CME

Management of Patients With Ulcer Bleeding

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This guideline presents recommendations for the step-wise management of patients with overt upper gastrointestinal bleeding. Hemodynamic status is first assessed, and resuscitation initiated as needed. Patients are risk-stratified based on features such as hemodynamic status, comorbidities, age, and laboratory tests. Pre-endoscopic erythromycin is considered to increase diagnostic yield at first endoscopy. Pre-endoscopic proton pump inhibitor (PPI) may be considered to decrease the need for endoscopic therapy but does not improve clinical outcomes. Upper endoscopy is generally performed within 24 h. The endoscopic features of ulcers direct further management. Patients with active bleeding or non-bleeding visible vessels receive endoscopic therapy (e.g., bipolar electrocoagulation, heater probe, sclerosant, clips) and those with an adherent clot may receive endoscopic therapy; these patients then receive intravenous PPI with a bolus followed by continuous infusion. Patients with flat spots or clean-based ulcers do not require endoscopic therapy or intensive PPI therapy. Recurrent bleeding after endoscopic therapy is treated with a second endoscopic treatment; if bleeding persists or recurs, treatment with surgery or interventional radiology is undertaken. Prevention of recurrent bleeding is based on the etiology of the bleeding ulcer. *H. pylori* is eradicated and after cure is documented anti-ulcer therapy is generally not given. Nonsteroidal anti-inflammatory drugs (NSAIDs) are stopped; if they must be resumed low-dose COX-2-selective NSAID plus PPI is used. Patients with established cardiovascular disease who require aspirin should start PPI and generally re-institute aspirin soon after bleeding ceases (within 7 days and ideally 1–3 days). Patients with idiopathic ulcers receive long-term anti-ulcer therapy.

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Ulcers are the most common cause of hospitalization for upper gastrointestinal bleeding (UGIB), and the vast majority of clinical trials of therapy for nonvariceal UGIB focus on ulcer disease. This guideline provides recommendations for the management of patients with overt UGIB due to gastric or duodenal ulcers. "Overt" indicates that patients present with symptoms of hematemesis, melena, and/or hematochezia. We first discuss the initial management of UGIB in patients without known portal hypertension, including initial assessment and risk stratification, pre-endoscopic use of medications and gastric lavage, and timing of endoscopy. We then focus on the endoscopic and medical management of ulcer disease, including endoscopic findings and their prognostic implications, endoscopic hemostatic therapy, post-endoscopic medical therapy and disposition, and prevention of recurrent ulcer bleeding.

Each section of the document presents the key recommendations related to the section topic, followed by a summary of the supporting evidence. A summary of recommendations is provided in **Table 1**.

A search of MEDLINE via the OVID interface using the MeSH term "gastrointestinal hemorrhage" limited to "all clinical trials" and "meta-analysis" for years 1966–2010 without language restriction as well as review of clinical trials and reviews known to the authors were performed for preparation of this document. The GRADE system was used to grade the strength of recommendations and the quality of evidence (1). The quality of evidence, which influences the strength of recommendation, ranges from "high" (further research is very unlikely to change our confidence in the estimate of effect) to "moderate" (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate) to "low" (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), and "very low" (any estimate of effect is very uncertain). The strength of a recommendation is graded as strong when the desirable effects of an intervention clearly outweigh the undesirable effects and is graded as conditional when uncertainty exists about the trade-offs (1). In addition to quality of evidence and balance between desirable and undesirable effects, other factors affecting the strength of recommendation include variability in values and preferences of patients, and whether an intervention represents a wise use of resources (1).

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Table 1. Summary and strength of recommendations

Initial assessment and risk stratification
1. Hemodynamic status should be assessed immediately upon presentation and resuscitative measures begun as needed (Strong recommendation).
2. Blood transfusions should target hemoglobin ≥7 g/dl, with higher hemoglobins targeted in patients with clinical evidence of intravascular volume depletion or comorbidities, such as coronary artery disease (Conditional recommendation).
3. Risk assessment should be performed to stratify patients into higher and lower risk categories and may assist in initial decisions such as timing of endoscopy, time of discharge, and level of care (Conditional recommendation).
4. Discharge from the emergency department without inpatient endoscopy may be considered in patients with urea nitrogen <18.2 mg/dl; hemoglobin ≥13.0 g/dl for men (12.0 g/dl for women), systolic blood pressure ≥110 mm Hg; pulse <100 beats/min; and absence of melena, syncope, cardiac failure, and liver disease, as they have <1% chance of requiring intervention (Conditional recommendation).
Pre-endoscopic medical therapy
5. Intravenous infusion of erythromycin (250 mg ~30 min before endoscopy) should be considered to improve diagnostic yield and decrease the need for repeat endoscopy. However, erythromycin has not consistently been shown to improve clinical outcomes (Conditional recommendation).
6. Pre-endoscopic intravenous PPI (e.g., 80 mg bolus followed by 8 mg/h infusion) may be considered to decrease the proportion of patients who have higher risk stigmata of hemorrhage at endoscopy and who receive endoscopic therapy. However, PPIs do not improve clinical outcomes such as further bleeding, surgery, or death (Conditional recommendation).
7. If endoscopy will be delayed or cannot be performed, intravenous PPI is recommended to reduce further bleeding (Conditional recommendation).
Gastric lavage
8. Nasogastric or orogastric lavage is not required in patients with UGIB for diagnosis, prognosis, visualization, or therapeutic effect (Conditional recommendation).
Timing of endoscopy
9. Patients with UGIB should generally undergo endoscopy within 24 h of admission, following resuscitative efforts to optimize hemodynamic parameters and other medical problems (Conditional recommendation).
10. In patients who are hemodynamically stable and without serious comorbidities endoscopy should be performed as soon as possible in a non-emergent setting to identify the substantial proportion of patients with low-risk endoscopic findings who can be safely discharged (Conditional recommendation).
11. In patients with higher risk clinical features (e.g., tachycardia, hypotension, bloody emesis or nasogastric aspirate in hospital) endoscopy within 12 h may be considered to potentially improve clinical outcomes (Conditional recommendation).
Endoscopic diagnosis
12. Stigmata of recent hemorrhage should be recorded as they predict risk of further bleeding and guide management decisions. The stigmata, in descending risk of further bleeding, are active spurting, non-bleeding visible vessel, active oozing, adherent clot, flat pigmented spot, and clean base (Strong recommendation).
Endoscopic therapy
13. Endoscopic therapy should be provided to patients with active spurting or oozing bleeding or a non-bleeding visible vessel (Strong recommendation).
14. Endoscopic therapy may be considered for patients with an adherent clot resistant to vigorous irrigation. Benefit may be greater in patients with clinical features potentially associated with a higher risk of rebleeding (e.g., older age, concurrent illness, inpatient at time bleeding began) (Conditional recommendation).
15. Endoscopic therapy should not be provided to patients who have an ulcer with a clean base or a flat pigmented spot (Strong recommendation).
16. Epinephrine therapy should not be used alone. If used, it should be combined with a second modality (Strong recommendation).
17. Thermal therapy with bipolar electrocoagulation or heater probe and injection of sclerosant (e.g., absolute alcohol) are recommended because they reduce further bleeding, need for surgery, and mortality (Strong recommendation).
18. Clips are recommended because they appear to decrease further bleeding and need for surgery. However, comparisons of clips vs. other therapies yield variable results and currently used clips have not been well studied (Conditional recommendation).
19. For the subset of patients with actively bleeding ulcers, thermal therapy or epinephrine plus a second modality may be preferred over clips or sclerosant alone to achieve initial hemostasis (Conditional recommendation).
Medical therapy after endoscopy
20. After successful endoscopic hemostasis, intravenous PPI therapy with 80 mg bolus followed by 8 mg/h continuous infusion for 72 h should be given to patients who have an ulcer with active bleeding, a non-bleeding visible vessel, or an adherent clot (Strong recommendation).
21. Patients with ulcers that have flat pigmented spots or clean bases can receive standard PPI therapy (e.g., oral PPI once daily) (Strong recommendation).
Repeat endoscopy
22. Routine second-look endoscopy, in which repeat endoscopy is performed 24 h after initial endoscopic hemostatic therapy, is not recommended (Conditional recommendation).
23. Repeat endoscopy should be performed in patients with clinical evidence of recurrent bleeding and hemostatic therapy should be applied in those with higher risk stigmata of hemorrhage (Strong recommendation).
24. If further bleeding occurs after a second endoscopic therapeutic session, surgery or interventional radiology with transcathether arterial embolization is generally employed (Conditional recommendation).

