79	>180	
Circulatory status	Normal	HR>100mmHg	SBP<100mmHg	
Comorbidities	None	None	Heart failure	Renal failure Liver failure Disseminated Cancer
Findings on EGD	Mallory–Weiss tear or no lesion	All other diagnosis	Malignancy of the UGIT	
Stigmata of bleeding	Low risk		High risk	

- Low-risk stigmata of bleeding - clean base ulcer, pigmented spots
- High-risk stigmata of bleeding - adherent clot, visible vessel, active bleeding

FIGURE 2. Complete (preendoscopic and postendoscopic) Rockall score. Reproduced with permission from [1]. EGD, esophagogastroduodenoscopy; HR, heart rate; NVUGIB, nonvariceal upper gastrointestinal bleeding; UGIT, upper gastrointestinal tract.

appeared to predict high-risk endoscopic stigmata and bleeding-related mortality with similar efficacy to the Glasgow–Blatchford score.

PREENDOSCOPIC MEDICAL MANAGEMENT

Preendoscopic medical management mainly with acid suppression has been studied extensively and shown to be beneficial in patients with NVUGIB.

Proton pump inhibitor

Administration of high-dose intravenous (i.v.) PPI (80-mg bolus followed by an 8-mg/h infusion) is routinely used today for patients presenting with suspected NVUGIB. This is largely based on a Cochrane meta-analysis [20] that included six randomized trials and 2223 patients. Compared with patients who received placebo or a histamine-2 receptor antagonist, high-dose PPI infusion prior to endoscopy resulted in fewer high-risk endoscopic stigmata of hemorrhage (37.2 versus 46.5%; OR 0.67; 95% CI 0.54–0.84) and reduced the need for endoscopic hemostasis (8.6 versus 11.7%; OR 0.68; 95% CI 0.5–0.93). There was, however, no significant reduction in rebleeding, surgery, or mortality with the use of high-dose i.v. PPI.

Prokinetic agents

The use of i.v. prokinetic agents prior to performing upper endoscopy may provide better visualization during endoscopy. In those patients suspected to have retained blood/clots in their upper gastrointestinal tract, i.v. erythromycin improves visualization and leads to less need for repeat endoscopy (OR 0.55; 95% CI 0.32–0.94); however, there is no effect on rebleeding rates, length of hospital stay, need for transfusions, surgery, or mortality [21].

Timing of endoscopy

Following hemodynamic stabilization, patients should undergo 'early' upper endoscopy (now routinely defined as within 24 h of patient presentation) [7,8]. Some high-risk patients, such as those with acute coronary syndrome or a suspected bowel perforation, may benefit from deferring endoscopy until their clinical situation is more fully evaluated and stabilized. Low-risk patients, identified using a preendoscopy risk stratification score (e.g., Glasgow–Blatchford), can be considered for outpatient management [22]. Very early or emergent upper endoscopy (i.e., performed within 2–12 h of patient presentation) has not been shown to confer any additional benefit or alter patient outcomes compared with early (12–24 h) endoscopy [23].

ENDOSCOPIC MANAGEMENT

Endoscopic management of acute NVUGIB can be challenging and appropriate knowledge and experience with all the various endoscopic hemostasis techniques and equipment is essential for adequate patient management.

ENDOSCOPIC RISK STRATIFICATION

In peptic ulcer bleeding, the endoscopic appearance of the ulcer bed can inform the endoscopist of the risk of ongoing/recurrent bleeding, help predict patient outcome, and guide endoscopic hemostasis as well as postendoscopy pharmacological management. The Forrest classification (Fig. 3) [24] is used to stratify ulcer stigmata into high and low-risk categories. High-risk stigmata includes Forrest type Ia (spurting bleeding), Ib (oozing bleeding), IIa (nonbleeding visible vessel), and IIb (adherent clot). Low-risk stigmata includes Forrest type IIc (flat pigmented spot) and type III (ulcer with clean base). The risk of ongoing bleeding or rebleeding is significantly greater when high-risk stigmata are present [23]. Table 1 summarizes the various endoscopic stigmata according to the Forrest classification and their corresponding prevalence, and risk for rebleeding without and following endoscopic hemostasis [25–27].

