Management of Upper Gastrointestinal Bleeding

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Upper gastrointestinal bleeding secondary to ulcer disease is common and results in substantial patient morbidity and medical expense. After initial resuscitation to stabilize the patient, carefully performed endoscopy provides an accurate diagnosis and identifies high-risk ulcer patients who are likely to rebleed with medical therapy alone and will benefit most from endoscopic hemostasis. For patients with major stigmata of ulcer hemorrhage—active arterial bleeding, nonbleeding visible vessel, and adherent clot—combination therapy with epinephrine injection and either thermal coagulation (multipolar or heater probe) or endoclips is recommended. High-dose intravenous proton pump inhibitors are recommended as concomitant therapy after successful endoscopic hemostasis. Patients with minor stigmata or clean-based ulcers will not benefit from endoscopic treatment and should receive high-dose oral proton pump inhibitor therapy. Effective medical and endoscopic management of ulcer hemorrhage can significantly improve outcomes and decrease the cost of medical care by reducing rebleeding, transfusion requirements, and the need for surgery.

Introduction

Upper gastrointestinal (UGI) bleeding occurs frequently and is a common cause of hospitalization or inpatient bleeding. Such bleeding results in substantial patient morbidity, mortality, and medical care expense. Ulcer disease is the most common cause of severe UGI hemorrhage, causing about 40% to 50% of cases, and UGI bleeding is the most common complication of peptic ulcer disease [1]. Although other nonvariceal conditions such as Mallory-Weiss tear, angiodysplasia, watermelon stomach, or Dieulafoy's lesion may also cause UGI hemorrhage, these occur much less often [2]. This article will review important aspects of the management of UGI bleeding secondary to ulcers.

Initial Approach to the Patient

The initial management of the patient with UGI bleeding should include evaluation of the severity of the hemorrhage, patient resuscitation, a brief medical history and physical examination, and consideration of possible interventions [1]. Clinical assessment should focus on the patient's hemodynamic state, with a view to early resuscitation. Initial medical therapy should be aimed at restoring blood volume by fluid replacement to ensure that tissue perfusion and oxygen delivery are not compromised. Airway protection with endotracheal intubation to prevent aspiration should be strongly considered in patients with ongoing hematemesis, altered mental or respiratory status, or severe neuromuscular disorders [1,2].

Intravenous erythromycin (a motilin receptor agonist that stimulates gastrointestinal motility) improves the quality of endoscopic examinations in patients with UGI hemorrhage by promoting the emptying of intragastric blood. A recent cost-effectiveness study confirmed that giving intravenous erythromycin before endoscopy for acute UGI bleeding resulted in cost savings and an increase in quality-adjusted life-years [3]. Because of these benefits, intravenous erythromycin before endoscopy is recommended for patients with UGI hemorrhage.

After initial resuscitation and initiation of medical therapy, urgent endoscopy is preferred for diagnosis and treatment because of its high accuracy and low complication rate. Endoscopy using large single-channel or double-channel therapeutic endoscopes is diagnostic in about 95% of patients with severe UGI bleeding. Endoscopy may also reveal stigmata of recent hemorrhage on ulcers, with important prognostic value, helping to triage patients into low-risk and high-risk. Some stigmata are associated with increased rebleeding, and patients without stigmata of hemorrhage rarely rebleed. By consensus, stigmata are divided into either active bleeding (arterial spurting or oozing) or recent hemorrhage (nonbleeding visible vessel [NBVV]), overlying clot without oozing, or flat, dark slough or spots) [1]. Analysis of randomized controlled trials from the Center for Ulcer

Research and Education (CURE) shows that medically treated patients have different rebleeding rates according to their stigmata of ulcer hemorrhage. Without endoscopic therapy, the rebleeding rate of ulcers with active arterial bleeding is 90%, the rate with NBVV is 50%, and the rate with nonbleeding, adherent clots is 33% [1]. Rebleeding rates are much lower for ulcer with oozing (10%), flat spots (7%), or clean bases (3%). Based on the high rebleeding rates with medical treatment alone, endoscopic therapy is recommended for all patients with active arterial bleeding, NBVV, or adherent clots. Persistent oozing also may be treated endoscopically, although rebleeding occurs less frequently. A large US multicenter trial illustrates the prevalence of these stigmata. Of 4090 hospitalized patients (2033 with duodenal ulcer and 2057 with gastric ulcer), 10.3% had active bleeding (arterial or oozing), 12.2% had NBVV, 8.3% had adherent clot, 9.9% had flat spot, and 58.4% had a clean ulcer base [4].

Newer techniques such as endoscopic Doppler ultrasound may provide more objective findings in patients with ulcer hemorrhage. Reports have suggested substantial interobserver disagreement in the interpretation of endoscopic stigmata of recent hemorrhage. The use of Doppler ultrasound has shown that some visible vessels do not demonstrate an arterial signal, whereas some ulcers with a clean base or pigmented spot show an arterial signal. Persistence of a positive Doppler signal after endoscopic treatment correlates with rebleeding, suggesting that endoscopic ultrasound may also be a useful guide to the completion of hemostasis if treatment is continued until the underlying blood-flow signal is extinguished [5]. A recent decision analysis comparing Doppler-based management of acute ulcer hemorrhage with standard treatment showed an average cost savings ranging from $560 to $1160 per patient in the Doppler-directed group [6•].

