
Endoscopic Therapy for Peptic Ulcer Bleeding

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Abstract

Among the gastrointestinal emergencies, acute upper gastrointestinal bleeding (UGIB) remains a challenging clinical problem owing to significant patient morbidity and costs involved with management. Peptic ulcer bleeding (PUB) contributes to the majority of causes of UGIB with a growing concern of its impact on the elderly and the increasing use of NSAIDs as precipitating bleeding episodes. Apart from initial critical assessment and care, endoscopy remains as the preferred initial management of PUB. Early use of high-dose proton pump inhibitor therapy is cost-effective and reduces the need for endotherapy as well as rebleed rates. Current endoscopic modalities offer a wide range of choices in high-risk PUB (active arterial bleeding or non-bleeding visible vessel). A combination of injection (epinephrine) along with thermal or endoclips therapy offers the best strategy for overall successful clinical outcomes. The role of endotherapy for adherent clots is controversial. A second-look endoscopy may be beneficial in high-risk patients. A multidisciplinary team approach should be part of all treatment protocols for the ideal management of UGIB.

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Peptic ulcer bleeding (PUB) continues to account for 28–59% of all episodes of upper gastrointestinal bleeding (UGIB) [1]. Recent epidemiological estimates show incidence rates for UGIB of about 60 per 100,000 population [2]. Though the prevalence of ulcers related to *Helicobacter pylori* are steadily declining at least in the Western world, these have been overtaken by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) as underlying causes of ulcer. The mortality rate from peptic ulcer disease has continued to rise progressively with age along with complications of perforation and hemorrhage [3]. Much of the increase in the frequency of peptic ulcer disease, particularly gastric ulcer, in the elderly is attributable to the high prevalence of NSAID use in this population. In addition to the use of NSAIDs for inflammatory conditions, increasing numbers of elderly patients take aspirin for cardiovascular and neurologic prophylaxis. Wilcox [4] reported that 65% of patients who had UGIB were taking aspirin or other NSAIDs, often administered without a prescription. In elderly patients, the risk of serious, adverse gastrointestinal events in patients taking non-selective NSAIDs is 5 times that of controls, whereas the risk in younger patients is slightly more than 1.5. Associated comorbidities in the older patient shifts the mortality rates upward approaching 7–10%, thus early diagnosis and treatment remains critical in such patients to best improve outcome [5].

Endoscopy with hemostatic therapy has clearly been shown to aid in proper diagnosis, prognosticate requirement for blood transfusions and in the majority of instances obviates the need

Table 1a. Rockall risk prediction score [12]

Variable	Score			
	0	1	2	3
Age, years	<60	60–79	>79	
Shock	BP >100 mm Hg pulse <100 bpm	BP >100 mm Hg pulse >100 bpm	BP <100 mm Hg pulse >100 bpm	
Comorbidity	none		cardiac disease, any other major comorbidity	renal failure, liver failure, disseminated malignancy
Endoscopic diagnosis	Mallory-Weiss tear, no lesion	all other diagnoses	malignancy of the upper GI tract	
Major SRH	none, or dark spots		blood in the upper GI tract, adherent clot or spurting vessel	

BP = Blood pressure; GI = gastrointestinal; SRH = stigmata of recent hemorrhage; bpm = beats per minute. Clinical score (pre-EGD) = age + shock + comorbidity; Minimal score = 0; Risk category clinical score: low = 0. Complete score (post-EGD) = clinical score + diagnosis + SRH; Maximum score (complete) = 11; Risk category (complete score): low <2, intermediate 3–4; high >5.

for surgical intervention [6–8]. In most management protocols, endoscopy is well accepted as the first-line management tool. This chapter will focus on the role of endoscopic therapy as part of the broader concept of a gastrointestinal bleeding/hemostatic-team-directed management for bleeding peptic ulcers.

Procedural Aspects

Initial Assessment, Evaluation and Preparation of the Patient

Initial assessment and evaluation of the patient starts in the emergency room or at the bedside if the patient bled during hospitalization. Hematemesis and/or melena are the commonest manifestations of UGIB. Significant bleeding results in hemodynamic alterations reflected by resting tachycardia (pulse ≥ 100 bpm), hypotension (systolic blood pressure <100 mm Hg), or postural changes (increase in the pulse ≥ 20 bpm or a drop in the systolic blood pressure of ≥ 20 mm Hg on standing). Clues such as dry mucous membranes, non-distensible neck veins, and decreased urinary output also point towards significant intravascular volume depletion.

Clinical assessment will best determine the fluid requirement needed for hemodynamic stabilization [9]. Large-bore intravenous (IV) access, judicious use of crystalloids; plasma expanders or

Table 1b. Glasgow-Blatchford's score risk prediction score

Admission risk marker	Score
A. Blood urea, mmol/l*	
≥25	6
10–<25	4
8–<10	3
6.5–<8	2
<6.5	0
B. H, g/l	
<100 in men and women	6
100–<120 in men only	3
100–<120 in women	1
120–<130 in men	
≥120 in women	0
≥130 in men	
C. SBP, mm Hg	
<90	3
90–99	2
100–109	1
≥110	0
D. Other markers	
Cardiac failure	2
Hepatic disease	2
Presentation with syncope	2
Presentation with melena	1

Total score: A+B+C+D. Range of scores is from 0 to 23; maximum score is 23, high risk, >0.

* Blood urea conversion: 1 mg/dl equals 0.357 mmol/l.

packed red cells can be dictated by the clinical setting. The use of nasogastric tube lavage is controversial though this might be helpful to prognosticate outcome when visualizing fresh blood and to confirm an upper gastrointestinal source for patients without hematemesis [10]. Erythromycin, a motilin receptor agonist, promotes gastric motility and thereby enhances visualization during endoscopy. A recent cost-effective analysis showed the strategy of administering erythromycin prior to endoscopy for UGIB improves overall cost saving as well as quality-adjusted life years [11].