Many well conducted clinical trials, meta-analyses, and evidence-based consensus statements have concluded that endoscopic hemostasis significantly reduces ulcer rebleeding rates, need for surgery, and mortality in patients with high-risk endoscopic stigmata [7,8]. Endoscopic therapy in the subgroup of high-risk patients who have an adherent clot has been advocated yet remains controversial. The recommended endoscopic therapy for adherent clots is preinjecting circumferentially around the ulcer/clot with diluted epinephrine (generally an admixture with normal isotonic saline of 1 : 10 000 in 1–2 ml aliquots) followed by shaving down the clot with a colon polyp snare without disrupting the pedicle/attachment of the clot. Once the clot is carefully removed, the underlying stigmata (often a nonbleeding visible vessel; however, oozing or spurting bleeding may be induced with clot removal despite the preinjection of epinephrine) are then treated accordingly [28,29]. A meta-analysis [23] of randomized trials in patients with an adherent clot did not show a significant benefit for endoscopic over medical treatment [relative risk

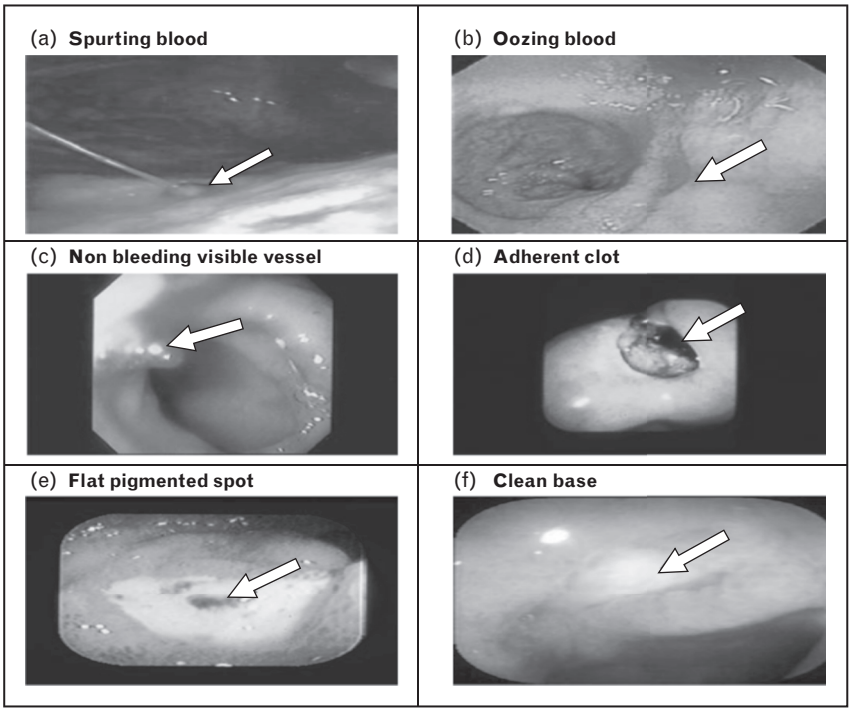

FIGURE 3. Endoscopic stigmata of bleeding peptic ulcer. High-risk endoscopic stigmata are those that spurt blood (Forrest Ia, Panel A), ooze blood (Forrest Ib, Panel B), contain a nonbleeding visible vessel (Forrest IIa, Panel C), or have an adherent clot (Forrest IIb, Panel D). Low-risk endoscopic stigmata are those that have a flat pigmented spot (Forrest IIc, Panel E) or an ulcer with clean base (Forrest III, Panel F). Reproduced with permission from [24].

(RR) = 0.31; 95% CI 0.06–1.77]. Similarly, a separate meta-analysis [28] also demonstrated that endoscopic therapy did not significantly reduce rebleeding (RR = 0.48; 95% CI 0.18–1.30]) compared with medical therapy. It should be noted that high-dose i.v. PPI may be adequate in certain populations [30].

ENDOSCOPIC HEMOSTASIS STRATEGIES

A variety of endoscopic treatment modalities exist for the management of acute NVUGIB, including injection, thermal (contact and noncontact) or mechanical therapy, or the combination thereof.