Medical Management

The main goals of medical management are reduction of morbidity, mortality, risk of rebleeding, transfusion needs, duration of hospitalization, and need for interventions (endoscopy, angiography, or surgery). Histamine H_2-receptor antagonists (H_2RAs), somatostatin and its analogues, and proton pump inhibitors (PPIs) have been the most extensively studied agents used in the medical management of nonvariceal UGI bleeding.

The use of acid-reducing medications is based on studies showing that acid and pepsin interfere with the hemostatic process of ulcers and nonvariceal UGI lesions. In vitro studies have demonstrated that an acid environment adversely influences both the intrinsic and extrinsic pathways, acid inhibits platelet aggregation, and acid affects pepsin activity, with maximal clot lysis at pH 2 but limited effect at pH above 5 [7]. These results suggest that increasing intragastric pH to greater than 6 could improve the coagulation process. Because clinical trials have shown that ulcer rebleeding occurs mainly during the first 72 hours, acid suppression should be maintained for at least 72 hours after hemostasis.

Although H_2RAs were the first medications available to inhibit acid secretion, the results of both pharmacokinetic studies and clinical trials do not support their use for the medical management of nonvariceal UGI bleeding. Intravenous H_2RAs are ineffective in maintaining a sustained high gastric pH because tolerance develops within 12 hours of the infusion [8].

Somatostatin or octreotide may have theoretical advantages (decreased splanchnic blood flow and secretion of gastric acid and pepsin, with stimulation of mucus production), but there is no firm evidence to recommend them over PPI therapy for nonvariceal UGI hemorrhage.

PPIs reduce both basal and stimulated acid secretion by inhibiting H^+,K^+-ATPase, the proton pump of the parietal cell. Several studies have shown that the infusion of PPIs provides sustained, high intragastric pH [9] and that an omeprazole infusion (80 mg bolus followed by 8 mg/h) can maintain intragastric pH steadily above 6 over a 72-hour period [10] without the development of tolerance. In the United States, the only PPIs available in an intravenous formulation are pantoprazole and esomeprazole.

Several randomized controlled trials have demonstrated the efficacy of high-dose PPI infusion for 3 days after successful endoscopic treatment of patients with bleeding ulcers and high-risk stigmata of hemorrhage [11,12]. Lau and coworkers [12] showed that after primary hemostasis had been achieved by endoscopic coagulation, high-dose omeprazole infusion reduced the rate of rebleeding, transfusion requirements, and duration of hospitalization. Sung and colleagues [13] reported that a combination of endoscopic therapy and omeprazole infusion was superior to omeprazole infusion alone in preventing recurrent bleeding in ulcer patients with NBVV and adherent clots. These studies illustrate that intravenous PPI infusion is beneficial after endoscopic hemostasis but not as a stand-alone therapy. More recently, several reviews and meta-analyses of PPI use in peptic ulcer bleeding have confirmed that PPIs reduce rebleeding, surgery, transfusion requirements, and duration of hospitalization without decreasing mortality [14–17].

Further review of the available studies suggests important differences between the outcomes of Asian and non-Asian patients in randomized controlled trials; when analyzed separately, results clearly differed [16]. PPI therapy for bleeding ulcer significantly reduced 30-day mortality in the Asian trials but not in the non-Asian studies. The effects of PPI therapy on rebleeding and the need for surgery were also markedly greater in the Asian trials than in non-Asian trials [16]. Possible reasons for these differences include younger patients in Asian studies (age 57 years vs 66 years in non-Asian trials) with fewer comorbidities; a lower parietal cell mass in Asian patients, leading to a more profound decrease in acid secretion; a higher rate of *Helicobacter pylori* infection in Asian patients, which is associated with a greater PPI effect on acid suppression

[18]; and greater likelihood that Asian patients are slow metabolizers of PPIs. Each of these factors would produce greater PPI antisecretory effect in Asian patients than in non-Asians.

Three recent studies have compared intravenous PPIs (pantoprazole 80 mg bolus and 8 mg/h continuous infusion for up to 72 hours) with intravenous H_2RAs (ranitidine) in the management of ulcer patients with high-risk stigmata who had been successfully treated with endoscopic hemostasis. One study showed no benefit in rebleeding or mortality with PPIs [19]. In another US study, there was a trend toward less rebleeding with pantoprazole than with ranitidine [20]. The small number of patients may have limited this trial's ability to detect a true treatment difference. A Chinese study compared intravenous pantoprazole (40 mg bolus followed by 40 mg every 12 hours for 3 days) to ranitidine (50 mg bolus followed by 50 mg every 18 hours for 3 days) and reported significantly lower rebleeding rates with pantoprazole after endoscopic hemostasis but similar results for transfusion requirements, hospital stay, need for surgery, and mortality [21].