Early and timely prediction of the outcomes of gastrointestinal hemorrhage poses a major question in clinical management. Poor clinical outcomes are consistently related to advanced age, presence of comorbidities, most notably cirrhosis, renal failure, or cardiopulmonary disease, presence of red hematemesis, hematochezia or bright red nasogastric aspirate, hemodynamic instability and laboratory abnormalities such as coagulopathy and anemia. Several independent risk factors for outcome have been established with reasonable accuracy and validated using clinical, laboratory as well as endoscopic parameters. Some of the primary outcomes measured by these scoring systems have been mortality as determined by the Rockall score (table 1a), recurrent hemorrhage for the Baylor score, and need for clinical intervention for the Glasgow-Blatchford's score (table 1b) [12, 13]. In a recent prospective study of low-risk

Table 2. Endoscopic stigmata of PUB

Endoscopic finding	Risk of rebleeding	Risk of bleeding after endoscopic therapy
High-risk lesions		
Active bleeding	90%	45–50%
Non-bleeding visible vessel		
Adherent clot	50%	20–30%
Low-risk lesions		
Oozing without visible vessel	10–20%	5–8%
Flat spot	5–10%	4%
Clean base	3–5%	1–3%

patients with UGIB, the Glasgow-Blatchford's score outscored the Rockall score in predicting the need for intervention or death. Using this in clinical practice, 68% of patients could be classified as low risk and thereby managed as outpatients [14]. These risk scoring systems, however, have had variable predictive outcomes and it is questionable whether they have been accepted widely into daily clinical practice primarily relating to concerns regarding accuracy, user friendliness and clinical applicability. Nonetheless, it is increasingly recognized that such outcome predictors are needed to best triage patients to further reduce morbidity and mortality secondary to gastrointestinal bleeding.

The site of performing the endoscopy varies between each center depending on the expertise and personnel involved. In high-risk patients who are hemodynamically instable, most centers recommend the ICU setting. Some centers have facilities in the emergency room itself where endoscopy can be performed safely. The advantage of an easy-access mobile endoscopic travel-cart fully equipped with all the necessary accessories in these situations is being increasingly recognized. We prefer to perform endoscopy in the hospital endoscopy suite in low-risk patients or those who have been downgraded from a higher risk category. Further triaging for hospital admission and need for ICU monitoring can be established by the endoscopic findings and outcome of endoscopic therapy, if performed. In the patient with more severe bleeding, a double channel endoscope (therapeutic endoscope) is useful mainly for the purpose of lavage, better visualization, and ability to use the 10-Fr heater probe (HP), although there are no clear data on its advantages. In patients with ulcers located in the posterior wall of the stomach or duodenum, a colonoscope may facilitate endoscopic therapy as the working channel is located on the right side (i.e. 5-o'clock position) [15]. In addition, the channel of the colonoscope allows passing a 10-Fr HP.

Informed written consent is obtained from each patient explaining the risks, benefits, alternatives and the procedure technique including sedation and therapeutic intervention. If the patient is unable to give consent, it is obtained from the legal guardian. The standard of care should follow hospital protocols.

Sedation aims for quieter well-relaxed patients which is important for successful endoscopic therapy. The combination of a narcotic and benzodiazepine is most commonly employed for conscious sedation. Continuous hemodynamic monitoring including oxygen saturation is

Table 3. Modalities available for endoscopic therapy

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1. Injection therapy
 - a. Epinephrine
 - b. Hypertonic saline
 - c. Sclerosant (absolute alcohol, polidoconol)
 - d. Tissue adhesives: cyanoacrylate, thrombin/fibrin glue

 2. Thermal therapy
 - a. Contact: HP, bipolar (gold probe, BICAP)
 - b. Non-contact: APC, Nd:YAG laser

 3. Mechanical therapy
 - a. Endoclips
 - b. Endoscopic band ligation

 4. Dual therapy (combination of above modalities)

mandatory. The administration of conscious sedation has been usually gastroenterologist-directed; however, many centers now use the help of a nurse anesthetist. An anesthesiologist may be considered in high-risk situations where endotracheal intubation may be necessary. The growing use of propofol for moderate sedation is recognized though the role of non-anesthetist administered propofol sedation in acute UGIB is debatable and more data is needed before this can be widely recommended [16].

The stigmata of hemorrhage seen at endoscopy can be classified as (i) high-risk lesions – spurt blood (Forrest grade IA), ooze blood (grade IB), a non-bleeding visible vessel (grade IIA) or adherent clot (grade IIB), or (ii) low-risk lesions are those with a flat, pigmented spot (grade IIC) or clean base (grade III) (table 1; fig. 1–11). Those lesions with high risk (active bleeding or non-bleeding visible vessel) should receive endoscopic therapy as many studies now demonstrate a reduction in rebleeding, the major cause of morbidity and mortality in UGIB [17].

Accessories and Techniques for Endoscopic Therapy

Many techniques are available for effective endoscopic hemostatic therapy. These can be categorized based upon their mechanism of action: (a) injection therapy, (b) thermal coagulation, (c) mechanical therapy, or (d) a combination of these (table 3; fig. 1–11).

Injection Therapy

This form of therapy aims at controlling bleeding by means of hydrostatic tamponading pressure, vasoconstriction, and/or possibly a secondary inflammatory reaction. It is the simplest and commonest used technique. The advantages of this technique are that it is easy to learn and requires only a sclerotherapy needle for implementation. The disadvantages are that the area injected should be accurate for best results or, if not well placed, could mask the visible area for treatment. Also, the effects are short lasting, as the injected fluid gradually dissipates [18].

Commonly used forms of injection therapy include: (1) Epinephrine, this is diluted (1:10,000) and administered through a 25-gauge retractable sclerotherapy needle. Volumes of

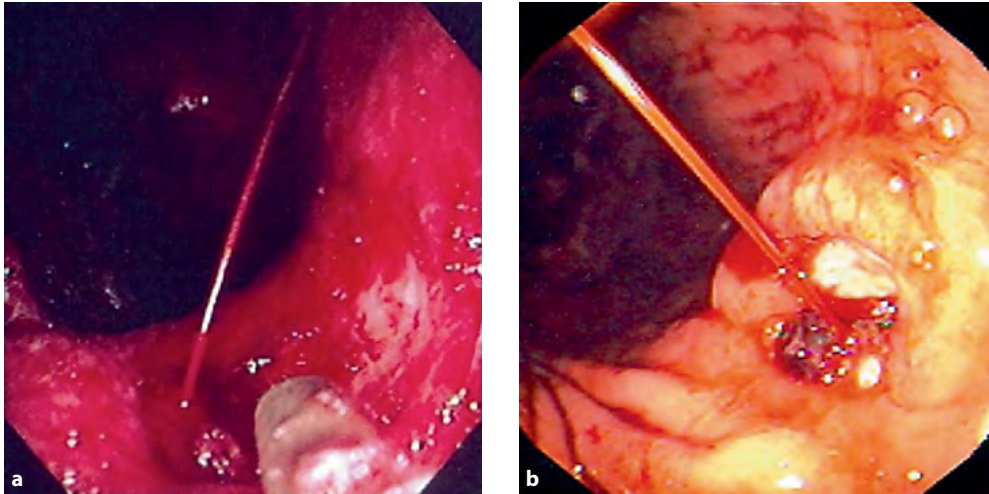


Fig. 1. Spurting ulcer. **a** Active spurting from a large ulcer on the angularis. The 10-Fr HP is seen exiting the endoscope channel. **b** Active spurting from a benign-appearing gastric ulcer on the angularis.

