CME

ACG Clinical Guideline: Upper Gastrointestinal and Ulcer Bleeding

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We performed systematic reviews addressing predefined clinical questions to develop recommendations with the GRADE approach regarding management of patients with overt upper gastrointestinal bleeding. We suggest risk assessment in the emergency department to identify very-low-risk patients (e.g., Glasgow-Blatchford score = 0–1) who may be discharged with outpatient follow-up. For patients hospitalized with upper gastrointestinal bleeding, we suggest red blood cell transfusion at a threshold of 7 g/dL. Erythromycin infusion is suggested before endoscopy, and endoscopy is suggested within 24 hours after presentation. Endoscopic therapy is recommended for ulcers with active spurting or oozing and for nonbleeding visible vessels. Endoscopic therapy with bipolar electrocoagulation, heater probe, and absolute ethanol injection is recommended, and low- to very-low-quality evidence also supports clips, argon plasma coagulation, and soft monopolar electrocoagulation; hemostatic powder spray TC-325 is suggested for actively bleeding ulcers and over-the-scope clips for recurrent ulcer bleeding after previous successful hemostasis. After endoscopic hemostasis, high-dose proton pump inhibitor therapy is recommended continuously or intermittently for 3 days, followed by twice-daily oral proton pump inhibitor for the first 2 weeks of therapy after endoscopy. Repeat endoscopy is suggested for recurrent bleeding, and if endoscopic therapy fails, transcatheter embolization is suggested.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B962.

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INTRODUCTION

Gastrointestinal (GI) bleeding is the most common GI diagnosis necessitating hospitalization in the United States, accounting for over half a million admissions annually (1,2). Upper GI bleeding (UGIB) refers to bleeding originating from sites in the esophagus, stomach, or duodenum. Nearly 80% of patients visiting emergency departments for UGIB are admitted to the hospital with that principal diagnosis (2).

This document will consider patients with manifestations of overt UGIB, which include hematemesis (vomiting of red blood or coffee-grounds material), melena (black, tarry stool), or hematochezia (passage of red or maroon material per rectum). We will consider the initial management of the overall population of patients with UGIB up to and including the time of endoscopic evaluation. We will restrict our recommendations regarding endoscopic therapies and postendoscopic management to patients with ulcer bleeding, the most common cause of UGIB and the diagnosis for which most randomized controlled trials (RCTs) of therapy have been performed.

METHODS

The panel members, with input from the American College of Gastroenterology (ACG) Practice Parameters Committee, formulated clinically pertinent focused questions related to management of an acute UGIB episode and framed each question in the PICO (population, intervention, comparator, and outcome) format. The PICO format includes the population the question and guideline statement apply to (e.g., patients with UGIB), the intervention or action being assessed (e.g., proton pump inhibitor [PPI]), the comparator the intervention is compared with (e.g., placebo), and the outcome(s) of interest (e.g., further bleeding). A systematic English-language literature search of bibliographic databases (including Embase, Ovid MEDLINE, and ISI Web of Science) from database inception through October 2019 was performed for each PICO. Any citation identified as potentially relevant by a panel member after dual independent review of titles and abstracts was retrieved in full form for review by the panel. RCTs and meta-analyses of RCTs were sought. Observational studies were only sought when RCTs directly addressing the PICO were not available. We did not rely on abstracts published >5 years

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Table 1. List of guideline statements with strength of recommendation and quality of evidence

Risk stratification
1. We suggest that patients presenting to the emergency department with upper gastrointestinal bleeding (UGIB) who are classified as very low risk, defined as a risk assessment score with ≤1% false negative rate for the outcome of hospital-based intervention or death (e.g., Glasgow-Blatchford score = 0–1), be discharged with outpatient follow-up rather than admitted to hospital (conditional recommendation, very-low-quality evidence).
Red blood cell transfusion
2. We suggest a restrictive policy of red blood cell transfusion with a threshold for transfusion at a hemoglobin of 7 g/dL for patients with UGIB (conditional recommendation, low-quality evidence).
Pre-endoscopic medical therapy
Prokinetic therapy with erythromycin
3. We suggest an infusion of erythromycin before endoscopy in patients with UGIB (conditional recommendation, very-low-quality evidence).
Proton pump inhibitor (PPI) therapy
4. We could not reach a recommendation for or against pre-endoscopic PPI therapy for patients with UGIB.
Endoscopy for UGIB
Timing of endoscopy
5. We suggest that patients admitted to or under observation in hospital for UGIB undergo endoscopy within 24 hr of presentation (conditional recommendation, very-low-quality evidence).
Need for endoscopic hemostatic therapy for ulcers with active bleeding or nonbleeding visible cessels
6. We recommend endoscopic therapy in patients with UGIB due to ulcers with active spurting, active oozing, and nonbleeding visible vessels (strong recommendation, moderate-quality evidence).
Need for endoscopic hemostatic therapy for ulcers with adherent clot
7. We could not reach a recommendation for or against endoscopic therapy in patients with UGIB due to ulcers with adherent clot resistant to vigorous irrigation.
Choice of endoscopic hemostatic therapy for bleeding ulcers
8. We recommend endoscopic hemostatic therapy with bipolar electrocoagulation, heater probe, or injection of absolute ethanol for patients with UGIB due to ulcers (strong recommendation, moderate-quality evidence).
9. We suggest endoscopic hemostatic therapy with clips, argon plasma coagulation, or soft monopolar electrocoagulation for patients with UGIB due to ulcers (conditional recommendation, very-low- to low-quality evidence).
10. We recommend that epinephrine injection not be used alone for patients with UGIB due to ulcers but rather in combination with another hemostatic modality (strong recommendation, very-low- to moderate-quality evidence).
11. We suggest endoscopic hemostatic therapy with hemostatic powder spray TC-325 for patients with actively bleeding ulcers (conditional recommendation, very-low-quality evidence).
12. We suggest over-the-scope clips as a hemostatic therapy for patients who develop recurrent bleeding due to ulcers after previous successful endoscopic hemostasis (conditional recommendation, low-quality evidence).
Antisecretory therapy after endoscopic hemostatic therapy for bleeding ulcers
13. We recommend high-dose PPI therapy given continuously or intermittently for 3 d after successful endoscopic hemostatic therapy of a bleeding ulcer (strong recommendation, moderate- to high-quality evidence).
14. We suggest that high-risk patients with UGIB due to ulcers who received endoscopic hemostatic therapy followed by short-term high-dose PPI therapy in hospital continue on twice-daily PPI therapy until 2 wk after index endoscopy (conditional recommendation, low-quality evidence).
Recurrent ulcer bleeding after successful endoscopic hemostatic therapy
15. We suggest that patients with recurrent bleeding after endoscopic therapy for a bleeding ulcer undergo repeat endoscopy and endoscopic therapy rather than undergo surgery or transcatheter arterial embolization (conditional recommendation, low-quality evidence for comparison with surgery, very-low-quality evidence for comparison with transcatheter arterial embolization)
Failure of endoscopic hemostatic therapy for bleeding ulcers
16. We suggest patients with bleeding ulcers who have failed endoscopic therapy next be treated with transcatheter arterial embolization (conditional recommendation, very-low-quality evidence).

before October 2019 or with only interim results presented without subsequent publication in full form. Relevant studies from review of reference lists of retrieved manuscripts or known to the authors also were considered. The critical outcome was further bleeding, which includes persistent and recurrent bleeding. Further bleeding was recommended as the primary endpoint for RCTs of UGIB management by an International Consensus Panel because prevention of further bleeding is the primary clinical goal for patients with UGIB (3). Mortality was defined as an important outcome but not critical for decision-making because death is uncommon in patients with UGIB (~2% in the United States (2)), and sample sizes for most RCTs are not based on assessment of mortality.

Other potential outcomes (e.g., length of hospitalization and surgery) were predefined for some individual PICOs. Meta-analyses performed for this guideline (fixed effect if $I^2 < 50\%$; random effects if $I^2 \geq 50\%$) as well as calculations of risk ratio (RR) and absolute risk difference for individual studies were performed with RevMan version 5.3 software (Cochrane Collaboration, Copenhagen, Denmark).

Each recommendation statement includes an assessment of the strength of the recommendation and the quality of evidence based on the GRADE methodology (4,5), followed by a summary of evidence outlining the key data and considerations behind the recommendation. The quality of evidence is rated using 4 categories. "High" quality indicates we are confident the true effect lies close to the estimate of the effect. "Moderate" indicates we are moderately confident in the effect estimate: The true effect is likely to be close to the effect estimate, but possibly is substantially different. "Low" indicates our confidence in the effect estimate is limited, and the true effect may be substantially different. "Very low" indicates we have very little confidence in the effect estimate, and the true effect is likely to be substantially different. The grade of evidence provided with each statement is based on the critical outcome, further bleeding, unless otherwise specified. The strength of recommendation reflects the level of confidence that the desirable effects of an action outweigh the undesirable effects and is based on the quality of evidence for efficacy, safety, values and preferences of patients, availability, and resource use. "Strong" recommendations begin with the words "we recommend" and are made when we are confident the desirable effects of an action clearly outweigh the undesirable effects. Strong recommendations imply that most informed patients would choose the recommended management and clinicians should provide the intervention to most patients. "Conditional" recommendations begin with the words "we suggest" and indicate the desirable and undesirable effects of an action are closely balanced or appreciable uncertainty exists about the balance. In this case, informed patients' choices will vary based on their values and preferences, with many not wanting the intervention; informed clinicians' choices also may vary, and they must ensure their patients' values and preferences are incorporated in decisions regarding management.

Each PICO, followed by the evidence table that summarizes the evidence and the grading of the quality of evidence from relevant studies for that PICO, is provided in the Supplementary Material (see Supplementary Digital Content, http://links.lww.com/AJG/B962). The list of guideline statements is provided in Table 1.

GUIDELINE STATEMENTS

Risk stratification

1. We suggest that patients presenting to the emergency department with UGIB who are classified as very low risk, defined as a risk assessment score with ≤1% false negative rate for the outcome of hospital-based intervention or death (e.g., Glasgow-Blatchford score = 0–1), be discharged with outpatient follow-up rather than admitted to hospital (conditional recommendation, very-low-quality evidence).

Summary of evidence. The goal of identifying very-low-risk patients is to allow a subset of patients to be safely discharged from the emergency department with outpatient follow-up, thereby reducing costs with little or no chance that patients will be at risk of poor outcomes that require or might have been prevented with in-hospital management. Thus, the primary benefit for this recommendation is economic because of fewer hospitalizations.