Two of these studies included only patients negative for *H. pylori* [19,20], and PPIs are less effective in reducing acid secretion in these patients than in those who are *H. pylori* positive [18]. Also, most subjects were rapid metabolizers of PPIs according to cytochrome P450 2C19 status. These two studies may be more generalizable to the United States and other heterogeneous populations in which most patients with ulcer bleeding are likely to be *H. pylori* negative and extensively metabolize PPIs.

Based on published randomized clinical trials, the recommended dose of PPIs for patients with high-risk endoscopic findings is the equivalent of omeprazole 80 mg by intravenous bolus, followed by an 8-mg/h infusion for 72 hours. However, PPIs are not approved by the US Food and Drug Administration for such medical therapy of either UGI or peptic ulcer bleeding. After the patient's condition stabilizes, intravenous PPI therapy may be switched to oral PPI therapy. Patients with low-risk endoscopic findings—clean ulcer base or flat spot—should be treated with high-dose oral PPIs (double the standard dose).

Recent studies suggest that North American patients may require an even higher equivalent dose of intravenous PPI. Howden et al. [22] showed that a 90-mg bolus of intravenous lansoprazole, followed by an intravenous infusion of 9 mg/h in *H. pylori*–negative subjects, maintained intragastric pH greater than 6 for only 36% of the first 24 hours and only 61% of the second 24-hour period. Another intravenous PPI, pantoprazole (80 mg bolus followed by an 8 mg/h infusion for 24 hours) produced intragastric pH greater than 6 for only 28% of the 24-hour observation period [23].

This was the pantoprazole dose that was used in the two negative trials (pantoprazole vs ranitidine) [19,20], so the lack of effect on rebleeding may have been secondary to ineffective acid suppression in heterogeneous, non-Asian populations. This limitation may explain why these two trials did not provide the beneficial clinical outcomes in UGI bleeding that were noted in Asian studies.

Two other aspects of PPI use for nonvariceal UGI bleeding have recently been considered: pre-endoscopic use and the use of oral PPIs. A retrospective report suggested that use of PPIs (both intravenous and oral) before endoscopy in ulcer hemorrhage patients significantly reduced adverse outcomes such as rebleeding, surgery, duration of hospitalization, and mortality [24].

A prospective, randomized, placebo-controlled study in Hong Kong showed that an intravenous bolus and infusion of omeprazole before endoscopy in patients with UGI hemorrhage decreased the need for endoscopic therapy, decreased the number of actively bleeding peptic ulcers, and decreased duration of hospitalization [25••]. A meta-analysis including a total of 1512 patients confirmed that PPI therapy before endoscopy in patients with UGI bleeding significantly decreased the proportion of patients with stigmata of hemorrhage, but it did not demonstrate any significant benefit in important clinical outcomes such as mortality, rebleeding, or surgery [26]. Two recent cost-effectiveness analyses suggest that the use of intravenous PPIs prior to endoscopy in patients with UGI bleeding was cost-effective in China [27] but was only slightly more effective and more costly in North America [28]. Therefore, in patients with UGI hemorrhage, intravenous PPI therapy before endoscopy appears reasonable in view of its previously documented benefits and negligible risks.

Oral dosing may be an alternative option for the management of nonvariceal UGI bleeding. In another Asian population, a high dose of oral omeprazole (40 mg twice daily) reduced rebleeding significantly more than placebo in ulcer patients with NBVV or adherent clots who did not receive endoscopic therapy [29]. More recent trials have suggested that 1) high-dose oral PPI (pantoprazole 40 mg twice daily [30] or omeprazole 40 mg/d [31]) is just as effective as an intravenous infusion after endoscopy therapy; 2) oral PPI (omeprazole 40 mg twice daily) was similar to intravenous omeprazole in effectiveness in ulcer patients with low-risk stigmata of hemorrhage [32]; and 3) oral PPI (rabeprazole 20 mg twice daily) was as effective as endoscopic treatment with hemoclips [33].

In another recent report in patients with bleeding ulcers, frequent oral PPI treatment with lansoprazole (120 mg initially, then 30 mg every 3 hours) achieved intragastric 24-hour pH control similar to the control achieved with intravenous lansoprazole (90-mg bolus followed by 9 mg/h infusion). The intragastric pH increased to a pH of 6 more rapidly (1 hour earlier) with the intravenous PPI than with the oral PPI, but the pH effects were comparable afterward [34•].

High-dose intravenous PPI treatment is expensive; oral PPIs are much less costly. Cost-effectiveness analyses in patients with high-risk endoscopic stigmata who had successful endoscopic therapy have shown that both intravenous and oral PPI treatment are more cost-effective than intravenous H_2RAs [35] or placebo [36]. When intravenous

PPI was compared with oral PPI, divergent results were obtained; one analysis favored intravenous use [36] and the other supported oral dosing [35].

Endoscopic Therapy

Several different techniques have been developed for endoscopic treatment of ulcer bleeding. An ideal endoscopic hemostasis technique should possess the following features:

- reproducible effectiveness
- easy and rapid application
- low complication rate
- low cost
- portability to the bedside
- widespread availability

Endoscopic techniques have been grouped into three general types according to whether tissue contact is necessary to achieve hemostasis. A combined-therapy group (dilute epinephrine injection plus thermal or mechanical treatment) is considered separately.