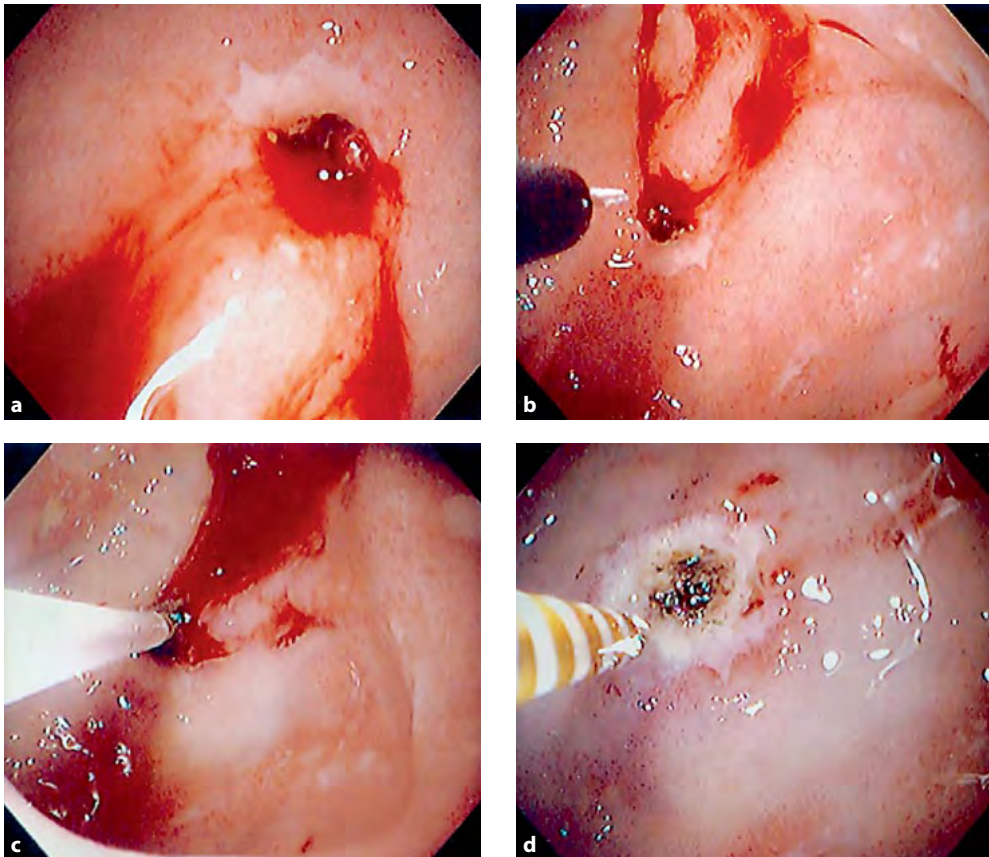


Fig. 2. Oozing visible vessel. **a** Oozing lesion seen in the anterior duodenal bulb with a fleshy component inferiorly. **b** The injection needle is exiting the channel of the diagnostic endoscope. **c** 3 cc's of dilute epinephrine are injected. **d** Black eschar (footprint) after endoscopy thermal therapy with the Bicap probe.

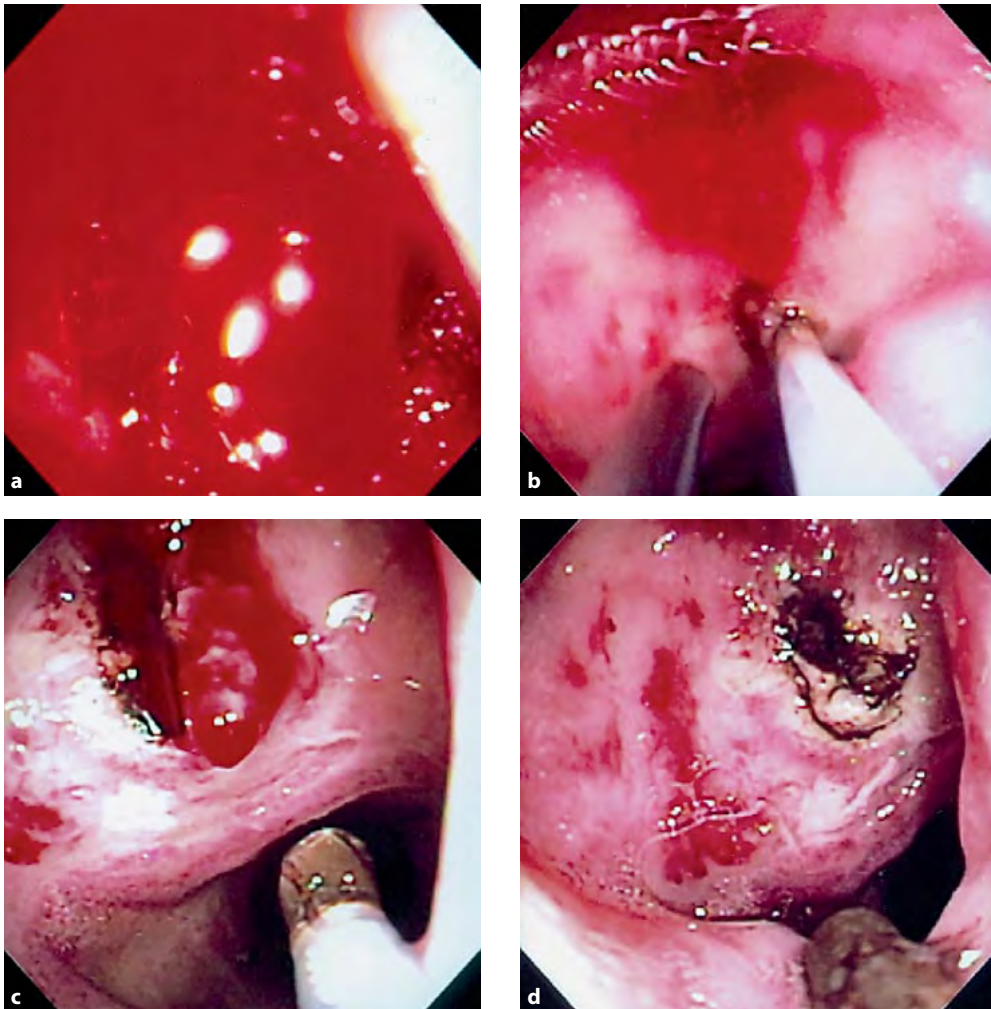


Fig. 3. Active bleeding. **a** Large amount of fresh blood in the duodenal bulb. After washing the lesion, the bleeding source was identified. **b** Both injection and endoscopic therapy are applied to arrest bleeding. **c** 10-Fr thermal probe exiting the therapeutic channel of the therapeutic endoscope. Partial therapy provided as a visible vessel is still present. **d** Further pulses of thermal therapy applied to the bleeding lesion.