Table 1. Continued.

Hospitalization
25. Patients with high-risk stigmata (active bleeding, visible vessels, clots) should generally be hospitalized for 3 days assuming no rebleeding and no other reason for hospitalization. They may be fed clear liquids soon after endoscopy (Conditional recommendation).
26. Patients with clean-based ulcers may receive a regular diet and be discharged after endoscopy assuming they are hemodynamically stable, their hemoglobin is stable, they have no other medical problems, and they have a residence where they can be observed by a responsible adult (Strong recommendation).
Long-term prevention of recurrent bleeding ulcers
27. Patients with *H. pylori*-associated bleeding ulcers should receive *H. pylori* therapy. After documentation of eradication, maintenance antisecretory therapy is not needed unless the patient also requires NSAIDs or antithrombotics (Strong recommendation).
28. In patients with NSAID-associated bleeding ulcers, the need for NSAIDs should be carefully assessed and NSAIDs should not be resumed if possible. In patients who must resume NSAIDs, a COX-2 selective NSAID at the lowest effective dose plus daily PPI is recommended (Strong recommendation).
29. In patients with low-dose aspirin-associated bleeding ulcers, the need for aspirin should be assessed. If given for secondary prevention (i.e., established cardiovascular disease) then aspirin should be resumed as soon as possible after bleeding ceases in most patients: ideally within 1–3 days and certainly within 7 days. Long-term daily PPI therapy should also be provided. If given for primary prevention (i.e., no established cardiovascular disease), anti-platelet therapy likely should not be resumed in most patients (Conditional recommendation).
30. In patients with idiopathic (non-*H. pylori*, non-NSAID) ulcers, long-term antiulcer therapy (e.g., daily PPI) is recommended (Conditional recommendation).

PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug; UGIB, upper gastrointestinal bleeding.

INITIAL ASSESSMENT AND RISK STRATIFICATION

Recommendations.

1. Hemodynamic status should be assessed immediately upon presentation and resuscitative measures begun as needed (Strong recommendation, low-quality evidence).

2. Blood transfusions should target hemoglobin ≥7 g/dl, with higher hemoglobins targeted in patients with clinical evidence of intravascular volume depletion or comorbidities such as coronary artery disease (Conditional recommendation, low-to-moderate-quality evidence).

3. Risk assessment should be performed to stratify patients into higher and lower risk categories, and may assist in initial decisions such as timing of endoscopy, time of discharge, and level of care (Conditional recommendation, low-quality evidence).

4. *Discharge from the emergency department without inpatient endoscopy may be considered in patients with urea nitrogen < 18.2 mg/dl; hemoglobin ≥13.0 g/dl for men (12.0 g/dl for women), systolic blood pressure ≥110 mm Hg; pulse < 100 beats/min; and absence of melena, syncope, cardiac failure, and liver disease, as they have < 1% chance of requiring intervention (Conditional recommendation, low-quality evidence).*

Summary of evidence. Based on other models of hemorrhage (2), the first step in management of patients presenting with overt upper gastrointestinal bleeding (UGIB) is assessment of hemodynamic status and initiation of resuscitative measures as needed. In addition to intravenous fluids, transfusion of red blood cells may be required. Randomized trials in euvolemic patients without current bleeding (3) and in cirrhotics with UGIB (4) indicate that transfusions should be given to maintain hemoglobin ≥7 g/dl. A restrictive transfusion policy is also supported by an older randomized trial of 50 patients without known varices in which patients transfused ≥2 units within 24 h of admission had significantly more rebleeding than those not transfused unless Hgb was <8 g/dl (5). Higher hemoglobin levels may need to be targeted in patients with other illnesses (e.g., coronary artery disease) (6) and in those with intravascular volume depletion (i.e., hypotension and tachycardia) in whom the hemoglobin is "artificially" elevated before repletion with intravascular fluid. Intubation may be considered to protect the airway and prevent aspiration in patients with severe ongoing hematemesis and/or altered mental status; it may also be necessary in some patients (e.g., those with comorbidities) to safely and effectively provide sedation for endoscopy.

Risk assessment of patients is clinically useful to determine which patients are at higher risk of further bleeding or death, and may inform management decisions such as timing of endoscopy, time of discharge, and level of care (e.g., ward vs. step-down vs. intensive care).

Instruments used to assess risk include the pre-endoscopic Rockall score (7) and the Blatchford score (8). The pre-endoscopic Rockall score (range, 0–7) uses only clinical data available immediately at presentation, which are related to the severity of the bleeding episode (systolic blood pressure and pulse) and to the patient (age and comorbidities). It has been shown to predict the risk of further bleeding and death in a population of patients hospitalized with UGIB (7). The Blatchford score (range, 0–23) uses clinical data (systolic blood pressure, pulse, melena, syncope, hepatic disease, and heart failure) and laboratory data (hemoglobin and blood urea nitrogen) available early after admission. It has been shown to predict the risk of intervention (transfusion and endoscopic or surgical therapy) and death in a population of patients presenting to hospital with UGIB (8).

In general, risk assessment with scoring systems such as Blatchford or Rockall is not able to unequivocally identify individual patients who will require intervention, with one exception. Patients with a Blatchford score of 0 (urea nitrogen <18.2 mg/dl; hemoglobin ≥13.0 g/dl for men (12.0 g/dl for women), systolic blood pressure ≥110 mm Hg; pulse <100 beats/min; absence of melena, syncope, cardiac failure, and liver disease), which may occur in up to ~5–20% of those presenting with UGIB, have <1% chance of requiring intervention (8–11).

In a prospective series, Stanley *et al.* (9) did not admit patients presenting to emergency departments with UGIB who had Blatchford scores of 0 unless necessary for other reasons. Of

123 patients with scores of 0, 84 were not admitted. Among the 23 patients receiving outpatient endoscopy no ulcers, varices, or malignancies were found and no interventions were needed. Among the remainder, none were readmitted with UGIB or died during ≥6 months of follow-up. Thus, discharge from the emergency department without inpatient endoscopy may be considered in very low-risk patients with Blatchford scores of 0.

PRE-ENDOSCOPIC MEDICAL THERAPY

Prokinetic therapy

Recommendations.

5. Intravenous infusion of erythromycin (250 mg ~30 min before endoscopy) should be considered to improve diagnostic yield and decrease the need for repeat endoscopy. However, erythromycin has not consistently been shown to improve clinical outcomes (Conditional recommendation, moderate-quality evidence).

Summary of evidence. Prokinetic agents given before endoscopy have been proposed to improve visualization at endoscopy. Three fully published randomized trials of erythromycin given intravenously before endoscopy were identified in a recent systematic review (12). Infusions of erythromycin 250 mg or 3 mg/kg were given over 5 or 30 min and endoscopy was performed 20–60 min after the infusion finished (13–15). All trials showed significant improvement in their primary end point related to visualization of mucosa.

However, a more clinically appropriate question is whether use of erythromycin translates into more diagnoses made at initial endoscopy or better clinical outcomes. Meta-analysis of these three trials (13–15) reveals a very modest but significant benefit (relative risk (RR) = 1.13, 1.02–1.26; number needed to treat (NNT) = 9) in diagnosis at first endoscopy. Erythromycin did not significantly reduce clinical outcomes such as blood transfusions, hospital stay, or surgery, but did decrease the proportion of patients undergoing a second endoscopy (12). Only two abstracts assessing metoclopramide were identified in this meta-analysis, and no significant benefits were found in this small sample (12).

Since this meta-analysis, a study reporting on the non-randomized cohort of patients with variceal bleeding from within a randomized trial found better visualization and shorter hospital stay with erythromycin, but no significant decreases in transfusions or repeat endoscopy (16). A randomized comparison of erythromycin, standard-bore nasogastric (NG) tube, or erythromycin plus NG tube in 253 patients with UGIB revealed no significant differences in visualization, diagnosis at first endoscopy, second-look endoscopy, further bleeding, or transfusions (17).

Proton pump inhibitor therapy

Recommendations.

6. Pre-endoscopic intravenous proton pump inhibitor (PPI) (e.g., 80 mg bolus followed by 8 mg/h infusion) may be considered to decrease the proportion of patients who have higher risk stigmata of hemorrhage at endoscopy and who receive endoscopic therapy. However, PPIs do not improve clinical outcomes such as further bleeding, surgery, or death (Conditional recommendation, high-quality evidence).

