

Endoscopic Management of Acute Non Variceal Upper Gastrointestinal Bleeding

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ABSTRACT

Acute upper gastrointestinal bleeding (UGIB) is a common cause of hospitalization, with incidences ranging from 48 to 160 cases per 100,000 adults per year. The management of acute non-variceal UGIB includes the performance of an early endoscopy within 24 hours, and the treatment of high-risk lesions using various endoscopic mono- or combination therapies (all favored over epinephrine injection alone). Beyond the endoscopic approach, adequate resuscitation and risk stratification before endoscopy are important in optimizing the care of patients with UGIB. A repeat endoscopy is warranted in rebleeding, whereas “second-look” endoscopy should not be performed routinely, but only in selected patients. Key elements are reviewed along with the current evidence with a focus on the endoscopic approach and therapy of non-variceal UGIB.

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Key words: Acute upper gastrointestinal bleeding; Gastrointestinal hemorrhage; Non-variceal upper gastrointestinal bleeding; Peptic ulcer bleeding; Risk stratification; Endoscopy; Management

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Abbreviations

BUN: Blood urea nitrogen, CI: confidence interval, GBS: Glasgow Blatchford Risk Score, GI: gastrointestinal, H2RA: H2 receptor antagonist, HRS: high-risk stigmata, INR: international normalized ratio, IV: intravenous, LOS: length of stay, LRS: low risk stigmata, NVUGIB: non-variceal upper gastrointestinal bleeding, OR: odds ratio, PPI: proton-pump inhibitor, RCT: randomized controlled trial, ROC: receiver operating characteristic, TAE: transarterial embolization, UGIB: upper gastrointestinal bleeding

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is a common cause of hospitalization leading to significant expenditures with reported incidences of 48 to 160 cases per 100 000 adults per year and mortality of 10% to 14%^[1]. Recent data suggest a decrease in the incidence and mortality of UGIB by 22.7% and 16.9% respectively^[2]. Its management has also evolved over the last decades, especially with regards to the endoscopic approach and therapy.

We discuss the acute management of non-variceal UGIB focusing on endoscopy. We review pre-endoscopic management including resuscitation, risk stratification, and proton pump inhibitor (PPI) and prokinetic use; the timing of endoscopy; the various available endoscopic methods, including novel therapies; second-look endoscopy and predictors of endoscopic treatment failure. While the pre-endoscopic approach targets all patients presenting with acute upper GI bleeding, especially non variceal, the data on endoscopy and post-endoscopy stem more specifically from patients with peptic ulcer bleeding. International consensus guidelines on UGIB^[1,3] and societal guidelines^[4-7] on the management of patients with ulcer bleeding provide specific management recommendations.

PRE-ENDOSCOPIC

Resuscitation and transfusion

The assessment of patients with acute UGIB should start with evaluation of their hemodynamic status. This directs resuscitation, and allows prompt risk stratification. Blood transfusions should be administered to patients with a hemoglobin <70g/L^[1], along with intravenous fluids. Such restrictive target is associated with improved outcomes; notably decreased in-hospital mortality in critically

ill patients^[8], as well as higher six-week survival, and decreased rebleeding in patients with UGIB^[9] compared to a more liberal approach targeting hemoglobin levels above 100g/L, and 90g/L respectively. A Cochrane review on transfusion in UGIB reports a non-significant trend towards increased rebleeding and mortality with transfusions^[10]. Early transfusions within 12 hours led to a two-fold increase in rebleeding (odds ratio (OR) 2.26, 95% CI 1.76-2.90)^[11]. Similar trends in rebleeding (OR 1.8, 95% CI 1.2-2.8) were seen with transfusion within 24 hours^[12].

However, the applicability of a restrictive strategy should be individualized to each patient, and may not apply to those, for instance with severe bleeding^[13]. In fact, the recent observations reported by Villanueva *et al.* were limited to patients with Child-Pugh class A and B cirrhosis; such trends were not seen in class C patients or those with peptic ulcer disease. Moreover, they excluded individuals with massive exsanguination and acute coronary syndrome (9). A large ongoing clinical trial in the United Kingdom should soon provide additional clarity (14).