up to 35–45 ml may be given in increments of 0.5 to 1.5 ml targeting four quadrants of the ulcer. Park et al. [19] showed that larger volumes (35–45 ml) were more effective in providing hemostasis as compared to standard volumes (15–25 ml) though there are no clear guidelines as to the ideal volume required. (2) Non-constrictive agents such as distilled water, normal or hypertonic saline, 50% dextrose. Studies show an initial hemostasis rate comparable to epinephrine; however, when compared to hemoclips the recurrent bleeding rates are generally higher in the injection group. These agents work by their local compressive action. (3) Other agents which include sclerosants such as ethanol and polidocanol have been used but side effects such as tissue necrosis have resulted in complications including even perforation. Tissue adhesives (cyanoacrylate) and fibrin glue are other injectable solutions which have yielded variable results.

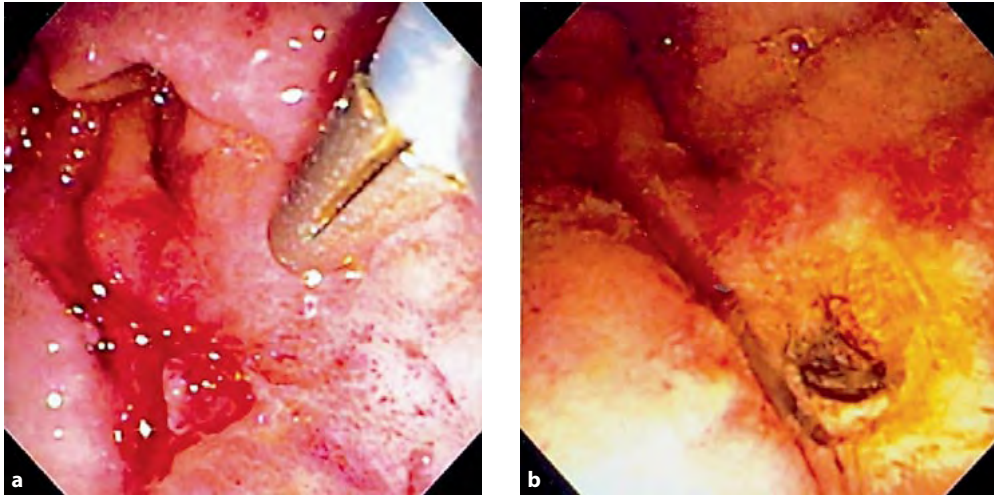


Fig. 4. Non-bleeding visible vessel on the inferior margin of a sphincterotomy site. **a** The 7-Fr probe is used to ablate the area resulting in a large footprint. **b** Mucosal depression resulting from multiple pulses with the thermal probe.

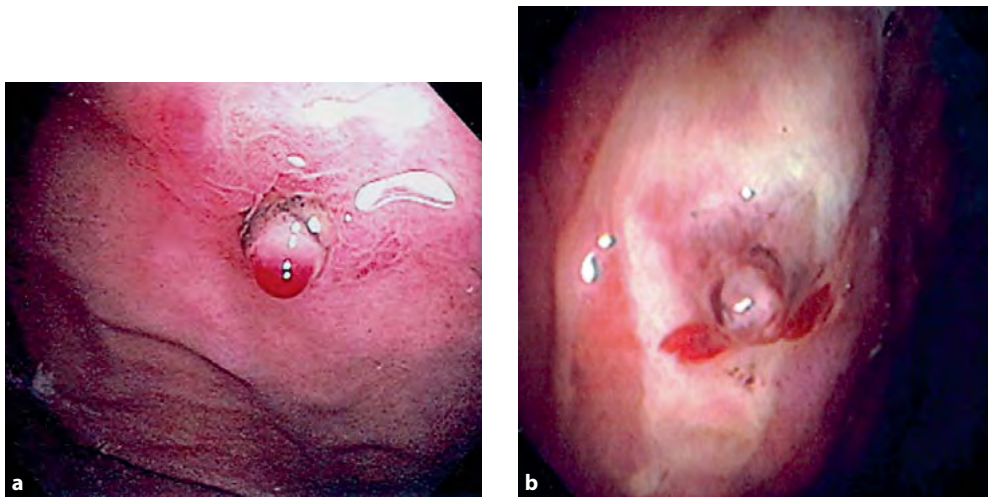


Fig. 5. Non-bleeding visible vessel. **a** Nipple-like projection on the angularis. No underlying ulcer is obvious. **b** Nipple-like projection from the base of a large gastric ulcer.

Thermal Coagulation

Thermal forms of therapy can be classified as either (a) contact or (b) non-contact.

Contact Therapies. These ensure appositional pressure resulting in a heat-sink effect in addition to tissue coagulation with contraction of blood vessels. These include the bipolar probe or the HP which can weld arteries (coaptive coagulation) as large as 2.5 mm in diameter in controlled laboratory conditions [20].