Table 2. Glasgow-Blatchford score

Risk factors at admission	Factor score
Blood urea nitrogen (mg/dL)	
18.2 to <22.4	2
22.4 to <28.0	3
28.0 to <70.0	4
≥70.0	6
Hemoglobin (g/dL)	
12.0 to <13.0 (men); 10.0 to <12.0 (women)	1
10.0 to <12.0 (men)	3
<10.0	6
Systolic blood pressure (mm Hg)	
100–109	1
90–99	2
<90	3
Heart rate (beats per minute)	
≥100	1
Melena	1
Syncope	2
Hepatic disease[a]	2
Cardiac failure[a]	2

[a]Hepatic disease and cardiac failure were not defined in the original report of the Glasgow-Blatchford score. One more recent study defined hepatic disease as known history, or clinical and laboratory evidence, of chronic or acute liver disease and cardiac failure as known history, or clinical and echocardiographic evidence, of cardiac failure (6).

Composite outcomes are commonly used in studies of risk assessment scores (6–10). We relied primarily on the composite outcomes as defined in the studies we reviewed, considering them preferable to single outcomes of further bleeding or mortality for identifying very-low-risk patients. The composite outcome in the 4 individual studies we assessed included hospital-based interventions for bleeding (transfusion and hemostatic therapies) and death (6–8,10), while the systematic review of other studies additionally included rebleeding leading to readmission in their composite outcome (9) (see Supplementary Table 1.2, Supplementary Digital Content, http://links.lww.com/AJG/B962).

Achieving a high sensitivity, which minimizes false negatives, is key when making decisions regarding outpatient management. False negatives occur when patients who will require intervention or die are incorrectly classified by the risk assessment tool as not requiring intervention or dying. This may result in discharging a patient who will require intervention or die. The goal would be no false negatives (100% sensitivity), but providers and patients can determine the level of certainty required to feel comfortable with discharge from the emergency department.

Patients with a Glasgow-Blatchford score (GBS, Table 2) of 0 have point estimates of 99%–100% sensitivity with lower bounds of 95% confidence interval (CI) of 98% (7–9), although specificities are poor with point estimates ranging from 8% to 22% (see Supplementary Table 1.2, Supplementary Digital Content, http://links.lww.com/AJG/B962). Patients with a GBS = 0–1 have sensitivity point estimates of 99%, with lower bounds of 95% CI of 97%–98% (7,8); specificities are higher with point estimates ranging from 27% to 40%. Two large multicenter studies reported GBS = 0–1 in 19%–24% of patients presenting with UGIB (6,7). A recent machine learning model from Shung et al. (8) can be set to provide sensitivities of 99% (comparable with GBS = 0–1) or 100% (comparable with GBS = 0) with specificities that are higher than GBS.

Figure 1 illustrates the calculation of sensitivity and specificity for a hypothetical cohort of 250 patients presenting with UGIB using the GBS threshold of 1 to identify very-low-risk patients. A 99% sensitivity means that for every 100 of these patients who will require hospital-based intervention or die, there will be 1 false negative—i.e., 1 patient with GBS = 0–1 is falsely categorized as not requiring intervention or dying. As mentioned, specificities are poor at high sensitivities. Figure 1 shows that among the 150 patients who will not require intervention or die, only 50 are correctly classified by a GBS = 0–1 (33% specificity, 67% rate of false positives). Thus, most patients who do not require intervention or die, and likely would not benefit from hospitalization, are not classified as very low risk. Improvement in specificity while maintaining high sensitivity is a key goal in development of new risk assessment models.

The panel considered if a sensitivity below 100% was acceptable and concluded that aiming for a sensitivity of 99% was reasonable because the greater specificity with the slightly lower sensitivity allows a greater number of patients to be discharged. Two risk stratification tools seem to provide sensitivities of 99% (with lower bound of 95% CI of 97%–98%): GBS = 0–1 and the Shung machine learning model (see Supplementary Table 1.2, Supplementary Digital Content, http://links.lww.com/AJG/B962). The panel mentioned only GBS in the recommendation because GBS has been widely studied in a variety of settings while the Shung model has only been evaluated in 1 setting at present. Importantly, the suggested threshold of 1% false negatives (99% sensitivity) for the outcome of hospital-based intervention or death serves as a guide for assessing prognostic models developed in the future. Patient and provider preferences regarding certainty of risk and desire for outpatient vs inpatient management should play an important role in decisions regarding thresholds. Decisions need to be individualized based on patient age, comorbidities, reliability, social support, and accessibility to medical care after discharge.

Although observational studies suggest GBS and a machine learning model identify very-low-risk patients with high sensitivity, evidence is scant to document that discharging such patients from the emergency department with outpatient management can indeed be performed with little or no risk as compared to admitting such patients. Only 1 study meeting the criteria for this PICO was identified: a before-after study (10) (see Supplementary Table 1.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). Before implementing a rule that patients with GBS = 0 would not be admitted unless necessary for other reasons, 0 of 105 patients with GBS = 0 required hospital-based intervention (transfusion, endoscopic, or surgical therapy) or died within 30 days. After implementing the rule, 0 of the 84 patients with GBS = 0 who were not admitted required hospital-based intervention or died on follow-up (10). In addition, a retrospective case series noted that, after initiating a protocol in which patients with acute UGIB and GBS = 0–1 would be discharged from the emergency department with outpatient care if no other reason for admission, 0 of 103 patients with GBS = 0–1 who were discharged required hospital-based intervention or died within 30 days (11).

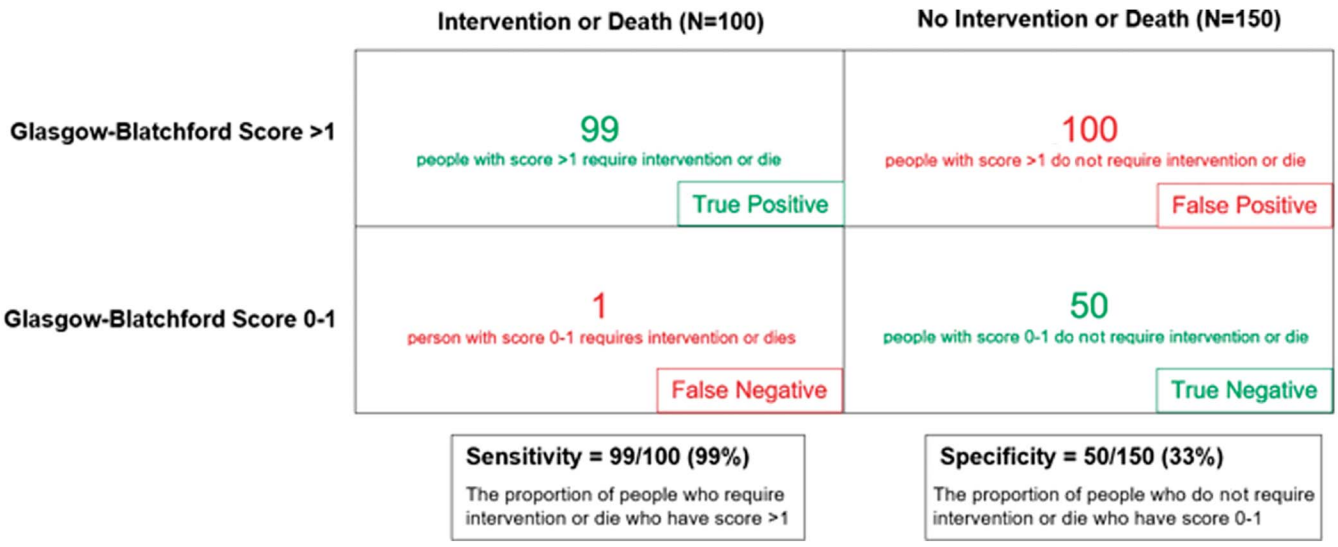

Figure 1. Two-by-two table to determine sensitivity and specificity for hypothetical population of 250 patients presenting with upper gastrointestinal bleeding using Glasgow-Blatchford score cutoff of 1. The upper row includes patients with scores >1, and the lower row includes those with scores of 0–1 (defined as very low risk). The left column shows the 100 patients who will require hospital-based intervention or die, with sensitivity calculated by the formula true positives divided by total number requiring intervention or dying (99/100 = 99%). The right column shows the 150 patients who will not require hospital-based intervention or die, with specificity calculated by the formula true negatives divided by total number not requiring intervention or dying (50/150 = 33%).

Conclusion. Use of a risk assessment tool to identify patients with ≤1% risk of transfusion, hemostatic intervention, or death who may be discharged with outpatient management should reduce hospitalizations and costs. A GBS = 0–1 should meet this requirement and allows more patients to be discharged than GBS = 0, which was the threshold suggested in the 2012 ACG Guidelines (1).

Red blood cell transfusion

2. We suggest a restrictive policy of red blood cell (RBC) transfusion with a threshold for transfusion at a hemoglobin of 7 g/dL for patients with UGIB (conditional recommendation, low-quality evidence).

Summary of evidence. For the general population of patients with anemia, not restricted to UGIB, current US guidelines make a strong recommendation for a restrictive RBC transfusion threshold of 7 g/dL in hospitalized hemodynamically stable patients, including critical care patients, and a threshold of 8 g/dL in those undergoing orthopedic or cardiac surgery and those with existing cardiovascular disease (12). The guideline recommendation stated that a threshold of 7 g/dL was likely comparable with 8 g/dL, but randomized trial evidence was not available in all patient categories; evidence was judged insufficient to make a recommendation in patients with acute coronary syndrome. These recommendations were based on a systematic review indicating that restrictive transfusion policies reduced the number of patients receiving RBC transfusion by 43% with no evidence of an impact on clinically important outcomes (13).

Two RCTs met our criteria for assessment of restrictive vs liberal transfusion policy in UGIB (14,15) (Table 3, see Supplementary Table 2.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). Villaneuva et al. (14) performed a randomized comparison of 7-g/dL vs 9-g/dL thresholds in 899 patients with 45-day mortality as the primary outcome. Patients with massive exsanguinating bleeding and those with symptomatic peripheral vasculopathy, stroke, or transient ischemic attack in the previous 90 days were excluded. Transfusion was less common in the restrictive arm (49% vs 86%, $P < 0.001$). The restrictive arm had lower mortality (5% vs 9%, $P = 0.02$; adjusted hazard ratio [HR] = 0.55, 95% CI 0.33–0.92), less further bleeding (10% vs 16%, $P = 0.01$; adjusted HR = 0.68, 0.47–0.98), and fewer transfusion reactions (3% vs 9%, $P = 0.001$) and cardiac complications (11% vs 16%, $P = 0.04$) (Table 3).

Jairath et al. (15) performed a cluster randomized trial in which participating sites rather than individual patients were randomly assigned to a study arm. Three hospitals were allocated to an 8-g/dL threshold and 3 hospitals to a 10-g/dL threshold, with exsanguinating hemorrhage as the only exclusion criterion. Recruitment was higher in the liberal policy arm with an unequal distribution of participants into the restrictive and liberal study arms (43% vs 57%); evidence of potential selection bias also was noted. The difference in the proportion receiving transfusion between the restrictive and liberal groups was less than would be anticipated (33% vs 46%, $P = 0.23$), likely due at least in part to lower adherence to the transfusion policy in the liberal group. Differences between restrictive and liberal policies were not significant in 28-day mortality (5% vs 7%), further bleeding (5% vs 9%), transfusion reactions (1% vs 2%), or thromboembolic/ischemic events (4% vs 7%) (Table 3).