The major thermal endoscopic therapies are multipolar electrocoagulation (MPEC), heater probe, and argon plasma coagulation (APC). The contact probes (heater and MPEC probes) can be applied *en face* or tangentially for peptic ulcers with major stigmata of hemorrhage. Target irrigation, suctioning using therapeutic endoscopes, and tamponade of the bleeding point allow the localization of the ulcer stigma and permit endoscopic treatment. Large-diameter probes (3.2 mm) and slow coagulation provide the most effective hemostasis and prevention of rebleeding by coaptive coagulation of the underlying artery in the ulcer base [1,4]. APC coagulates poorly through blood and provides only superficial coagulation (≤ 1 mm unless it touches the mucosa and becomes a monopolar coagulator), which is ineffective for the treatment of larger underlying vessels [1].

Injection techniques use epinephrine (usually 1:10,000 or 1:20,000), sclerosants, or clotting factors (non-USA) and are the most frequently used technique for emergency hemostasis, either alone or in combination with thermal or mechanical techniques. Mechanical techniques such as hemoclips may provide hemostasis by grasping underlying vessels or closing acute lesions.

Injection treatment

Injection therapy for ulcer bleeding has been advocated because it is easy to use, inexpensive, and widely available, and many endoscopists have had prior experience sclerosing esophageal varices [1,4].

Epinephrine injection (1:10,000 to 1:20,000) provides local tamponade, vasoconstriction, and improved platelet aggregation to promote hemostasis. Saline injection alone causes local vessel compression or tamponade. Sclerosants such as alcohol, ethanolamine, and polidocanol cause tissue necrosis. Alcohol may predispose to ulceration and possible perforation.

The technique involves injection through a sclerotherapy catheter with a 25-gauge retractable needle in four quadrants around an actively bleeding point or nonbleeding vessel. Dilute epinephrine/saline solution (1:10,000–1:20,000) is injected in increments of 0.5 to 1.5 mL, up to a total of 25 to 30 mL. If alcohol is used, 0.1-mL to 0.2-mL increments are injected, up to a maximum of 1 mL. Caution is recommended with alcohol, to avoid tissue damage, necrosis, and perforation and not to exceed 1 mL injection volume. Alcohol injection should not be repeated if rebleeding occurs, and alcohol injection should not be combined with thermal modalities.

This technique of epinephrine injection is effective for active ulcer bleeding (arterial or oozing) and prevention of NBVV rebleeding. Adding a second endoscopic treatment to epinephrine injection significantly reduces the rate of recurrent bleeding, surgery, and mortality [37]. A Cochrane Database Review confirmed that in patients with bleeding ulcers and major stigmata of hemorrhage, the risk of further bleeding was significantly reduced regardless of which second procedure (electrocoagulation, heater probe, or endoclip) was added to injection of epinephrine [38••].

Electrocoagulation

Electrical current generates heat that can coagulate tissue, including arteries. In bipolar electrocoagulation or MPEC, the current flows between two or more electrodes separated by 1 to 2 mm at the probe tip. Current flow is concentrated closer to the tip than with a monopolar probe, providing less depth of tissue injury and less potential for perforation [39].

Electrocoagulation involves applying a large-diameter probe (3.2 mm diameter) directly on the ulcer stigmata or bleeding site to compress the underlying vessel with moderate appositional (tamponade) pressure before coagulation. The pressure on the stigmata temporarily interrupts blood flow through the underlying vessel, reduces the heat sink effect, and, with application of heat, can coaptively seal large arteries. The use of low energy (12–16 W on a BICAP II generator) and long duration (10 seconds) can weld the walls of arteries up to 2 mm in diameter (Table 1). Coaptive coagulation with low power settings and long duration provides deeper coagulation, especially useful for therapy of large, chronic ulcers or large arteries [39]. Electrocoagulation is effective for actively bleeding ulcer, NBVV, or adherent clot.

Heater probe

The probe effectively transfers heat from its end or sides to tissues, allowing heat transfer whether applied perpendicularly or tangentially. Teflon coating of heater probes lessens sticking. The technique involves use of a large (3.2 mm) heater probe and firm tamponade directly on the bleeding point or visible vessel. Coagulation occurs with an energy setting of 25 to 30 joules, using four to five pulses (a total

Table 1. Thermal coagulation versus hemoclipping for nonvariceal upper gastrointestinal hemorrhage

Parameter	Thermal coagulation	Hemoclipping
Ease of emergency use	Easy	Relatively easy
Tangential treatment	Easy	More difficult
Irrigation with device	Yes	No
Different sizes of probes or clips	Yes	Yes
Different brands of devices	Yes	Yes
Increase in tissue injury (lesion size/depth)	Yes	No
Time to lesion healing	Longer	Shorter

of 125–150 J) per tamponade station (before changing the probe position) [39] (Table 1). The heater probe is effective for actively bleeding ulcer, NBVV, or adherent clot.