The two available bipolar probes include the Gold Probe (Microinvasive, Boston Scientific Corp., Natick, Mass., USA) and the BICAP or bipolar circumactive probe (Circon-ACMI,

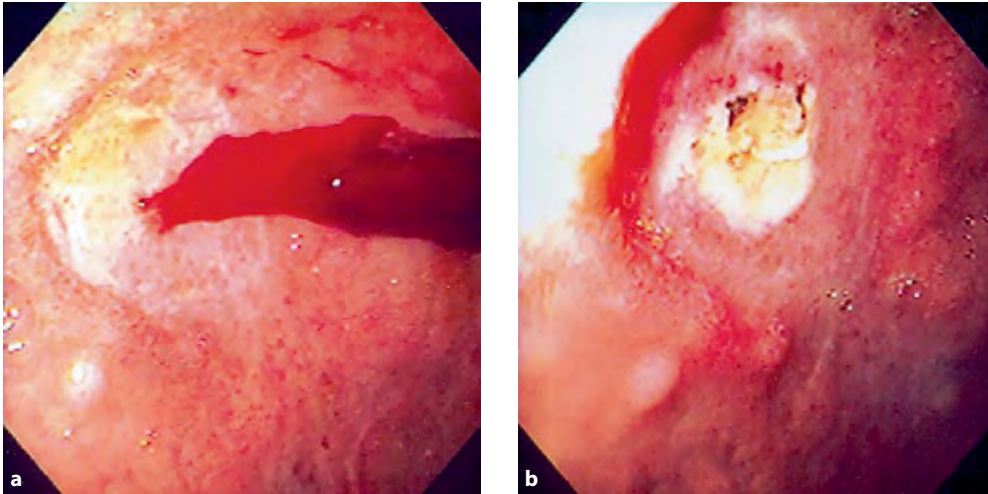


Fig. 6. Oozing lesion. **a** Oozing from a ulcer in the duodenal bulb. **b** After washing, no raised lesions are apparent. Thermal therapy was given.

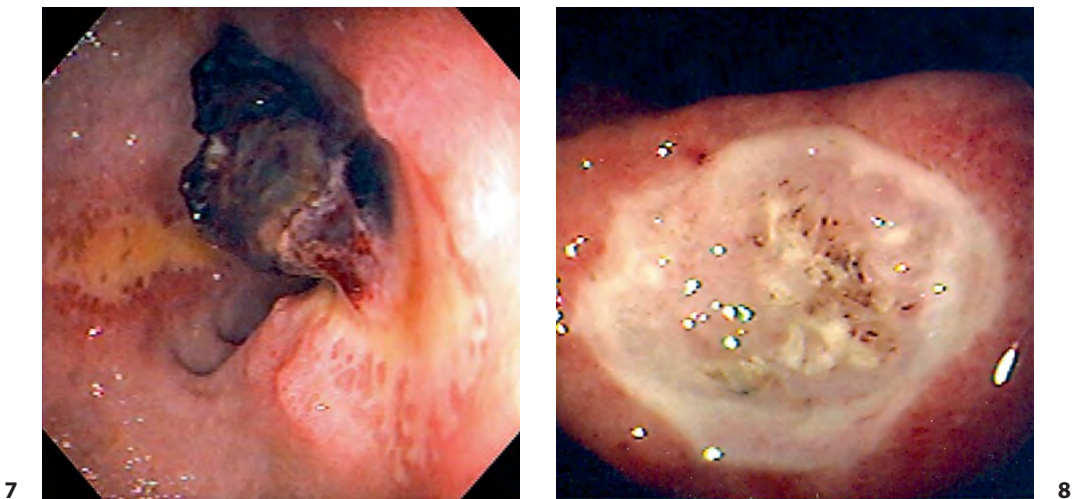


Fig. 7. Large clot extending from the base of a duodenal ulcer posteriorly. Small ulcers are also present in the bulb. **Fig. 8.** Multiple spots on a benign-appearing gastric ulcer.

Stamford, Conn., USA). The probes are available in diameters of 2.4–3.2 mm and have alternating positive and negative electrodes which concentrate diathermic coagulation concentrated around the tip providing lesser depth of tissue injury and lower risk for perforation. A central opening provides for working via a foot pedal-operated irrigation pump. Simultaneous injection can be provided through the same catheter. The probe is forcefully opposed directly on the major stigmata of bleeding and pulse treatment of 5–10 s with a power of 10–15 W are applied until target coagulation is achieved.

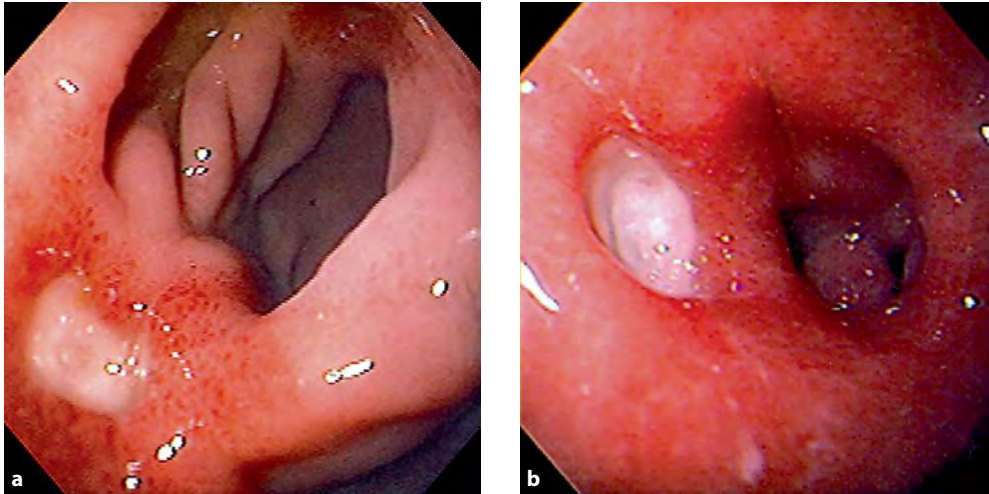


Fig. 9. Clean-based lesions. **a** Clean-based ulcer in the duodenal bulb. **b** Benign-appearing clean-based ulcer in the antrum in a patient using aspirin.

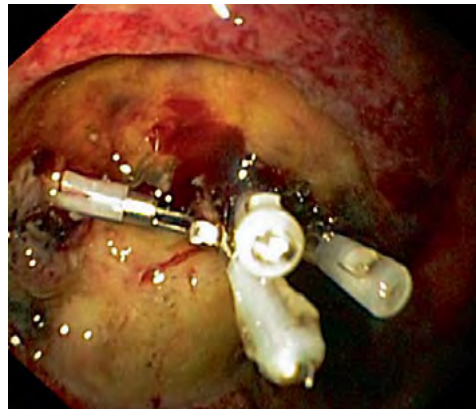


Fig. 10. Bleeding ulcer with visible vessel. Successful deployment of endoclips to achieve hemostasis.