Based on the above evidence, the panel suggested a restrictive transfusion policy. A threshold for transfusion at hemoglobin of 7 g/dL (i.e., transfusion administered when hemoglobin falls below 7 g/dL) was chosen because the RCT demonstrating benefit of restrictive transfusion in UGIB used a threshold of 7 g/dL (14). Furthermore, a meta-analysis of RCTs in patients with any transfusion indication found no significant difference in the effect on mortality with restrictive vs liberal transfusion between the subgroup of RCTs using a restrictive threshold of 8–9 g/dL (RR = 1.05, 0.78–1.40) and the subgroup using 7 g/dL (RR = 0.94, 0.74–1.19) (13).

Given the exclusion of exsanguinating UGIB from these RCTs and the knowledge that hemoglobin levels in hypotensive patients will be lower after fluid resuscitation even in the absence of further bleeding, the panel agreed it is reasonable to transfuse hypotensive patients before hemoglobin levels reach 7 g/dL. Given a paucity of randomized trial evidence in patients with UGIB and pre-existing cardiovascular disease and the current guideline recommendation to use 8 g/dL in patients with pre-existing cardiovascular disease, the panel agreed this threshold was reasonable in patients with UGIB and pre-existing cardiovascular disease. This population must be differentiated from those who present with acute coronary syndrome. Evidence is very limited in the latter, although meta-analysis of 2 small studies in patients with anemia and acute coronary syndrome (N = 141) or stable coronary artery disease undergoing cardiac catheterization (N = 14) indicated a possible suggestion of increased mortality with restrictive transfusion using a threshold of 8 g/dL or hematocrit 24% (RR = 3.88, 0.83–18.13) (13,16,17). Thus, a threshold higher than 8 g/dL may be considered in patients with UGIB and acute coronary syndrome, based on very limited evidence.

Conclusion. A restrictive RBC transfusion policy in which patients are transfused when hemoglobin falls below 7 g/dL seems to reduce further bleeding and death, a conclusion unchanged from the 2012 ACG Guidelines (1). Hypotensive patients may be transfused at higher hemoglobin levels given equilibration that occurs with fluid resuscitation and a threshold of 8 g/dL is reasonable in patients with pre-existing cardiovascular disease.

Pre-endoscopic medical therapy

Prokinetic therapy with erythromycin.

3. We suggest an infusion of erythromycin before endoscopy in patients with UGIB (conditional recommendation, very-low-quality evidence).

Summary of evidence. The rationale for using a prokinetic agent such as erythromycin is to propel blood and clot distally from the upper GI tract and improve visualization at endoscopy, thereby improving diagnostic yield. Increasing the diagnostic yield ideally would improve clinically important outcomes such as further bleeding by increasing the proportion of patients who receive appropriate management (e.g., endoscopic therapy and medical therapy) based on endoscopic findings. The panel also predefined other potentially meaningful benefits: reduction in repeat endoscopies (if the correct diagnosis is made more often on index endoscopy) and reduction in hospital stay (more frequent diagnoses on index endoscopy may allow earlier discharge in patients found to

have low-risk findings, and fewer repeat endoscopies may reduce prolongations in hospital stay that occur due to waiting for repeat procedures).

Our search identified a systematic review, of 8 RCTs (18) and 1 additional RCT published after the systematic review that included 29 patients assigned to erythromycin or gastric lavage (19) (Table 4, see Supplementary Table 3.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). Only 1 of these 9 RCTs provided results for our critical outcome of further bleeding (19): 1/14 (7.1%) with erythromycin vs 2/15 (13.3%) with gastric lavage; difference = −6%, −28% to 16%. Mortality results were provided in 3 RCTs with our meta-analysis of these trials for erythromycin vs placebo/no treatment revealing RR = 0.81, 0.41–1.60 (20–22). The meta-analysis of 8 RCTs documented reduction in need for repeat endoscopy (odds ratio [OR] = 0.51, 0.34–0.77) and days of hospitalization (mean difference = −1.75, −2.43 to −1.06) (18). Units of blood transfused tended to be lower with erythromycin (mean difference = −1.06, −2.24 to 0.13 with significant heterogeneity [I^2 = 89%]) (18).

Although evidence was lacking for benefit of erythromycin in reducing further bleeding and mortality, erythromycin provided meaningful reductions in repeat endoscopies and length of hospitalizations: e.g., the upper bound of the 95% CI suggested at least a 1-day decrease in hospitalization. The economic benefit of reduced procedures and hospital stay, as well as the presumed desire of patients to avoid additional procedures and hospital days, relatively low cost, and ease of administration, led the panel to a conditional recommendation for use of pre-endoscopic erythromycin. The available evidence (enrollment criteria in RCTs) did not suggest benefit was restricted to a specific subgroup of patients with acute UGIB. Evidence assessing the prokinetic agent metoclopramide is scant, coming only from older abstracts, and does not provide support for its use (23–25).

An intravenous infusion of 250 mg is recommended because this or similar dose was most commonly used in the RCTs. The infusion was given over 5–30 minutes (most often 20–30 minutes) and followed by endoscopy 20–90 minutes later (18,19). Intravenous erythromycin can prolong the QT interval, with effect related to rate of infusion and dose, and is very rarely associated with ventricular tachyarrhythmias such as torsade de pointes. However, review of case reports indicates this occurs with repeated and/or higher doses (26,27). Nevertheless, some, but not all, studies excluded patients with factors that potentially increase the risk of torsade de pointes, which may include QT prolongation on baseline electrocardiogram, cardiac disease, electrolyte abnormalities, hepatic dysfunction, concurrent antiarrhythmic therapy, and drugs that prolong QT interval and are CYP3A4 substrates (e.g., terfenadine and astemizole) (19,20,22,26,28,29).

Conclusion. Infusion of 250 mg of erythromycin 20–90 minutes before endoscopy may reduce the need for repeat endoscopy and length of hospitalization, although is not documented to improve clinical outcomes such as further bleeding. The 2012 ACG Guidelines indicated such an infusion "should be considered" (1).

PPI therapy.

4. We could not reach a recommendation for or against pre-endoscopic PPI therapy for patients with UGIB.

Summary of evidence. Systematic review revealed 3 placebo-controlled RCTs assessing pre-endoscopic PPI therapy (30–32) (see Supplementary Table 4.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). However, in 2 of these trials (30,31), all patients remained in their assigned treatment arm (placebo or PPI) after endoscopy. Because standard practice requires PPI therapy in patients with ulcers, these 2 trials are not congruent with current clinical practice. This study design also is methodologically problematic because if patients in the placebo arm who require PPIs remain on placebo after endoscopy while those in the PPI arms receive PPIs after endoscopy, bias in favor of the PPI arms is introduced. These 2 trials therefore do not allow for assessment of postendoscopic endpoints such as further bleeding and mortality, leading the panel to rely solely on the trial by Lau et al. for these outcomes. All 3 studies were used to assess outcomes up to the time of endoscopy such as need for endoscopic treatment.

Lau et al. (32) found no evidence of benefit for PPI (intravenous omeprazole, 80-mg bolus followed by 8-mg/hr infusion) vs placebo in further bleeding (11/314 [3.5%] vs 8/317 [2.5%]; difference = 1%, −2 to 4%) or mortality (8/314 [2.5%] vs 7/317 [2.2%]; difference = 0%, −2% to 3%) (Table 5). Similarly, our meta-analysis of the 2 other excluded studies (30,31) did not show benefit in further bleeding or mortality despite bias toward PPI therapy. Our meta-analysis of the 3 studies (30–32) revealed reduced endoscopic hemostatic treatment at index endoscopy with PPI vs placebo (RR = 0.73, 0.57–0.94), likely related to lower rates of high-risk stigmata of recent hemorrhage at endoscopy.

Table 3. Outcomes in randomized trials of restrictive vs liberal transfusion strategy

	Villaneuva et al. (14)		Jairath et al. (15)[a]	
	Restrictive strategy (N = 444)	Liberal strategy (N = 445)	Restrictive strategy (N = 257)	Liberal strategy (N = 383)
Hemoglobin threshold (g/dL)	7	9	8	10
Further bleeding, n (%)	45 (10.1)	71 (16.0)	13 (5.1)	31 (8.1)
Relative effect size (95% CI)	Adjusted HR = 0.68 (0.47–0.98)		RR = 0.62 (0.33–1.17)	
Absolute effect size (95% CI)	Difference = −6% (−10% to −1%)		Difference = −3% (−7% to 1%)	
Mortality, n (%)	23 (5.2)	41 (9.2)	14 (5.4)	25 (6.5)
Relative effect size (95% CI)	Adjusted HR = 0.55 (0.33–0.92)		RR = 0.83 (0.44–1.57)	
Absolute effect size (95% CI)	Difference = −4% (−7% to −1%)		Difference = −1% (−5% to 3%)	

CI, confidence interval; HR, hazard ratio; RR, risk ratio.
[a]Cluster randomized trial in which participating sites rather than individual patients were randomly assigned to a study arm.

Thus, limited low-quality evidence suggests no benefit of pre-endoscopic PPI therapy in further bleeding or mortality, although the CIs for these outcomes are wide. In the absence of evidence for clinical benefit, the panel could not make a recommendation for pre-endoscopic PPI therapy. Nevertheless, the panel did not recommend against pre-endoscopic PPI therapy, given the imprecision of the evidence and other very indirect evidence. Randomized trial data (see statement 13) indicate that postendoscopic high-dose PPI therapy reduces further bleeding after endoscopic therapy in patients with ulcers with high-risk stigmata (33) and in patients with ulcers with adherent clots not treated with endoscopic therapy (34,35), raising the possibility that pre-endoscopic PPI therapy might provide some benefit in a minority of patients with UGIB. Furthermore, in patients who will not undergo endoscopy and endoscopic hemostatic therapy or in whom it will be delayed, the panel felt pre-endoscopic PPI therapy might be given based on very indirect evidence from a meta-analysis of RCTs in patients who did not consistently receive endoscopic hemostatic therapy that showed reduced rebleeding (OR = 0.38, 0.18–0.81), but not mortality, with PPI vs placebo or histamine-2-receptor antagonist (H2RA) (36).

Pre-endoscopic PPI therapy may modestly reduce need for endoscopic treatment. Providers and patients who place a high value on reducing the need for endoscopic therapy may choose to use pre-endoscopic PPI therapy. Economic considerations also will vary across different healthcare locations: The additional cost of PPI therapy for all patients with UGIB vs the reduction in cost by avoiding endoscopic therapy in a small number of patients may impact decisions. Economic analyses were identified but not incorporated because models did not use the primary clinical outcome data reported by Lau et al. in the effectiveness analyses.

