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Review Article

REVIEW ARTICLE

An update on the management of non-variceal upper gastrointestinal bleeding

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Abstract

Upper gastrointestinal bleeding (UGIB) continues to be a common gastrointestinal emergency that carries significant morbidity and mortality. The epidemiology of UGIB has been changing over the last few decades with an overall decrease in peptic ulcer disease and increase in the prevalence of other etiologies including vascular lesions and malignancy. Appropriate risk assessment and patient stratification are crucial to ensuring that optimal care is delivered to patients and some risk assessment tools have shown excellent ability to define a low-risk group who can be managed as outpatients safely. Regardless of the etiology of UGIB, resuscitative interventions by primary care providers remain the most important initial measures to improve the outcome for patients including hemodynamic stabilization, an appropriate blood transfusion strategy, with or without acid-lowering agents, while also providing subsequent urgent endoscopic assessment and intervention. In addition, with increasing use of antithrombotic agents in clinical practice and its associated risk of bleeding, the management of such agents in the acute setting has become a real challenge to all physicians. In this article, we provide an up-to-date, evidence-based, practical review of recent changes and advances in UGIB with a focus on non-variceal etiologies.

Key words: UGIB; peptic ulcer; endoscopic hemostasis; risk assessment; antithrombotic

Introduction and epidemiology

Ulcers are the most common etiology of non-variceal upper gastrointestinal bleeding (UGIB). We therefore focus this review on peptic ulcer bleeding and briefly also address other etiologies of non-variceal UGIB. Indeed, ulcers are the most common cause of hospitalization for UGIB, accounting for >250,000 hospitalizations annually in the USA [1], with readmission rates of 14.6% [2]. The hospitalization rate for upper gastrointestinal (GI) hemorrhage in the USA decreased from 81 to 67 per 100,000 population from 2002 to 2012 [3]. Peptic ulcer disease remains the most common cause of hemorrhage, followed by gastritis and esophagitis. Interestingly, although the hospitalization rate has decreased by 30% for peptic ulcer hemorrhage, it has increased for Dieulafoy's lesions (33%), angiodysplasia (32%), and neoplasm (50%). The all-cause upper GI hemorrhage case fatality rate over this same time span decreased from 2.6% to 1.9%, with the largest reductions in mortality occurring for patients with UGIB bleeding from esophagitis (39%), neoplasm (36%), and Mallory–Weiss tear (MWT) (36%). Summary data suggest that weekend admission is associated with a significant increase in mortality in patients with non-variceal UGIB [4].

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Causes of UGIB

UGIB can be caused by several pathologies that affect the upper GI tract and broadly can be divided into non-variceal and variceal etiologies; we only discuss the former in this review. Historically, most cases of severe UGIB are related to peptic ulcer disease (PUD) (50%–60%) followed by variceal bleeding (4%–16%) [5–7]. However, more recent data suggest that the epidemiology is changing with a decreasing incidence of PUD (20%–40%) while other causes are being encountered more commonly [8–10]. Specifically, hospitalization secondary to esophagitis, Dieulafoy's lesion, angiodysplasia, and neoplasms has increased [3]. Here, we will review some of the most important non-PUD, non-variceal causes of UGIB (Table 1) [3, 11–13]. Unless specified, the reference to high-risk lesions refers to findings equivalent to those of peptic ulcers exhibiting Forrest Ia, Ib, IIa, and IIb endoscopic stigmata [14].

Esophagitis

Erosive esophagitis is an important cause of non-variceal upper GI bleeding (NVUGIB) that is accounting for an increasing proportion of patients with UGIB (8%–13%) [15, 16]. A multivariable analysis identified several independent risk factors for bleeding from erosive esophagitis, namely moderate-severe esophagitis (Grade 3 or 4 esophagitis, using the Savary–Miller classification [17]) (odds ratio [OR] 25.5, 95% confidence interval [CI] 9.6–67.9), the presence of cirrhosis (OR 5.7, 95% CI 1.7–18.9), an Eastern Cooperative Oncology Group performance status of $\geq$3 (OR 4.6, 95% CI 1.5–14.2), and concomitant anticoagulant therapy (OR 3.9, 95% CI 1.2–12.5) [16]. Patients with UGIB secondary to erosive esophagitis tend to have a more favorable outcome compared with those with other causes of UGIB, including shorter hospital stays, lower rebleeding rates, and lower mortality [18]. The mainstay of therapy is acid suppression as endoscopic therapy is rarely required and reserved for high-risk lesions.

Gastritis/duodenitis

Gastritis/duodenitis is rarely the only cause of bleeding and may have multiple etiologies, many of which share the same risk factors as PUD (including non-steroidal anti-inflammatory drug use, *Helicobacter pylori* infection, alcohol, radiation, and chronic bile reflux). A study estimated that gastritis is responsible for 18% of all episodes of UGIB, with hospitalization rates related to UGIB secondary to gastritis decreasing by 55% from 2002 to 2012 [3]. Bleeding from gastritis/duodenitis is usually self-limited and the treatment consists of acid suppressive therapy and, rarely, endoscopic therapy is required in patients exhibiting high-risk lesions.

Table 1. Causes of upper gastrointestinal bleeding [3, 12]

Etiology	Approximate prevalence
Peptic ulcer disease (PUD)	40%–63%
Esophageal/gastric varices	4%–16%
Gastritis/duodenitis	18%–22%
Esophagitis	8%–20%
Angiodysplasia	4%–6%
Mallory–Weiss tear	5.0%–7.4%
Gastric antral vascular ectasias	2.3%–4.0%
Malignancy	2.6%–4%
Dieulafoy's lesion	1.5%–2.3%
Cameron lesion	<1%
Hemobilia	<1%
Hemosuccus pancreaticus	<1%
Aorto-enteric fistula	<1%
No lesions identified	10%–15%

Mallory–Weiss tear (MWT)

These patients typically present with hematemesis or coffee ground emesis after a history of non-bloody vomiting with a longitudinal mucosal tear in the distal esophagus or proximal stomach. Most bleeding episodes from MWT are self-limited, but occasionally hemorrhage can be severe, requiring urgent assessment. MWT accounts for ~5%–7% of all causes of UGIB [3, 19]. Most only require acid suppressive therapy to help with mucosal healing; however, some patients will require endoscopic interventions. Despite the high efficacy of epinephrine injection (hemostasis 93%), the risk of rebleeding is 5.8%–6.6% when used as monotherapy in MWT, which is higher than for other endoscopic interventions [20, 21], as is also the case for PUD [22]. The most-studied endoscopic hemostatic modalities when treating MWT have been hemoclips and band ligation, often resulting in successful hemostasis (~100%) with low rebleeding rates, making them the preferred endoscopic intervention in patients presenting with actively bleeding MWT [23, 24]. Topical hemostatic agents can be considered as an alternative option in such patients [25, 26]. Contact thermal therapy should be used with extreme caution given the risk of complications, including perforation, especially when used in the esophagus for a bleeding MWT.

Vascular lesions

A useful a system to classify these lesions is the Yano–Yamamoto classification that was originally described for vascular lesions in the small bowel but can be useful as a framework for other upper GI vascular lesions (Figure 1) [27]. The major vascular lesions resulting in NVUGIB include angiodysplasia (Type 1), Dieulafoy's lesions (Type 2), and arteriovenous malformations (Type 3), and these are further discussed below.

Angiodysplasia

These are small tortuous, dilated, thin-walled vessels and the most common vascular abnormalities of the GI tract. They are responsible for a minority of UGIB (4%–6%) [3, 28, 29]. Angiodysplasia is more commonly seen in older patients (>60 years) and the prevalence increases with age [30]. Furthermore, several conditions have been associated with increased prevalence of GI angiodysplasia, including chronic kidney disease (CKD), aortic stenosis, von Willebrand disease [31–33], and left ventricular assist devices [34–36]. The endoscopic management of angiodysplasia commonly utilizes argon plasma coagulation (APC), contact thermal coagulation, or hemoclips; radiofrequency ablation (RFA) has also been reported [37].