Injection therapy

Diluted epinephrine (1 : 10 000 or 1 : 20 000) is the most commonly used. Tamponade resulting from volume effect and possibly local vasoconstriction are the mechanisms of action. Another class of injectable agents are tissue adhesives including thrombin, fibrin, and cyanoacrylate glues, which

Table 1. Rates of rebleeding before and after endoscopic therapy and rates of surgery and mortality with no endoscopic therapy, stratified by the endoscopic stigmata

Endoscopic stigmata	Forrest classification	Prevalence (%)	Persisting bleeding or rebleeding with no endoscopic treatment (%)	Rebleeding after endoscopic hemostasis (%)	Surgery for bleeding with no endoscopic treatment (%)	Mortality with no endoscopic treatment (%)
Active bleeding	Types Ia and Ib	12–18	55–90	15–30	35	11
Nonbleeding visible vessel	Type IIa	8–22	43–50	15–30	34	11
Adherent clot	Type IIb	8–17	22–33	0–5	10	7
Flat pigmented spot	Type IIc	16–20	10	not applicable	6	3
Clean base	Type III	42–55	5	not applicable	0.5	2

are used to create a primary seal at the site of bleeding. In a small case series [31▪], cyanoacrylate was successfully used as a spray to arrest acute NVUGIB unresponsive to traditional therapy. Dilute epinephrine injection is inferior in preventing rebleeding and surgery when compared with bipolar electrocoagulation, clips, or fibrin glue [23]. When epinephrine is combined with another modality, a significant reduction in rebleeding and surgery compared with epinephrine injection alone is seen (RR = 0.34; 95% CI 0.23–0.5; number needed to treat = 5) [7,23]. Current consensus statements state that epinephrine injection alone is inadequate (unless no other hemostasis modality is available to the endoscopist) as definitive hemostasis therapy and should be used in combination with an additional hemostasis modality.

Thermal devices

These are divided into contact and noncontact modalities. Contact thermal devices include heater probes and bipolar electrocautery probes. Noncontact thermal devices include argon plasma coagulation. Heat generated from these devices leads to edema, coagulation of tissue proteins, contraction of vessels, and indirect activation of the coagulation cascade, resulting in a hemostatic bond [32]. Heater and bipolar electrocautery probes also use local tamponade (mechanical pressure of the probe tip directly on the bleeding site) combined with heat or electrical current to coagulate blood vessels, a process known as 'coaptive coagulation'. Argon plasma coagulation is primarily used for the treatment of superficial mucosal lesions, such as vascular malformations/gastric antral vascular ectasias. Thermal contact therapy with heater probe or bipolar electrocoagulation is more effective in reducing ulcer rebleeding, need for surgery, and mortality when compared with no treatment or epinephrine injection alone. There is no real difference in efficacy of contact thermal devices. A benefit of combination therapy with epinephrine along with contact thermal therapy over thermal therapy alone has also been suggested [23,28] especially for Forrest Ia and Ib lesions.

Mechanical therapy

These include clips and band ligation devices. Endoscopic clips are directly deployed onto a bleeding site and typically slough off within days to weeks following placement. Hemostasis is achieved by mechanical compression of the bleeding site. Clips were found to be more effective than epinephrine alone in reducing rebleeding and surgery. Comparative trials with other modalities found no significant differences in the rates of rebleeding or surgery [23]. Emerging data suggest that an over-the-scope clip (Ovesco, Tübingen, Germany) developed for the closure of perforations and fistulas is also effective for the management of peptic ulcer hemorrhage [33]. Endoscopic band ligation devices, commonly used in esophageal variceal bleeding, also have been reported to be effective in the treatment of NVUGIB (e.g., Dieulafoy's lesion) [34].

Second-look endoscopy

Hemodynamic instability, active bleeding at endoscopy, ulcer size larger than 2 cm, ulcer location (high lesser gastric curvature or posterior duodenum), hemoglobin level below 10 g/dl, and the need for transfusion predict rebleeding [35]. A planned, second-look endoscopy that is performed within 24 h after index endoscopy is not routinely recommended because it provides only a limited reduction in the rate of rebleeding and may not be cost-effective when medical therapy with i.v., high-dose PPI is used [36,37]. Repeat endoscopy with possible repeat endoscopic hemostasis should be considered on a case-by-case basis if there are clinical signs of recurrent bleeding or if there is uncertainty regarding the effectiveness of hemostasis during initial endoscopy.