7. If endoscopy will be delayed or cannot be performed, intravenous PPI is recommended to reduce further bleeding (Conditional recommendation, moderate-quality evidence).

Summary of evidence. A Cochrane meta-analysis of six randomized trials (N = 2,223) of pre-endoscopic PPI therapy found no significant differences between PPI and control in mortality (6.1 vs. 5.5%; odds ratio (OR) = 1.12, 0.72–1.73), rebleeding (13.9 vs. 16.6%; OR = 0.81, 0.61–1.09), or surgery (9.9 vs. 10.2%, OR = 0.96, 0.68–1.35) (18). PPI therapy significantly reduced the proportion of participants with higher risk stigmata of hemorrhage (active bleeding, non-bleeding visible vessel, and adherent clot) at index endoscopy (37.2 vs. 46.5%; OR = 0.67, 0.54–0.84) and undergoing endoscopic therapy at index endoscopy (8.6 vs. 11.7%; OR = 0.68, 0.50–0.93). Similar results were seen in the highest quality study, which also was the only study employing high-dose bolus and continuous infusion intravenous PPI (19). Endoscopic therapy was performed in 19.1 vs. 28.4% (P = 0.007), and, among those with ulcers, active bleeding was significantly less common (6.4 vs. 14.7%; P = 0.01) and clean-based ulcers more common (64.2 vs. 47.4%; P = 0.001) with PPI therapy. PPI therapy should be discontinued after endoscopy unless the patient has a source for which PPIs may be beneficial (e.g., ulcers and erosions).

A Cochrane meta-analysis of randomized trials of patients with UGIB who did not consistently receive endoscopic hemostatic therapy reported that PPI therapy was associated with reduced rebleeding (OR = 0.38, 0.18–0.81 (with significant heterogeneity); NNT = 10) and surgery (OR = 0.62, 0.44–0.88; NNT = 17), but not mortality (20). This suggests that if endoscopy will be delayed or cannot be performed, PPI therapy may improve clinical outcomes.

Gastric lavage

Recommendations.

8. NG or orogastric lavage is not required in patients with UGIB for diagnosis, prognosis, visualization, or therapeutic effect (Conditional recommendation, low-quality evidence).

Summary of evidence. A variety of reasons have been advanced to perform NG lavage in patients with gastrointestinal (GI) bleeding: to determine if the source of bleeding is in the upper GI tract, to provide prognostic information, to clear blood and clots and allow better visualization at endoscopy, and to treat UGIB.

Documentation of a UGI source. NG aspirates with blood or coffee-ground material clearly document UGIB, and a bloody NG aspirate increases the likelihood of finding active bleeding or a non-bleeding visible vessel as compared with coffee-grounds or a clear NG aspirate (21,22). However, a clear or bile-stained NG aspirate may be seen in up to 18% of patients with an upper GI source (22–27). For example, in a Canadian UGIB registry, 13% of patients with UGIB had a clear or bile-stained aspirate; 15% of patients with a clear/bile-stained aspirate had active bleeding or non-bleeding visible vessel compared with 23% with coffee-grounds and 45% with bloody aspirates (22). In a prospective study of patients presenting with hematochezia plus hypotension,

tachycardia, dropping hemoglobin, or transfusion, and a negative NG aspirate, 15% had an upper GI source (27). Although some suggest that a non-bloody bile-stained aspirate indicates duodenal contents were sampled and rules out a UGI source, physicians are incorrect about 50% of the time when they report bile in the aspirate (25). In addition, testing NG aspirates for occult blood is not documented to be useful.

Prognostic value. Intuitively, a persistently bloody NG aspirate would seem likely to indicate a more severe UGIB episode. An NG aspirate with red blood is reported to be associated with more severe bleeding (proportion requiring >5 units of blood and surgery) (21,22), and increases the chance of identifying high-risk stigmata at the time of endoscopy (21,22). However, whether a bloody aspirate provides better prognostic information than other readily available data such as blood pressure and pulse is not known. In a prospective trial in 325 patients, the proportion with "shock" (systolic blood pressure <100 mm Hg and pulse >100 beats/minute) correlated with the NG aspirate finding: 11% with a clear aspirate, 36% with coffee-grounds, and 60% with bloody aspirate (28).

Improvement of visualization. The standard small-bore NG tube typically used for aspiration is not likely to effectively clear clots from the stomach. A large-bore orogastric tube is more likely to be successful in clearing the stomach with major UGIB. A small randomized comparison of a 40 French orogastric tube (with sedation) vs. no lavage in 38 patients showed a significantly higher proportion with excellent visualization in the fundus (the primary end point) and a trend in the antrum ($P=0.06$) (29). There was no significant difference in the proportion with the bleeding source defined (95 vs. 83%). The use of a large-bore orogastric tube is difficult and uncomfortable for patients and cannot be recommended routinely.

Endoscopic methods of aspiration designed to improve visualization, including use of a jumbo channel (6 mm) or an external auxiliary device, have been assessed in case series (30,31). Further study is needed to determine their potential role as compared with prokinetic therapy and NG aspiration.

Therapeutic effect. Older textbooks reported that NG lavage could stop bleeding in a majority of cases and recommended use of iced saline. However, UGIB stops spontaneously in a majority of patients without specific therapy, and studies in dogs with experimentally induced ulcers indicated that results with lavage are no better and may even be worse at temperatures of 0–4 °C (32).

ENDOSCOPY FOR DIAGNOSIS

Timing of endoscopy

Recommendations.

9. Patients with UGIB should generally undergo endoscopy within 24 h of admission, following resuscitative efforts to optimize hemodynamic parameters and other medical problems (Conditional recommendation, low-quality evidence).

10. In patients who are hemodynamically stable and without serious comorbidities endoscopy should be performed as soon as possible in a non-emergent setting to identify the substantial proportion of patients with low-risk endoscopic findings who can be safely discharged (Conditional recommendation, moderate-quality evidence).

11. In patients with higher risk clinical features (e.g., tachycardia, hypotension, bloody emesis or NG aspirate in hospital) endoscopy within 12 h may be considered to potentially improve clinical outcomes (Conditional recommendation, low-quality evidence).

Summary of evidence. Early endoscopy has been variably defined as endoscopy performed within 2–24 h of presentation. A variety of observational studies and a few randomized trials have assessed this issue, but marked variations in study design, definitions, end points, and methodologic rigor make synthesis of the results difficult. Two systematic reviews summarize these studies (33,34).

Studies of early endoscopy consistently show that patients undergoing endoscopy within 8 h of presentation have more high-risk stigmata (active bleeding, visible vessels, or adherent clots) than those with later endoscopies (34), thereby increasing the proportion who requires endoscopic therapy. However, observational studies do not document a benefit in clinical outcomes of endoscopy performed within 2–12 h of presentation (33,34). Observational studies do suggest a benefit of endoscopy within 24 h after admission in terms of decreased length of stay (35,36) and surgical intervention (35). Thus, endoscopy within 24 h appears appropriate in a population hospitalized with UGIB. However, risk stratification also may have a role in considerations regarding timing of endoscopy.

Low-risk patients. Lee *et al.* (37) performed a randomized trial comparing endoscopy within 2 h vs. endoscopy within 48 h in 110 patients who were hemodynamically stable, had no serious comorbidity, and had no reason to suspect variceal bleeding. No significant improvements in end points such as bleeding, surgery, or mortality were identified. However, the length of hospital stay, post-discharge unplanned physician visits, and costs were significantly decreased in the early endoscopy group. Forty-six percent of patients in the early endoscopy group could be discharged home immediately and had no rebleeding or repeat endoscopy during the next month.

In a second randomized trial comparing early endoscopy within 6 h vs. within 48 h in 93 patients with hemodynamic stabilization and absence of severe comorbidity, no significant benefits were seen in clinical end points or in resource utilization (38). Although discharge without hospitalization was recommended in the 40% of early endoscopy patients who met criteria for early discharge, this advice was followed in only 9%, suggesting that the financial benefit of early endoscopy can only be realized if physicians use the results of endoscopy in making management decisions.