International normalized ratio (INR) and platelet count

Most guidelines support the correction of coagulopathy when present, without however delaying endoscopy. INR value does not correlate with rebleeding risk, while it has been linked to increased mortality at a cut-off of 1.5 (OR 1.96, 95% CI 1.13-3.41)^[15]. This is contrasted to the platelet count not shown to be a predictor of either rebleeding or mortality, for which there is no high quality evidence to guide transfusion thresholds^[16].

Risk stratification

Along with resuscitation, risk-stratifying patients into high- and low-risk categories should be done early on using prognostic scales. Validated scales aid in the decisions regarding hospitalization and early discharge, and may guide timing of endoscopy^[1,4].

The Rockall score can be calculated using both pre-endoscopic (total=7), and post-endoscopic (total=11) data. It predicts risk for further bleeding and mortality using age (<60, 60-79, and >70 years old), the presence of shock (systolic blood pressure<100 mmHg and heart rate >100 beats per minute), comorbidities (ischemic heart disease, congestive heart failure, any major comorbidities; and renal or liver failure and disseminated malignancy) and endoscopic diagnosis (Mallory-Weiss tear, peptic ulcer disease, erosive disease, esophagitis, or evidence of malignancy), along with endoscopic findings (blood in stomach, adherent clot, visible vessel, and spurting vessel or pigmented spot or no stigmata)^[17]. Patients with risk scores of 0 and 1 had low incidences of rebleeding and no associated mortality^[17].

The Glasgow Blatchford risk score (GBS) (total=23) was elaborated to predict the need for interventions (i.e. transfusions, surgical and endoscopic therapy) (Table 1). It has the advantage of incorporating only pre-endoscopic variables (hemoglobin and blood urea nitrogen (BUN); heart rate and systolic blood pressure; history of syncope and melena; and heart failure or liver disease)^[18]. A GBS of 0 predicts a 0.5% risk for needing subsequent intervention. Stanley *et al.* used this cut-off to safely direct early discharge and outpatient endoscopy^[19]. A threshold of 0 displayed 100% sensitivity in predicting the need for endoscopic therapy, with a specificity of 6.3%^[20].

Comparing the above scores, the GBS' area under the receiver operating characteristic curve (0.90, 95% CI 0.88-0.93) outperformed the full Rockall (0.81, 96% CI 0.77-0.84), and pre-endoscopic Rockall score (0.70, 95% CI 0.65-0.75) in predicting the need for

intervention or death^[19]. Pre-endoscopic Rockall score has not proven to be a reliable predictor of low risk patients^[20]. A modified GBS that excludes syncope and BUN, was validated to identify patients at low risk for adverse outcomes^[21]. A similar modified score eliminates subjective components (presence of hepatic and cardiac disease, melena and syncope) performed as well as GBS^[22]. Several other risk scoring systems exist^[23,24], though many need further external validation^[24].

International consensus recommends early discharge of low risk patients after endoscopy^[1] according to a set of criteria previously summarized^[25], while American College of Gastroenterology guidelines for peptic ulcers bleeding even consider discharge before endoscopy for selected population^[4]. High risk patients should be hospitalized and monitored for 72 hours^[25]. The timing of endoscopy is further discussed below.

Prokinetics prior to endoscopy

The use of prokinetics before endoscopy should be considered in selected patients. Meta-analyses have shown that erythromycin led to decreased need for repeat endoscopy^[26], but failed to change the length of stay (LOS), transfusion requirements and need for surgery^[27,28]. Data in variceal bleeding however demonstrate improved visibility, decreased duration of endoscopy and LOS with erythromycin given 30 minutes prior to endoscopy performed within 12 hours of presentation^[29]. A subsequent meta-analysis with erythromycin included a large number of patients with variceal bleeding showed a significant increase in incidence of "empty stomach", decreased need for second endoscopy, transfusion and length of stay^[30]. Furthermore, the yield of erythromycin is similar to nasogastric tube lavage^[28].

It is noteworthy that most studies are limited to high-risk patients with red blood hematemesis or blood in the nasogastric aspirate. Current guidelines do not support the routine use of prokinetics, but rather recommend their use in selected patients with active bleeding and/or blood in the stomach^[1].