EMERGING DIAGNOSTIC AND THERAPEUTIC MODALITIES

In recent years several new modalities for the diagnosis and treatment of NVUGIB were introduced. These new technologies hold promise; however, they require further validation on larger scales.

Video capsule endoscopy

Recently, video capsule endoscopy (VCE) has been shown to be an effective and potentially cost-effective way to identify acute UGIB in the emergency department [38▪,39,40▪]. Capsule endoscopy identifies gross blood in the upper gastrointestinal tract, including the duodenum, significantly more often than nasogastric tube aspiration, and identifies inflammatory lesions, equally as well as EGD. Capsule endoscopy may also facilitate patient triage and earlier endoscopy, but at this point in time should not be considered a substitute for endoscopy [40▪].

Topical hemostatic agents

In selected patients, hemostatic sprays have been used with good overall results. Advantages include ease of use, lack of need for precise lesion targeting, access to lesions in difficult locations, and the ability to treat a larger surface area. Preliminary data suggest that TC-325 (Hemospray; Cook Medical

Inc, Winston-Salem, North Carolina, USA), a powder that rapidly concentrates clotting factors at the bleeding site, may be effective in peptic ulcer bleeding (spurting or oozing bleeding) [41,42▪]. EndoClot (EndoClot Plus Inc, Santa Clara, California, USA) consists of absorbable modified polymers and is intended to be used as an adjuvant hemostatic agent to control bleeding in the gastrointestinal tract. It rapidly absorbs water from serum and concentrates platelets, red blood cells, and coagulation proteins at the bleeding site to accelerate the clotting cascade. To date, there have been no peer-reviewed publications on this product's safety or efficacy in acute NVUGIB [42▪].

ANCILLARY MEASURES IN THE TREATMENT OF NONVARICEAL UPPER GASTROINTESTINAL BLEEDING

When conventional medical and endoscopic treatments fail to control NVUGIB, the use of alternative measures, both nonsurgical and surgical, may be necessary.

Endoscopic ultrasound

Preliminary data from a small number of patients suggest that endoscopic ultrasound (EUS) may have a potential role in selected patients with variceal and nonvariceal UGIB. Law *et al.* [43▪] reported on the outcome of 17 patients with refractory NVUGIB who were managed with EUS-guided therapy. A linear echoendoscope and a standard 22-gauge FNA needle were used to deliver an injection (sclerosing agent or glue) or coil directly to bleeding vessel. After EUS-guided hemostasis, 88% of the patients required no further treatment (median follow-up of 12 months).

Transarterial catheter embolization

Transarterial catheter embolization can be an effective alternative to surgery especially in patients at high operative risk. Transarterial catheter embolization is indicated in patients who fail endoscopic therapy. Today, with the use of superselective embolization techniques, high technical and clinical success rates (63–97%) can be achieved with a low rate of adverse events (e.g., ischemic complications) [44,45]. There is no consensus on the optimal embolic agent and the choice is usually influenced by availability, local expertise, and personal preference of the radiologist. Gelfoam (Pfizer, New York, USA), *N*-butyl cyanoacrylate, coils, and combinations of these agents have all been successfully used [45,46▪]. Laursen *et al.* [47▪] recently reported on $n = 105$ patients with peptic ulcer bleeding (Forrest Ia–IIb) who were randomized following successful endoscopic therapy to receive standard care or adjuvent arterial embolization. Rebleeding was observed in two patients in the embolization arm versus eight in the control arm ($P = 0.079$). Although these results did not reach statistical significance, the observed statistical trend may suggest that for selected patients at high risk for rebleeding, such an approach may be beneficial.

Surgery

Today, emergency surgery for NVUGIB is uncommon and usually reserved for patients with massive bleeding who fail endoscopic and/or interventional radiology therapy. Today, a limited surgical approach with oversewing of the bleeding vessel is preferred since supplementary postsurgical treatment with *H. pylori* eradication and PPI use cures PUD in most cases.

POSTENDOSCOPIC MANAGEMENT

Postendoscopic management is important in reducing rebleeding rates and treating the baseline disease.