Thus, both studies suggest that early endoscopy in patients who are hemodynamically stable and have no serious comorbidities can potentially result in lower costs by allowing early discharge in up to ~40–45% of patients, supporting performance of endoscopy

as soon as possible in patients with low-risk clinical features. However, the lack of clinical benefit argues against the need for endoscopy in an emergent setting (e.g., "middle of the night") for low-risk patients. Furthermore, as mentioned earlier, patients with very low risk based on pre-endoscopic assessment (e.g., Blatchford score of 0) may be considered for discharge from the emergency department without undergoing endoscopy (9).

High-risk patients. In a randomized trial comparing endoscopy within 12 h with endoscopy >12 h after presentation, without exclusion of higher risk patients, no significant benefit was identified in bleeding, surgery, or mortality. In subgroup analyses, patients who had a bloody NG aspirate pre-endoscopy (but not those with clear or coffee-grounds aspirates) had significantly fewer units of blood transfused and hospital days (28). As mentioned above, a majority of these patients with a bloody aspirate had systolic blood pressure <100 mm Hg and pulse >100 beats/minute. A recent observational study also found a significantly higher mortality in high-risk UGIB patients (Blatchford score ≥12) having endoscopy >13 h after presentation (44%) than in those having earlier endoscopy (0%, $P<0.001$) (39). Multivariate analysis found that presentation-to-endoscopy time was the only variable significantly associated with mortality.

Thus, limited data, from subgroup analysis of a randomized trial and an observational study, raise the possibility that patients with high-risk clinical features may have improved clinical outcomes if endoscopy is performed within 12 h of presentation.

Risk of early endoscopy. The potential risk of endoscopy, often performed during off hours in sick patients, must be considered. A prospective, non-randomized study indicated an increased risk of oxygen desaturation in patients undergoing endoscopy within 2 h as compared with endoscopy at 2–24 h (40). This study highlights the fact that early endoscopy has the potential to further increase complications if performed too early, before appropriate resuscitation and stabilization.

Endoscopic diagnosis of ulcer and stigmata of recent hemorrhage

Recommendations.

12. Stigmata of recent hemorrhage (SRH) should be recorded as they predict risk of further bleeding and guide management decisions. The stigmata, in descending risk of further bleeding, are active spurting, non-bleeding visible vessel, active oozing, adherent clot, flat pigmented spot, and clean base (Strong recommendation, high-quality evidence).

Summary of evidence. The definition of an ulcer is a histological one, requiring extension into the submucosa or deeper. In contrast, erosions are breaks that remain confined to the mucosa. This is clinically relevant because serious bleeding does not occur from an erosion due to the absence of veins and arteries in the mucosa. Rather serious bleeding occurs when an ulcer erodes into vessels in the submucosa or deeper. Swain *et al.* (41) assessed the histological characteristics of gastric ulcers with visible vessels in 27 patients who required surgery for further bleeding, and identified arteries in the ulcer base in 26 (96%) of the 27 specimens.

Table 2. Classification and prevalences of stigmata of recent hemorrhage in 2,401 patients hospitalized with bleeding ulcers at 72 US endoscopy centers (48)

Stigmata of hemorrhage	Forrest classification	Prevalence
Active spurting bleeding	IA	12% (spurting + oozing)
Active oozing bleeding	IB	
Non-bleeding visible vessel	IIA	8%
Adherent clot	IIB	8%
Flat pigmented spot	IIC	16%
Clean base	III	55%

Although the definition of an ulcer relates to histological depth, in practice no objective measure of the depth of an ulcer is performed. Currently, the endoscopic diagnosis of an ulcer is based on the interpretation of the endoscopist that unequivocal depth is present at endoscopic visualization.

Ulcer surface area dimensions or diameter can be estimated with the use of a device of known dimension, such as an open biopsy forceps. Ulcers larger than 1–2 cm are associated with increased rates of further bleeding with conservative therapy and after endoscopic therapy (42–44).

SRH are terms that describe the appearance of an ulcer base at endoscopy in patients with ulcer bleeding. SRH provide prognostic information regarding the risk of rebleeding, need for therapeutic intervention, and death (45,46). SRH are therefore used to stratify patients with ulcer bleeding and guide management decisions including endoscopic and medical therapy, admission vs. discharge, and level of care in hospital. In the absence of clinical evidence of bleeding, however, the presence of SRH does not appear to be associated with a risk of subsequent bleeding (47).

Descriptive terms for SRH are generally used in North America whereas the Forrest classification is common in Europe and Asia. The descriptive terms for SRH and corresponding Forrest classifications are shown in **Table 2** with US prevalences. Most patients with ulcer bleeding have low risk characteristics of clean bases or flat spots identified at endoscopy (48). Active bleeding may be broken down into arterial spurting and oozing, although most studies of prevalence have combined these categories. A recent large prospective trial found that only 68 (17%) of 397 patients enrolled with actively bleeding ulcers had arterial spurting (49). **Table 3** shows pooled rates of further bleeding, surgery, and death without endoscopic therapy stratified by SRH.

Most studies and meta-analyses of ulcer hemorrhage outcomes combine both spurting and oozing bleeding into an "active ulcer bleeding" category. However, results from prospective trials suggest they should be viewed separately because the risk of further bleeding with spurting probably is substantially higher than the risk with oozing. In non-randomized cohorts of patients receiving only conservative therapy (without endoscopic therapy) in two studies, the rate of further bleeding requiring surgery was higher in those with spurting than those with oozing (7/10 (70%) vs. 7/24 (29%) and 5/8

Table 3. Stigmata of recent hemorrhage and average rates (with ranges) of further bleeding, surgery, and mortality in prospective trials without endoscopic therapy (45)

Stigmata	Further bleeding (*N* =2,994)	Surgery for bleeding (*N* =1,499)	Mortality (*N* =1,387)
Active bleeding	55% (17–100%)	35% (20–69%)	11% (0–23%)
Non-bleeding visible vessel	43% (0–81%)	34% (0–56%)	11% (0–21%)
Adherent clot	22% (14–36%)	10% (5–12%)	7% (0–10%)
Flat pigmented spot	10% (0–13%)	6% (0–10%)	3% (0–10%)
Clean ulcer base	5% (0–10%)	0.5% (0–3%)	2% (0–3%)

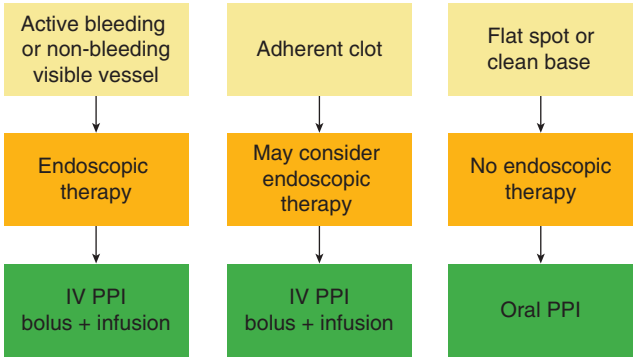

Figure 1. Recommended endoscopic and medical management based on stigmata of hemorrhage in ulcer base. IV, intravenous; PPI, proton pump inhibitor.

(63%) vs. 7/35 (20%)) (50,51). In a study restricted to UGIB patients requiring intensive care unit admission, transfusion-requiring further bleeding occurred in 23/24 (88%) with spurting and 3/28 (11%) of those with oozing (52). Data from eight prospective trials including UGIB patients with oozing treated conservatively without endoscopic therapy reveal a pooled rate of further bleeding of 39% (range, 10–100%) (50,51,53–58) and further bleeding requiring emergency surgery in 26% (range, 20–38%) (50,51,55,56).

Marked differences can be seen across different reports in the relative proportions of SRH and may relate to several factors. One potential explanation is the timing of the endoscopy, as discussed above, with more high-risk SRH identified with earlier endoscopy. Another potential explanation is inter-observer disagreement among endoscopists. Considerable variability has been reported among endoscopists in classifying SRH from photographs or video clips (59,60). Improvements in agreement may be achieved with training (e.g., instruction with review of photographs or videos, atlases) (49,59,61). It is also possible that differing patient characteristics (e.g., severity of comorbidities) may influence the prevalence of SRH.

Another potential difference in reported proportions of SRH may relate to variability in irrigation of clots. Vigorous irrigation with a water pump device will wash away overlying clot and reveal underlying SRH in a substantial portion of patients. Syringe irrigation followed by only 10 s of water pump irrigation removed clots in 33% of patients in one study (62). In another study water pump irrigation for up to 5 min removed clots in 43% of patients, revealing high-risk stigmata mandating endoscopic therapy in 30% and low-risk stigmata in 13%; no therapy was provided to the 57% with adherent clots and the rebleeding rate was only 8% (63). Thus, vigorous irrigation of clots on an ulcer base is recommended to more accurately determine underlying SRH and more accurately assess the risk of rebleeding.