Nasogastric tube

Nasogastric tube lavage is not necessary^[4], but can be considered prior to endoscopy^[1]. A bloody aspirate is linked to increased risk of finding a high risk lesion, though a clear or bilious aspirate cannot rule it out^[31]. Fifteen percent of patients in the latter group have high-risk stigmata (HRS) at endoscopy^[31]. While it may also decrease time to endoscopy, it has not been shown to improve mortality, length of stay or transfusion requirements^[32].

Table 1 Risk stratification – Modified from Glasgow Blatchford risk score (GBS)^[18, 22].

Clinical parameters		Score
Objective findings	Heart rate (beats/min)	≥100 1
	Systolic blood pressure (mmHg)	100-109 1
		90-99 2
	Blood urea nitrogen (mmol/L)	<90 3
		6.5-7.9 2
		8.0-9.9 3
		10.0-24.9 4
	Hemoglobin (g/dL)	≥25 6
		Men Women 12.0-12.9 10-12 1
		10.0-11.9 3
<10.0 <10 6		
Subjective findings ^[2]	Comorbidities	Heart failure 2
		Liver disease 2
	Presentation	Melena 1
		Syncope 2

Proton-pump inhibitors prior to endoscopy

It is well established that PPI use following successful endoscopic therapy in patients with HRS decreases rebleeding, need for surgery and repeat endoscopy and mortality (the latter specifically in high-risk patients having first undergone successful endoscopic therapy) as reviewed elsewhere^[33]. In contradistinction, the initiation of PPI prior to endoscopy has yet to show comparable results. In a Cochrane review, pre-endoscopic PPI led to a decreased proportion of patients with HRS, as well as the need for endoscopic intervention^[34], but does not reduce rebleeding, surgery or mortality. Nevertheless, the initiation of PPI while awaiting endoscopy should be considered, preferably using an 80 mg intravenous bolus followed by an 8mg/hr infusion^[1,4].

The decision to use PPI before endoscopy should be individualized, as additional data are still needed to define their optimal use in this setting. In the absence of impact on major clinical endpoints, cost may become a more relevant variable. Cost-effectiveness analysis in US and Canadian settings reveal that pre-endoscopic PPI is slightly more costly and effective compared to PPI after endoscopy^[35]. Such conclusions may vary depending on the elapsed time to endoscopy (early versus delayed), the underlying stigmata of recent bleeding (favoring HRS), as well as the proportion of patients with variceal bleeding^[36]. Financially, the benefits of PPI use before endoscopy may depend on, and be limited to the duration of hospitalization; which becomes a major driver in determining overall cost. The use of pre-endoscopic PPI becomes a dominant strategy when LOS of patients with low-risk stigmata (LRS) is less than 3 days, and those with HRS increases beyond 6^[35]. Most importantly, PPI should not replace or delay endoscopy; potential rare associated complications may also influence clinical decision-making^[1,36].

Timing of endoscopy

Early endoscopy within 24 hours of presentation is recommended for most patients with UGIB. It allows for safe early discharge of low-risk patients^[39,40]. Very early endoscopy (<12hr) may be associated with increased findings of advanced stigmata, but does not impact on rebleeding or mortality^[40].

While some suggest very early endoscopy in selected high-risk patients^[4,41] such as those with bloody naso-gastric aspirate^[40] or high Blatchford risk score^[42], the body of evidence that support such practice changes outcomes is limited^[41]. Current international guidelines thus do not advocate for routine endoscopy in less than 12 hours in patients with suspected non-variceal UGIB^[1], as opposed to variceal bleeding where endoscopy should be performed within 12 hours^[43]. Additional evidence for the availability out-of-hours endoscopy just failed to reach significance with regards to

mortality^[44]; on the other hand, mortality has been reported to be increased in some high-risk patients undergoing early endoscopy^[45].

ENDOSCOPY

Endoscopic modalities used in the management of acute UGIB are classified into injection, thermal and mechanical therapies. Endoscopic hemostasis should be performed for all lesions exhibiting HRS (Table 2) given high rates of rebleeding and improved outcomes with endoscopic treatments^[46,47]. We review indications for endoscopic therapy, describe endoscopic treatment options and discuss the evidence for their use in UGIB. We also briefly report on emerging novel endoscopic technologies.