Gastric antral vascular ectasia

Gastric antral vascular ectasia (GAVE) is a condition in which ectatic and sacculated mucosal vessels form stripes that rise to form the characteristic endoscopic appearance previously known as "watermelon stomach." GAVE can occur alone or may be associated with systemic conditions including systemic sclerosis, CKD, bone marrow transplantation, and cirrhosis [38]. GAVE is a rare cause of UGIB accounting for ~4% of all cases

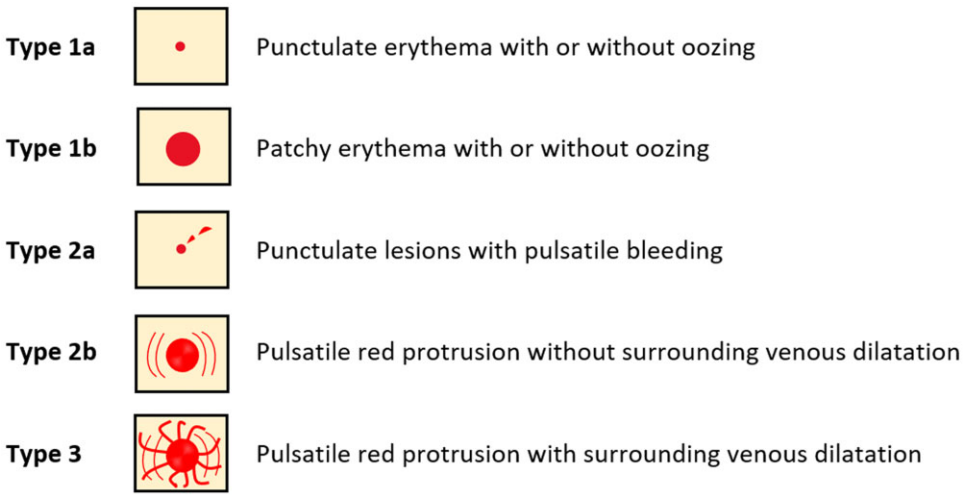

Figure 1. The Yano–Yamamoto classification of vascular lesions (modified from the study by Yano *et al.* [27])

[39]. The most commonly used endoscopic hemostatic tools to treat GAVE include band ligation, APC, and RFA. A meta-analysis of four randomized–controlled trials (RCTs) (204 patients) found higher endoscopic eradication of GAVE (risk difference [RD] 0.29, 95% CI 0.14–0.44) and less recurrent bleeding (RD 0.29, 95% CI 0.15–0.44) with band ligation as compared with APC [40], while APC required more endoscopic sessions to achieve eradication. Another meta-analysis of 24 observational studies (508 patients) suggested greater hemostasis rates with RFA compared with APC (97% vs 66%, respectively; $P < 0.001$), with significantly fewer mean treatment sessions (2.10 vs 3.39, $P < 0.001$) and less severe complications (1.92% vs 5.12%, $P < 0.001$) [41].

Dieulafoy's lesion

This terminology refers to an intact large-diameter (1–3 mm) submucosal artery that protrudes through the mucosa in the absence of an ulcer (Figure 2). Such lesions are usually located in the proximal part of the stomach (fundus) but can be seen also in the duodenum and small bowel. Even though a Dieulafoy's lesion is a rare (~1.5%) cause of UGIB, it is an important etiology to consider since it can cause recurrent and even massive bleeding, and can be difficult to localize given the intermittent nature of the hemorrhage [3], especially as the overlying mucosa is by definition completely normal in appearance. Endoscopic treatment of such lesions is similar to PUD-related bleeding including injection therapy, thermal contact therapy, hemoclips, or band ligation [42–43]. Endoscopic tattooing is recommended after successful endoscopic therapy to ensure easier localization in cases of rebleeding.

Malignancy

Neoplastic lesions of the upper GI tract are important causes of NVUGIB and can be challenging to manage. They account for ~3% of all severe UGIB [3, 44]. Tumor bleeding usually results in diffuse bleeding that can be extremely difficult to manage using standard endoscopic therapy such as hemoclips, injection therapy, and contact or non-contact thermal coagulation. Recently, a more novel endoscopic approach has been to utilize topical hemostatic agents. A recent meta-analysis found higher odds of hemostasis using topical hemostatic agents compared with conventional endoscopic tools in malignant GI bleeding

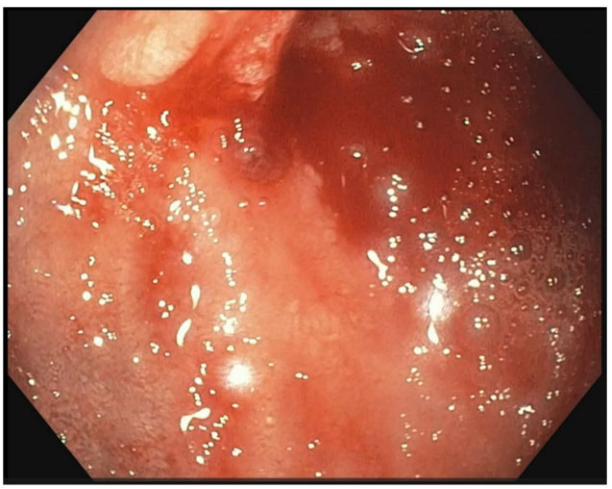

Figure 2. Actively bleeding Dieulafoy's lesion in the small bowel

subgroup analysis (OR 14.7, 95% CI 2.2–100.6) [45]. These promising results suggest that topical hemostatic agents may become the preferred first-line therapy for UGIB secondary to malignancy, but further high-quality studies are required to confirm these preliminary observations.

Risk assessment

Along with initial assessment and resuscitation, it is important to risk-stratify patients into low- and high-risk categories using validated risk assessment scores to ensure appropriate patient disposition from the initial point of care (the emergency room, in-hospital ward, or intensive care unit in most cases). Several scoring systems have been developed [46]; we will discuss the more commonly cited ones, including the Glasgow-Blatchford score (GBS); the altered mental status, systolic blood pressure, and age of ≥65 years (AIMS65) score; the Rockall score (RS); and the Age, Blood tests, and Co-morbidities (ABC) score. Some of these scores including Progetto Nazionale Emorragia Digestiva (PNED), Baylor Bleeding Score (BBS), and Cedars-Sinai Medical Centre Predictive Index (CSMCPI) require endoscopic assessment for generation of a full score, limiting their application in initial risk stratification in clinical practice. Despite poor uptake,

some guidelines now recommend some of these, as we will discuss below [22, 47].

Rockall Score (RS)

The RS is calculated using a pre-endoscopic (age, co-morbidities, and shock) and an endoscopic (etiology of bleeding and the presence of active bleeding) component [48]. The clinical or pre-endoscopic Rockall score (pRS) was proposed and can be calculated by omitting the endoscopic criteria, but this decreases the predictive power of the score. Although limited, the RS has been shown to have more accuracy in predicting mortality (with an optimal cut-off of ≥4 for clinical and ≥5 for full Rockall) than the risk of rebleeding [49]. However, the RS does poorly in predicting the risk of rebleeding or the need for surgical/radiological therapies and moderately in predicting the need for endoscopic therapy and blood transfusion [50, 51].

Glasgow Blatchford Score (GBS)

The GBS is a validated scoring system that was derived and aimed to identify patients who will require inpatient management [52] based solely on the initial assessment of a patient in the emergency room (Table 2). A low GBS score (0–1) has been shown to exhibit high sensitivity (98.6%) for identifying patients at low risk of requiring a hospital-based intervention (red blood cell transfusion, endoscopic treatment, interventional radiology, or surgery) and therefore who can be safely discharged from the emergency department with outpatient follow-up [53]. Furthermore, a GBS score of ≥7 can help to identify high-risk patients who are predicted to require endoscopic intervention (sensitivity 80%) [53]. In addition, it performs well at predicting the need for blood transfusion [51, 54]. However, the GBS is not accurate in predicting death and rebleeding [53, 55].

AIMS65 score

Another validated scoring system, the albumin, international normalized ratio (INR), altered mental status, systolic blood pressure and age ≥ 65 years (AIMS65) was developed from a large cohort in the USA with the aim of providing an easily calculated bedside risk score [56]. This score is based on five parameters with equal weight [57, 58]. Despite its ease of use, the ability to apply it during the initial patient assessment in the emergency room, and its accuracy in predicting inpatient mortality, the AIMS65 score does not discriminate low-risk patients who can be safely discharged home from the emergency room [59].

Table 2. The Glasgow-Blatchford score (GBS) [52]

Admission risk marker	Value	Score
Blood urea, mmol/L	6.5–8	2
	8–10	3
	10–25	4
	>25	6
Hemoglobin for men, g/dL	12–13	1
	10–12	3
	<10	6
Hemoglobin for women, g/dL	10–12	1
	<10	6
Systolic blood pressure, mmHg	100–109	1
	90–99	2
	<90	3
Pulse, per minute	≥100	1
History/co-morbidities	Melena	1
	Syncope	2
	Hepatic disease[a]	2
	Cardiac failure[b]	2

[a]Known history or clinical/laboratory evidence of chronic or acute liver disease.
[b]Known history of or clinical/echocardiographic evidence of cardiac failure.

ABC score

More recently, the ABC score was derived from an international cohort that included 3,012 UGIB patients [60]. The ABC score had good performance for predicting mortality in patients with UGIB. In the setting of UGIB, patients with a low ABC score (≤3), medium ABC score (4–7), and high ABC score (≥8) had 30-day mortality rates of 1%, 7%, and 25%, respectively [60]. The ABC score was externally validated and was found to display good prediction of mortality (receiver-operating characteristic [ROC] 0.78 [0.73; 0.83]) [61] but not the need for endoscopic intervention [62].

Comparison of risk assessment tools (Table 3)

Low-risk patients

A meta-analysis that used a composite end point (30-day mortality, recurrent bleeding, and need for intervention) concluded that GBS with a cut-off of 0 was superior to other risk scores in identifying low-risk patients [63], providing strong evidence to support the superiority of the GBS in identifying low-risk patients compared with other available clinical assessment tools while some of the newer assessment scales (ABC [61] and CANUKA [55]) show promising initial results in identifying low-risk patients.