Endoclips

Several devices, including metallic clips, endoloops, and rubber band ligation, have been described for the mechanical endoscopic treatment of bleeding ulcers. Endoclips have been the most extensively studied [40]. Clipping devices are designed to grasp the submucosa, seal bleeding vessels, or approximate the sides of lesions during endoscopy. The clips produce hemostasis in a manner similar to surgical ligation. They do not interfere with ulcer healing [40].

Precise deployment is critical. An *en face* approach allows optimal capture of the target site and surrounding tissue. A single clip may be sufficient to grasp an NBVV, but placing two additional clips to ligate proximally and distally from the bleeding point is suggested (Table 1). Endoclips are effective for active arterial bleeding, NBVV, or adherent clot [41]. A recent meta-analysis compared the effects of hemoclips to injection or thermocoagulation (heater probe or electrocoagulation) for bleeding ulcer treatment. Hemoclips significantly improved definitive hemostasis when compared with injection alone, and were comparable to thermocoagulation [42].

Endoclipping is limited by the vessel size (> 2 mm in diameter), difficulty in accessing ulcers (such as those in the proximal lesser curve or posterior duodenal bulb), fibrotic lesions, and single clip deployment (although multiple clips are often needed) [40]. Studies have shown that not all clips are equally effective. They differ in size, shape, deployment characteristics, ability to grasp and release a bleeding point and to rotate, and in long-term retention [43], as well as in clinical efficacy [44]. For example, in one pilot study evaluating a specific clip brand, the TriClip (Cook Ireland Ltd., Limerick, Ireland), the overall hemostasis failure rate was 33%, and the clips were dislodged in 41% of patients at the follow-up endoscopy 24 hours after placement [45]. In another comparative trial, hemoclips were superior to TriClips in achieving primary hemostasis in patients with major stigmata of ulcer hemorrhage [44]. All hemoclips appear to be safe and do not cause significant tissue inflammation or injury.

Combination therapy

Combination treatment with epinephrine injection and thermal therapy (MPEC or heater probe) or endoclips has theoretical advantages because each technique has different mechanisms of action for hemostasis. Combining the mechanisms of action of each hemostasis technique may provide a beneficial additive effect. Both epinephrine injection and thermal devices activate platelet coagulation and produce tamponade of the vessel. Epinephrine also produces vessel constriction, and thermal probes cause coaptive coagulation. Endoclips cause vessel ligation and can be used to close lesions [1].

The combination therapy technique involves dilute epinephrine injection into four quadrants around stigmata in the ulcer base, followed by thermal coagulation with a heater probe or multipolar probe, or deployment of endoclips. Combination therapy has become the standard treatment for actively bleeding ulcers and nonbleeding adherent clot. A recent meta-analysis compared combination therapy (epinephrine injection plus other injection or thermal or mechanical method) with monotherapy (injection, thermal, or mechanical therapy alone) in high-risk patients with bleeding ulcer. The authors found that dual therapy achieved significantly better outcomes than epinephrine injection alone but was not significantly superior to thermal or mechanical monotherapy [46•].

Recommendations for endoscopic therapy based on stigmata of ulcer hemorrhage

Active arterial bleeding

Combination therapy with epinephrine injection (1:10,000 or 1:20,000) and thermal coagulation (multipolar or heater probe) is recommended. Coaptive coagulation is the goal. Successful endoscopic hemostasis occurs in nearly 100% of lesions, and rebleeding occurs in less than 10% to 20%. By comparison, continued bleeding or rebleeding occur in 85% to 95% of patients treated with medical therapy [1,39]. Combination therapy with epinephrine and hemoclipping is a newer alternative [39,47,48••].

Ulcer oozing without other stigmata of hemorrhage

If oozing from an ulcer base persists despite irrigation and observation, any endoscopic monotherapy (thermal probes, injection, or mechanical method) is effective. Rebleeding rates are less than 5%, compared with rebleeding rates varying from 10% to 27% with medical therapy alone [1,4].

Nonbleeding visible vessel

Monotherapy with thermal coagulation (heater probe or MPEC) is effective. With large-diameter probes (3.2 mm

in diameter), firm tamponade, and slow coagulation with a low power setting to flatten the visible vessel, rebleeding rates are less than 5% to 10%, versus 50% with medical therapy alone [39].

Nonbleeding adherent clot

Combination therapy should be used, including four-quadrant epinephrine injection around the base of the clot, use of a rotatable polypectomy snare to shave down the clot using a cold-guillotine technique, and thermal coaptive coagulation or hemoclipping to treat the residual clot or NBVV. The rebleeding rate after combination therapy in a CURE trial was less than 5%, compared with 35% with medical therapy alone [49]. A recent meta-analysis confirmed the benefit of endoscopic combination therapy for adherent clot overlying an ulcer [50••].

Flat spots or clean-based ulcers

Endoscopic hemostasis provides no benefit in patients with these endoscopic findings, who have a very low rebleeding rate on medical therapy alone—7% for flat spots and 3% for clean-based ulcers.

Re-treatment

Rebleeding after endoscopic therapy of UGI ulcers, which occurs in 10% to 25% of patients, is a challenging problem [51]. One large randomized trial showed a significant reduction in complication rates in patients re-treated endoscopically with epinephrine injection and heater probe, compared with emergency surgery. These results, together with our own experience, suggest that repeat endoscopic therapy is warranted for rebleeding after initial hemostasis for ulcer hemorrhage. Endoscopic combination therapy is recommended for re-treatment.