Conclusion. Available evidence indicates no benefit of pre-endoscopic PPI therapy for clinical outcomes, preventing a recommendation for its use. Given a modest reduction in endoscopic therapy and the unproven possibility that PPIs might benefit a select minority of patients and/or those in whom endoscopic therapy is unavailable or delayed, we did not recommend against its use. Other guidelines have produced highly variable statements, ranging from recommendations for (37) to against (38) pre-endoscopic PPI therapy. In previous guidelines, we indicated that pre-endoscopic PPI therapy may be considered to decrease the need for endoscopic therapy but did not improve clinical outcomes (1,39). However, since then, consensus on the appropriate manner of presenting guideline recommendations has evolved. Guidelines should provide a recommended action (40). Therefore, statements such as "may be considered," which do not recommend for or against an action such as giving PPI therapy, are no longer used.

Endoscopy for UGIB

Timing of endoscopy.

5. We suggest that patients admitted to or under observation in hospital for UGIB undergo endoscopy within 24 hours of presentation (conditional recommendation, very-low-quality evidence).

Summary of evidence. Making an earlier diagnosis is not sufficient to justify early endoscopy; evidence of benefit in clinical, economic, or patient-centered outcomes is required. Potential benefits of early endoscopy include more accurate prognosis to guide management (e.g., timing of refeeding and discharge) and earlier provision of endoscopic or medical therapy based on endoscopic findings (41). Potential harms may include death or complications if endoscopy is performed before appropriate resuscitation and management of active comorbidities as well as poorer outcomes with after-hours endoscopy.

The panel considered studies in overall populations of patients with UGIB as well as in studies restricted to patients with clinical features predicting low risk or high risk of further bleeding and death. This statement was limited to patients who had been admitted to hospital or placed in a hospital observation unit. Patients identified as very low risk who are discharged from the emergency department with outpatient follow-up (discussed in Statement 1) were not considered. Observational studies were included because of a lack of RCTs directly addressing the PICOs. Because fundamental differences likely exist in important characteristics that may influence outcomes between patients who receive and who do not receive early endoscopy in nonrandomized studies, we only included observational studies that attempted adequate statistical adjustment in assessment of outcomes.

Overall population with UGIB. No RCT assessed endoscopy within 24 hours vs >24 hours, although an RCT compared endoscopy performed ≤12 hours vs >12 hours after presentation in consecutive patients with UGIB (42) (see Supplementary Table 5.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). The authors reported results only in those with endoscopically confirmed ulcer bleeding and found no reduction in further bleeding (6/162 [3.7%] vs 8/163 [4.9%]) or mortality

Table 4. Randomized trials of pre-endoscopic erythromycin infusion vs no erythromycin or placebo: results of systematic review and meta-analyses

Outcome	No. of studies (no. of subjects)	Erythromycin vs no erythromycin/placebo effect size (95% CI)
Further bleeding	1 study (N = 29) (19)	RR = 0.54 (0.05–5.28)
Mortality	3 studies (N = 278) (20–22)	RR = 0.81 (0.41–1.60)
Second-look endoscopy	8 studies (N = 598) (18)	OR = 0.51 (0.34–0.77)
Hospital days	5 studies (N = 375) (18)	Mean difference = −1.75 (−2.43 to −1.06)
Units of red cells transfused	6 studies (N = 544) (18)	Mean difference = −1.06 (−2.24 to 0.13)[a]

CI, confidence interval; OR, odds ratio; RR, risk ratio.
[a]Heterogeneity (I^2 = 89%).

(1/162 [0.6%] vs 1/163 [0.6%]). Very-low-quality evidence from observational studies suggests that patients hospitalized with UGIB who undergo endoscopy within 1 day of admission have a shorter hospital stay (43–45) than those who do not. Two of these observational studies (43,45) identified a lower risk of surgery and another reported a reduction in mortality with endoscopy within 1 day of admission (46). It is uncertain whether endoscopy reported as within 1 day of admission in database studies truly occurred within 24 hours of admission; some potentially might occur the next calendar day beyond 24 hours after admission (44–46).

Low-risk clinical features. Two small RCTs in patients with low-risk clinical features (hemodynamically stable with no severe comorbidities) found that endoscopy within 2–6 hours of initial evaluation identified low-risk endoscopic findings (e.g., clean-based ulcer, nonbleeding Mallory-Weiss tear) that should allow discharge with outpatient follow-up in at least 40% of patients (47,48) (see Supplementary Table 6.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). A reduction in inpatient care was identified in only one of these studies (48) because in the second study attending physicians failed to follow the endoscopists' recommendation for outpatient care in ~80% of those with low-risk endoscopic findings (47). Differences in further bleeding or mortality were not identified. Because neither RCT assessed endoscopy within 24 hours vs >24 hours, we also reviewed a large cohort study of 5,415 hemodynamically stable patients without significant comorbidities (American Society of Anesthesiologists score 1–2) with endoscopically documented bleeding ulcers (49). Endoscopy within 24 hours from admission showed a trend to lower in-hospital mortality (adjusted OR = 0.59, 0.33–1.05) but not 30-day mortality (adjusted OR = 1.02, 0.50–2.09).

High-risk clinical features. Previous guidelines have suggested considering endoscopy within 12 hours in patients with high-risk features such as hemodynamic instability (1,37,50) or cirrhosis (51), although supporting evidence is extremely limited (see Supplementary Table 7.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). Relevant studies identified included 2 observational studies using statistical adjustment—and results were conflicting. A nationwide Danish cohort study of consecutive patients with endoscopically confirmed ulcer bleeding found increased mortality in high-risk patients with very early or late endoscopy (49). In-hospital mortality was lower with endoscopy 6–24 hours after admission in hemodynamically unstable patients and 12–36 hours after admission in hemodynamically stable patients with significant comorbidities (American Society of Anesthesiologists score 3–5) as compared to endoscopy outside these timeframes. This study raised the possibility that very early endoscopy may cause harm if hemodynamic resuscitation and management of other active comorbidities is not undertaken before endoscopy. By contrast, a single-center Korean cohort study reported 28-day mortality was reduced with endoscopy within 6 hours vs 6–48 hours after presentation (52).

A large RCT, identified as a 2015 abstract reporting interim results and subsequently fully published in 2020, compared urgent endoscopy within 6 hours of gastroenterology consultation with a control group assigned to endoscopy 6–24 hours after consultation in 516 patients predicted to be at high risk based on GBS ≥12 (53). Neither further bleeding (28/258 [10.9%] vs 20/258 [7.8%]; difference = 3%, −2% to 8%) nor mortality (23/258 [8.9%] vs 17/258 [6.6%]; difference = 2%, −2% to 7%) was reduced with earlier endoscopy (Table 6). Similarly, no benefit was seen in duration of hospitalization or transfusion requirements, although endoscopic hemostatic treatment was 11.6% more frequent in the urgent endoscopy group. Because of the lag from presentation to randomization, the study actually compared endoscopies at means of 10 and 25 hours after presentation, with 55% of the control group having endoscopy >24 hours after presentation. These data raise the possibility that intervals even greater than 24 hours may be acceptable.

This trial excluded patients with hypotensive shock who failed to stabilize after initial resuscitation, a group representing only 5% of their high-risk patients (53). Based on anecdotal experience, the panel believes such patients require urgent intervention with endoscopy or interventional radiology.

Table 5. Double-blind placebo-controlled randomized trial of omeprazole bolus followed by continuous infusion started before endoscopy in patients presenting to emergency department with hematemesis or melena (32)

Outcome	Omeprazole (N = 314)	Placebo (N = 317)
Hours of infusion before endoscopy, mean ± SD	14.7 ± 6.3	15.2 ± 6.2
Further bleeding (30 d), n (%)	11 (3.5)	8 (2.5)
Death (30 d), n (%)	8 (2.5)	7 (2.2)
Hospital days, mean ± SD	4.5 ± 5.3	4.9 ± 5.1
Units of blood transfused, mean ± SD	1.54 ± 2.41	1.88 ± 3.44
Endoscopic therapy, n (%)	60 (19.1)[a]	90 (28.4)

[a] $P = 0.007$ vs placebo.

Conclusion. The panel suggests that patients admitted or under observation in hospital with overt UGIB, whether predicted to be at low risk or high risk of further bleeding and death, undergo upper endoscopy within 24 hours of presentation. This decision was based on evidence of potential economic benefit (reduced length of stay) (43–45,48) as well as possible clinical benefit in mortality and need for surgery in observational studies (43,45,46,49). We chose to use the time from presentation rather than from admission, given the likely wide variation in times from presentation to admission across different institutions. Although observational studies supporting a 1-day threshold used admission rather than presentation as the starting point, the panel was concerned that institutions with lengthy delays between presentation and admission might have unacceptably long periods to endoscopy if time from admission was used. Given a large observational study raising the possibility of harm with very early endoscopy in patients with hemodynamic instability or significant comorbidities (49) and a large randomized trial indicating no benefit of very early endoscopy in high-risk patients (53), the panel agreed that resuscitation and attention to other active comorbidities should be undertaken as necessary before endoscopy and did not include the suggestion from the 2012 ACG Guidelines that endoscopy within 12 hours "may be considered" in patients with high-risk clinical features (1). The panel noted this practice seems different from approaches for hemorrhagic shock because of trauma, which may include rapid

hemostatic intervention with limited crystalloid administration and low blood pressure targets. Whether such approaches are beneficial in a subset of patients with shock because of UGIB is uncertain. Data in hemodynamically stable patients without severe comorbidities (47,48) support endoscopy as soon as possible within routine hours because it may allow early discharge in a substantial proportion of patients who have low-risk endoscopic findings, thereby reducing length of hospitalization and costs. Suggested initial management from time of presentation through endoscopy is shown in Figure 2.

Need for endoscopic hemostatic therapy for ulcers with active bleeding or nonbleeding visible vessels.

6. We recommend endoscopic therapy in patients with UGIB due to ulcers with active spurting, active oozing, and nonbleeding visible vessels (strong recommendation, moderate-quality evidence).

Summary of evidence. A 2009 meta-analysis of 19 RCTs reported marked benefit of endoscopic therapy vs no endoscopic therapy for the outcome of further bleeding in patients with active bleeding (RR = 0.29, 0.20–0.43; number needed to treat [NNT] = 2, 2–2) and nonbleeding visible vessels (RR = 0.49, 0.40–0.59; NNT = 5, 4–6) (33) (see Supplementary Table 8.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). Benefit in mortality was not documented. No subsequent relevant RCTs were identified.