High-risk patients

Cut-offs for defining "high-risk" groups varies between studies but in general the following cut-offs have been proposed: ABC score ≥ 8, AIMS65 score ≥ 3, GBS ≥ 12, and pRS ≥ 6 [61]. Comparative studies have concluded that the AIMS65 was better than both the GBS and pRS at predicting in-hospital mortality [53, 64]. On the other hand, all assessment tools showed modest predictive ability in prognosticating the need for endoscopic therapy, limiting its use in clinical practice [65–67]. Two of the largest comparative studies both concluded that the GBS was superior to the AIMS65 and pRS for the composite end point of hospital-based interventions (area under the ROC [AUROC] 0.86–0.93 for the GBS compared with 0.66 and 0.68–0.72 for the AIMS65 and pRS, respectively) [53, 68]. However, a more recent study that also included the ABC score concluded that the most commonly used assessment tools (GBS, AIMS65, pRS, and ABC) all exhibited poor discriminative ability for that composite end point (mortality, transfusion, endoscopic, radiological or surgical interventions) with none of the tools achieving an AUROC of >0.65 [61].

Based on the available evidence, the current UGIB guidelines (including the international consensus, American College of Gastroenterology [ACG] and European Society of Gastrointestinal Endoscopy [ESGE]) only recommend the GBS using a cut-off of ≤1 to identify low-risk patients who can be safely managed as outpatients with high certainty (false negative for requiring in-hospital interventions of <1%) [22, 47, 69].

Table 3. Comparison of RS, pRS, GBS, AIMS65, and ABC scores (from the study by Oakland *et al.* [46] with modification)

Score	Parameters	External validation AUROC				
		Mortality	Rebleeding	Endoscopic intervention	Surgery or interventional radiology	Blood transfusion
RS	Age, shock, co-morbidity, diagnosis (endoscopic), evidence of bleeding (endoscopic)	0.66–0.73	0.52–0.64	0.76	0.64	0.70–0.76
pRS	Age, shock, co-morbidity	0.64–0.93	0.52–0.66	0.51–0.75	0.49–0.62	0.59–0.75
GBS	Blood urea, hemoglobin, sBP, heart rate, melena, syncope, hepatic, and cardia diseases	0.63–0.80	0.56–0.71	0.58–0.78	0.61–0.71	0.70–0.93
AIMS65	Albumin, INR, mental status, sBP, age	0.69–0.91	0.57–0.60	0.75	NR	0.66–0.76
ABC	Age, urea, albumin, creatinine, co-morbidities (altered mental status, liver cirrhosis, disseminated malignancy, American Association of Anesthesiologists score)	0.78–0.85	0.58	0.68	NR	0.61

RS, Rockall Score; pRS, Pre-endoscopy Rockall; GBS, Glasgow-Blatchford score; AIMS65, Albumin, INR, mental status, sBP, and age ≥65 years; ABC, Age, Blood tests, and Co-morbidities; AUROC, Area Under the Receiver-Operating Characteristics; sBP, systolic blood pressure; NR, not reported; INR, International Normalized Ratio; HR, heart rate.

Blood transfusion

High-quality evidence supports the use of a restrictive transfusion strategy in patients presenting with stable UGIB without underlying cardiovascular disease. A meta-analysis of five RCTs (1,965 patients) found both significantly lower mortality and rebleeding rates in patients allocated to a restrictive vs a liberal transfusion strategy amongst patients bleeding from both variceal and non-variceal causes [70].

Patients with underlying, especially active, cardiovascular disease may be at higher risk of developing ischemic events at lower hemoglobin levels and generally require higher hemoglobin levels. A meta-analysis of 11 studies in patients with cardiovascular disease found no significant differences between liberal and restrictive strategies (none in the context of UGIB, though) with regard to 30-day mortality or acute pulmonary edema, although patients in the liberal group exhibited a lower risk of cardiovascular events (relative risk [RR] 0.56, 95% CI 0.37–0.85) [71].

Currently, the most recent practice guidelines (from both the ACG and ESGE) recommend a restrictive transfusional approach in patients with UGIB without underlying cardiovascular disease to be initiated at a threshold level of 7 g/dL and aiming for a post-transfusion target hemoglobin value of 7–9 g/dL [22, 47]. Both guidelines suggest a more liberal transfusion strategy (transfusion when hemoglobin level is ≤8 g/dL) for patients with underlying cardiovascular disease, aiming for a post-transfusion target hemoglobin of ≥10 g/dL. A liberal blood transfusion strategy may also be more appropriate for UGIB patients who present initially with hemodynamic instability.

Prokinetic agents

The most-studied prokinetic agent is the macrolide antibiotic erythromycin because of its motilin-like properties, given 30–120 minutes before endoscopy as an infusion at a dose of 250 mg [47]. The effectiveness of erythromycin as a prokinetic agent in the setting of UGIB has been tested in nine RCTs and summarized in a meta-analysis that included eight of these [72, 73]. In their meta-analysis ($n = 598$ patients), Rahman *et al.* [72] found that erythromycin administration was associated with statistically significant improvements in adequate gastric mucosal visualization (OR 4.14, 95% CI 2.01–8.53, $P < 0.01$) and a reduced need for second-look endoscopy (OR 0.51, 95% CI 0.34–0.77, $P < 0.01$). Furthermore, the length of hospital stay was shorter among patients who received pre-endoscopy erythromycin (MD −1.75, 95% CI −2.43–1.06, $P < 0.01$). However, the use of erythromycin did not improve any clinically important outcomes such as blood transfusion or need for emergency surgery [72]. Despite the potential for adverse events when erythromycin is used, including prolongation of the QT interval that could rarely result in a tachydysrhythmia, no such adverse events have been reported in the RCTs studying erythromycin for UGIB [72]. Another prokinetic agent, metoclopramide, was investigated in two small studies published in abstract form only and the data did not support its routine use [74].

The most recent UGIB guidelines (ACG and for patients with clinically severe or ongoing active bleeding, the ESGE) recommended using erythromycin before endoscopy for acute UGIB to improve visualization and reduce the need for a second-look endoscopy [22, 47].

Pre-endoscopy proton-pump inhibitors

Pre-endoscopy proton-pump inhibitors (PPIs) have been proposed as a treatment for UGIB and to improve patient clinical outcomes. Studies have shown that this intervention can reduce the need for endoscopic therapy through the downstaging of bleeding lesions but failed to show any associated improvement in important clinical outcomes such as mortality, rebleeding, or the need for surgery [75–77].

Current practice guidelines have differed in their recommendations on the use of PPI pre-endoscopy. These have either suggested against using pre-endoscopy PPI (British Society of Gastroenterology [78]) or could not make a recommendation for or against its use (ACG guidelines [22]). Some experts still suggest using PPI prior to endoscopy to downgrade any high-risk lesions (American Gastroenetrology Association [AGA] expert review [79]) that may be particularly useful when timely endoscopy cannot be performed, or the patient presents contraindications to undergo early endoscopic evaluation (within the first 24 hours of presentation). The administration of PPI before endoscopy, however, has been found to be cost-effective among patients presenting with suspected UGIB [80] and is especially so in the context of a probable non-variceal cause of bleeding or if endoscopy will be delayed [81, 82].

Importantly, regardless of the decision to use pre-endoscopy PPI, adequate resuscitation should be performed followed by a timely endoscopy.

Timing of endoscopy

In general, "urgent endoscopy" has been defined as endoscopy within 12 hours whereas "early endoscopy" is defined as endoscopy performed within 24 hours [47]. Early endoscopy, as defined, is performed within the 24 hours following presentation, has resulted in the best outcomes and has remained the recommended approach for over a decade [22]; it has resulted in better patient outcomes including lower in-hospital mortality, fewer procedures, shorter hospital stay, and lower total hospital costs [83, 84]. On the other hand, performing endoscopy in the acute setting of a patient with a suspected UGIB may carry some risks including the potential for inadequate resuscitation before the procedure and a need to perform endoscopy during off-hours when fewer endoscopy resources are available and/or endoscopist fatigue is present, resulting in lower-quality examination with sub-par hemostasis and worsened outcomes [69, 85].

Such considerations are highlighted by a recent large nationwide Danish cohort study of high-risk patients in which increased mortality amongst very sick patients was noted when urgent (as well as late, beyond 24 hours) endoscopy was performed [86].

Recently, a high-quality RCT (516 patients) compared urgent endoscopy (within 6 hours of gastroenterology consultation) with a control group (within 24 hours of gastroenterology consultation) among patients with predicted high-risk UGIB (GBS $\geq$ 12) [87]. This study found no significant difference in the 30-day mortality, further bleeding, duration of hospitalization, or transfusion requirements between the urgent and the early endoscopy arms. However, it is important to recognize that many of these studies excluded patients who presented with hypotensive shock who fail to stabilize after initial resuscitation and this group may need more urgent intervention after careful and adequate resuscitation on a case-by-case basis.

The current practice guidelines agree that all patients with NVUGIB should undergo early upper endoscopy (within 24 hours of presentation) but only after adequate resuscitation [22, 47, 69]. Furthermore, ESGE guidelines, based on high-quality evidence, specifically do not recommend performing urgent endoscopy ($\leq$12 hours) due to lack of improvement in patient outcomes. The same guideline also does not suggest emergent endoscopy ($\leq$6 hours) for NVUGIB since this may be associated with worse patient outcomes [47]. It is very important to recognize that these recommendations only apply for suspected NVUGIB, while suspected variceal UGIB has different recommendations [88]. Indeed, the guidelines for patients with acute variceal bleeding suggest performing a gastroscopy within 12 hours, based on low- to very-low-quality evidence [88].