Indication for endoscopic therapy in non-variceal upper gastrointestinal bleeding (UGIB)

While patients with low risk endoscopic stigmata do not warrant endoscopic treatment, it is specifically the group of patients with active bleeding-either spurting or oozing blood-as well as patients with a non-bleeding visible vessel or an adherent clot who benefit from endoscopic therapy to improve outcomes^[48], as detailed below^[1,4].

Data from trials featuring sequential endoscopic evaluations of bleeding stigmata depict an evolution from HRS to LRS, where the majority of rebleeding occurs within the first 72 hours (49). Ulcer with flat pigmented spot or clean base are associated with low incidences of rebleeding with reported rates of 10-13%, and 5% respectively^[49,50]. Meta-analysis found that endoscopic therapy (injection or thermal) of ulcers with HRS (active bleeding and non-bleeding visible vessel) significant decreased rebleeding, surgery and mortality^[46,47]. The benefit was not seen in patients with flat pigmented spots or adherent clots. Table 2 summarizes a selection of large databases with proportional prevalence and bleeding outcomes. Such comparative analysis is limited by varying study methodologies, and patient selection.

Endoscopic treatment modalities

Injection therapy: Injection therapy includes epinephrine, hypertonic saline, sclerosants (polidocanol, ethanolamine, absolute alcohol and sodium tetradecyl sulfate), and tissue adhesives (cyanoacrylate, thrombin and fibrin glue). All injection therapies primarily achieve hemostasis through local tissue and vascular tamponade^[5,53]. Additionally, thrombin and fibrin injection can create a tissue seal at the site of bleeding, whereas sclerosants provoke direct tissue injury and induce thrombosis. This is associated with more tissue necrosis, limiting sclerosant use to < 1mL^[5,53].

Table 2 Endoscopic identification of stigmata of recent bleeding and associated prevalence and outcomes.

Stigmata of recent hemorrhage	Forrest Classification	Prevalence in patients with UGIB Modified from RUGBE ^[51]	Prevalence in ulcer bleeding Modified from CORI ^[52]	Prevalence in ulcer bleeding Modified from Laine ^[50]	Rate of further bleeding Modified from Laine ^[50]
		Registry of 1869 patients 1999-2002 Canada	Database of 3874 EGDs 2000-2004 USA	Pooled data from prospective trials	
Spurting vessel	Active bleeding	IA	3%	18%	55%
Oozing vessel		IB	9%		
Non-specified active bleeding	No-active bleeding	High-risk stigmata	2%	17%	22%
Non-bleeding visible vessel		IIA	10%		
Adherent clot		IIB	7%		
Flat pigmented spot	Low-risk stigmata	IIC	5%	20%	10%
Clean base		III	47%	42%	5%
Unknown			12		

Epinephrine is the most commonly used agent, benefiting from its low cost, high availability and ease of use. In addition to local tamponade, it induces vasoconstriction and platelet aggregation. Epinephrine is usually diluted at a concentration of 1:10,000 or 1:20,000 or less, and injected with increments of 0.5mL to 1.5mL to all quadrants around the stigmata of recent hemorrhage^[54]. Although there are no strict criteria regarding the quantity, a higher total volume^[55] – around 30 mL^[56] – may optimize hemostasis and has been associated with decreased rebleeding^[56,57]. Epinephrine injection alone, however, does not provide adequate hemostasis in UGIB and should be used in combination with other modalities (see below). It does achieve comparable rates of initial hemostasis, and is a good adjunct to control bleeding.

Thermal therapy: Thermal modalities are comprised of electrocautery probe (monopolar, bipolar or multipolar), heater probe (HP), argon plasma coagulation (APC), and laser - the last two being non-contact modalities. Most frequently used in UGIB are electrocautery probe (mainly bipolar and multipolar) and heater probe which achieve hemostasis through coaptive coagulation; which provides local tamponade and vessel occlusion via the application of pressure using the probe tip, followed by heat or electrical current to coagulate the vessel. The tissue coagulation further induces intravascular platelet aggregation. Alternatively, APC uses argon to conduct electricity to treat superficial lesions (<1-2mm deep)^[58]. It does not allow physical compression and becomes a monopolar probe if contact is made with the tissue with the risk of submucosal gas accumulation. Monopolar probes, which induce more tissue injury and perforation, are rarely used as are lasers in the contemporary management of UGIB.