Proton pump inhibitor

Acid suppression is essential for ulcer healing and reducing the risk of rebleeding. A Cochrane systematic review and meta-analysis showed that PPIs significantly reduced rebleeding (OR 0.49; 95% CI 0.37–0.65), the need for urgent surgery (OR 0.61; 95% CI 0.48–0.78), and the need for repeat endoscopic treatment (OR 0.53; 95% CI 0.41–0.68). In the subgroup of patients with high-risk stigmata, a significant reduction in mortality was observed with the use of PPI (OR 0.53; 95% CI 0.31–0.91) [48]. The optimal dose and route of administration lacks consensus between guidelines [49▪▪]. In clinical practice, most patients after endoscopic hemostasis are treated with a high-dose i.v. PPI protocol (80 mg i.v. bolus followed by continuous i.v. infusion of 8 mg/h) for 72 h. Low-risk patients can be adequately managed with oral PPIs. Following initial treatment, oral PPIs combined with *H. pylori* eradication is recommended for all patients with PUD.

Nonsteroidal anti-inflammatory drug and acetylsalicylic acid

PPIs should be used in all patients with previous ulcer bleeding who require ongoing treatment with antithrombotic agents [7,8]. In the case of ASA, the risk of rebleeding versus prevention of coronary artery disease needs to be considered. Resumption of ASA immediately following endoscopic hemostasis results in a trend toward increased rebleeding rates but a significantly lower all-cause mortality (hazard ratio 0.2; 95% CI 0.05–0.9) [50]. It is reasonable to suggest that at least for patients with a high cardiovascular risk profile, ASA treatment should

be resumed as soon as possible (within 1–3 days) following an episode of NVUGIB [51].

ADDITIONAL CAUSES OF NONVARICEAL UPPER GASTROINTESTINAL BLEEDING AMENABLE TO ENDOSCOPIC HEMOSTASIS

Taken together these causes may account for up to 50% of NVUGI cases. Published literature on management is scant and consists mainly of small studies and case series.

Esophagitis

Esophagitis is most commonly seen in patients who are already in hospital for another reason and have an in-dwelling nasogastric tube. Upper endoscopy is important for diagnosis; however, endoscopic hemostasis is rarely required unless a focal ulcer with stigmata of recent hemorrhage is found. Patients should be treated with PPI for 8–12 weeks followed by repeat endoscopy to rule out underlying Barrett's esophagus.

Mallory–Weiss tear

Mallory–Weiss tear is a mucosal laceration at the gastroesophageal junction often, but not always, due to antecedent vomiting or retching. Bleeding is usually self-limited and the rates of rebleeding are approximately 10% [52]. Patients with ongoing or severe bleeding require endoscopic therapy. Bipolar electrocoagulation, epinephrine injection, clips, and band ligation have all been used successfully; however, there are no prospective comparative studies [53].

Dieulafoy's lesion

Dieulafoy's lesion is a large-caliber submucosal arteriole that protrudes through the mucosa and can cause massive acute UGIB. It is usually located in the stomach, most often in the fundus, but can appear anywhere in the gastrointestinal tract. Endoscopic hemostasis can be accomplished with banding, clipping, contact thermal coagulation, or with the use of an injectable agent including sclerosant, glue, or epinephrine [54].

Angioectasias and gastric antral vascular ectasias

Mucosal vascular lesions typically cause chronic blood loss rather than acute overt UGIB. These lesions can be sporadic or associated with an underlying disorder such as cirrhosis, chronic renal failure, collagen-vascular disease, valvular heart disease, or Osler–Weber–Rendu. Argon plasma coagulation, contact thermal coagulation, or band ligation are most commonly used and are associated with a decrease in transfusion requirements. Multiple endoscopic treatment sessions are usually required [55].

Upper gastrointestinal tumors

Endoscopic hemostasis of these lesions has proven less effective with higher rates of rebleeding. Various endoscopic treatment modalities have been described with no clear recommendations. More recently, successful preliminary experience with the hemostatic powder TC-325 (Hemospray) to control bleeding from upper gastrointestinal tract tumors has been reported [56].