Endoscopic hemostatic modalities

During the initial endoscopic assessment of patients with NVUGIB, an important step is to localize the site of the bleeding and categorize the lesion as “high-risk” vs “low-risk” using an endoscopic assessment system, specifically the Forrest classification [14] (Table 4). In this classification, patients with Forrest Ia, Ib, IIa, and IIb are considered high-risk lesions for persistent or recurrent bleeding and warrant endoscopic therapy while Forrest IIc and III are low-risk lesions [89, 90]. Recently, the classification of Forrest Ib lesions (oozing bleed) as high-risk has been questioned as the risk of rebleeding may have been overestimated previously and is, in fact, lower compared with Forrest IIa and IIb lesions [91]. Nevertheless, the current recommendation is to manage such lesions (i.e. Forrest Ib) as high-risk when encountered endoscopically [47].

The approach to peptic ulcers with adherent clot (Forrest IIb) is controversial, as the available data have conflicting conclusions when it comes to the benefit of endoscopic therapy for such lesions for which guidelines are equivocal [22]. If the expertise (including radiological and surgical backup) is available and the ulcer is located in a favorable location, an attempt may be made to remove the adherent clot and apply endoscopic hemostatic therapy.

Endoscopic hemostatic tools

The available tools can be broadly categorized into thermal coagulation, mechanical therapy, injection therapy, and more recently topical hemostatic agents. Endoscopic therapy is indicated for ulcers with active bleeding or stigmata of recent hemorrhage (based on Forrest classification). Here we will discuss some of the commonly used endoscopic hemostatic tools including appropriate indication and efficacy data.

Injection therapy

Several agents can be used including dilute epinephrine, sclerosing agents (e.g. ethanol and ethanolamine), and tissue adhesives (e.g. thrombin and cyanoacrylate). Dilute epinephrine (1:10,000 or 1:20,000) is the most commonly used injectable therapy and works mostly by causing tissue tamponade and partly by vasoconstriction. It is typically injected in 0.5- to 2-mL aliquots around the ulcer base. Epinephrine monotherapy has been shown to be less effective than standard endoscopic tools such as bipolar electrocoagulation and clips with higher risk of further bleeding (RR 2.2, 95% CI 1.04–4.64) [22]. The combination of epinephrine injection with another endoscopic therapy has been shown to be superior to epinephrine injection monotherapy when it comes to risk of further bleeding (RR 0.34, 95% CI 0.23–0.50) [92]. The major advantage of epinephrine injection is that it is easy to administer, and it is particularly useful when active bleeding is encountered to temporarily slow down the bleeding to provide a clear field until a more definite endoscopic intervention is applied (i.e. clips or electrocoagulation).

Through-the-scope clips

Mechanical hemostasis can be achieved by using clips that include through-the-scope (TTS) clips and over-the-scope clips (OTSC). TTS clips are typically applied at the bleeding site, resulting in mechanical compression, achieving hemostasis (Figure 3). Despite the widespread use of the TTS clips for hemostasis, the evidence to support their efficacy is actually quite limited [92–94]. TTS clips can be used for a variety of bleeding lesions including PUD and vascular lesions (e.g. Dieulafoy’s lesions). However, the use of such clips can be technically challenging in certain locations (e.g. proximal lesser curvature of stomach and posterior duodenum) and in fibrotic ulcers. As discussed previously, this mode of hemostasis can be combined with epinephrine injection, achieving superior outcomes compared with epinephrine monotherapy [92].

Table 4. Forrest classification of non-variceal upper gastrointestinal bleeding lesions and approximate prevalence [13, 90]

Forrest class	Definition	Lesional risk of continued bleeding	Prevalence	Risk of rebleeding without endoscopic treatment	Medical treatment	Endoscopic treatment
Ia	Active spurting bleed	High-risk	7%	55% (including oozing bleed [Forrest 1b])	High-dose PPI IV for 72 hours	Yes
Ib	Oozing bleed	High-risk	27%	See text[a]	High-dose PPI IV for 72 hours	Yes
IIa	Non-bleeding visible vessel	High-risk	26%	43%	High-dose PPI IV for 72 hours	Yes
IIb	Adherent clot	High-risk	11%	22%	High-dose PPI IV for 72 hours	After clot removal
IIc	Flat-pigmented spot	Low-risk	4%	10%	Low-dose PPI PO	No
III	Clean-base ulcer	Low-risk	25%	5%	Low-dose PPI PO	No

[a]Recent data suggest rebleeding risk is lower than previously reported [91].
PPI, proton-pump inhibitors; IV, intravenous; PO, oral.

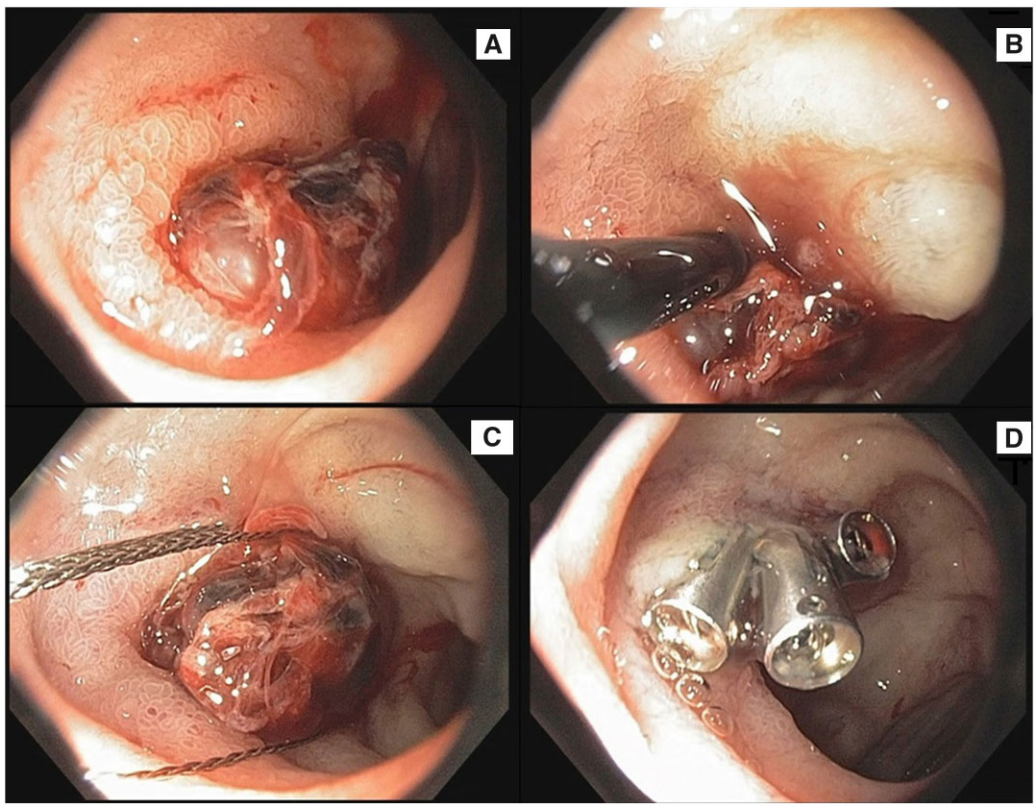

Figure 3. Images of hemostasis with the use of through-the-scope clips (TTS). (A) Adherent clot on a duodenal ulcer; (B) the edge of the ulcer is injected with dilute epinephrine; (C) the clot is removed using a snare; (D) definite hemostasis is achieved using through-the-scope endoscopic clips.

OTSC

The OTSC (or cap-mounted clip) technology has increasingly been used for many different endoscopic therapeutic indications (Figure 4). It has been shown to be efficacious as rescue compared to standard therapy (TTS clips, principally) in decreasing persistent bleeding amongst patients presenting with high-risk endoscopic bleeding ulcer lesions who have experienced recurrent bleeding [95]. Since that time, additional RCTs assessing its role as primary therapy in NVUGIB have suggested its efficacy in decreasing rebleeding at 7 and 30 days, as has a recent meta-analysis that regrouped both observational studies and RCTs [96]. However, a number of methodological limitations leading to lower certainty of evidence have been raised that have questioned adopting this technology as primary therapy in NVUGIB, let alone peptic ulcer bleeding [97]. The cost-effectiveness of this technology also requires further characterization if used in first intent of endoscopic hemostasis. Currently, the OTSC is recommended as rescue therapy for patients with NVUGIB experiencing persistent or recurrent bleeding [22, 47].