Electrocautery should be applied with firm pressure, optimally using low power (15 Watts) of longer duration (10 to 12 seconds)^[59]. Treatment should be repeated until flattening of the vessel or coagulation of the stigmata^[60]. Similarly heater probes should be manipulated using similar pressure, with repeated pulses delivering 25-30 Joules of energy per pulse, for a total of 4 to 5 pulses per application^[58].

Mechanical therapy: Mechanical devices cause local tamponade of vessels via direct approximation of the submucosa surrounding the bleeding site^[54]. They exhibit the advantage of not inducing tissue injury. The most common devices include endoscopic clips and band ligation devices; the latter being mostly used in variceal bleeding, though it has been reported effective in Dieulafoy lesions^[61]. Technical skills with regards to the proper positioning and deployment of clips are critical in achieving optimal effectiveness. The location of certain lesions (i.e. posterior wall of duodenal bulb, posterior wall gastric body, and lesser curvature of stomach) is an additional factor that may further limit the use of clips^[62].

Comparison of endoscopic modalities in acute UGIB

Several RCTs have compared the different endoscopic strategies with medical treatment only; with other modalities; as well as monotherapy versus combination therapy. Despite considerable heterogeneity amongst the different trials, all measured similar outcomes of recurrent bleeding, initial hemostasis, need for surgery and overall mortality. To date, five meta-analyses assess the optimal endoscopic therapy in peptic ulcer bleeding with high-risk stigmata^[48,62-65] (Table 3).

Endoscopic therapy displays significant benefits in decreasing rebleeding, lowering the need for surgery and mortality when compared to no endoscopic therapy^[46] for the treatment of peptic ulcers with high risk stigmata. It is well established that epinephrine

injection should not be used as monotherapy, and needs to be combined with a second modality. Thermal therapy, injection of sclerosant, and clips all seem effective as monotherapy, and can be used in combination with other modalities^[1,4].

An earlier meta-analysis by Calvet *et al.* compared the use of epinephrine injection to epinephrine injection followed by a second endoscopic therapy using 16 studies with a total of 1673 patients^[63]. Hemostatic modalities included various injectates (epinephrine, thrombin, ethanolamine, ethanol, sodium tetradecyl sulfate, polidocanol injection, and fibrin glue), and thermal modalities (laser, heat probe, bipolar electrocoagulation), as well as clips in patients with Forrest Ia, Ib, IIa, and IIb lesions. Trials with routine second-look endoscopy, which use repeat endoscopic therapy upon the presence of bleeding or HRS on follow-up endoscopy, were also included. The authors concluded that the addition of a second endoscopic agent after epinephrine injection decreases further bleeding, mortality and emergency surgery. This was irrespective of the second modality.

Marmo *et al* conducted a meta-analysis comparing dual endoscopic therapy versus monotherapy in the treatment of high-risk peptic ulcers based on 22 studies with a total of 2474 patients^[64]. Authors compared injection plus either (1) thermal; (2) mechanical (hemoclips); or (3) a second injection method to injection only (mainly epinephrine). Dual therapy with thermal or mechanical hemostasis was also compared to thermal and mechanical monotherapy respectively. Dual therapy showed significant decreased recurrent bleeding and need for surgery, but not mortality compared to epinephrine injection only. No combination therapy proved to be better than thermal or mechanical monotherapy.

Sung *et al* looked at endoscopic clipping versus injection and thermocoagulation in a meta-analysis featuring 15 randomized trials with 1156 patients by comparing clips to injection, clips plus injection to injection, and clips to thermocoagulation, both with or without injection^[62]. In addition patients with ulcers with high-risk stigmata, Dieulafoy lesions were also included. While a high degree of heterogeneity was noted across the studies; results show decreased rebleeding and need for surgery, but not mortality with clips (with or without injection) compared to injection alone. Initial hemostasis was however unchanged, and the benefits of clips were comparable to thermocoagulation.