ENDOSCOPIC THERAPY

Who should receive endoscopic therapy?

Recommendations.

13. Endoscopic therapy should be provided to patients with active spurting or oozing bleeding or a non-bleeding visible vessel (Strong recommendation, high-quality evidence) (**Figure 1**).

14. Endoscopic therapy may be considered for patients with an adherent clot resistant to vigorous irrigation. Benefit may be greater in patients with clinical features potentially associated with a higher risk of rebleeding (e.g., older age, concurrent illness, inpatient at time bleeding began) (Conditional recommendation, moderate-quality evidence).

15. Endoscopic therapy should not be provided to patients who have an ulcer with a clean base or a flat pigmented spot (Strong recommendation, high-quality evidence).

Summary of evidence. Meta-analysis of trials of endoscopic therapy vs. no endoscopic therapy for patients with an actively bleeding ulcer (spurting and oozing combined) shows a significant decrease in further bleeding (RR = 0.29, 0.20–0.43) with an NNT of only 2 (64). The need for urgent intervention and surgery is also significantly decreased. Meta-analysis of patients with a non-bleeding visible vessel in an ulcer reveals a significant decrease in further bleeding (RR = 0.49, 0.40–0.59; NNT = 5) as well as urgent intervention and surgery (64).

Although spurting and oozing bleeding are combined in most randomized trials and meta-analyses, as discussed above the rate of further bleeding appears to be substantially lower with oozing. Nevertheless, the 39% pooled rate of rebleeding in patients who were treated conservatively does support performing endoscopic therapy for oozing. Better efficacy may be expected after endoscopic therapy in patients with oozing than in those with other high-risk stigmata. In a cohort of patients within the placebo arm of a randomized trial of high-dose PPI vs. placebo after endoscopic therapy, the rates of further bleeding at 72 h were lower with oozing (4.9%) than with spurting (22.5%), clots (17.7%), or non-bleeding visible vessels (11.3%) (65).

Meta-analysis of randomized trials in patients with an adherent clot does not show a significant benefit (RR = 0.31, 0.06–1.77) (64). However, significant heterogeneity is present among the studies. Two US trials reported significant benefit of endoscopic hemostasis, with pooled rebleeding rates for endoscopic vs. medical therapy of 3 vs. 35% (61,66). The other studies, from Europe and Asia, showed no suggestion of any benefit. The one study using therapy matching current recommendations (vigorous irrigation; bolus and continuous infusion of PPI following endoscopy) reported

no rebleeding in the 24 control patients with clots receiving only medical therapy (67). The reasons for the marked variation in results are uncertain but potential explanations might include differences in severity of comorbidities (US studies done primarily in tertiary care centers), etiology of the ulcer disease (*H. pylori* ulcers may be more common outside the US), and response to PPIs (greater in *H. pylori*-positive patients and in Asia).

Patients with clean-based ulcers or flat pigmented spots rarely have serious recurrent bleeding (45) and therefore would not derive significant benefit from endoscopic therapy.

What endoscopic therapies should be used?

Recommendations.

16. Epinephrine therapy should not be used alone. If used, it should be combined with a second modality (Strong recommendation, high-quality evidence).

17. Thermal therapy with bipolar electrocoagulation or heater probe and injection of sclerosant (e.g., absolute alcohol) are recommended because they decrease further bleeding, need for surgery, and mortality (Strong recommendation, high-quality evidence).

18. Clips are recommended because they appear to decrease further bleeding and need for surgery. However, comparisons of clips vs. other therapies yield variable results and currently used clips have not been well studied (Conditional recommendation, low-to-moderate quality evidence).

19. For the subset of patients with actively bleeding ulcers, thermal therapy or epinephrine plus a second modality may be preferred over clips or sclerosant alone to achieve initial hemostasis (Conditional recommendation, low-to-moderate-quality evidence).

Summary of evidence. The primary end point recommended in trials of UGIB is prevention of further bleeding, which includes initial hemostasis in actively bleeding patients plus prevention of rebleeding in those with initial hemostasis and in those without active bleeding at presentation (68). Endoscopic therapies that have shown efficacy in randomized trials include thermal therapy (e.g., bipolar electrocoagulation, heater probe, monopolar electrocoagulation, argon plasma coagulation, and laser), injection (epinephrine, sclerosants (e.g., absolute ethanol, polidocanol, and ethanolamine), thrombin or fibrin glue (thrombin plus fibrinogen)), and clips (64).

Randomized trials indicate epinephrine injection is effective at achieving initial hemostasis in patients with active bleeding, with results not significantly different from other therapies (64). However, epinephrine monotherapy is less effective than other monotherapies in preventing further bleeding (RR = 1.72, 1.08–2.78; NNT = 9) and surgery based on meta-analysis of three trials employing bipolar electrocoagulation, clips, or fibrin glue as comparators (64). Furthermore, epinephrine plus a second modality (e.g., bipolar electrocoagulation, sclerosant, and clip) is significantly more effective than epinephrine alone in reducing further bleeding (RR = 0.34, 0.23–0.50; NNT = 5) and surgery (64). However, if a second-look endoscopy is performed and higher risk lesions are retreated, the benefit of combined therapy vs. epinephrine alone is not seen (64).

Thermal contact therapy with bipolar electrocoagulation or heater probe is significantly more effective than no endoscopic therapy in achieving initial hemostasis (RR = 11.70, 5.15–26.56), reducing further bleeding (RR = 0.44, 0.36–0.54; NNT = 4), surgery, and mortality (RR = 0.58, 0.34–0.98; NNT = 33) in a meta-analysis of 15 randomized trials (64). No significant differences were seen in randomized trials comparing these two thermal modalities. The term "multipolar electrocoagulation" is used in some studies. The multipolar probe and other bipolar probes all deliver bipolar electrocoagulation; the difference in terms relates only to the configuration of the electrodes on the probe tip. Thus, meta-analyses combine multipolar and bipolar electrocoagulation trials.

Results of two small studies suggested benefit of epinephrine plus bipolar electrocoagulation vs. bipolar electrocoagulation alone, but results with thermal monotherapy were poorer in these trials than most other studies (69,70). A larger high-quality study found that injection of thrombin plus heater probe was not better than heater probe alone (71). Thus, although limited information suggests that epinephrine followed by thermal contact therapy may be more efficacious than thermal therapy alone, data are insufficient to recommend that thermal contact devices should not be used alone as monotherapy.

However, there may be practical reasons to pre-inject epinephrine before other therapies for specific SRH. Anecdotally, for active bleeding, injection of epinephrine may slow or stop bleeding allowing improved visualization for application of subsequent therapy. In addition, if clot removal is planned for adherent clots resistant to irrigation, pre-injection of epinephrine may reduce the rate of severe bleeding induced by clot removal.

Sclerosant injection also significantly reduces further bleeding (RR = 0.56, 0.38–0.83; NNT = 5) as well as surgery and mortality as compared with no endoscopic therapy based on meta-analysis of three randomized trials of absolute alcohol (64). Because the volume of sclerosants must be limited due to concern for tissue necrosis, sclerosant therapy alone may not be optimal for actively bleeding ulcers. Among actively bleeding patients in a randomized trial comparing absolute alcohol vs. no therapy, initial hemostasis was achieved in only 46% with alcohol vs. 8% in controls (64). Epinephrine injection before sclerosant therapy for actively bleeding ulcers seems reasonable although this has not been compared with sclerosant alone in randomized trials.

Trials comparing thermal therapy with sclerosant therapy show no significant difference in further bleeding, surgery, or mortality, although thermal therapy showed significantly fewer urgent interventions (surgery, repeat endoscopic therapy, or interventional radiology) and a trend to less further bleeding (RR = 0.69, 0.47–1.01) (64).