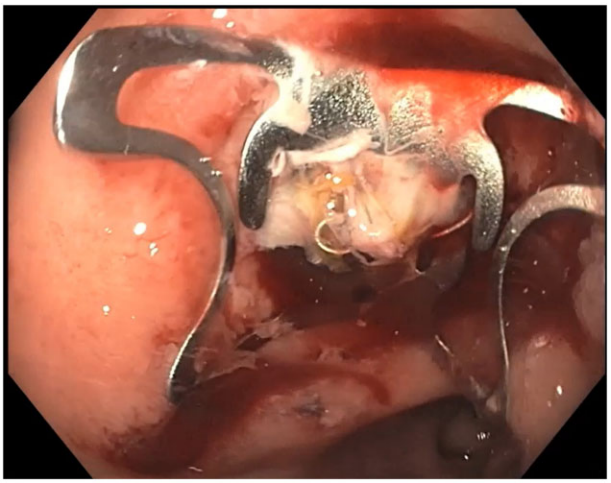

Figure 4. Image of hemostasis with the use of the over-the-scope clip (OTSC). Duodenal ulcer causing severe gastrointestinal bleeding that was refractory to endoscopic therapy with through-the-scope endoscopic clips and angiographic coiling (seen at the base of the ulcer); an OTSC was applied with successful hemostasis.

Contact thermal therapy

Thermal therapies achieve hemostasis by generating heat that leads to coagulation of tissue and contraction of the blood vessels. Several contact thermal devices are available including bipolar electrocoagulation, heater probes, and soft monopolar electrocoagulation. Bipolar electrocoagulation probes achieve hemostasis by coaptive coagulation that involves applying pressure directly over the bleeding vessel with the probe while applying cautery. The current recommendation is to use the large 3.2-mm probe with firm pressure over the vessel and the application of heat energy for 8–10 seconds [22]. Available data support the use of thermal contact therapy devices with a meta-analysis of 15 RCTs concluding that such tools reduce further bleeding (RR 0.44, 95% CI 0.36–0.54) and mortality (RR 0.58, 95% CI 0.34–0.98) compared with no endoscopic therapy [92]. The monopolar hemostatic forceps soft coagulation (MHFSC) (Figure 5), which has been primarily developed for the treatment of bleeding during endoscopic resection [98], can also be used to manage other bleeding lesions. MHFSC achieves hemostasis by applying heat energy using the closed forceps tip to the bleeding site or by grasping the bleeding vessel with the open forceps and applying direct thermal soft coagulation. A RCT that included 112 patients compared MHFSC with TTS clips for peptic ulcer bleeding [99]. This study showed a higher initial hemostasis success rate with MHFSC compared with TTS clips (98.2% vs 80.4%, $P = 0.004$) and less recurrent bleeding (3.6% vs 17.7%, $P = 0.04$). This study, along with other RCTs [100–102], confirmed the safety of MHFSC when used to manage NVUGIB with no reported serious adverse events such as perforation. MHFSC is currently conditionally supported by the ACG guidelines whereas the bipolar electrocoagulation is strongly recommended given the stronger quality of evidence to support its use in NVUGIB [22].

Non-contact thermal therapy

APC is a non-contact thermal modality that produces a superficial tissue coagulation (~1–2 mm). APC is frequently used to manage superficial vascular lesions such as angiodysplasia and GAVE (see other causes of UGIB section). However, the application of APC in peptic ulcer bleeding is less well supported. A RCT concluded that APC is associated with less further bleeding than water injection [103], while other RCTs concluded that APC (with or without epinephrine injection) is as effective as heater probes [104] and TTS clips [105] in managing peptic ulcer bleeding. However, the overall evidence to use APC in peptic ulcer bleeding is less robust than other endoscopic modalities and hence the ACG gave a conditional recommendation for using it in peptic ulcer bleeding [22].

Recent advances in endoscopic hemostasis

Topical hemostatic agents

One of the most recent developments in the field of UGIB treatment is the introduction of topical hemostatic agents. These are non-contact modalities that have hemostatic properties and are applied locally to the site of the bleeding relatively easily compared with other modalities. Unlike other endoscopic hemostatic modalities, topical hemostatic agents can be applied widely onto an area of bleeding, which is especially advantageous in diffusely bleeding lesions such as malignancy.

The most commonly studied agent is TC-325 (Hemospray®, Cook Medical, Bloomington, USA), which is a biologically, silica-based, inert powder that creates a mechanical barrier over bleeding sites when it comes in contact with moisture in the GI tract [106]. It is delivered by a spray catheter without direct contact with the bleeding lesion (Figure 6) [107]. Multiple observational and randomized studies have assessed the safety and efficacy of TC-325 in the management of suspected UGIB [25, 108–113]. TC-325 was found to have high immediate hemostasis when used as primary or rescue therapy (>90% immediate hemostasis rate) [114]. TC-325 has also, more specifically, been found to be effective in managing malignant hemorrhagic lesions of the GI tract—especially given the diffuse nature of the bleeding [109]. However, the main concern with TC-325, given its mechanism of action, is recurrent bleeding once the powder washes off 12–24 hours later, re-exposing the bleeding lesion [115, 116], which is an issue for lesions with delayed risks of rebleeding that have been reported to be ≥72 hours for bleeding ulcers treated endoscopically. Randomized comparative studies have failed to show higher rates of rebleeding when TC-325 is more formally assessed in comparable groups of patients to conventional endoscopic interventions [25, 112]. The largest RCT to date that has compared TC-325 with conventional endoscopic therapy was recently published by Lau *et al.* [113]. The study, which included 224 patients with NVUGIB, concluded that TC-325 was non-inferior to conventional endoscopic therapy in achieving control of bleeding (90.1% vs 81.4%, respectively) and 30-day recurrent bleeding (8.1% vs 8.8%, respectively) or 30-day mortality (12.6% vs 12.4%, respectively) (Table 5). An important consideration when applying this agent is the technical failure that can occur secondary to catheter blockade due to premature activation of the topical agent inside the catheter upon exposure to moisture. These issues can usually be avoided by following the manufacturer's instructions.

Much less information is available about other topical hemostatic agents that are discussed below. The EndoClot Polysaccharide Hemostatic System (PHS) (EndoClot Plus, California, USA) is a hemostatic, absorbable, modified polymer particle powder that has been used in UGIB [117]. EndoClot PHS consists of a white powder that combines with blood, drawing out water to form a gel matrix that adheres to the mucosa,

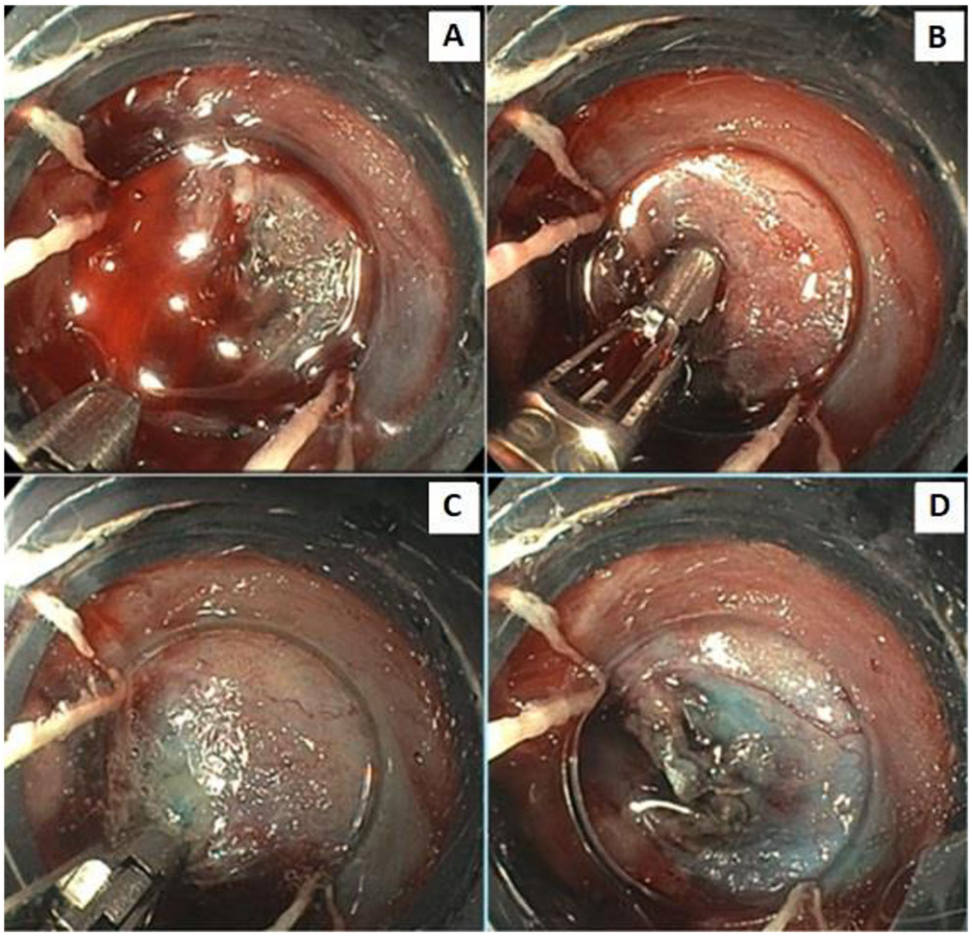

Figure 5. The images of post-esophageal endoscopic mucosal resection bleeding managed by monopolar hemostatic forceps soft coagulation (MHFSC). (A) Active spurting bleeding noted after mucosal resection; (B) the MHFSC is used to grasp the bleeding vessel resulting in mechanical tamponade; (C) soft coagulation is then applied to the bleeding vessel; (D) successful hemostasis is achieved.