More recently, Barkun *et al.* performed a meta-analysis of 41 trial enrolling 4,261 patients that only included contemporary endoscopic therapies (injectates; heater probe, monopolar and bipolar electrocoagulation, microwave and argon plasma coagulation, and clips) in patients with high-risk bleeding ulcers^[65], while excluding placebo/sham-controlled trials. Any endoscopic therapy outperformed pharmacotherapy in reducing rebleeding, but not surgery or mortality. Injection therapy was inferior to the other modalities, except when compared to thermocoagulation, in which case a strong trend favoring the latter was detected for rebleeding but failed to reach significance. Authors had insufficient data to support the dual use of injection and thermal or mechanical therapy. In a subgroup analysis, injection followed by thermocoagulation was however superior to thermal monotherapy. Highlighted were the infrequent use of high dose intravenous PPI limited to one trial, and the impact of contemporary acid suppression therapy on the outcome of selected patients, such as those with adherent clots. The authors concluded by suggesting thermal therapy or clips can be used alone or in combination.

The meta-analysis by Laine *et al* yielded similar conclusions^[48]. Authors excluded RCTs using second-look endoscopy (and re-

treatment when needed), and defined only clinically evident rebleeding as primary outcome measure. Modalities such as laser or injection of adhesive were not considered. Endoscopic therapy compared to pharmacotherapy decreased further bleeding and need for surgery, except in the adherent clot subgroup where no differences were detected. Epinephrine was found to be inferior to other modalities for reducing further bleeding, but had comparable rates of initial hemostasis. Again, clips and thermal therapy, with or without injection, had similar efficacy. Furthermore, PPI therapy after endoscopy was associated with lower rebleeding, surgery and mortality.

Adherent clot

The approach to endoscopic findings of clots in ulcers should first involve irrigation in an attempt to dislodge the clot and expose the underlying stigmata. The identification of adherent clots can be made only after failure of aggressive irrigation to displace clots for up to 5 minutes^[66]. Laine showed that vigorous washing exposed the stigmata in 43% patients (70% showed HRS and 30% LRS) with adherent clots in the remaining 57%^[66]. Similar findings were reported by Lin *et al* with 33% clots dislodged with washing^[67].

Rates of rebleeding from adherent clots without endoscopic therapy vary widely in the literature^[46,66-72]. This may be due in part to poor inter-observer agreement^[73,74] and variable degrees of prior irrigation^[75]. Two RCTs showed that endoscopic treatment of adherent clots decreases rebleeding compared to medical therapy^[68,69], while others showed no added benefits^[70-72]. A single RCT used high dose IV PPI bolus plus infusion, and reported no rebleeding in the acid suppression only group^[70]. A meta-analysis examining this issue suggested significant improvement in outcomes attributable to endoscopic treatment in this patient population^[76], yet was criticized because of statistical shortcomings^[77]. A recent meta-analysis on the subject found no benefits in clinical outcomes^[48]; authors however note the presence of significant heterogeneity between the trial populations.

Current recommendations support vigorous irrigation (up to 5 minutes), and consider endoscopic treatment of adherent clot, especially in high-risk population; while acknowledging that high dose IV PPI may be adequate in certain populations^[1,4]. Endoscopic approach involves epinephrine injection in 4 quadrants followed by cold guillotining the clot to expose underlying stigmata and then treat the underlying stigmata^[60,68,69].

Novel therapies

Several new endoscopic therapies have emerged in the treatment of UGIB. Hemostatic sprays have shown promising preliminary results, and other newer mechanical devices have also been used in anecdotal cases.

Hemostatic spray

Two main powder-based topical hemostatic agents have been used in early clinical settings to treat GI bleeding. The Ankaferd Blood Stopper is a herbal derivative that promotes cell aggregation and coagulation through various cellular interactions. The hemostatic agent TC-325 HemosprayTM (Cook Medical Inc., Bloomington, IN, USA) is an inorganic compound that achieves rapid hemostasis by becoming cohesive and adhesive in contact with moisture. This creates a quick mechanical barrier over the bleeding site allowing hemostasis^[78-80], the compound is then naturally sloughed off over days. HemosprayTM has not been approved for external use by the FDA and is delivered via a catheter attached to a pressurized carbon

dioxide canister. Sung *et al.* achieved immediate hemostasis in 19/20 patients with actively bleeding peptic ulcer, without major adverse effects, with 72-hour rebleeding noted in two patients^[81].