Clips have not been compared with no endoscopic therapy but are more effective than injection of epinephrine or water in reducing further bleeding and surgery (64). On comparison with other standard therapies (thermal or sclerosant, with or without epinephrine), clips were less effective at initial hemostasis than thermal therapy (heater probe) (64), but not significantly different in other outcomes such as further bleeding. However, these studies were

heterogeneous with one showing clips to be significantly better and two others indicating clips were significantly worse than the comparators in their effect on further bleeding. Thus, more data are needed on the role of clips alone in the acute management of UGIB. Variables to consider in assessing the heterogeneous study results include variation among different endoscopists and among different types of clips. Newer clips in current use are easier to apply and vary in size, rigidity, depth of attachment, and duration of retention (72,73); however, they have not been well studied in randomized trials. Clips also have the theoretical benefit of not inducing tissue injury, unlike thermal therapies and sclerosants—and therefore may be preferred in patients on antithrombotic therapy and those undergoing retreatment for rebleeding.

Despite showing efficacy in randomized trials, laser, monopolar electrocoagulation, argon plasma coagulation, and injection of thrombin or fibrin glue are not recommended as first-line therapies due to less robust evidence, potential for slightly higher risk of adverse effects, availability, ease of use, and/or cost (64).

Techniques for endoscopic hemostatic therapy. Endoscopic hemostatic modalities are generally applied to the bleeding site to halt bleeding and in the immediate area of the SRH in the ulcer base with the intent to close or obliterate the underlying vessel and prevent rebleeding. The technique used to treat adherent clots in the two studies reporting benefit of endoscopic therapy was epinephrine injection into all four quadrants of the ulcer followed by mechanical clot removal (e.g., snare; manipulation with forceps, probe, or tip of endoscope) and application of thermal therapy (61,66).

Dilute (1:10,000 or 1:20,000 in saline) epinephrine is generally injected in 0.5–2 ml aliquots in and around the stigmata of hemorrhage in the ulcer base. Although large volumes of epinephrine (e.g., 30–45 ml) are reported to be more effective as monotherapy (74–76), no studies have documented the optimal volume when used in combination with other modalities. We recommend injection until active bleeding slows or stops or, for non-bleeding stigmata, in all four quadrants next to the SRH in the ulcer base.

Absolute alcohol is generally administered in 0.1–0.2 ml aliquots with a limitation of 1–2 ml (77) due to the concern for tissue injury with higher volumes. Five percent ethanolamine is administered in 0.5–1.0 ml aliquots; widely variable total volumes of 0.5–14 ml have been reported in randomized trials for ulcer bleeding (78–80).

Bipolar electrocoagulation should be performed with the endoscope tip as close as possible to the bleeding ulcer; the large (3.2 mm) probe should be applied en face or at the least possible angulation with firm/maximal pressure (81,82). A setting of ~15 W and 8–10 s applications are recommended (81,83,84). Multiple applications should be applied in the ulcer base on and around the SRH, until bleeding has stopped, the vessel is flattened, and the base is whitened. Recommendations for the heater probe are identical with a setting of 30 J being used.

Clips should be placed over the bleeding site and on either side of the SRH in an attempt to seal the underlying artery.

MEDICAL THERAPY AFTER ENDOSCOPY

Recommendations.

20. After successful endoscopic hemostasis, intravenous PPI therapy with 80 mg bolus followed by 8 mg/h continuous infusion for 72 h should be given to patients who have an ulcer with active bleeding, a non-bleeding visible vessel, or an adherent clot (Strong recommendation, high-quality evidence) (**Figure 1**).

21. Patients with ulcers that have flat pigmented spots or clean bases can receive standard PPI therapy (e.g., oral PPI once-daily) (Strong recommendation, moderate-quality evidence).

Summary of evidence. Meta-analysis of randomized trials of intravenous PPI therapy (80 mg bolus followed by 8 mg/h continuous infusion) vs. placebo/no treatment for 72 h after endoscopic therapy of high-risk stigmata reveals a significant reduction in further bleeding (RR = 0.40, 0.28–0.59; NNT = 12), surgery (RR = 0.43, 0.24–0.76; NNT = 28), and mortality (RR = 0.41, 0.20–0.84; NNT = 45) (64).

In a recent large randomized trial of bolus followed by continuous infusion PPI vs. placebo after successful endoscopic hemostasis, subgroup analysis of patients with oozing bleeding showed a very low rebleeding rate with placebo (8/163 (4.9%)) (65). The results of this subgroup analysis suggest that intensive PPI therapy may not be needed for oozing bleeding without other SRH.

Meta-analysis of trials of intermittent oral or intravenous PPI vs. placebo/no therapy reveals a significant reduction in further bleeding (RR = 0.53, 0.35–0.78), but no significant difference in surgery, urgent intervention, or mortality. Meta-analysis of five fully published randomized trials that compare bolus followed by continuous infusion PPI vs. intermittent PPI therapy after endoscopic therapy for high-risk stigmata reveals an absolute risk reduction in further bleeding with intermittent PPI of 1% (95% CI −3 to 5%) (85–89). Most of these trials were relatively small, methodologic concerns have been raised about the single large trial, and rates of rebleeding were very low in all arms of the studies (3–14%). For these reasons, it is difficult to conclude that the two treatments are "equivalent". Nevertheless, these data do suggest that intermittent PPI therapy may suffice after endoscopic therapy for high-risk stigmata.

Rates of serious rebleeding with lower risk stigmata (clean base, flat pigmented spot) are low (45) and thus standard antisecretory therapy to heal the ulcer is all that is recommended in patients with these findings.

REPEAT ENDOSCOPY

Recommendations.

22. Routine second-look endoscopy, in which repeat endoscopy is performed 24 h after initial endoscopic hemostatic therapy, is not recommended (Conditional recommendation, moderate-quality evidence).

23. Repeat endoscopy should be performed in patients with clinical evidence of recurrent bleeding and hemostatic therapy should be applied in those with higher risk stigmata of hemorrhage (Strong recommendation, high-quality evidence).

24. If further bleeding occurs after a second endoscopic therapeutic session, surgery or interventional radiology with transcathether

arterial embolization is generally employed (Conditional recommendation, low-quality evidence).

Summary of evidence. Second-look endoscopy is generally defined as routine repeat endoscopy within 24 h after initial endoscopy and hemostatic therapy. Repeat endoscopic hemostatic therapy is typically given to patients with higher risk SRH. A meta-analysis of randomized trials assessing second-look endoscopy reported a small but significant reduction in rebleeding in patients undergoing second-look endoscopy (absolute risk reduction = 6.2% (1.3–11.1%; NNT = 16)) with no significant benefit in reducing surgery or death (90). A subsequent meta-analysis found no significant benefit when hemostatic therapy was epinephrine injection or fibrin glue injection, but did identify a significant difference in rebleeding for the two randomized trials employing thermal therapy (RR = 0.29, 0.11–0.73) (91).

However, these studies were done before the currently accepted practice of adding intensive PPI therapy after endoscopic therapy, which has been shown to reduce further bleeding. In a randomized trial of single endoscopy plus high-dose intravenous PPI vs. routine second-look endoscopy without PPI, rebleeding occurred in 8.2 vs. 8.7% (RR = 1.1, 0.4–2.7) (91).

The expense of second-look endoscopy also must be considered. A large number of unnecessary endoscopies will be performed since most patients do not have recurrent bleeding. In addition, second-look endoscopies do not prevent further bleeding in all patients, and repeat endoscopic therapy is successful in most patients with rebleeding (92). An economic analysis suggests that intravenous PPI therapy would be the dominant strategy as compared with second-look endoscopy if the PPI therapy reduced rebleeding to 9% or if it cost $10 per day (93). Recent randomized trials report rebleeding rates < 9% (49,91) in patients with high-risk ulcer bleeding treated with endoscopic and PPI therapy. Furthermore, intensive PPI therapy is considered as standard therapy after endoscopic therapy of high-risk SRH (as discussed above) and would be employed even if second-look endoscopy is done.

If a population at very high risk of recurrent bleeding after endoscopic hemostasis could be identified, this group potentially could derive benefit from second-look endoscopy. Although several characteristics are reported to be associated with an increased risk of bleeding after hemostatic therapy, no grading system has been validated to reliably identify a very high-risk population (44).

Repeat endoscopy with endoscopic therapy is appropriate in patients with clinical evidence of rebleeding. A randomized trial comparing endoscopic therapy vs. surgery for recurrent bleeding after endoscopic hemostatic therapy revealed that 73% of patients with recurrent bleeding can be successfully treated with repeat endoscopic therapy and avoid the need for surgery, with a lower rate of complications than those treated with surgery (92). If further bleeding occurs after the second endoscopic treatment, surgery or interventional radiology (transcatheter arterial embolization) is reported to be successful in achieving hemostasis. A recent review of case series of angiographic embolization in patients with UGIB failing endoscopic and medical therapy revealed a technical success rate > 90% and a rebleeding rate of 33%, which was widely variable across studies (9–66%) (94).