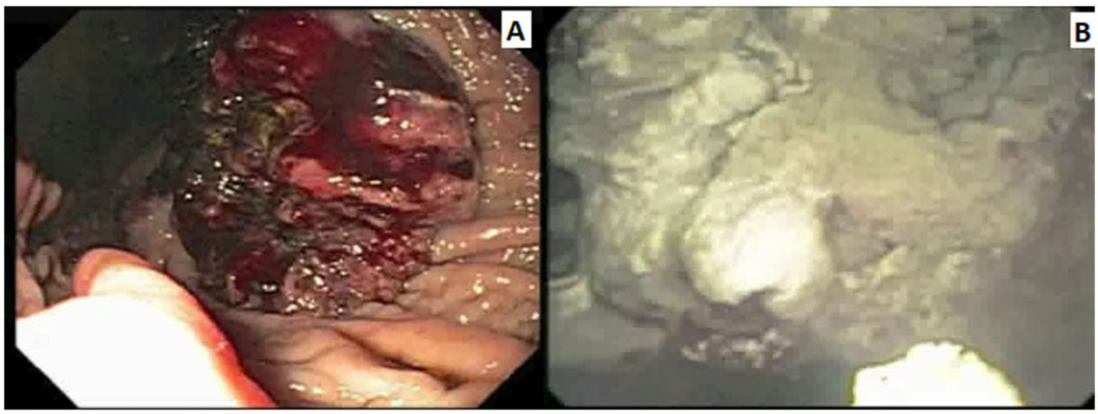

Figure 6. The images of hemostasis with the use of topical hemostatic agent TC-325. (A) Actively oozing gastric adenocarcinoma; (B) hemostasis achieved following application of the topical hemostatic agent TC-325.

creating a physical barrier [118]. Similarly to TC-325, it is delivered via a spray catheter without direct contact with the mucosa and is dispensed over a large field of distribution. The duration of adherence to the mucosa is unknown but is thought to range from 1 to 48 hours [118]. A few observational studies concluded that this agent is safe and effective in achieving hemostasis in NVUGIB (as a primary or rescue therapy) with reported immediate hemostasis of 64%–100% [117, 119, 120]. The 30-day rebleeding in these studies varied between 3.3% and 20%.

Another recently introduced topical agent is PuraStat (PuraStat^{TM}, 3D-Matrix, Europe Ltd, France), which is a synthetic self-assembling peptide agent that forms a transparent hydrogel at neutral pH [121]. Once PuraStat is applied to a bleeding area, it will rapidly form a hydrogel barrier to produce

Table 5. Primary and secondary outcomes of trial by Lau *et al.* [113]

Outcome	TC-325 ($n = 111$)	Standard treament ($n = 113$)	Odds ratio (95% CI)
Control of bleeding within 30 days	90.1%	81.4%	8.7 (0.95)*
Failed immediate hemostasis	2.7%	9.7%	0.26 (0.07-0.95)
30-day rebleeding	8.1%	8.5%	0.91 (0.37-2.22)
Need for further treatment of bleeding	9.0%	10.6%	0.83 (0.34-2.02)
30-day mortality	12.6%	12.4%	1.02 (0.46-2.25)

CI, confidence interval.
*Between-group difference (1-sided 95% CI)

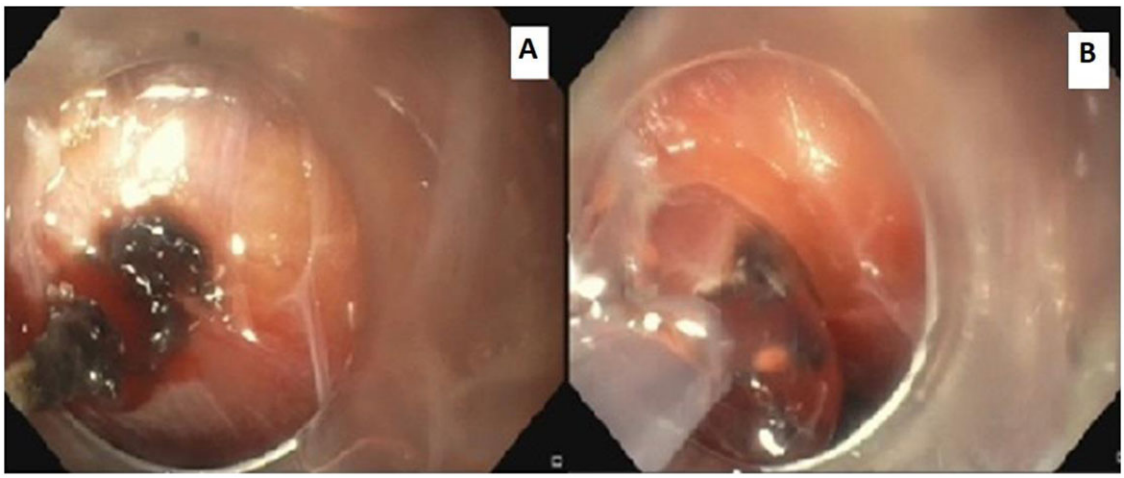

Figure 7. Images of hemostasis with the use of topical hemostatic agent PuraStat. (A) Active bleeding during per-oral endoscopic myotomy; (B) bleeding managed by applying PuraStat gel to the bleeding site.

hemostasis (Figure 7). A main advantage of PuraStat compared with other topical agents is its transparent nature that does not obscure endoscopic view, allowing multi-modality therapy at the index endoscopy. Furthermore, some *in vitro* model and animal studies have shown a tissue-regenerating capability of this agent that may promote ulcer healing [122, 123]. A few studies in patients with NVUGIB showed that PuraStat was successful in achieving hemostasis in >80% of lesions [121, 124, 125]. Rebleeding can occur in ≤17% of patients [121].

Other topical agents that have been described in the literature but with even sparser data and availability include the recently Food and Drug Administration (FDA)-approved biocompatible natural polymer Nexpowder Endoscopic Hemostasis System (Medtronic plc, Dublin, Ireland) and the older Ankaferd Blood Stopper (Ankaferd Health Products Ltd, Turkey). These agents have different compositions but exhibit mechanisms of action similar to those of the other topical hemostatic powders.

The ESGE guideline suggests using topical agents in the case of persistent bleeding refractory to standard hemostatic modality [47]. More recently, the ACG guidelines made a conditional recommendation suggesting the use of TC-325 in patients with actively bleeding ulcers. Future guidelines will likely support the use of these agents as a first-line treatment for NVUGIB, with perhaps its most useful role standing out in the management of malignant bleeding given the accumulating evidence from RCTs and observational studies to support its efficacy compared with conventional endoscopic therapy. Additional unpublished analysis from a recent meta-analysis found higher immediate hemostasis with TC-325 compared with conventional endoscopic therapy in malignant bleeding with no difference in the rebleeding rate (Figure 8) [45].

Doppler endoscopic probe

Adoption of the Forrest endoscopic risk stratification has assisted in the management of patients with NVUGIB (especially with bleeding ulcers) for almost 50 years [14]. Attempts to improve on this endoscopic risk assessment have included the development of a TTS endoscopic Doppler probe or Doppler endoscopic probe (DEP) that can detect arterial submucosal blood flow during endoscopy by passing a probe through the operating channel of the endoscope [126]. This endoscopic diagnostic modality may be used prior to endoscopic treatment to estimate the intrinsic rebleeding risk of a lesion and the subsequent need for endoscopic hemostasis, and/or after treatment to assess its effectiveness.

A recent systematic review and meta-analysis of available observational and interventional studies assessing DEP identified 14 studies [127]. Although the certainty of evidence overall was low, patients with a bleeding lesion displaying a positive DEP signal prior to or following any possible endoscopic hemostasis were at greater risk of overall rebleeding (odds ratio [OR] 6.54 [2.36, 18.11] and OR 25.96 [6.74, 100.0], respectively). Furthermore, the use of DEP at the index upper endoscopy significantly reduced overall rebleeding rates (OR 0.27 [0.14, 0.54]). All evaluable outcomes including overall rebleeding, bleeding-related mortality, and need for surgery were improved with DEP characterization of management guidance but not all-cause mortality [127]. DEP has also recently been shown to be a cost-effective approach when compared with traditional sole visual approaches of lesional risk stratification in patients with NVUGIB [128]. Although initially described almost 40 years ago, its dissemination has remained poor and it has been the subject of disparate recommendations, if any, by learned societies owing to the limited data characterizing this modality and its certainty [22].