Complications of endoscopic hemostasis

Potential complications include perforation or precipitation of bleeding from an NBVV. In a meta-analysis of injection or thermal probe coagulation, hemorrhage was induced in 0.4% of patients and perforation in 0.7%. Perforations are more frequent after endoscopic re-treatments [1].

Follow-up Medical Management

After the initial bleed is treated endoscopically and hemostasis is achieved, medical management with PPIs is recommended for 6 to 8 weeks, unless the patient is also *H. pylori* positive, requires low-dose aspirin maintenance, or uses a nonselective NSAID. Patients positive for *H. pylori* should receive eradication therapy and should be retested to document *H. pylori* eradication 6 to 10 weeks after completion of the antibiotics. Patients needing long-term aspirin or NSAIDs should receive PPI maintenance treatment indefinitely to reduce ulcer recurrence [1,4].

Conclusions

UGI bleeding secondary to ulcer hemorrhage is a frequent cause of hospitalization and inpatient bleeding, resulting in substantial patient morbidity and mortality. Randomized controlled trials and meta-analyses show that PPIs improve clinical outcomes in patients with ulcer hemorrhage. Patients with high-risk endoscopic stigmata should receive high-dose intravenous PPI therapy after successful endoscopic treatment. Patients with low-risk endoscopic stigmata should receive an oral PPI at twice the usual clinical dose. High-dose intravenous PPI therapy before endoscopy appears reasonable but is expensive. For patients with major stigmata of ulcer hemorrhage—active arterial bleeding, NBVV, and adherent clot—combination therapy with epinephrine injection and either thermal coagulation (MPEC or heater probe) or endoclips is recommended. Patients with minor stigmata or clean-based ulcer do not benefit from endoscopic hemostasis and should be triaged to less intensive care and be considered for early discharge.

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Kovacs TOG, Jensen DM: **Recent advances in the endoscopic diagnosis and therapy of upper gastrointestinal, small intestinal, and colonic bleeding.** *Med Clin N Am* 2002, **86:**1319–1356.
2. Kovacs TOG: **Mallory-Weiss tears, angiodysplasia, watermelon stomach and Dieulafoy's: a potpourri.** *Tech Gastrointest Endosc* 2005, **7:**139–147.
3. Winstead NS, Wilcox CM: **Erythromycin prior to endoscopy for acute upper gastrointestinal hemorrhage: a cost-effectiveness analysis.** *Aliment Pharmacol Ther* 2007, **26:**1371–1377.
4. Kovacs TOG, Jensen DM: **Endoscopic treatment of peptic ulcer bleeding.** *Curr Treat Opt Gastroenterol* 2007, **10:**143–148.
5. Wong RCK: **Endoscopic Doppler US probe for acute peptic ulcer hemorrhage.** *Gastrointest Endosc* 2004, **60:**804–812.
6. • Chen V, Wong RCK: **Endoscopic Doppler ultrasound versus endoscopic stigmata—directed management of acute peptic ulcer hemorrhage: a multimodel cost analysis.** *Dig Dis Sciences* 2007, **52:**149–160.

An interesting cost analysis showing cost savings with the use of Doppler ultrasound–directed management rather than standard treatment of bleeding ulcer.

7. Green FW Jr, Kaplan MM, Curtis LE, et al.: **Effects of acid and pepsin on blood coagulation and platelet aggregation: a possible contributor to prolonged gastroduodenal mucosal hemorrhage.** *Gastroenterology* 1978, **74:**38–43.
8. Labenz J, Peitz U, Leusing C, et al.: **Efficacy of primed infusions with high dose ranitidine and omeprazole to maintain high intragastric pH in patients with peptic ulcer bleeding: a prospective, randomized, controlled study.** *Gut* 1997, **40:**36–41.