The HP (Olympus, Tokyo, Japan) uses a simple heating device in a Teflon-coated hollow aluminum cylinder with an inner coil rather than electric current. The heat generated can be given directly or tangentially by the distal tip. Probes are available in diameters of 2.3–3.2 mm. The probe temperature can rise up to 250°C (482°F). Four to five bursts of energy of 30 J/pulse are applied for adequate coagulation.

Non-Contact Therapies. The use of Nd:YAG laser for endotherapy is rarely used today primarily owing to the increased depth of coagulation resulting in high rates of perforation as well as the excessive maintenance costs. The underlying mechanism of action is the conversion of light to heat energy by the directed beam which coagulates the bleeding site.

Argon plasma coagulation (APC) as a non-contact thermoblative technique is now available at many endoscopic units. It has advantages of being safe given the depth of penetration (<1 mm) and relative ease of use. There are disadvantages though of providing only superficial coagulation which may thus miss larger deeper vessels.

Mechanical Therapies

The endoscopic mechanical modality currently available is the hemoclip which are metallic devices designed to grasp the mucosa, seal and approximate vessels without interfering with underlying mucosal regeneration and healing [21]. They need precise deployment since inadvertent clipping of only the tip of the vessel can result in potentiating or initiating vigorous bleeding. End on clipping with axial push of surrounding tissue results in better anchoring is preferred over tangential clipping slipping on fibrotic ulcer bases. Difficult areas such as the gastric fundus, lesser curve and posterior duodenal bulb present challenging territories for effective application. Similarly, clipping in the setting of underlying coagulopathy can also aggravate bleeding. Most clips slough off within days or weeks of deployment and may vary based upon the type of clip.

Current available hemoclips available are (a) QuickClip 2, Olympus USA, Corp. which is a rotatable clip device produced in two sizes (opening width of 8 or 12 mm), (b) Resolution Clip, Boston Scientific, Inc. which cannot be rotated but can be reopened after closure if repositioning is required (opening width of 11 mm), (c) TriClip, Wilson Cook, Inc. is a three-pronged endoclip (opening width of 12 mm) and (d) Inscope (Ethicon Endosurgery Inc.) multclip applicator with four endoclips (opening width of 14 mm). Jenson et al. [22] studied the hemostatic capability of the three aforementioned clips in a randomized canine model for bleeding ulcers and showed that all had an initial success rate of 100% with long-term retention rate higher in the resolution clip group.

Endoscopic Combination Therapy

Endoscopic therapy using a combination of the above-discussed methods is favored to monotherapy alone considering the theoretical additive effect of each modality and given the different mechanisms of action of each technique.

Outcomes of Endoscopic Therapy

In a multicenter trial, Rutgeerts et al. [23] studied the effects of single and multiple injections of fibrin glue and polidocanol. Repeated fibrin glue had more benefit in reducing the rebleed rates as compared to single injection of fibrin or polidocanol though the final outcome of rebleed was similar in all the groups. Their use has generally been declining owing to the difficulty in their administration and costs.

Comparative data between the heater and bipolar probes show different outcomes. In the study by Hui et al. [24], 91 patients were randomized to YAG laser, HP or bipolar coagulation. Recurrent bleeding rates were 10% for bipolar probe, 19% for HP and 10% for YAG laser coagulation. Need for surgery was higher in the HP group (13%) as compared to 7% in either of the other groups. In another prospective randomized study of 80 patients, Lin et al. [25] compared HP with bipolar coagulation and demonstrated a permanent hemostasis rate of 92% with the HP and 85% in the bipolar group. Chung et al. [26] compared these HP therapy with adrenaline and reported no difference between the groups with regard to transfusion requirement (4.5 vs. 3.8 units), emergency surgery (20 vs. 22%), hospital stay (8 vs. 7 days), and mortality (2 vs. 4) initial control of bleeding, rebleeding and mortality. In a randomized trial of 185 patients, APC was compared with HP (both groups received epinephrine injection). There was no significant difference between these two endoscopic techniques in achieving initial hemostasis as well as rebleeding rates, blood transfusion requirements, length of hospital stay and mortality [27]. The Cochrane review, which included this study in addition to one comparing APC with

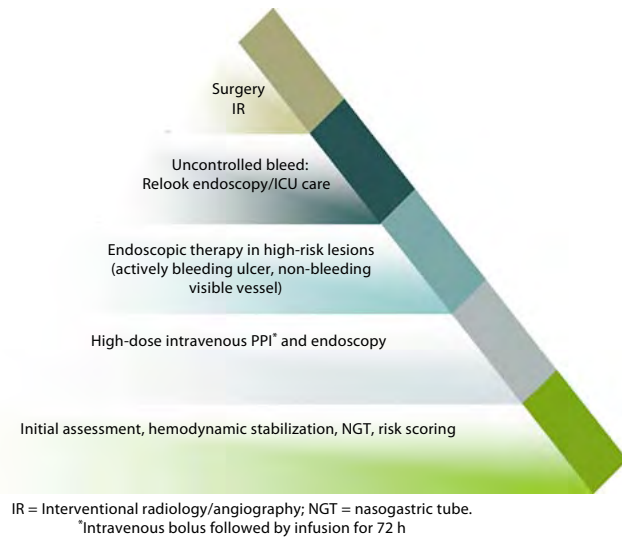


Fig. 11. The PUB pyramid [56].

sclerotherapy, concluded that there was no evidence to suggest that APC was superior to other endoscopic therapies [28].

Cipolleta et al. [29] studied the use of hemoclips initially for bleeding peptic ulcers where they were compared to HP thermocoagulation. They reported a lower risk of recurrent bleeding in the hemoclip group (1.8%) versus the heater group (21%). The efficacy of clips however was limited by difficulty in successful deployment as evidenced in separate trials by Lin et al. [30] and Gevers et al. [31]. A recent meta-analysis showed that the rate of initial hemostasis was insignificantly increased in the control group compared with the hemoclip group (92 vs. 96%) (odds ratio [OR] 0.58, 95% confidence interval [CI] 0.19–1.75). The rebleeding rate was decreased with hemoclips compared with controls (8.5 vs. 15.5%) (OR 0.56, 95% CI 0.30–1.05), though this was not statistically significant. Current evidence from meta-analyses and randomized controlled trials suggests that the hemoclip is equivalent to other endoscopic modalities in terms of initial hemostasis, rebleeding rates, emergency surgery, and mortality for treatment of PUB [32]. Newer mechanical devices such as endoscopic suturing, loops and stapling hold promise but await future trials.