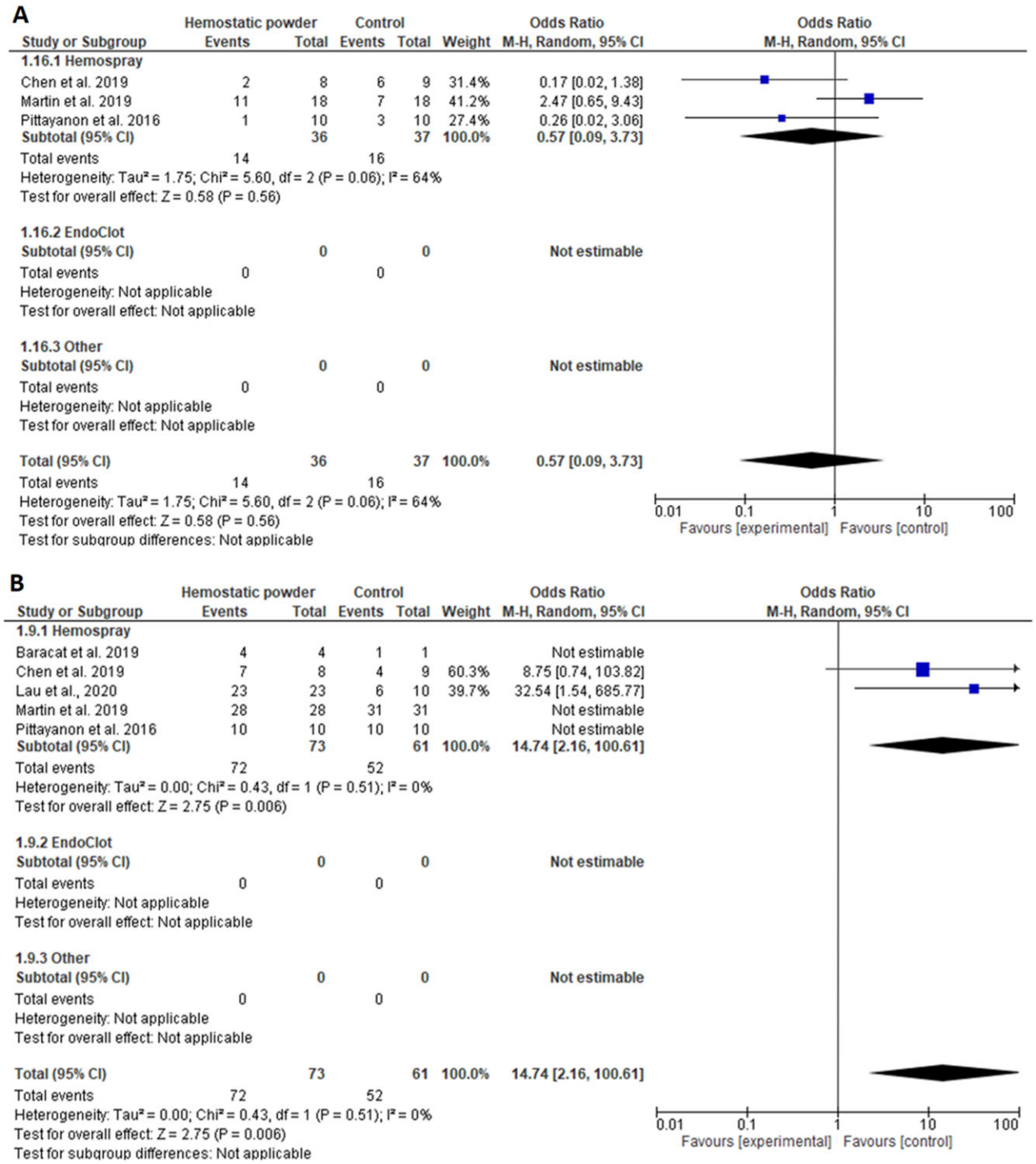

Figure 8. Forrest plots of trials comparing topical hemostatic agents with conventional endoscopic modalities in malignant gastrointestinal bleeding [45]. (A) immediate hemostasis; (B) rebleeding.

Post-endoscopy PPIs

Multiple RCTs have been performed assessing PPI post-successful endoscopic therapy and have been summarized in a Cochrane review [129] that has regularly been updated and reported by the international consensus group in 2019 [69] comparing PPI treatment with placebo or H2 receptor antagonists (H2RA) in acute bleeding from PUD. There is continued evidence that PPI therapy vs no PPIs or H2RA reduces mortality (OR 0.56, 95% CI 0.34–0.94) and rebleeding risk (OR 0.43, 95% CI 0.29–0.63) [69]. Similar conclusions were reached by the ACG guidelines that concluded (based on seven RCTs and high-quality evidence) that high-dose PPI (defined as ≥80 mg daily for 3 days) compared with placebo or no treatment significantly reduced further bleeding (RR 0.43, 95% CI 0.33–0.56), mortality (RR 0.41, 95% CI 0.22–0.79), and surgery (0.42, 95% CI 0.25–0.71) [22].

It remains unclear whether PPI infusion (80 mg bolus followed by 8 mg/hour infusion for 3 days) is superior to intermittent PPI (40 mg twice daily). Sachar *et al.* [130] performed a meta-analysis of 13 RCTs comparing these two PPI regimens in patients with confirmed high-risk bleeding ulcers. Intermittent PPI therapy was non-inferior to PPI infusion in terms of rebleeding, mortality, and urgent interventions. It has also been suggested by some that high-dose oral PPI (≥80 mg/day) displays similar efficacy (rebleeding, surgery, and mortality) when compared with intravenous PPI [131], although a recent trial suggested that very large numbers of patients would be required to confirm non-inferiority, let alone equivalence [132]. A cost-effectiveness analysis concluded that high-dose intravenous PPI was more cost-effective than high-dose oral PPI [133]. The most recent guidelines recommend high-dose PPI therapy (high-quality evidence) given continuously or intermittently (moderate-quality evidence) after successful endoscopic therapy for PUD [22, 47].

Among high-risk ulcers that received 72-hour PPI infusion, patients are typically treated with short-term high-dose oral PPI after discharge. One RCT included patients with a RS of >6 exhibiting high-risk ulcers that were treated successfully endoscopically followed by high-dose PPI infusion for 72 hours, randomizing them to twice-daily oral 40-mg esomeprazole for 11 days vs a single daily dose [49]. The former group was significantly less likely to experience further bleeding at 28 days compared with once-daily 40-mg esomeprazole (10.8% vs 28.7%, respectively) [49]. This practice is supported by the ACG guidelines that issued a conditional recommendation for twice-daily PPI for 2 weeks after the index endoscopy [22].

Recurrent bleeding

Some patients will NVUGIB fail conventional endoscopic therapy or experience recurrences after initial hemostasis that are associated with increased morbidity and mortality [134]. Indeed, ∼15% of patients will fail an initial hemostatic attempt at the initial index endoscopy, with ≤25% of patients rebleeding after an initial successful endoscopic treatment [135]. The management of such patients can be a challenge but recent developments in endoscopic and non-endoscopic therapies now provide more options that can potentially improve the outcomes for such patients. The approach to failed initial endoscopic hemostasis has been discussed earlier.

Recurrent bleeding is defined as recurrence of bleeding after successful hemostasis. It usually presents as ongoing hematemesis, recurrent melena, hemodynamic instability, or drop of hemoglobin of >2 g/dL [136]. A meta-analysis of 14 studies has identified significant predictors of rebleeding. Pre-endoscopic characteristics have included initial haemodynamic instability, a presenting low hemoglobin value, and greater transfusional needs. Endoscopic predictors of rebleeding were active bleeding, large ulcer size, and a posterior duodenal ulcer or a high lesser gastric curvature ulcer location [137] as well as persistent Doppler signal [138]. A RCT that compared repeat endoscopic intervention with surgery was able to show that repeat endoscopic therapy can control bleeding in 73% of patients [139]. Furthermore, the same study showed a significantly lower risk of complications and cost with endoscopic therapy compared with surgery and no increase in risk of mortality. Despite the safety of repeat endoscopic interventions, care should be taken when using repeat heater probes since this has been associated with some cases of perforation [139]. In these cases, the use of mechanical hemostatic modalities (e.g. TTS clips and OTSC) or topical hemostatic agents is preferred. More recently, a small RCT included 66 patients with recurrent bleeding were treated with OTSC and this modality was found to be superior to standard therapy (TTS clips in 94%) in decreasing further bleeding (15.2% vs 57.6%), $P < 0.001$), without a difference in mortality, although the trial was underpowered for this latter outcome [95].

In spite of the high success rate of repeat endoscopic therapy in controlling the majority of recurrent ulcer bleeds, some will fail such therapy and require non-endoscopic interventions, namely surgery or transcatheter arterial embolization (TAE). A meta-analysis of 13 observational studies showed that despite TAE exhibiting higher rebleeding rates compared with surgery (OR 2.44; 95% CI 1.77–3.36), TAE was associated with significantly lower risk of complications (OR 0.45, 95% CI 0.30–0.47) and comparable mortality to surgery [140]. Furthermore, TAE was associated with shorter hospital stay compared with surgery [141]. Despite the lower efficacy of TAE, given its excellent safety profile and shorter hospital stay, it is the preferred rescue therapy for patients with failed endoscopic therapy. Current evidence does not support prophylactic TAE even among high-risk patients [142].

Based on the available data, the ACG guidelines suggest repeating endoscopy and endoscopic therapy in patients who have recurrent bleeding and selecting TAE as second-line therapy if endoscopic re-intervention fails [22].