Table 6. Randomized trial of endoscopy <6 hours vs 6–24 hours after gastroenterology consultation in patients with hematemesis or melena and Glasgow-Blatchford score ≥12 (53)

Outcome	Endoscopy <6 hr (N = 258)	Endoscopy 6–24 hr (N = 258)
Hours from presentation to endoscopy, mean ± SD	9.9 ± 6.1	24.7 ± 9.0
Further bleeding (30 d), n (%)	28 (10.9)	20 (7.8)
Death (30 d), n (%)	23 (8.9)	17 (6.6)
Hospital days, median (range)	5 (4–9)	5 (3–8)
Units of blood transfused, mean ± SD	2.4 ± 2.3	2.4 ± 2.1
Endoscopic therapy, n (%)	155 (60.1)[a]	125 (48.4)

[a]$P = 0.01$ vs endoscopy 6–24 hours.

Most RCTs and the meta-analysis cited combine spurting and oozing bleeding into a single "active-bleeding" category. Spurting active bleeding is much less common than oozing; e.g., a large prospective trial reported 68 (17%) of 397 patients with actively bleeding ulcers had spurting (54). In addition, further bleeding seems to be more frequent in patients with spurting vs oozing active bleeding (55,56). Nevertheless, further bleeding in patients with oozing managed without endoscopic therapy is still high enough to

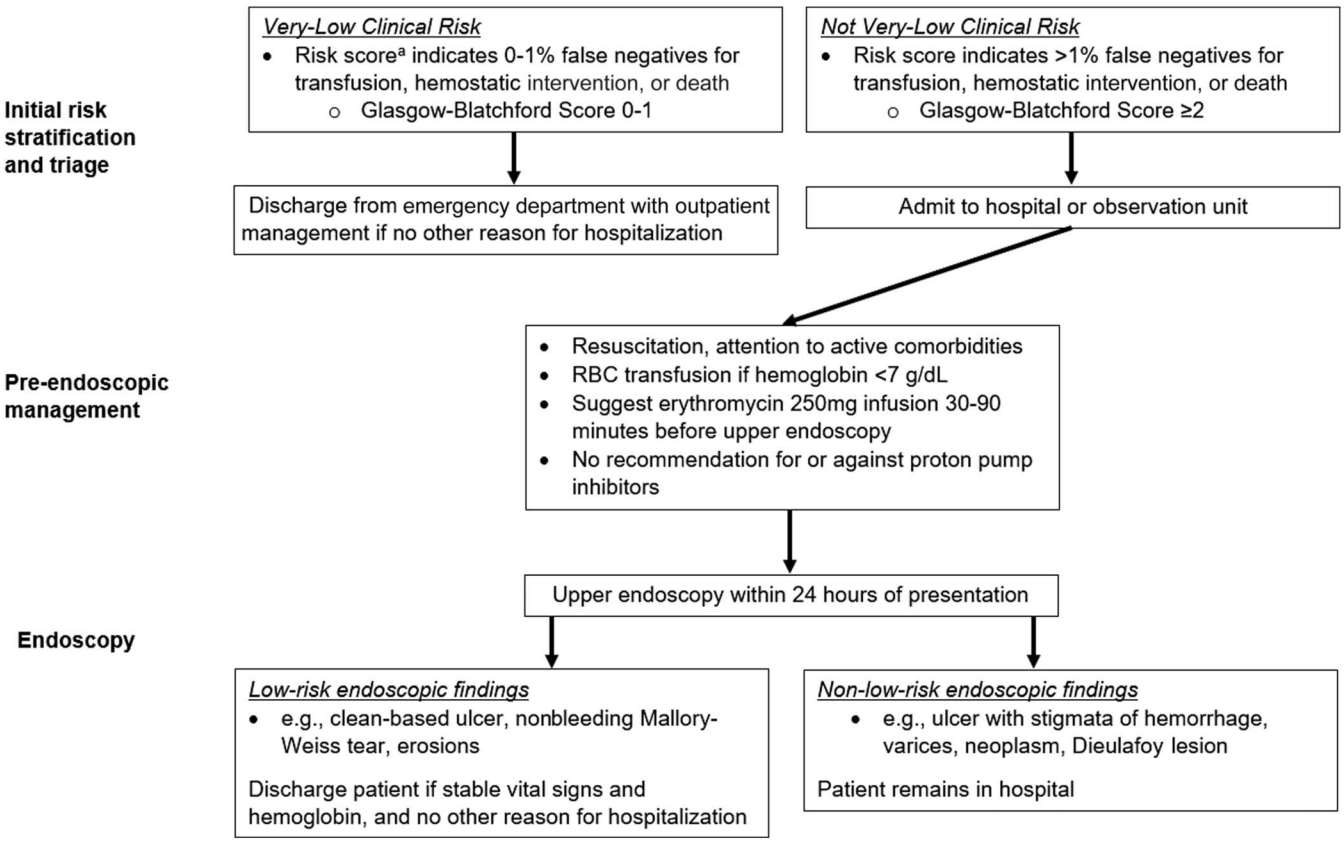

Figure 2. Initial management of patients presenting with overt upper gastrointestinal bleeding. [a]Future risk assessment tools may be used if score discriminates risk of transfusion, hemostatic intervention or death with 99–100% sensitivity (0%–1% false negatives). RBC, red blood cell.

support a recommendation for endoscopic therapy. A summary of 8 prospective trials that included patients with oozing managed without endoscopic therapy revealed a pooled rate of further bleeding of 39% (range 10%–100%) (1). Of note, the definition of oozing may vary widely among endoscopists. Some trials require continuous bleeding for 5 minutes of observation to be labeled as active oozing (57), which should reduce categorization of minor and transient bleeding (e.g., after scope trauma) as active oozing.

Conclusion. As indicated in the 2012 ACG Guidelines (1), endoscopic therapy provides important clinical benefit in patients with UGIB due to ulcers with high-risk findings of active bleeding and nonbleeding visible vessels.

Need for endoscopic hemostatic therapy for ulcers with adherent clot.

7. We could not reach a recommendation for or against endoscopic therapy in patients with UGIB due to ulcers with adherent clot resistant to vigorous irrigation.

Summary of evidence. The most recent meta-analysis of RCTs assessing this question did not find benefit of endoscopic therapy vs no endoscopic therapy in patients with clots for outcomes of further bleeding (RR = 0.31, 0.06–1.77) or mortality (RR = 0.90, 0.23–3.58) (33), and no subsequent relevant RCTs were identified (see Supplementary Table 9.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). Nevertheless, heterogeneity was present for the outcome of further bleeding, requiring closer assessment of the individual trials.

Two small US RCTs (N = 56, 32) reported high rates of rebleeding in the control group and significant reductions with endoscopic therapy (58,59). Neither study used vigorous irrigation of clots (e.g., irrigation using water pump before declaring the clots adherent) or postendoscopic high-dose PPI therapy, and both studies were terminated early, with 47% and 59% of the predetermined sample sizes enrolled. By contrast, an RCT from Hong Kong using vigorous irrigation and high-dose bolus/continuous infusion PPI therapy after endoscopy reported that 0 of 24 patients receiving PPI without endoscopic therapy had recurrent bleeding (35) The potential benefit of PPI therapy alone also is supported by a double-blind RCT of omeprazole 40 mg twice-daily vs placebo without endoscopic therapy in either arm: Recurrent bleeding occurred in 0 of 64 patients with PPI vs 13 (21%) of 61 given placebo (34). The panel was unable to identify baseline patient characteristics that reliably allowed identification of a subset of patients likely to benefit from endoscopic therapy.

Issues such as local endoscopic expertise and experience, individual patient characteristics, preference for endoscopic intervention vs conservative management, and cost of endoscopic therapy may play a role in provider decisions. Accessibility for application of endoscopic therapy based on ulcer location and availability of interventional radiological or surgical back-up if uncontrollable bleeding is provoked are other factors to be considered. When performing endoscopic therapy for clots, some endoscopists use mechanical manipulation to remove or reduce the clot (e.g., cold snare guillotine, tip of hemostatic probe). We know of no trials comparing manipulation vs no manipulation nor comparing different methods of manipulation to inform decisions about its use.

Conclusion. Given the small size of the individual studies, the marked inconsistency in results, and the inability to identify the causes of heterogeneity among trials, the panel felt they could neither recommend for nor against endoscopic therapy in patients with adherent clots. The panel believed either course of management could be considered acceptable based on available evidence. The 2012 ACG Guidelines suggested endoscopic therapy "may be considered" (1), but as noted above, such statements are no longer considered acceptable because guidelines should provide a recommended action (40).

Choice of endoscopic hemostatic therapy for bleeding ulcers.

8. We recommend endoscopic hemostatic therapy with bipolar electrocoagulation, heater probe, or injection of absolute ethanol for patients with UGIB due to ulcers (strong recommendation, moderate-quality evidence).
9. We suggest endoscopic hemostatic therapy with clips, argon plasma coagulation, or soft monopolar electrocoagulation for patients with UGIB due to ulcers (conditional recommendation, very-low- to low-quality evidence).
10. We recommend that epinephrine injection not be used alone for patients with UGIB due to ulcers but rather in combination with another hemostatic modality (strong recommendation, very-low- to moderate-quality evidence).
11. We suggest endoscopic hemostatic therapy with hemostatic powder spray TC-325 for patients with actively bleeding ulcers (conditional recommendation, very-low-quality evidence).
12. We suggest over-the-scope clips as a hemostatic therapy for patients who develop recurrent bleeding due to ulcers after previous successful endoscopic hemostasis (conditional recommendation, low-quality evidence).

Summary of evidence. We assessed RCTs of endoscopic hemostatic therapy vs no endoscopic therapy or vs other forms of endoscopic therapy (see Supplementary Table 10.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). We excluded studies with second-look endoscopy in which routine repeat endoscopy with endoscopic retreatment was performed (typically ~1 day after index endoscopy) because this impacts our predefined outcomes (further bleeding and mortality) and is not a recommended or standard practice in the United States. In addition, although certain baseline characteristics have been associated with increased risk of rebleeding after endoscopic therapy, we did not formally assess use of other prophylactic therapies after successful endoscopic therapy. Nevertheless, prophylactic transcatheter arterial embolization (TAE) after endoscopic treatment, even in patients with high-risk features, cannot be recommended based on an RCT in 241 patients with ulcers at high risk of further bleeding (60).

Bipolar electrocoagulation/heater probe. A meta-analysis of 15 RCTs showed that the thermal contact devices bipolar electrocoagulation and heater probe reduce further bleeding (RR = 0.44, 0.36–0.54; NNT = 4, 3–5) and mortality (RR = 0.58, 0.34–0.98; NNT = 33, 21–1,000) compared with no endoscopic therapy (33) (Table 7). The modalities likely are similar in efficacy: Meta-analysis of 3 RCTs showed RR for further bleeding with heater probe vs bipolar electrocoagulation of 1.01 (95% CI 0.57–1.80) (33). Previous recommendations for thermal contact

devices include use of the large 3.2-mm probe with firm/maximal pressure at settings of ~15 W with 8- to 10-second applications for bipolar electrocoagulation and 30 J for heater probe (1).