CONCLUSION

Even in the modern era, NVUGIB remains associated with significant morbidity and mortality. Advances in medical and endoscopic therapies have led to improved patient outcome and reduced need for surgery. Clinical and endoscopic risk stratification assists in patient management and has important prognostic implications. Multiple endoscopic modalities can be used to arrest acute bleeding. Combination therapy with epinephrine injection with an additional modality yields the lowest rates of rebleeding and is most commonly used. Emerging technologies and therapeutic agents are gaining acceptance; however, further validation of these hemostasis modalities in large-size prospective comparative trials is needed.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Rockall TA, Logan RF, Devlin HB, Northfield TC. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Steering Committee and members of the National Audit of Acute Upper Gastrointestinal Haemorrhage. BMJ 1995; 311:222–226.
2. Corley DA, Stefan AM, Wolf M, *et al.* Early indicators of prognosis in upper gastrointestinal hemorrhage. Am J Gastroenterol 1998; 93:336–340.
3. Lingenfelser T, Ell C. Gastrointestinal bleeding in the elderly. Bailliere's Best Pract Res Clin Gastroenterol 2001; 15:963–982.
4. Tsoi KKF, Chiu PWY, Chan FKL, *et al.* The risk of peptic ulcer bleeding mortality in relation to hospital admission on holidays: a cohort study on 8222 cases of peptic ulcer bleeding. Am J Gastroenterol 2012; 107:405–410.
5. Boonpongmanee S, Fleischer DE, Pezzullo JC, *et al.* The frequency of peptic ulcer as a cause of upper-GI bleeding is exaggerated. Gastrointest Endosc 2004; 59:788–794.

6. Villanueva C, Colomo A, Bosch A, *et al.* Transfusion strategies for acute upper
■■ gastrointestinal bleeding. N Engl J Med 2013; 368:11–21.

A very important article on transfusion strategies in UGIB.

7. Barkun AN, Bardou M, Kuipers EJ, *et al.* International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Int Med 2010; 152:101–113.
8. Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol 2012; 107:345–360.
9. Huang ES, Karsan S, Kanwal F, *et al.* Impact of nasogastric lavage on outcomes in acute GI bleeding. Gastrointest Endosc 2011; 74:971–980.
10. Hearnshaw SA, Logan RFA, Palmer KR, *et al.* Outcomes following early red blood cell transfusion in acute upper gastrointestinal bleeding. Aliment Pharmacol Ther 2010; 32:215–224.
11. Shingina A, Barkun AN, Razzaghi A, *et al.* Systematic review: the presenting international normalised ratio (INR) as a predictor of outcome in patients with upper nonvariceal gastrointestinal bleeding. Aliment Pharmacol Ther 2011; 33:1010–1018.
12. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ETTL. New oral anticoagulants
■■ increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. Gastroenterology 2013; 145:105–112.

A systematic review of current knowledge regarding new anticoagulants and risk of UGIB.

13. Lu Y, Loffroy R, Lau JYW, Barkun A. Multidisciplinary management strategies
■ for acute nonvariceal upper gastrointestinal bleeding. Br J Surg 2014; 101:e34–e50.

A recent comprehensive review of NVUGIB.

14. Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. Lancet 2000; 356:1318–1321.
15. Bryant RV, Kuo P, Williamson K, *et al.* Performance of the Glasgow–Blatchford
■ score in predicting clinical outcomes and intervention in hospitalized patients with upper GI bleeding. Gastrointest Endosc 2013; 78:576–583.

A recent study addressing the validity and accuracy of the Glasgow-Blatchford score in hospitalized patients.

16. Stanley AJ, Dalton HR, Blatchford O, *et al.* Multicentre comparison of the Glasgow Blatchford and Rockall scores in the prediction of clinical end-points after upper gastrointestinal haemorrhage. Aliment Pharmacol Ther 2011; 34:470–475.
17. Schiefer M, Aquarius M, Leffers P, *et al.* Predictive validity of the Glasgow Blatchford Bleeding Score in an unselected emergency department population in continental Europe. Eur J Gastroenterol Hepatol 2012; 24:382–387.
18. Cheng DW, Lu YW, Teller T, *et al.* A modified Glasgow Blatchford Score improves risk stratification in upper gastrointestinal bleed: a prospective comparison of scoring systems. Aliment Pharmacol Ther 2012; 36:782–789.
19. Tammaro L, Buda A, Paolo MC, *et al.* A simplified clinical risk score predicts
■ the need for early endoscopy in nonvariceal upper gastrointestinal bleeding. Dig Liver Dis 2014; 46:783–787.