HOSPITALIZATION FOR PATIENTS WITH UGIB

Recommendations.

25. Patients with high-risk stigmata (active bleeding, visible vessels, clots) should generally be hospitalized for 3 days assuming no rebleeding and no other reason for hospitalization. They may be fed clear liquids soon after endoscopy (Conditional recommendation, low-quality evidence).

26. Patients with clean-based ulcers may receive a regular diet and be discharged after endoscopy assuming they are hemodynamically stable, their hemoglobin is stable, they have no other medical problems, and they have a residence where they can be observed by a responsible adult (Strong recommendation, moderate-quality evidence).

Summary of evidence. Clear liquid diet can be provided after endoscopic therapy. This recommendation is based on the fact that patients with recurrent bleeding may have to undergo urgent interventions such as endoscopy, interventional radiology, or surgery. Clear liquids allow sedation or anesthesia to be administered within 2 h after the last ingestion (95). Thus, we suggest clear liquid diet for ~2 days in patients who are at higher risk for rebleeding. However, given the excellent results obtained with current endoscopic and medical therapy some investigators have raised the possibility of early refeeding in higher risk patients. A randomized trial of normal diet vs. nothing by mouth for 24 h after endoscopic therapy for oozing or non-bleeding visible vessels found no significant difference in rebleeding (2 vs. 6%) (96). This trial may not simulate standard practice; however, because second-look endoscopy with retreatment was performed at 24 h.

With a low risk of recurrent bleeding, regular diet may be instituted. A randomized trial of patients with lower risk lesions (e.g., Mallory-Weiss tears, ulcers with clean base or flat pigmented spots) revealed no significant differences in outcomes with immediate refeeding of regular diet vs. delayed refeeding (clear liquids at 36 h and regular diet at 48 h) (97). Although patients with flat spots in this trial had similar outcomes with immediate refeeding, the 8% rebleeding rate and 5% rate of urgent intervention may argue for clear liquid diet in these patients for 1–2 days. Data to guide the duration of hospitalization for patients with flat pigmented spots are lacking.

Several trials have demonstrated that patients with UGIB who have low-risk features may be discharged on the first hospital day (or worked up and discharged as an outpatient) without negative consequences (9,33,98). Criteria vary across studies but generally include low-risk clinical features (e.g., stable vital signs and hemoglobin, no serious comorbidities), low-risk endoscopic features (e.g., clean-based ulcer, erosive disease, Mallory-Weiss tear), and satisfactory home/social support.

Other patients with higher risk stigmata (active bleeding, visible vessel, and clot) generally remain in the hospital for 3 days assuming no rebleeding or other medical issues. This is based primarily on older studies suggesting that recurrent bleeding almost always

(~≥ 95%) occurred within 3 days (43,99–101). More recent results of randomized trials suggest that a substantial minority of patients may have recurrent bleeding after 3 days—most often occurring within 7 days (49,102,103). For example, in a recent large randomized trial of patients with higher risk bleeding ulcers treated with endoscopic therapy, 24% of the 82 patients with rebleeding in the 30-day study rebled beyond 3 days, with equal proportions in the group receiving continuous infusion PPI and those receiving placebo after endoscopic therapy (49). Six percent of rebleeding occurred after 7 days (49).

Although patients should be educated about symptoms of UGIB and the need to return to hospital if these symptoms develop, we do not recommend hospital stays be routinely extended beyond 3 days in patients without further bleeding or other medical problems.

LONG-TERM PREVENTION OF RECURRENT BLEEDING ULCERS

Recommendations.

27. Patients with H. pylori-associated bleeding ulcers should receive H. pylori therapy. After documentation of eradication, maintenance antisecretory therapy is not needed unless the patient also requires non-steroidal anti-inflammatory drugs (NSAIDs) or antithrombotics (Strong recommendation, high-quality evidence) (**Figure 2**).

28. In patients with NSAID-associated bleeding ulcers, the need for NSAIDs should be carefully assessed and NSAIDs should not be resumed if possible. In patients who must resume NSAIDs, a COX-2-selective NSAID at the lowest effective dose plus daily PPI is recommended (Strong recommendation, high-quality evidence).

29. In patients with low-dose aspirin-associated bleeding ulcers, the need for aspirin should be assessed. If given for secondary prevention (i.e., established cardiovascular disease) then aspirin should be resumed as soon as possible after bleeding ceases in most patients: ideally within 1–3 days and certainly within 7 days. Long-term daily PPI therapy should also be provided. If given for primary prevention (i.e., no established cardiovascular disease), antiplatelet therapy likely should not be resumed in most patients (Conditional recommendation, moderate-quality evidence).

30. In patients with idiopathic (non-H. pylori, non-NSAID) ulcers, long-term antiulcer therapy (e.g., daily PPI) is recommended (Conditional recommendation, low-quality evidence).

Summary of evidence. Patients with bleeding ulcers have an unacceptably high rate of recurrent bleeding if no strategy is employed to reduce this risk. For example, in patients with duodenal ulcer bleeding (*H. pylori* not assessed, no NSAID use) followed in a double-blind trial after ulcer healing, bleeding recurred within 1 year in nearly 40% (104). In a systematic review of randomized trials of patients with *H. pylori*-associated bleeding ulcers (105), the rate of recurrent bleeding in studies with 12-month follow-up was 26% (106–109). In *H. pylori*-positive NSAID users with bleeding ulcers followed for 6 months after ulcer healing, recurrent bleeding ulcers occurred with resumption of NSAIDs in 19% of those given only *H. pylori* therapy (110), while in *H. pylori*-positive low-dose aspirin users who presented with ulcer complications and were followed for a median of 12 months after ulcer healing and *H. pylori* eradication, recurrent bleeding ulcers occurred with resumption of low-dose aspirin in 15% (111). Finally, in a prospective cohort of patients with idiopathic bleeding ulcers (*H. pylori* negative, no NSAID use) followed for 7 years, the incidence of recurrent ulcer bleeding was 42% (112).

H. pylori ulcers

Biopsy-based *H. pylori* testing is recommended by ACG *H. pylori* guidelines in patients presenting with a bleeding ulcer (113). Because some studies suggest sensitivity may be decreased with acute UGIB, confirmation of a negative test with a subsequent non-endoscopic test has also been recommended (113,114). However, if histological examination of the biopsy specimens shows no mucosal mononuclear cell infiltrate, the predictive value for absence of *H. pylori* approaches 100%, while a neutrophilic infiltrate has >95% positive predictive value for *H. pylori* infection (115).

A meta-analysis of randomized trials showed that *H. pylori* eradication therapy for prevention of recurrent ulcer bleeding is significantly more effective than short-term antisecretory therapy alone (rebleeding 4.5 vs. 23.7%; OR = 0.18, 0.10–0.35) (105). Furthermore, *H. pylori* eradication was also more effective than long-term maintenance antisecretory therapy with PPI or histamine-2 receptor antagonist (H2RA) (although most patients received H2RA: 1.6 vs. 5.6%; OR = 0.24, 0.09–0.67) (105). A systematic review of studies assessing rebleeding in patients with documented *H. pylori* eradication revealed a 1.3% incidence of rebleeding over mean follow-up periods of 11–53 months (105).