Role of *H. pylori* infection

Helicobacter pylori is the main etiological factor in PUD and its eradication has been demonstrated to significantly reduce the rate of ulcer recurrence [143]. An updated Cochrane database systematic review that included 55 RCTs showed a superior duodenal ulcer healing with *H. pylori* eradication compared with both ulcer-healing drugs and no therapy. Furthermore, the eradication therapy resulted in lower risk of recurrence of both gastric and duodenal ulcers [144]. More importantly, a meta-analysis found an 82% lower risk of ulcer rebleeding in the *H. pylori* eradication group compared with non-eradication group in the absence of antisecretory therapy (number need to treat [NNT] 5, 95% CI 4–8) [145]. The same study also demonstrated a 75% lower risk of ulcer rebleeding when *H. pylori* is eradicated compared with no-eradication with continued antisecretory therapy (NNT 20, 95% CI 12–100). These data support routine testing and eradication of *H. pylori* in all patients presenting with peptic ulcer disease-related UGIB.

Another important clinical question is the timing of testing since most *H. pylori* detection tests exhibit lower sensitivity in the setting of an acute UGIB, which may prompt some to delay testing, with false negative rates of ≤55% [146]. On the other hand, delays in eradication (even as short as 8 days after peptic ulcer diagnosis) have been shown to increase the risk of rehospitalization due to recurrent symptoms from a complicated ulcer [147, 148]. These considerations support the recommendation of testing for *H. pylori* during the index hospitalization with a repeat attempt later (within 4 weeks) if the initial results are negative for the aforementioned [47].

Antithrombotic and UGIB

An ever-increasing number of patients presenting with UGIB events are taking antithrombotics. Recent guidelines by the ACG have reviewed and updated the available literature on this important topic (Figure 9) [149, 150]. In the acute setting of UGIB in a patient prescribed a vitamin K antagonist, there is no role

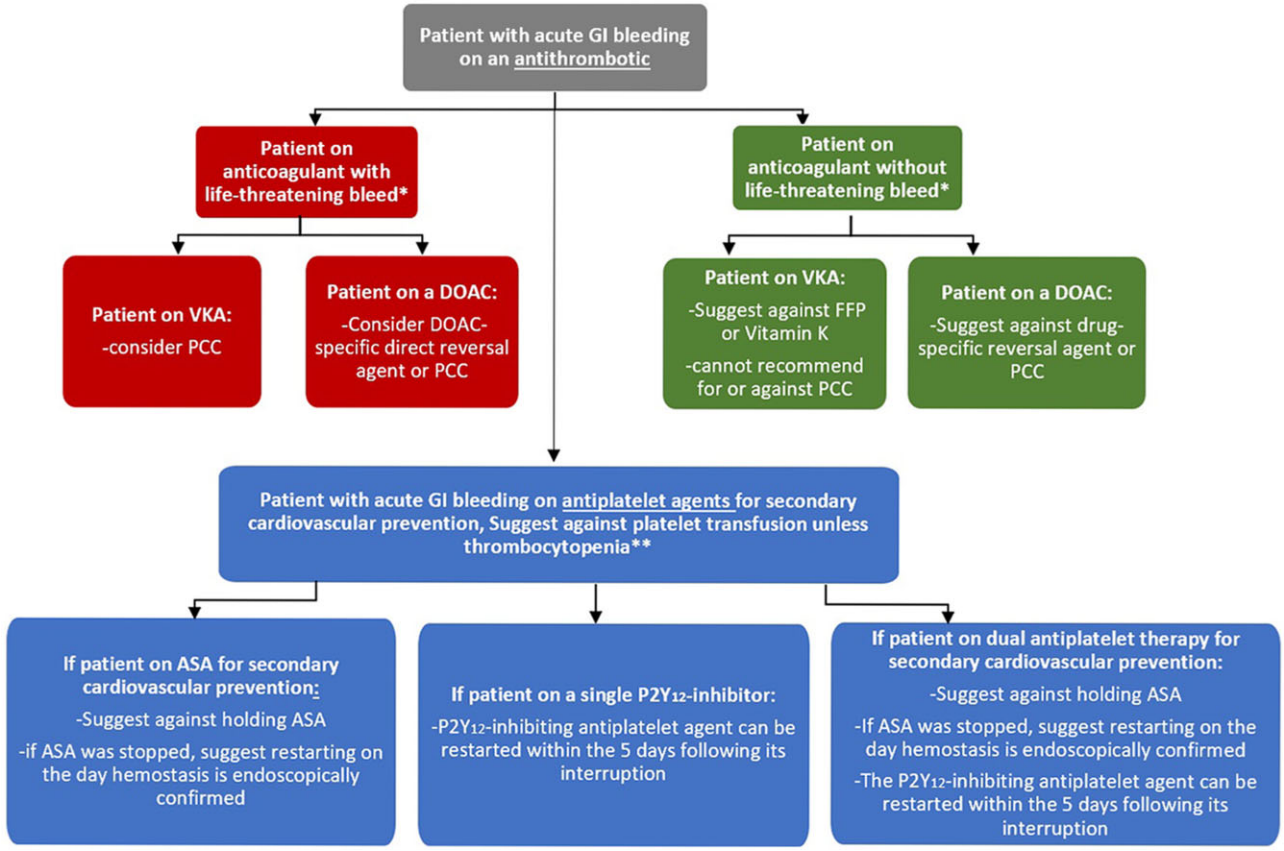

Figure 9. Management of patients on antithrombotics in the setting of acute gastrointestinal bleeding (modified from the study by Barkun *et al.* [150]). *Life-threatening hemorrhage is defined as major clinically overt or apparent bleeding resulting in hypovolemic shock or severe hypotension requiring pressors or surgery or associated with a decrease in hemoglobin of >5 g/dL, requiring transfusion of <5 units of packed red blood cells, or causing death; **defined as <100,000/μL; GI, gastrointestinal; VKA, vitamin K antagonist; PCC, prothrombin complex concentrate; FFP, fresh frozen plasma; DOAC, direct oral anticoagulants; ASA, aspirin.

for the administration of vitamin K because of its delayed onset of action. Similarly, there is no indication for administering fresh frozen plasma because of the potential increased risk of transmission of infectious agents and, even more so, because of the very low certainty of evidence supporting such an approach [149]. No recommendation could be made by the ACG guidelines panel members as to the routine use of prothrombin complex concentrate (PCC) because of insufficient evidence. However, PCC's more rapid and reliable correction of an INR provides a biological rationale for its theoretical efficacy in the setting of acute UGIB, in addition to a decreased required volume of administration when compared with fresh frozen plasma.

The ACG guidelines identified the context of a life-threatening bleed as one for which a separate specific set of recommendations differ from those for a routine patient presenting with an UGIB. Life-threatening hemorrhage is defined as major clinically overt or apparent bleeding resulting in hypovolemic shock or severe hypotension requiring pressors or surgery; or associated with a decrease in hemoglobin of >5 g/dL, requiring transfusion of ≤5 units of packed red blood cells; or causing death [149]. For patients in this clinical situation, PCC administration could be considered as reversal for either a vitamin K antagonist or a direct oral anticoagulant. Also, only in this special situation of a life-threatening hemorrhage should a drug-specific reversal agent be considered in a patient having taken a direct oral anticoagulant within the past 24 hours, despite limited evidence of benefit and high costs.

As for the management of patients receiving antiplatelet agents, among patients with an acute GI bleed prescribed aspirin (ASA) or P2Y12-inhibiting antiplatelet agents, platelet transfusions are not recommended in the absence of thrombocytopenia (<100,000/μL). Indeed, there is a possible increase in mortality with its use in GI bleeding and other medical conditions, as well as a lack of benefit in decreasing further hemorrhage. Among patients with an acute GI bleed on ASA for cardiovascular prevention, ASA should not be held unless given for primary prophylaxis, in which case it should be discontinued. If stopped, the ACG panel members suggested resuming ASA on the day hemostasis is endoscopically confirmed. Supporting evidence for this approach includes a trend for reduced mortality in patients with acute myocardial infarction and peptic ulcer bleeding with ASA continuation [151], as well as a decreased mortality in patients with high-risk ulcer bleeding whose ASA was resumed immediately after endoscopic hemostasis [152]. Although no additional recommendations could be made for patients on a sole P2Y12-inhibiting antiplatelet agents or dual antiplatelets due to lack of evidence, a reasonable approach could be to adopt a strategy similar to that of patients on ASA, or bridge using ASA until the P2Y12-inhibiting antiplatelet agent can be restarted within the 5–7 days following its interruption [47, 153].

With regard to secondary prophylaxis, in patients with previous ulcer bleeding requiring continued cardiovascular prophylaxis with anticoagulant therapy (vitamin K antagonists, direct

oral anticoagulants) or antiplatelet agents, it is suggested to continue PPI therapy for as long as the patient requires the antithrombotic treatment [47, 69].

Conclusions

UGIB continues to be a common medical emergency with significantly associated morbidity and mortality. The last few decades have seen tremendous advances in the management of UGIB including improvement in risk stratification, better understanding of the optimal supportive resuscitative measures, and development of new and improved endoscopic hemostatic tools and less morbid radiological transarterial embolization techniques. Nevertheless, some areas of uncertainty remain, including the optimal risk assessment tool to identify high-risk populations, the optimal therapy for malignant UGIB, and the optimal indication for OTSC in UGIB patients. High-quality research is now needed to answer such important questions.

Authors' Contributions

A.A.A. was responsible for drafting and revising the manuscript; A.N.B. was responsible for drafting and revising the manuscript. Both authors have read and approved the final version of the manuscript.

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Conflict of Interest

None declared.

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