A new preendoscopic risk stratification score.

20. Sreedharan A, Martin J, Leontiadis GI, *et al.* Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. Cochrane Database Syst Rev 2010; 7:CD005415.
21. Barkun AN, Bardou M, Martel M, *et al.* Prokinetics in acute upper GI bleeding: a meta-analysis. Gastrointest Endosc 2010; 72:1138–1145.
22. Stanley AJ, Ashley D, Dalton HR, *et al.* Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation. Lancet 2009; 373:42–47.
23. Laine L, Mcquaid KR. Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analyses of randomized controlled trials. YJCGH AGA Inst 2009; 7:33–47.
24. Gralnek IM, Barkun AN, Bardou M. Current concepts: management of acute bleeding from a peptic ulcer. N Engl J Med 2008; 359:928–937.
25. Lau JY, Chung SC, Leung JW, *et al.* The evolution of stigmata of hemorrhage in bleeding peptic ulcers: a sequential endoscopic study. Endoscopy 1998; 30:513–518.
26. Guglielmi A, Ruzzenente A, Sandri M, *et al.* Risk assessment and prediction of rebleeding in bleeding gastroduodenal ulcer. Endoscopy 2002; 34:778–786.
27. Hearnshaw SA, Logan RFA, Lowe D, *et al.* Use of endoscopy for management of acute upper gastrointestinal bleeding in the UK: results of a nationwide audit. Gut 2010; 59:1022–1029.
28. Kahi CJ, Jensen DM, Sung JJY, *et al.* Endoscopic therapy versus medical therapy for bleeding peptic ulcer with adherent clot: a meta-analysis. Gastroenterology 2005; 129:855–862.
29. Bleau BL, Gostout CJ, Sherman KE, *et al.* Recurrent bleeding from peptic ulcer associated with adherent clot: a randomized study comparing endoscopic treatment with medical therapy. Gastrointest Endosc 2002; 56:1–6.
30. Sung JJY, Chan FKL, Lau JYW, *et al.* The effect of endoscopic therapy in patients receiving omeprazole for bleeding ulcers with nonbleeding visible vessels or adherent clots: a randomized comparison. Ann Intern Med 2003; 139:237–243.
31. Walia SS, Sachdeva A, Kim JJ, *et al.* Cyanoacrylate spray for treatment of
■ difficult-to-control GI bleeding. Gastrointest Endosc 2013; 78:536–539.

Novel approach in the treatment of persistent UGIB not amenable to standard therapies.

32. Conway JD, Adler DG, Diehl DL, *et al.* Endoscopic hemostatic devices. Gastrointest Endosc 2009; 69:987–996.
33. Kirschniak A, Subotova N, Zieker D, *et al.* The Over-The-Scope Clip (OTSC) for the treatment of gastrointestinal bleeding, perforations, and fistulas. Surg Endosc Other Interv Tech 2011; 25:2901–2905.
34. Alis H, Oner OZ, Kalayci MU, *et al.* Is endoscopic band ligation superior to injection therapy for Dieulafoy lesion? Surg Endosc Other Interv Tech 2009; 23:1465–1469.
35. García-Iglesias P, Villoria A, Suarez D, *et al.* Meta-analysis: predictors of rebleeding after endoscopic treatment for bleeding peptic ulcer. Aliment Pharmacol Ther 2011; 34:888–900.
36. Marmo R, Rotondano G, Bianco MA, *et al.* Outcome of endoscopic treatment for peptic ulcer bleeding: is a second look necessary? A meta-analysis. Gastrointest Endosc 2003; 57:62–67.
37. Spiegel BMR, Ofman JJ, Woods K, Vakil NB. Minimizing recurrent peptic ulcer hemorrhage after endoscopic hemostasis: the cost-effectiveness of competing strategies. Am J Gastroenterol 2003; 98:86–97.
38. Meltzer AC, Ward MJ, Gralnek IM, Pines JM. The cost-effectiveness analysis
■ of video capsule endoscopy compared to other strategies to manage acute upper gastrointestinal hemorrhage in the ED. Am J Emerg Med 2014; 32:823–832.