The benefits of dual therapy have been studied in several trials with most studies offering an additional hemostatic therapy to epinephrine injection. The Cochrane database systematic review included 17 studies with 1,763 patients [33]. A second procedure reduced further the bleeding rate from 18.8 to 10.4% (OR 0.51), and need for emergency surgery from 10.8 to 7.1% (OR 0.63). The mortality fell by half from 5 to 2.5% (OR 0.50). They concluded that there was improvement after combination therapy with epinephrine regardless of the choice of modality. These findings were similar to a previous meta-analysis by Calvet et al. [34], though another study by Marmo et al. [35] addressing dual vs. monotherapy in high-risk ulcers suggested that single endoscopic treatment by means of thermal probes or clips (non-injection-based monotherapies) is as effective as dual treatments and probably safer. These results encourage the endoscopist to use more than one modality other than injection alone especially in high-risk ulcer bleeds.

The role of endoscopic therapy in non-bleeding ulcers with adherent clots is still controversial. The fear of dislodging a stable clot provoking bleeding has been of concern. In a meta-analysis by Kahi et al. [36] of 6 studies (240 patients) where the clot was removed, subsequently

performed endoscopic therapy was shown to be superior to medical therapy alone in decreasing rebleeding rates (relative risk [RR] 0.35, 95% CI 0.14–0.83) while the results were comparable with other outcomes such length of hospital stay, need for surgery, transfusion requirements or mortality.

The recent combined meta-analysis broadly outlines the effectiveness of various therapy modalities for bleeding ulcers [37]. The authors concluded that endoscopic therapy was effective for active bleeding (RR 0.29, 95% CI 0.20–0.43) and a non-bleeding visible vessel (RR 0.49, 95% CI 0.40–0.59). Clearly, dual therapy was more beneficial than epinephrine alone (table 4). These results are echoed by another systematic review [38].

Limitations and Complications

Complications of endoscopic therapy are limited including aspiration pneumonia and perforation. A pooled analysis for all these modalities revealed a complication rate of 0.5% (95% CI 0.4–0.8) [37]. Clips and epinephrine had the lowest rates of perforations while the HP group had the highest. Endoscopic therapy is limited by factors such as an unstable patient, poor sedation, inadequate visualization due to blood, difficult areas of reach such as the posterior wall of duodenum, junction between the first and second part of duodenum, and lesser curve.

Post-Procedure Care

Patients with hemodynamic unstable acute gastrointestinal bleeding are usually managed in the ICU till they are stabilized. Close monitoring with serial hemoglobin levels are required thereby assessing the patient for downgrading to onward transfer to the ward and then on for discharge. Despite initial success, rebleeding occurs in 10–20% of patients, directly or indirectly related to the size or site of ulcer, associated comorbidities, technical difficulties and endoscopic expertise. Further rebleeding is documented by any further changes in stools and color, vital signs and hematocrit keeping in mind laboratory variability. The benefit of a second-look endoscopy was evaluated by Chiu et al. [39]. They found several predictors for peptic ulcer rebleeding by logistic regression analysis including: American Society of Anesthesiologists (ASA) grade III or grade IV status (OR 3.81, 95% CI 1.27–11.44), ulcer size >1.0 cm (OR 4.69, 95% CI 1.60–13.80), and a finding of persistent stigmata of recent hemorrhage at the scheduled second endoscopy (OR 6.65, 95% CI 2.11–20.98). In the meta-analysis by Marmo et al. [40], they concluded that a systematic second-look endoscopy with retreatment significantly reduced the risk of recurrent bleeding compared to controls, although such an approach did not substantially reduce the need for subsequent surgery or mortality.

The role of Doppler ultrasound has been shown to help in guiding the use and predicting the failure of endoscopic therapy of PUB especially in high-risk patients [41]. Further studies are required to show the beneficial cost-effectiveness of these endoscopic tools and such trials are underway.

Acute PUB in anticoagulated patients requires optimal management even though there are no clear guidelines available due to lack of prospective trials. Therapy should therefore be addressed on an individual case-by-case basis requiring normalizing or targeting the INR to <1.6 with fresh-frozen plasma and/or vitamin K. This includes discontinuing the anticoagulant such as warfarin, coumadin, aspirin or antiplatelet agents. A combination endoscopic therapy will be preferred than a monotherapy. The timing of resuming anticoagulation is controversial due to

lack of clear data and would have to be decided depending on the underlying medical condition and the overall patient's clinical and endoscopic characteristics [42].

Concurrent Medical Therapy

Acid Suppression

The rationale for acid suppression stems from the fact that gastric juice is an anticoagulant by decreasing platelet aggregation (even disintegration), promoting clot lysis due to pepsin activating by acid, and further increasing the fibrinolytic activity that is impaired. Based on in vitro and animal data, a pH of 6–6.5 is targeted to reverse these effects and maintain clot stability. Proton pump inhibitors (PPI) are effective in maintaining the gastric pH above 4.0 though recent studies cast doubt on their ability to maintain a gastric pH of 6 or more [43]. Khuroo et al. [44] initially showed the efficacy of oral omeprazole (40 mg twice daily for 5 days) compared to placebo in a randomized trial of 220 patients from India. Acid suppression prevented recurrent bleeding in patients with ulcers who had stopped bleeding spontaneously. Lau et al. [45] randomized patients to receive high-dose IV omeprazole (bolus of 80 mg followed by an infusion 8 mg/h). Rebleeding rates within the first 3 days were 4.2% in the omeprazole group compared to 20% in the placebo group, while rebleeding within 30 days was 6.7 vs. 22.5% respectively ($p < 0.001$). Similarly, the need for surgery and 30-day mortality were significantly reduced in the PPI group. Sung et al. [46] clearly demonstrated that a combination of endoscopic therapy with omeprazole IV infusion was better than omeprazole alone with regard to 30-day rebleeding rates, requirement for blood transfusions and 30-day mortality. Current data shows that IV PPI provides more rapid increase in gastric pH, reaching a mean pH of 6 approximately 1 h sooner than oral PPI [47]. The Cochrane meta-analysis which included 24 trials (4,373 patients) concludes that the use of PPI significantly decreased rebleeding (OR 0.40, 95% CI 0.24–0.67), need for urgent surgery (OR 0.50, 95% CI 0.33–0.76), and the risk of death (OR 0.53, 95% CI 0.31–0.91) [48].