Sclerosant injection. A meta-analysis of 3 RCTs revealed that injection with absolute ethanol reduced further bleeding (RR = 0.56, 0.38–0.83; NNT = 5, 4–13) and mortality (RR = 0.18, 0.05–0.68; NNT = 9, 8–24) compared with no endoscopic therapy (33) (Table 7). Typically, aliquots of 0.1–0.2 mL per injection are used, with maximum volume restricted to 1–2 mL to minimize serious tissue injury (61–63). Another sclerosant agent, polidocanol, also has been studied, generally in combination with epinephrine. A meta-analysis of 6 RCTs comparing epinephrine plus polidocanol injection therapy vs no endoscopic treatment revealed a trend to less further bleeding (RR = 0.60, 0.36–1.00 with heterogeneity [I^2 = 58%]) and no significant difference in mortality (RR = 0.80, 0.40–1.61) (33) (Table 7). The panel therefore recommended injection with absolute ethanol but did not recommend polidocanol.

The 2 endoscopic treatments with strong recommendations, thermal contact therapy with bipolar electrocoagulation or heater probe and injection of absolute ethanol, were compared in 5 RCTs and a meta-analysis of these trials revealed a trend to less further bleeding with thermal contact therapy (RR = 0.69, 0.47–1.01), based on low-quality evidence, and no significant difference in mortality (RR = 1.60, 0.57–4.52) (33) (Table 7). The panel did not recommend thermal contact therapy over ethanol injection, given the moderate-quality evidence of ethanol's benefit in both further bleeding and mortality as compared to no endoscopic therapy.

Clips. Evidence for clips is less robust, with a lack of randomized comparisons with no endoscopic treatment. Clips were compared with epinephrine monotherapy in 2 RCTs (64,65). Our meta-analysis of these trials provided low-quality evidence of decreased further bleeding (RR = 0.20, 0.07–0.56) without benefit in mortality (RR = 2.11, 0.60–7.44) with clips (Table 7). Clips have been compared with thermal contact therapies in 4 RCTs, and significant differences were not identified in further bleeding (RR = 1.31, 0.36–4.75) or mortality (RR = 1.16, 0.38–3.52) (33) (Table 7). Thus, 2 RCTs of clips vs a substandard therapy (epinephrine monotherapy) provide indirect low-quality evidence that clips are more effective than no treatment for further bleeding. However, although the RCTs comparing clips and thermal contact devices show no significant difference, the evidence was very low quality and CI of the estimates of treatment effect were broad and cannot be taken to indicate equivalence. Therefore, the panel agreed on a conditional recommendation for clips. Previous recommendations for application of clips include placement of clips over the bleeding site and on either side of the bleeding site in an attempt to seal the underlying artery (1).

Argon plasma coagulation. Evidence for argon plasma coagulation (APC) is also less robust than for bipolar electrocoagulation, heater probe, and absolute ethanol. APC was compared with water injection in an RCT (66) with less further bleeding (4/58 [6.9%] vs 12/58 [20.7%]; difference = −14%, −26% to −1%) and comparable mortality (2/58 vs 2/58). Three RCTs comparing APC ± epinephrine injection with other modalities were identified (67–69). Our meta-analysis of these trials showed no significant difference in further bleeding (RR = 0.82, 0.21–3.19 with heterogeneity [I^2 = 73%]) or mortality (RR = 0.85, 0.30–2.44) (Table 7). Given indirect very-low-quality evidence that APC is more effective than no treatment because it has less further bleeding than a substandard therapy (water injection) and additional very-low-quality evidence that APC is not different from other modalities, the panel agreed to a conditional recommendation for APC. APC in supporting RCTs was performed using gas flow settings of 1–2 L/min and power settings of 40–70 W for duodenal and gastric ulcers with distance between probe and mucosa of 2–10 mm (66–69). Frequent suction to remove smoke and reduce distension is recommended.

Soft monopolar electrocoagulation. A 1992 systematic review identified 3 RCTs comparing monopolar electrocoagulation vs no endoscopic treatment with results indicating reduction in further bleeding (70). However, guidelines generally have not included monopolar electrocoagulation because of the perceived potential for higher risk of adverse events with greater tissue injury (1). More recently, a modification in monopolar electrocoagulation, soft coagulation mode, was developed for hemostasis in endoscopic submucosal dissection and subsequently applied for treatment of bleeding ulcers. By using a continuous wave with maximal voltage reduced to 200 V, coagulation without carbonization or cutting is provided (71) with the goal of improved safety. Monopolar hemostatic forceps are used for soft coagulation: The closed tip can be applied to the bleeding site or the forceps can be used to grasp the bleeding site (71–75). Soft monopolar electrocoagulation in RCTs was performed using soft coagulation mode at settings of 50–80 W with 1- to 2-second applications (72–75).

We therefore considered soft monopolar electrocoagulation and identified 4 RCTs comparing this with other modalities (clips and heater probe) (72–75). Because 3 studies used routine second-look endoscopy, only 1 study could be relied on to assess further bleeding and mortality (75). This comparison of soft coagulation vs clips, with initial epinephrine injection in all actively bleeding ulcers, revealed reduced further bleeding with soft coagulation (3/56 [5.4%] vs 19/56 [33.9%], difference = −33%, −54% to −13%). Deaths in this study (zero in both groups), and the other 3 RCTs, were uncommon and similar in the treatment groups. Because most RCTs could not be relied on for outcomes of further bleeding and mortality, we also assessed persistent bleeding after hemostatic therapy at index endoscopy, an outcome not confounded by second-look endoscopy. Persistent bleeding trended lower with soft coagulation on meta-analysis of the 4 RCTs (RR = 0.35, 0.12–1.03), although heterogeneity was present (I^2 = 61%) and quality of evidence was very low. No important adverse events, such as perforation, were reported among 237 patients receiving soft coagulation in the 4 RCTs. Given the previous indirect evidence suggesting efficacy of standard monopolar electrocoagulation and more recent limited evidence suggesting the efficacy of soft monopolar electrocoagulation may be at least as good as other hemostatic modalities, the panel supported a conditional recommendation for soft monopolar electrocoagulation.

Epinephrine injection. Epinephrine monotherapy is less effective for further bleeding than standard monotherapies such as bipolar electrocoagulation and clips: RR = 2.20, 1.04–4.64 with significant heterogeneity (I^2 = 56%) in our meta-analysis of 4 RCTs (64,65,76,77). Epinephrine plus a second modality is more effective than epinephrine monotherapy for further bleeding:

Table 7. Meta-analyses of randomized trials comparing endoscopic thermal, injection, or clip therapy with no endoscopic therapy or another endoscopic therapy

Endoscopic therapy	Comparator therapy	No. of studies	Risk ratio (95% confidence interval)	
			Further bleeding	Mortality
Endoscopic therapy vs no endoscopic therapy				
Thermal contact with bipolar electrocoagulation or heater probe	No endoscopic therapy	15 (33)	0.44 (0.36–0.54)	0.58 (0.34–0.98)
Absolute ethanol injection	No endoscopic therapy	3 (33)	0.56 (0.38–0.83)	0.18 (0.05–0.68)
Epinephrine + polidocanol injection	No endoscopic therapy	6 (33)	0.60 (0.36–1.00)[a]	0.80 (0.40–1.61)
One endoscopic therapy vs another endoscopic therapy				
Thermal contact with bipolar electrocoagulation or heater probe	Absolute ethanol injection	5 (33)	0.69 (0.47–1.01)	1.60 (0.57–4.52)
Clips	Epinephrine injection	2 (64,65)	0.20 (0.07–0.56)	2.11 (0.60–7.44)
Clips	Thermal contact with bipolar electrocoagulation or heater probe	4 (33)	1.31 (0.36–4.75)	1.16 (0.38–3.52)
Epinephrine injection + second modality	Epinephrine injection	7 (33)	0.34 (0.23–0.50)	0.52 (0.23–1.16)
Argon plasma coagulation ± epinephrine	Epinephrine injection + second modality	3 (67–69)	0.82 (0.21–3.19)[a]	0.85 (0.30–2.33)

[a]Heterogeneity ($I^2 > 50\%$).

RR = 0.34, 0.23–0.50 in meta-analysis of 7 RCTs (33) (Table 7). Thus, the panel recommends against the use of epinephrine alone. Epinephrine should always be used in combination with another hemostatic modality. Epinephrine is most commonly used in a 1:10,000 dilution, typically injected in 0.5- to 2.0-mL aliquots.

Epinephrine injection combined with other modalities. The panel also considered the question of whether modalities such as thermal contact devices or clips should always be used in combination with epinephrine injection. Endoscopists commonly use epinephrine in patients with active bleeding to reduce bleeding and improve visibility before application of the other modality or in patients with nonbleeding high-risk stigmata to prevent rebleeding during application of the other modality. Meta-analysis of 2 small RCTs comparing epinephrine before bipolar electrocoagulation vs bipolar electrocoagulation alone revealed lower further bleeding with combined therapy (RR = 0.35, 0.18–0.71) without a significant difference in mortality (RR = 0.49, 0.09–2.60) (33). Because rates of further bleeding (25%, 34%) were unusually high in the bipolar monotherapy arms and moderate-quality evidence indicates bipolar electrocoagulation or heater probe monotherapy reduces further bleeding and mortality, the panel did not believe this limited evidence allowed a suggestion that thermal contact devices should always be preceded by epinephrine injection. Meta-analysis of 2 small RCTs comparing clips plus epinephrine vs clips alone revealed no significant difference in further bleeding (RR = 1.10, 0.42–2.88) or mortality (RR = 0.63, 0.10–3.87) (64,78). However, in both studies, epinephrine was injected after clip placement. Some endoscopists use epinephrine after clip application rather than before to avoid local swelling with large volume injection that may make clip application more difficult or to treat residual bleeding after clip placement.

Hemostatic powder spray TC-325. We evaluated hemostatic powder spray, restricting our search to products commercially available in the United States at the time this document was developed. TC-325 only adheres to actively bleeding lesions, so its use in nonbleeding lesions is likely ineffective (79). A delivery catheter with its tip 1–2 cm from the bleeding site is used to apply TC-325 in 1- to 2-second bursts until the bleeding site is covered and bleeding stops.

Two published RCTs were identified but not relied on because both included routine second-look endoscopies (80,81). We were aware of a large RCT from Lau et al. (82) at the time of our literature search (clinicaltrials.gov NCT02534571), and results of the full trial were subsequently published in 2020. This noninferiority RCT compared TC-325 with standard therapy (clipping or contact thermocoagulation ± previous epinephrine injection) in 224 patients with actively bleeding nonvariceal lesions, including 130 with ulcers. Their primary outcome, further bleeding at 30 days, occurred in 8/65 (12.3%) with TC-325 and 10/65 (15.4%) with standard therapy in patients with ulcers: difference = −3%, −15% to 9%.