9. Merki HS, Wilder-Smith CH: **Do continuous infusions of omeprazole and ranitidine retain their effect after prolonged dosing?** *Gastroenterology* 1994, **106:**60–64.
10. Netzer P, Gaia C, Sandoz M, et al.: **Effect of repeated injection and continuous infusion of omeprazole and ranitidine on intragastric pH over 72 hours.** *Am J Gastroenterol* 1999, **94:**351–357.
11. Lin HJ, Lo WC, Cheng YC, et al.: **Role of intravenous omeprazole in patients with high-risk peptic ulcer bleeding after successful endoscopic epinephrine injection: a prospective, randomized, comparative trial.** *Am J Gastroenterol* 2006, **101:**500–505.
12. Lau JY, Sung JJ, Lee KK, et al.: **Effects of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers.** *N Engl J Med* 2000, **343:**310–316.
13. Sung JJY, Chan FKL, Lau JYW: **The effect of endoscopic therapy in patients receiving omeprazole for bleeding ulcers with non-bleeding visible vessels or adherent clots.** *Ann Intern Med* 2003, **139:**237–243.
14. Andriulli A, Annese V, Caruso N, et al.: **Proton-pump inhibitors and outcome of endoscopic hemostasis in bleeding peptic ulcers: a series of meta-analyses.** *Am J Gastroenterol* 2005, **100:**207–219.
15. Bardou M, Toubouti Y, Benhaberou-Brun D, et al.: **Meta-analysis: proton-pump inhibition in high-risk patients with peptic ulcer bleeding.** *Aliment Pharmacol Ther* 2005, **21:**677–686.
16. Leontiadis GI, Sharma VK, Howden CW: **Systematic review and meta-analysis: enhanced efficacy of proton pump inhibitor therapy for peptic ulcer bleeding in Asia—a post hoc analysis from the Cochrane Collaboration.** *Aliment Pharmacol Ther* 2005, **21:**1055–1061.
17. Leontiadis GI, Sharma VK, Howden CW: **Proton pump inhibitor treatment for acute peptic ulcer bleeding.** *Cochrane Database Syst Rev* 2006, **1:**CD002094.
18. van Herwaarden MA, Samson M, van Nispen CHM, et al.: **The effect of Helicobacter pylori eradication on intragastric pH during dosing with lansoprazole or ranitidine.** *Aliment Pharmacol Ther* 1999, **13:**731–740.
19. Barkun A, Racz I, van Rensburg C, et al.: **Prevention of peptic ulcer rebleeding using continuous infusion of pantoprazole vs ranitidine: a multicenter, multinational, randomized, double blind, parallel-group comparison [abstract].** *Gastroenterology* 2004, **126:**A-78.
20. Jensen DM, Pace SC, Soffer E, et al.: **Continuous infusion of pantoprazole versus ranitidine for prevention of ulcer rebleeding: A US multicenter, randomized, double-blind study.** *Am J Gastroenterol* 2006, **101:**1991–1999.
21. Hsu PI, Lo GH, Lo CC, et al.: **Intravenous pantoprazole versus ranitidine for prevention of rebleeding after endoscopic hemostasis of bleeding peptic ulcers.** *World J Gastroenterol* 2004, **10:**3666–3669.
22. Howden CW, Metz DC, Hunt B, et al.: **Dose-response evaluation of the antisecretory effect of continuous infusion intravenous lansoprazole regimen over 48 h.** *Aliment Pharmacol Ther* 2006, **23:**975–984.
23. Metz DC, Amer F, Hunt B, et al.: **Lansoprazole regimens that sustain intragastric pH > 6.0: an evaluation of intermittent oral and continuous intravenous infusion dosages.** *Aliment Pharmacol Ther* 2006, **23:**985–995.
24. Keyvani L, Murthy S, Leeson S, Targownik LE: **Pre-endoscopic proton pump inhibitor therapy reduces recurrent adverse gastrointestinal outcomes in patients with acute non-variceal upper gastrointestinal bleeding.** *Aliment Pharmacol Ther* 2006, **24:**1247–1255.
25.•• Lau JY, Leung WK, Wu JCY, et al.: **Omeprazole before endoscopy in patients with gastrointestinal bleeding.** *N Engl J Med* 2007, **356:**1631–1640.

Randomized, placebo-controlled trial in patients with ulcer hemorrhage showing that early intravenous infusion of high-dose omeprazole before endoscopy reduces the need for endoscopic therapy and decreases the number of actively bleeding ulcers.

26. Dorward S, Sreedharan A, Leontiadis GI, et al.: **Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding.** *Cochrane Database Syst Rev* 2006, CD005415.
27. Tsoi KK, Sung JJ: **Cost-effectiveness analysis of high-dose omeprazole infusion before endoscopy for patients with upper GI bleeding.** *Gastrointest Endosc* 2008, **67:**1056–1063.
28. Al-Sobah S, Burkun AN, Herba K, et al.: **Cost-effectiveness of proton-pump inhibition before endoscopy in upper gastrointestinal bleeding.** *Clin Gastroenterol Hepatol* 2008, **6:**418–425.
29. Khuroo MS, Yattoo GN, Javid G, et al.: **A comparison of omeprazole and placebo for bleeding peptic ulcer.** *N Engl J Med* 1997, **336:**1054–1058.
30. Bajaj JS, Dua KS, Hanson K, et al.: **Prospective, randomized trial comparing effect of oral versus intravenous pantoprazole on rebleeding after nonvariceal upper gastrointestinal bleeding: a pilot study.** *Dig Dis Sci* 2007, **52:**2190–2194.
31. Murthy S, Keyvani L, Leeson S, Targownik LE: **Intravenous versus high-dose oral proton pump inhibitor therapy after endoscopic hemostasis of high-risk lesions in patients with acute non-variceal upper gastrointestinal bleeding.** *Dig Dis Sci* 2007, **52:**1685–1690.
32. Yilmaz S, Bayan K, Juzunm Y, et al.: **A head to head comparison of oral vs. intravenous omeprazole for patients with bleeding peptic ulcers with a clean base, flat spots, and adherent clots.** *World J Gastroenterol* 2006, **12:**7837–7843.
33. Kim JI, Cheung DY, Cho SH, et al.: **Oral proton pump inhibitors are as effective as endoscopic treatment for bleeding peptic ulcer: a prospective, randomized, controlled trial.** *Dig Dis Sci* 2007, **52:**3371–3376.
34.• Laine L, Shah A, Bemanian S: **Intragastric pH with oral vs intravenous bolus plus infusion proton pump inhibitor therapy in patients with bleeding ulcers.** *Gastroenterology* 2008, **134:**1836–1841.