Timing of Acid Suppression

The use of PPI prior to endoscopy accelerates resolution of signs of bleeding in ulcers [32, 39]. In a randomized trial of 638 patients [49], one group received a high-dose IV bolus followed by omeprazole infusion, while the other group, placebo was followed by endoscopy the next morning. The infusion group had a significantly lower number of patients who required endoscopic therapy than placebo (23 vs. 37% $p = 0.007$) though there were no differences in outcomes of rebleeding rates, requirement of blood transfusions or mortality. These findings were supported by a Cochrane meta-analysis by Dorward et al. [50] showing the usefulness of early PPI therapy in downstaging stigmata of recent hemorrhage at index endoscopy. In a cost-effective analysis, PPI reduced the need for endoscopic therapy by 7.4% and resulted in a lower cost-effectiveness ratio per endoscopic therapy averted (USD 3,561) than placebo (USD 4,117) [51]. In the meta-analysis by Laine and McQuaid [37], PPI therapy as an adjunct after endoscopic hemostatic therapy was examined in three groups: (1) IV PPI (bolus + continuous infusion) vs. placebo, (2) IV PPI (bolus + continuous infusion) vs. H_2 receptor antagonists, and (3) oral or intermittent IV bolus vs. placebo. They concluded that PPI after endoscopic therapy reduced rebleeding, need for surgery, need for urgent intervention and mortality. The results were most consistent for bolus followed by continuous IV PPI infusion for 72 h. This data is further corroborated by

Table 4. Summary of meta-analyses of randomized controlled trials for endoscopic therapy in PUB (adapted from Laine et al. [37])

Study description	Endoscopic hemostatic technique	Number of studies compared for meta-analyses	Outcomes, RR (95% CI)			
			further bleeding	surgery	urgent Intervention	mortality
Meta-analyses for endoscopic hemostatic therapy versus no endoscopic therapy						
Thermal (HP, BPEC) vs. no endoscopic therapy	thermal therapy	2–3	0.44 (0.36–0.54)	0.39 (0.27–0.55)	0.50 (0.37–0.66)	0.58 (0.34–0.98)
Epinephrine + thermal contact vs. no endoscopic therapy	injection + thermal therapy	13–15	0.10 (0.03–0.40)	0.71 (0.19–2.62)	0.16 (0.04–0.69)	0.80 (0.27–2.37)
Sclerosant vs. no endoscopic therapy	injection therapy	3	0.56 (0.38–0.83)	0.24 (0.09–0.64)	0.65 (0.43–0.98)	0.18 (0.05–0.68)
Epinephrine + Sclerosant vs. no endoscopic therapy	injection therapy	6	0.60 (0.36–1.00)	0.61 (0.22–1.73)	0.62 (0.45–0.86)	0.80 (0.40–1.61)
Meta-analyses for epinephrine only versus other monotherapy and epinephrine dual therapy						
Monotherapy (BIPEC, fibrin glue, clip) vs. epinephrine	injection, thermal, mechanical	2–3	0.58 (0.36–0.93)	0.44 (0.20–0.98)	0.73 (0.44–1.21)	0.37 (0.10–1.37)
Epinephrine + second therapy (HP, BPEC, sclerosant, thrombin, clip vs. epinephrine)	injection, thermal, mechanical	4–7	0.34 (0.23–0.50)	0.33 (0.17–0.66)	0.39 (0.24–0.62)	0.52 (0.23–1.16)
Clips vs. epinephrine	mechanical, injection	2	0.22 (0.09–0.55)	0.22 (0.06–0.83)	NA	1.68 (0.23–12.45)
Clips vs. other therapy (HP, epinephrine + BPEC, sclerosants, epinephrine)	mechanical, thermal, injection	2–4	1.312 (0.36–4.75)	0.85 (0.32–2.26)	1.17 (0.09–14.46)	1.16 (0.38–3.52)

HP = Heater probe; BPEC = bipolar electrocoagulation.

a recent multicenter worldwide study examining the use of IV esomeprazole bolus 80 mg followed by 8 mg/h infusion over a 72-hour period versus placebo in patients following successful endoscopic hemostasis for PUB. At 72 h, fewer patients receiving IV esomeprazole had recurrent bleeding compared to placebo (5.9 vs. 10.3%), and the difference in rebleeding remained significant at 7 days. Endoscopic retreatment was also reduced from 11.6 to 6.4% significantly within 30 days of primary therapy. The data may be slightly skewed for more patients being *H. pylori* positive (approximately 70% of the treated group) and therefore further studies should confirm the similar efficacy in *H. pylori*-negative patients [52].

H. pylori Eradication

Several studies have conclusively shown the benefit of *H. pylori* eradication in reducing the rate of bleeding peptic ulcer [53]. Appropriate testing and treatment is a cost-effective strategy despite the low prevalence in the developed world. The rapid urease test in the setting of active bleeding has a lower sensitivity as compared to other tests such as the ¹³C breath test, serology or histology. The use of PPI also decreases the sensitivity of the CLO test, breath test and stool antigen test [54]. It is unknown how many days of PPI treatment are needed before the tests become less accurate [55]. Histology examining for chronic active gastritis is a reliable marker *H. pylori* infection which is not influenced by PPI therapy.

Conclusion

Endoscopy has clearly defined its role in the primary management of acute PUB which is by far the most important cause of UGIB. Initial triage and assessment obtained at the time of endoscopy form the base for initiating further treatment. We can to a large extent predict the outcomes and risk stratify by using clinical and endoscopic information. Early endoscopy is indicated in all high-risk patients. Empiric early use of PPI therapy with high-dose bolus and subsequent infusion prior to endoscopy may decrease bleeding stigmata and need for endoscopic therapy. A combination of PPI therapy along with endoscopic therapy offers the best hemostatic results. Endoscopic therapy should be used for all ulcers with active bleeding and non-bleeding vessels. Among the endoscopic therapies, epinephrine should not be used alone, while other treatments including thermal, injection or mechanical clips have all shown efficacy in controlling bleeding. Combinations of epinephrine injection along with either mechanical or thermal methods may be preferable to a single therapy approach although further studies may be needed. The role of endoscopic therapy in adherent clots is still uncertain, although intensive PPI therapy may be sufficient in this setting. PPI infusion must be continued after endoscopic therapy for at least 72 h before switching to oral therapy. *H. pylori* should be sought for, treated, and eradication confirmed by subsequent testing.

Recent advances in pharmacotherapy as well as endotherapy have favorably changed the management strategies for PUB. Endotherapy forms the basis for any further intervention, be it surgery or interventional radiology, thereby stressing the importance of a multidisciplinary targeted approach. All of these improvements together pave the way for future newer modalities and trials to help further improve outcomes while reducing costs in UGIB treatment.

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