Recent guidelines have suggested use of TC-325 as a temporizing measure that should be followed by use of a second definitive hemostatic modality (50,83). This is based on the fact that TC-325 powder sloughs off the mucosa and is eliminated from the GI tract within 24 hours after application (50,79,83) and further bleeding is common in observational studies of TC-325: e.g., 31% (95% CI 26%–37%) in a meta-analysis of 18 observational studies and 2 RCTs (84). By contrast, the results from Lau et al. suggest TC-325 may be effective as a single agent.

Given similar rates of further bleeding for TC-325 vs standard therapies and 95% CIs suggesting no more than a 9% higher rate of further bleeding with TC-325, the panel made a conditional recommendation for hemostatic powder spray TC-325 for actively bleeding ulcers. The panel believes that further research is necessary to confirm that TC-325 could be used as monotherapy, especially in patients with actively spurting bleeding which constituted only a small proportion

of patients in the study of Lau et al. Given that TC-325 was not superior to other standard endoscopic hemostatic therapies, cost becomes a major factor in deciding when to use TC-325. The panel suggested that in countries such as the United States, where the cost is extremely high (US list price $2,500 in November 2020), TC-325 should not be the initial modality used if other therapies can be readily applied. Factors such as ulcer location and size, endoscopist experience, and availability of therapies will impact choice of initial modality. An economic analysis suggested that standard endoscopic therapy followed by TC-325 if standard therapy failed was the dominant strategy (more effective and less costly) compared with standard therapy alone, TC-325 alone, or TC-325 followed by standard therapy if TC-325 failed (85). However, costs of TC-325 used in the model were far less than current US prices and rebleeding rates used were much higher than those from Lau et al., raising questions about the applicability of the results at present. Changes in cost of TC-325 may impact decisions regarding its use as initial therapy, and future economic analyses can assist in determining cost thresholds for such decisions.

Over-the-scope clips. Application of over-the-scope clips is performed similarly to endoscopic ligation: A cap device with a single clip is placed on the distal tip of the endoscope, the bleeding lesion is approached enface, the cap is placed over the lesion encircling it, the lesion is suctioned into the cap, and the clip is released. In patients who have recurrent bleeding after previous successful endoscopic hemostasis, an RCT revealed that over-the-scope clips were superior to standard therapy in further bleeding (5/33 [15.2%] vs 19/33 [57.6%], difference = −42%, −63% to −22%) without a significant different in mortality (86). Standard through-the-scope clips were the therapy used in 94% of the control group, potentially limiting generalizability of this study regarding comparisons of over-the-scope clips to other forms of hemostatic therapy.

We were aware of an RCT of over-the-scope-clips for initial treatment of UGIB (clinicaltrials.gov NCT03216395) at the time of our literature search and results were published in 2020. The trial compared epinephrine plus over-the-scope clips vs epinephrine plus bipolar electrocoagulation or clips in patients with severe UGIB because of Dieulafoy lesions (N = 5) or ulcers (N = 48) with active bleeding, visible vessels, clots, or Doppler-positive flat spots (87). Further bleeding for ulcers occurred in 1/23 (4%) vs 7/25 (28%) (difference = −24%, −43% to −4%) with no deaths. This RCT raises the possibility of over-the-scope clips as initial treatment. However, the limitations of the study leading to the rating of very low quality of evidence prevented us from modifying our recommendation regarding over-the-scope clips (see Supplementary Table 10.1, Supplementary Digital Content, http://links.lww.com/AJG/B962).

Conclusion. Evidence of clinical benefit with endoscopic therapy is most robust for thermal contact devices (bipolar electrocoagulation and heater probe) and absolute ethanol injection. Low- to very-low-quality evidence also suggests benefit for clips, APC, and soft monopolar electrocoagulation. Epinephrine monotherapy is less effective than other standard monotherapies and also less effective than epinephrine plus a second modality. Hemostatic powder spray TC-325 seems effective for actively bleeding ulcers, although current high cost may limit its use as the initial endoscopic therapy for this indication in the United States. Over-the-scope clips seem useful for patients with recurrent ulcer bleeding after previous successful endoscopic hemostasis. As compared to the 2012 ACG Guidelines (1), the current guideline statements are expanded to include APC, soft monopolar electrocoagulation, hemostatic powder spray TC-325, and over-the-scope clips.

Antisecretory therapy after endoscopic hemostatic therapy for bleeding ulcers

13. We recommend high-dose PPI therapy given continuously or intermittently for 3 days after successful endoscopic hemostatic therapy of a bleeding ulcer (strong recommendation, moderate- to high-quality evidence).

Summary of evidence. The hypothesis leading to use of high-dose PPI therapy in patients with bleeding ulcers, based on *in vitro* data, is that reduction of intragastric acid promotes clot formation and stability (88–90). Whether the target intragastric pH should be near 7 (88,89), or whether inhibition of pepsin-induced clot lysis at a pH >4–5 (89,90) is sufficient, is unknown.

We identified 7 RCTs with 8 randomized comparisons of high-dose PPI therapy (defined as ≥80 mg daily for at least 3 days) vs placebo (6 RCTs) (54,91–95) or no treatment (2 comparisons in 1 RCT) (96) after successful endoscopic hemostatic therapy (see Supplementary Table 11.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). Four comparisons included continuous intravenous PPI therapy with 80-mg bolus followed by 8-mg/hr infusion for 72 hours (54,91,95,96) and 4 included intermittent PPI therapy: 40 mg twice-daily orally (92,94), 20 mg q6h orally (93), and 80-mg bolus followed by 40 mg q12h intravenously (96). Seven comparisons were from Asia and 1 from Iran (93). This high-quality evidence showed PPI therapy markedly reduced further bleeding (RR = 0.43, 0.33–0.56), mortality (RR = 0.41, 0.22–0.79), and surgery (RR = 0.42, 0.25–0.71) compared with placebo/no treatment. Subgroup analyses revealed no evidence of a difference in treatment effect between continuous and intermittent PPI therapy (tests for subgroup difference $P \geq 0.90$). Sensitivity analysis restricted to the 4 studies not allowing for epinephrine monotherapy as endoscopic hemostatic therapy (91,92,94,95) also revealed benefit in further bleeding: RR = 0.35, 0.22–0.55.

We identified 9 RCTs comparing high-dose PPI therapy to H2RA therapy after successful endoscopic hemostatic therapy (see Supplementary Table 11.2, Supplementary Digital Content, http://links.lww.com/AJG/B962). Four RCTs used intravenous PPI 80-mg bolus followed by 8-mg/hr infusion (97–100), 1 used intravenous PPI 40-mg bolus followed 6.7-mg/hr infusion (101), and 4 used intermittent intravenous PPI therapy (40 mg q6h (102) or q12h (103); 80-mg bolus followed by 40 mg q8h (104) or twice-daily (105)). Six RCTs included United States (98) or European sites (99,100,102–104). This moderate-quality evidence showed a reduction in further bleeding with PPI vs H2RA therapy (RR = 0.56, 0.41–0.77), but neither mortality nor surgery was significantly lower with PPI. Again, no evidence of a difference in treatment effect was noted between continuous and intermittent PPI therapy (subgroup differences $P > 0.90$).

We identified 12 RCTs comparing 80-mg bolus followed by 8-mg/hr continuous infusion for 3 days to a less intensive PPI regimen after successful endoscopic hemostasis (96,106–116) (see

Supplementary Table 11.3, Supplementary Digital Content, http://links.lww.com/AJG/B962). Comparisons were to 40 mg/d in 4 RCTs (106,108,109,112), 40 mg twice-daily in 3 RCTs (113–115), 80 mg twice-daily in 1 RCT (107), 80-mg bolus and 40–80 mg q6–12h in 3 RCTs (96,110,111), and 40-mg bolus followed by 4-mg/hr infusion in 1 RCT (116). The meta-analytic estimate for further bleeding with bolus-continuous infusion vs less intensive regimens (RR = 1.12, 0.86–1.47; risk difference = 1%, −2% to 4%) trended to more rather than less further bleeding with bolus-continuous infusion PPI, although the lower bounds of the 95% CI were consistent with as much as a 14% relative risk reduction or 2% absolute risk reduction with the bolus-continuous infusion regimen. Subgroup analyses showed no significant differences related to dose, frequency, or route of PPIs.

The panel made a strong recommendation for high-dose PPI therapy given continuously or intermittently for 3 days after successful endoscopic hemostatic treatment, based on high-quality evidence documenting a large relative risk reduction in further bleeding and mortality as compared to placebo/no treatment and moderate-quality evidence documenting a benefit in further bleeding as compared to H2RAs. The magnitude of benefit in these RCTs was virtually identical with high-dose bolus followed by continuous infusion PPI (80-mg bolus, 8-mg/hr infusion) and intermittent PPI with average total daily doses of 80–160 mg (some with an initial 80 mg bolus).

The panel then considered dosing and route of high-dose PPI regimens. High-quality evidence supports an 80-mg bolus followed by 8-mg/hr infusion in patients receiving a high-dose continuous intravenous PPI regimen. By contrast, available data do not allow certainty regarding the optimal dosing of intermittent high-dose PPI therapy. Based on RCTs, intermittent doses of 40 mg 2 to 4 times daily, given either orally or intravenously, are suggested, with the higher total doses potentially desirable in western populations because PPIs are reported to have lesser pharmacodynamic and clinical effect in western than in Asian populations (117). An initial oral or intravenous bolus of 80 mg may be appropriate to potentially achieve a greater effect on intragastric pH on the first day of treatment (118). Intermittent doses can be given orally, assuming the patient is awake, alert, and without nausea, vomiting, or dysphagia. Oral administration seems to produce a pharmacodynamic effect similar to that of equivalent doses of intravenous PPI, although the initial rise in intragastric pH with oral PPI may lag ~15–60 minutes behind that of intravenous PPI (111,119,120). Choice of continuous infusion vs intermittent PPI therapy may be influenced by factors such as ease of administration and cost.

Conclusion. High-dose PPI therapy, defined as ≥80 mg daily for ≥3 days, given continuously or intermittently after endoscopic hemostatic therapy reduces further bleeding and mortality. Continuous therapy should be 80-mg bolus followed by 8-mg/hr infusion. By contrast, the optimal dosing with intermittent oral or intravenous therapy is uncertain, although we suggest 80-mg bolus followed by 40 mg 2–4 times daily. The current recommendation expands the recommendation from the 2012 ACG Guidelines (1) beyond continuous infusion PPI to include intermittent oral or intravenous high-dose PPI. Suggested endoscopic and medical therapy based on endoscopic features of ulcers is shown in Figure 3.