Randomized trial in patients with bleeding ulcer, comparing high-dose oral PPI to intravenous bolus plus infusion for the control of intragastric pH. The oral PPI effects were similar to those observed with intravenous PPIs.

35. Spiegel BMR, Dulai GS, Lim BS, et al.: **The cost-effectiveness and budget impact of intravenous versus oral proton pump inhibitors in peptic ulcer hemorrhage.** *Clin Gastroenterol Hepatol* 2006, **4:**988–997.
36. Barkun AN, Herba K, Adam U, et al.: **The cost-effectiveness of high-dose oral proton pump inhibition after endoscopy in the acute treatment of peptic ulcer bleeding.** *Aliment Pharmacol Ther* 2004, **20:**195–202.
37. Calvet X, Vergara M, Brullet E, et al.: **Addition of a second endoscopic treatment following epinephrine injection improves outcome in high-risk bleeding ulcers.** *Gastroenterology* 2004, **126:**441–450.
38.•• Vergara M, Calvet X, Gisbert JP: **Epinephrine injection versus epinephrine injection and a second endoscopic method in high risk bleeding ulcers.** *Cochrane Database Syst Rev* 2007, CD005584.

Excellent review demonstrating significant benefit in hemostasis outcomes by adding endoscopic treatment after epinephrine injection.

39. Jensen DM, Machicado GA: **Endoscopic hemostasis of ulcer hemorrhage with injection, thermal, and combination methods.** *Tech Gastrointest Endosc* 2005, **7:**124–131.
40. Technology Assessment Committee, Chuttani R, Barkun A, et al.: **Endoscopic clip application devices.** *Gastrointest Endosc* 2006, **63:**746–750.
41. Saltzman JR, Strata LL, Di Sena V, et al.: **Prospective trial of endoscopic clips versus combination therapy in upper GI bleeding.** *Am J Gastroenterol* 2005, **97:**1503–1508.
42. Sung JJ, Tsai KK, Lai LH, et al.: **Endoscopic clipping versus injection and thermo-coagulation in the treatment of non-variceal upper gastrointestinal bleeding: a meta-analysis.** *Gut* 2007, **56:**1364–1373.

43. Jensen DM, Machicado GA, Hirabayashi K: **Randomized controlled study of 3 different types of hemoclips for hemostasis of bleeding canine acute gastric ulcers.** *Gastrointest Endosc* 2006, **64:**768–773.

44. Lin HJ, Lo WC, Cheng YC, Peing CL: **Endoscopic hemoclip versus TriClip placement in patients with high-risk peptic ulcer bleeding.** *Am J Gastroenterol* 2007, **102:**539–543.

45. Chan CY, Yan KK, Siu WT, et al.: **Endoscopic hemostasis by using the TriClip for peptic ulcer hemorrhage: a pilot study.** *Gastrointest Endosc* 2008, **67:**35–39.

46.• Marmo R, Rotondano G, Piscopo R, et al.: **Dual therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers: a meta-analysis of controlled trials.** *Am J Gastroenterol* 2007, **102:**279–289.

Meta-analysis reporting improved hemostasis outcomes with combination therapy compared with epinephrine injection alone, but without substantial benefit over mechanical or thermal techniques.

47. Park CH, Joo YE, Kim HS, et al.: **A prospective, randomized trial comparing mechanical methods of hemostasis plus epinephrine injection to epinephrine injection alone for bleeding peptic ulcer.** *Gastrointest Endosc* 2004, **60:**173–179.

48.•• Lo CC, Hsu PI, Lo GH, et al.: **Comparison of hemostatic efficacy for epinephrine injection alone and injection combined with hemoclip therapy in treating high-risk bleeding ulcers.** *Gastrointest Endosc* 2006, **63:**767–773.

A prospective randomized controlled trial showing that combination therapy with epinephrine injection and hemoclip was superior to epinephrine injection alone for treating bleeding ulcers.

49. Jensen DM, Kovacs TOG, Jutabha R, et al.: **Randomized trial of medical or endoscopic therapy to prevent recurrent ulcer hemorrhage in patients with adherent clots.** *Gastroenterology* 2002, **123:**407–413.

50.•• Kahi CJ, Jensen DM, Sung JJY, et al.: **Endoscopic therapy versus medical therapy for bleeding peptic ulcer with adherent clot: a meta-analysis.** *Gastroenterology* 2005, **129:**855–862.

A meta-analysis of available studies evaluating the effect of endoscopic therapy for bleeding ulcer patients with adherent clot. The results show that endoscopic hemostasis reduces recurrent bleeding significantly more than medical treatment.

51. Lau JJ, Sung JJY, Lam Y, et al.: **Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers.** *N Engl J Med* 1999, **340:**751–756.