Mechanical devices and other: A variety of clips have been tested as alternative to endoscopic clips, such as the three-prong TriClipTM (Cook Medical Inc., Bloomington, IN, USA) and the over-the-scope clip OTSCTM (Ovesco Endoscopy, Tübingen, Germany)^[78]. The latter can grasp larger volume of tissue with higher compression force^[78,79]. It has been used successfully in cases of GI bleeding^[82]. Endoscopic Doppler ultrasound is an adjunct method that can guide endoscopic therapy by identifying underlying vasculature before proceeding to focal injection of vessels^[54,79,83]. Endoscopic sutures and expandable stents have yet to be tested for acute non variceal UGIB at the time of writing of this review^[78].

POST-ENDOSCOPY

Predictors of rebleeding after endoscopy

Rebleeding after initial hemostasis occurs in 10-20%^[44,51,84] of patients, and is in itself a predictor of mortality^[85]. Both clinical and endoscopic variables help predict the risk of rebleeding. Several independent prognosticators have been identified, and include comorbid illness, the presence of hemodynamic instability, active bleeding at endoscopy, large ulcer size (most commonly >2cm), ulcer location (posterior duodenal wall and lesser gastric curvature), hemoglobin value (most commonly <10g/L) and the need for transfusion^[84,85]. The presence of such factors may help identify and manage patients at an especially high-risk of rebleeding.

Second look endoscopy

Second look-endoscopy is a pre-planned repeat endoscopy at 16 to 48 hours after achieving initial endoscopic hemostasis. While meta-analyses show a decrease in rebleeding^[86-88] and surgery^[88] but not in mortality with second-look endoscopy, caution is needed in interpreting such results as to their applicability to contemporary practice. Indeed trials did not use high-dose IV PPI, except for one study in which repeat endoscopy did not change outcomes^[89]. Moreover, the benefits of second-look endoscopy were not robust when very-high risk patients were excluded^[88]. The added cost also needs to be considered^[90]. Hence, second-look endoscopy is not recommended in all UGIB patients, but should be reserved for those at an especially high risk for rebleeding^[1,4].

Endoscopy in rebleeding

Repeat endoscopy is recommended in the setting of clinically evident rebleeding after successful hemostasis^[1,4]. A RCT showed that a second attempt at endoscopic control of bleeding was achieved in 73% of patients. Compared to surgery, it is associated with lower complications without increased mortality^[91]. After a second episode of rebleeding, surgical and radiological options should be considered and are being increasingly used in contemporary practice for cases refractory to endoscopic treatment. A national UK audit on non-variceal UGIB revealed that surgery and transarterial embolization (TAE) was required in 2.3%, and 1.3% of all patients, respectively^[92]. Mortality was noted to be higher after surgery than after TAE, with rates of 29% (28/97 patients) versus 10% (6/60 patients), suggesting TAE may be an alternative for surgery in rebleeding^[92]. Several retrospective studies support TAE after failed endoscopic treatment as being at least comparable to surgery with regards to complications, without adversely affecting mortality in retrospective studies^[93-95].

DISCUSSION

The management of non-variceal UGIB has significantly evolved over the last decade, along with the emergence of high quality data. It is however important to be familiar with some of the limitations of the evidence in order to make informed decision when managing the patient at an individual level. Indeed, the benefits of certain measures are best shown in selected populations, such as the use of prokinetics and the performance of “second-look” endoscopy. Moreover, in some cases such as the use of pre-endoscopic IV PPI, the ideal setting has yet to be determined. With regards to the endoscopic management, no modality, or combination of modalities has been consistently shown to improve outcomes, except for the inferiority of epinephrine injection monotherapy. The clinical context, including local expertise and endoscopic visibility and anatomy should further direct the choice for the optimal endoscopic modality in each patient. While several guidelines are available to guide the management of non-variceal UGIB^[1,3,4-7], clinicians should individualize patient care.

CONCLUSION

The management of non-variceal UGIB should include adequate resuscitation, and prompt risk stratification followed by timely endoscopic evaluation aid in identifying patients at low and high-risk for complications. Patients with HRS should be observed in a monitored setting, and benefit from endoscopic therapy in combination with IV PPIs. Epinephrine injection should no longer be used as monotherapy, as other modalities are more effective, while novel therapies are emerging. The care for patients with NVUGIB must also include adapted acute management and secondary prevention of ulcers related to H. Pylori, and concomitant medications such as non-steroidal anti-inflammatory drugs and antiplatelet agents.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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