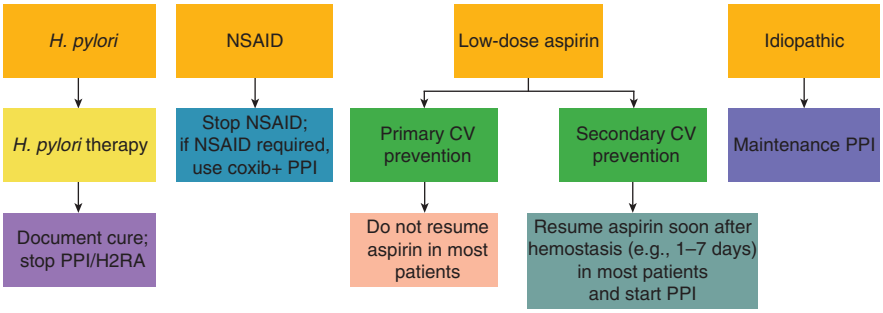

Figure 2. Recommended management to prevent recurrent ulcer bleeding based on etiology of ulcer bleeding. CV, cardiovascular; H2RA, histamine-2 receptor antagonist; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Because patients with *H. pylori* ulcers have such low rebleeding rates if they have eradication of the infection, it is important to document cure of the infection at ≥1 month following the end of *H. pylori* therapy. Endoscopic biopsy can be done if patients are undergoing repeat endoscopy for another reason (e.g., to document gastric ulcer healing), but a urea breath test or stool antigen test should be done if endoscopy is not needed (113). Antibody testing should not be employed since it remains positive in most patients after successful therapy (116). PPIs can cause falsely negative *H. pylori* testing in approximately one third of cases (117,118) so PPIs should be discontinued 2 weeks before testing to ensure optimal sensitivity (118). Some practitioners may use an H2RA during this period to decrease risk of recurrent ulcers in case *H. pylori* therapy was not successful.

NSAID ulcers

Randomized trials in NSAID users show that co-therapy with misoprostol, PPIs, and double-dose H2RAs or use of COX-2-selective inhibitors decrease endoscopic ulcers in patients taking NSAIDs (119,120) and that misoprostol and COX-2-selective NSAIDs also decrease complicated ulcers in arthritis patients (120,121). Although these trials suggest that the agents studied may be beneficial in patients who presented with a bleeding ulcer, they do not specifically address management of these high-risk patients.

Several randomized trials from Hong Kong have studied prevention of recurrent bleeding in NSAID users who presented with bleeding ulcers. In patients who were restarted on NSAID after ulcer healing, maintenance PPI therapy had a significantly lower risk of recurrent ulcer bleeding at 6 months as compared with *H. pylori* therapy only (4.4 vs. 18.8%; NNT = 7) (110). In a follow-up study, celecoxib was compared with diclofenac plus PPI after ulcer healing in patients who were *H. pylori* negative or had successful *H. pylori* therapy (122). The rates of recurrent ulcer bleeding at 6 months were 4.9% with celecoxib and 6.4% for diclofenac plus PPI; recurrent ulcers were seen at 6-month endoscopy in 19 and 26% of patients (123). Because rates of recurrent ulcer bleeding were relatively high with either protective strategy, a subsequent 12-month double-blind study of similar design compared celecoxib plus twice-daily PPI vs. celecoxib plus placebo (124). Recurrent ulcer bleeding occurred in 0 vs. 8.9% (NNT = 12). Thus, patients with a bleeding ulcer while on NSAIDs who must remain on NSAIDs should receive a COX-2-selective NSAID at the lowest effective dose plus PPI therapy.

Low-dose aspirin ulcers

Randomized trials in low-dose aspirin users show that PPIs and standard dose H2RAs reduce endoscopic ulcers (125–127) and that PPIs reduce UGIB in patients taking low-dose aspirin plus clopidogrel (128).

In a study of *H. pylori*-positive low-dose aspirin users with bleeding ulcers, the rates of recurrent ulcer bleeding at 6 months after resuming low-dose aspirin were 0.9% with PPI and 1.9% with *H. pylori* therapy (110). Although no placebo group was included, this trial raised the possibility that *H. pylori* eradication alone may reduce recurrent ulcer bleeding with low-dose aspirin. A subsequent trial performed in *H. pylori*-positive low-dose aspirin users with ulcer complications showed that after *H. pylori* eradication and ulcer healing, PPI therapy had significantly less recurrent ulcer bleeding than placebo at a median of 12 months (1.6 vs. 14.8%; NNT = 8) (111). Thus, in patients with bleeding ulcers who require continued antiplatelet therapy, once-daily PPI should be given.

The need for antiplatelet therapy should be reviewed in patients who have ulcer bleeding while taking low-dose aspirin. In patients taking aspirin for primary prophylaxis (no overt cardiovascular disease), the benefit of low-dose aspirin is relatively small: meta-analysis of randomized trials reveals an annual absolute risk reduction of 0.07% (NNT = 1,429) (129). Primary prevention is recommended only in patients at higher risk for cardiovascular events, based on risk assessment tools. In patients hospitalized with ulcer bleeding, the risk of subsequent bleeding likely outweighs the cardiovascular benefit in many or most patients on primary prophylaxis.

In contrast, the benefit of low-dose aspirin for secondary prophylaxis in patients with established cardiovascular disease is much larger (annual absolute risk reduction of 1.49% (NNT = 68)) (129) and failure to resume low-dose aspirin after ulcer bleeding is associated with an increased mortality (130). A randomized trial in low-dose aspirin users with established cardiovascular disease who presented with a bleeding ulcer showed that resumption of low-dose aspirin vs. placebo after endoscopic hemostasis and initiation of PPI therapy was associated with no significant increase in recurrent ulcer bleeding at 1 month (10.3 vs. 5.4%), but a significant decrease in mortality at 1 month and 2 months (1.3 vs. 12.9%) (130). Thus, it is important to resume antiplatelet therapy, along with PPI co-therapy, as early as possible in patients with established cardiovascular disease.

The timing of resumption of aspirin is not clear and data are primarily based on observational studies. A systematic review found that thrombotic events in patients with established cardiovascular disease occurred at a mean of 10.7 days after aspirin withdrawal (131), while another review of patients on secondary prevention stopping aspirin perioperatively reported the mean interval after discontinuation for acute cerebral events was 14.3 days and for acute coronary syndrome was 8.5 days (132). Recent joint consensus recommendations from US cardiology and GI organizations stated that "reintroduction of antiplatelet therapy in high-cardiovascular-risk patients is reasonable in those who remain free of rebleeding after 3–7 days" (133), while the study from Sung *et al.* (130) indicated a benefit of resumption of low-dose aspirin immediately after endoscopic hemostasis in patients with high-risk stigmata. Thus, the benefit-risk ratio of aspirin resumption must be carefully considered jointly by gastroenterologists, cardiologists, neurologists, and patients on a case-by-case basis. However, early resumption of antiplatelet therapy within 1–3 days after hemostasis, and certainly within 7 days, will be appropriate in most patients with established cardiovascular disease.

Idiopathic (non-*H. pylori*, non-NSAID) ulcers

Patients with idiopathic bleeding ulcers have a high rate of recurrence when followed without protective co-therapy (112).

Surreptitious NSAID use undoubtedly accounts for some of these ulcers. Although no randomized trials have assessed the benefit of medical co-therapy in this population, antiulcer therapy seems likely to reduce recurrent idiopathic ulcers and will also be effective at reducing recurrent ulcers in those surreptitiously using NSAIDs.

CONCLUSION

Management of the patient presenting with overt bleeding proceeds in a step-wise manner. The first step is assessment of hemodynamic status and initiation of resuscitative measures as needed. Patients are risk stratified based on clinical features such as hemodynamic status, comorbidities, age, and initial laboratory tests. Most patients should receive an upper endoscopy within 24 h or less, and endoscopic features of the ulcer assist in directing further management. Those with high-risk findings of active bleeding or non-bleeding visible vessel should receive endoscopic therapy and those with an adherent clot may receive endoscopic therapy; these patients should then receive intravenous PPI therapy with a bolus followed by continuous infusion. Those with flat spots or clean-based ulcers do not require endoscopic therapy or intensive intravenous PPI therapy. Recurrent ulcer bleeding after endoscopic therapy should be treated with a second endoscopic treatment, but if bleeding still persists or recurs treatment with surgery or interventional radiology is undertaken.

Prevention of recurrent bleeding is based on the presumed etiology of the bleeding ulcer. *H. pylori* should be eradicated if present and after cure is documented, no further therapy is needed. NSAIDs should be stopped; if they must be continued a low-dose of a COX-2-selective NSAID plus a PPI should be used. Patients with established cardiovascular disease who require aspirin or other antiplatelet agents should start PPI therapy and generally have antiplatelet therapy reinstituted as soon as possible after bleeding ceases (ideally within 1–3 days and certainly within 7 days). Those with idiopathic ulcers should receive long-term antiulcer therapy.

CONFLICT OF INTEREST

Guarantor of the article: Loren Laine, MD.

Specific author contributions: L. Laine: planning and conducting review; analysis/interpretation of data; drafting and revision of the manuscript. He approved final draft submitted. D. Jensen: planning and conducting review; analysis/interpretation of data; critical review and revision of the manuscript. He approved final draft submitted.

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