Recent study on the effectiveness and potential role of VCE in the management of UGIB.

39. Rubin M, Hussain SA, Shalomov A, *et al.* Live view video capsule endoscopy enables risk stratification of patients with acute upper GI bleeding in the emergency room: a pilot study. Dig Dis Sci 2011; 56:786–791.
40. Gralnek IM, Ching JYL, Maza I, *et al.* Capsule endoscopy in acute upper
■ gastrointestinal hemorrhage: a prospective cohort study. Endoscopy 2013; 45:12–19.

Recent study on the effectiveness and potential role of VCE in the management of UGIB.

41. Sung JJY, Luo D, Wu JCY, *et al.* Early clinical experience of the safety and effectiveness of Hemospray in achieving hemostasis in patients with acute peptic ulcer bleeding. Endoscopy 2011; 43:291–295.
42. Barkun AN, Moosavi S, Martel M. Topical hemostatic agents: a systematic
■ review with particular emphasis on endoscopic application in GI bleeding. Gastrointest Endosc 2013; 77:692–700.

A comprehensive review on the role of hemostatic agents in the treatment of UGIB.

43. Law R, Fujii-lau L, Wong LM, *et al.* Efficacy of endoscopic ultrasound-guided
■ hemostatic interventions for resistant nonvariceal bleeding. Clin Gastroenterol Hepatol 2014. [Epub ahead of print]

Novel approach in the treatment of persistent UGIB not amenable to standard therapies.

44. Walker TG, Salazar GM, Waltman AC. Angiographic evaluation and management of acute gastrointestinal hemorrhage. World J Gastroenterol 2012; 18:1191–1201.
45. Mirsadraee S, Tirukonda P, Nicholson A, *et al.* Embolization for nonvariceal upper gastrointestinal tract haemorrhage: a systematic review. Clin Radiol 2011; 66:500–509.
46. Yata S, Ihaya T, Kaminou T, *et al.* Transcatheter arterial embolization of acute
■ arterial bleeding in the upper and lower gastrointestinal tract with N-butyl-2-cyanoacrylate. J Vasc Interv Radiol 2013; 24:422–431.

Recent study on the role of angio-embolization for UGIB.

47. Laursen SB, Hansen JM, Andersen PE, Schaffalitzky de Muckadell OB.
■ Supplementary arteriel embolization an option in high-risk ulcer bleeding: a randomized study. Scand J Gastroenterol 2014; 49:75–83.

Recent study on the role of angio-embolization for UGIB.

48. Leontiadis GI, McIntyre L, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. Cochrane Database Syst Rev 2004; ((3)):CD002094.
49. Neumann I, Letelier LM, Rada G, *et al.* Comparison of different regimens of
■■ proton pump inhibitors for acute peptic ulcer bleeding. Cochrane Database Syst Rev 2013; 6:CD007999.

A comprehensive evidence-based review on the role of PPIs in the management of acute peptic ulcer bleeding.

50. Sung JJY, Lau JYW, Ching JYL, *et al.* Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. Ann Intern Med 2010; 152:1–9.
51. Sheasgreen C, Leontiadis GI. Recent advances on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Gastroenterol 2013; 26:191–197.
52. Bharucha AE, Gostout CJ, Balm RK. Clinical and endoscopic risk factors in the Mallory-Weiss syndrome. Am J Gastroenterol 1997; 92:805–808.
53. Morales P, Baum AE. Therapeutic alternatives for the Mallory-Weiss tear. Curr Treat Options Gastroenterol 2003; 6:75–83.
54. Norton ID, Petersen BT, Sorbi D, *et al.* Management and long-term prognosis of Dieulafoy lesion. Gastrointest Endosc 1999; 50:762–767.
55. Sebastian S, O'Morain CA, Buckley MJM. Review article: Current therapeutic options for gastric antral vascular ectasia. Aliment Pharmacol Therap 2003; 18:157–165.
56. Chen Y-I, Barkun AN, Soulellis C, *et al.* Use of the endoscopically applied hemostatic powder TC-325 in cancer-related upper GI hemorrhage: preliminary experience (with video). Gastrointest Endosc 2012; 75:1278–1281.