14. We suggest that high-risk patients with UGIB due to ulcers who received endoscopic hemostatic therapy followed by short-term high-dose PPI therapy in hospital continue on twice-daily PPI therapy until 2 weeks after index endoscopy (conditional recommendation, low-quality evidence).

Summary of evidence. The panel next considered PPI dosing for high-risk patients who have received recommended endoscopic hemostatic therapy followed by short-term high-dose PPI therapy. A single RCT was identified that included patients who presented with a Rockall score ≥6, underwent successful endoscopic hemostatic therapy for ulcers with active bleeding, nonbleeding visible vessel, or adherent clot, and received 3 days of bolus followed by continuous infusion PPI (121) (see Supplementary Table 12.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). Patients were randomly assigned to 40-mg oral esomeprazole twice-daily vs once-daily for 11 days and then all patients received 2 more weeks of esomeprazole 40 mg once-daily. Further bleeding was lower at both 14 days and the primary analysis at 28 days (10/93 [10.8%] vs 27/94 [28.7%]; difference = −18%, −29% to −7%). Twice-daily oral PPI for ~2 weeks was considered by the panel likely to be safe, well-tolerated, readily available, and relatively inexpensive. These factors, combined with the low-quality evidence of efficacy in reducing further

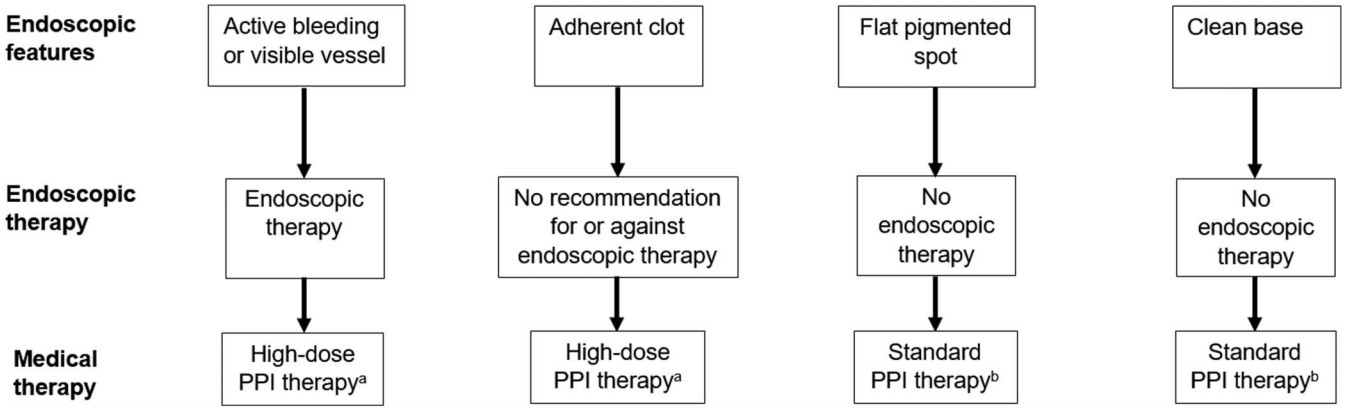

Figure 3. Endoscopic and medical therapy for ulcer bleeding based on endoscopic features of ulcer. [a]For continuous regimen, 80-mg bolus followed by 8-mg/min infusion for 3 days is recommended. For intermittent regimens, doses of 40 mg 2 to 4 times daily for 3 days are suggested, given orally if feasible, and an initial bolus of 80 mg may be appropriate. [b]Standard PPI therapy (e.g., oral PPI once-daily) has been recommended by previous guidelines (1,37) but is not assessed in the current document. PPI, proton pump inhibitor.

bleeding, led the panel to a conditional recommendation for twice-daily PPI until 2 weeks after index endoscopy in this population. After 2 weeks, the regimen used in the single relevant RCT (121) switched patients to a 2-week course of once-daily PPI. Available evidence does not allow us to determine whether longer courses of twice-daily PPI or overall PPI therapy would provide additional benefit in this population.

Conclusion. Twice-daily PPI therapy from days 4–14 after index endoscopy reduces further bleeding as compared to once-daily PPI in high-risk patients who received endoscopic therapy followed by 3 days of high-dose PPI therapy. This is a new recommendation based on evidence that became available after publication of the 2012 ACG Guidelines.

Recurrent ulcer bleeding after successful endoscopic hemostatic therapy

15. We suggest that patients with recurrent bleeding after endoscopic therapy for a bleeding ulcer undergo repeat endoscopy and endoscopic therapy rather than undergo surgery or transcatheter arterial embolization (conditional recommendation, low-quality evidence for comparison with surgery, very-low-quality evidence for comparison with transcatheter arterial embolization).

Summary of evidence. One RCT has assessed repeat endoscopy vs urgent surgery in patients with rebleeding after endoscopic therapy (122) (Table 8; see Supplementary Table 13.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). Lau et al. found more frequent further bleeding with endoscopy vs surgery (11/48 [22.9%] vs 3/44 [6.8%]; difference = 16%, 2%–30%) but no significant difference in mortality (5/48 [10.4%] vs 8/44 [18.2%]; difference = −8%, −23% to 7%). Surgery was subsequently required in 13/48 (27.1%) assigned to endoscopy while a second surgery was needed in 4/44 (9.1%) assigned to surgery (difference = 18%, 3%–33%). Complications were less common with endoscopy (7/48 [14.6%] vs 16/44 [36.4%]; difference = −22%, −39% to −4%) and occurred after salvage surgery in all but 1 patient in the endoscopy group. Length of hospital stay was similar in the 2 groups.

Given that a second application of endoscopic therapy was successful in prevention of further bleeding in approximately three-quarters of patients with recurrent ulcer bleeding after endoscopic therapy and was associated with far fewer complications than surgical therapy, the panel suggested repeat endoscopy rather than surgical therapy in this population. No RCTs compare repeat endoscopy with interventional radiology with TAE. However, given the relatively high success rate of repeat endoscopic therapy for recurrent bleeding after initial endoscopic therapy reported by Lau et al. (122) and in the RCT of over-the-scope clips cited above (86), as well as the safety, ease, and availability of endoscopy, the panel suggested repeat endoscopy rather than TAE in these patients, although evidence was considered very low quality.

Care should be taken when performing repeat endoscopic therapy. Two of 48 patients treated with repeat heater probe therapy in the RCT (122) developed perforation and a meta-analysis of adverse events in RCTs of endoscopic therapy revealed that approximately half of perforations reported with heater probe occurred in patients receiving 2 consecutive treatments (33). Although the evidence is uncontrolled and very low quality, these reports raise the possibility that thermal contact therapies such as heater probe, when given on consecutive endoscopies during the same hospitalization, may have an increased risk of perforation. Thus, alternate forms of hemostatic therapy may be considered if thermal contact was used at the initial endoscopy. In addition, occasional patients might be considered for treatment with TAE or surgery rather than repeat endoscopy based on clinical or endoscopic features. For example, in the randomized trial by Lau et al. (122), failure of repeat endoscopic hemostatic therapy was associated with hypotension at the time of rebleeding and ulcer size >2 cm.

Conclusion. In patient with recurrent bleeding after endoscopic therapy for a bleeding ulcer, repeat endoscopy and endoscopic therapy successfully prevents further bleeding in approximately three-quarters of patients, with fewer complications than surgical therapy. This recommendation is unchanged from the 2012 ACG Guidelines (1).

Failure of endoscopic hemostatic therapy for bleeding ulcers

16. We suggest patients with bleeding ulcers who have failed endoscopic therapy next be treated with transcatheter arterial embolization (conditional recommendation, very-low-quality evidence).

Summary of evidence. Failure of endoscopic therapy may have varying definitions; e.g., persistent bleeding after initial or subsequent endoscopic therapy and recurrent bleeding after repeat

Table 8. Randomized trial of endoscopic retreatment vs surgery in patients with recurrent bleeding after successful endoscopic therapy (122)

Outcome	Endoscopy (N = 48)	Surgery (N = 44)	Absolute difference (95% confidence interval)
Further bleeding, n (%)	11 (22.9)	3 (6.8)	16% (2% to 30%)
Death, n (%)	5 (10.4)	8 (18.2)	−8% (−22% to 7%)
Surgery for rebleeding or complication after initial assigned treatment, n (%)	13 (27.1)	4 (9.1)	18% (3% to 33%)
Complications, n (%)[a]	7 (14.6)	16 (36.4)	−22% (−39% to −4%)
Hospital days, median (range)	10 (2–111)	11 (4–42)	Not reported

[a]Complications included respiratory failure, myocardial infarction, cardiac arrhythmia, stroke, pneumonia, wound dehiscence or infection, acute renal failure, abdominal sepsis, recurrent bleeding, and tension pneumothorax. All complications but 1 in endoscopy group occurred after salvage surgery.

endoscopic therapy. A systematic review and meta-analysis of 13 observational studies in nonvariceal UGIB (all with high risk-of-bias) (123) and a subsequent population-based cohort study of all patients with peptic ulcer bleeding who failed endoscopic therapy in Stockholm from 2000 to 2014 (124) met criteria for assessment of TAE vs surgery (see Supplementary Table 14.1, Supplementary Digital Content, http://links.lww.com/AJG/B962). Results from the meta-analysis and additional cohort study were similar without a difference in mortality documented for TAE vs surgery: meta-analysis OR = 0.77, 0.50–1.18 (123); cohort study adjusted 30-day mortality HR = 0.70, 0.37–1.35 (124). Further bleeding was more common with TAE vs surgery (meta-analysis OR = 2.44, 1.77–3.36; cohort study adjusted HR = 2.48, 1.33–4.62), while major complications were less common with TAE (meta-analysis OR = 0.45, 0.30–0.67; cohort study: 9/109 [8.3%] vs 66/205 [32.2%], difference = −24%, −32% to −16%). Hospital stay was shorter with TAE in the cohort study: median 8 vs 16 days; adjusted acceleration factor = 0.59, 0.45–0.77.

Although surgery likely was more effective in reducing further bleeding, the fact that TAE was associated with markedly fewer complications and was not associated with increased mortality led the panel to suggest TAE was a reasonable initial choice in management of patients with bleeding ulcers who have failed endoscopic therapy. Nevertheless, the choice of TAE vs surgery may vary based on factors such as patient comorbidities and current medical status as well as local expertise and availability of procedures (e.g., expertise of local interventional radiologists in TAE for UGIB and experience of local surgeons in ulcer surgery). Furthermore, patients and providers may value the competing outcomes of further bleeding vs complications and length of hospitalization differently with those most concerned with further bleeding choosing surgery while those most interested in avoiding complications and lengthy hospitalization choosing TAE.

Conclusion. In patients who fail endoscopic therapy, TAE shows marked reductions in complications and hospital stay with no difference in mortality as compared to surgery, but does have a higher rate of further bleeding. New evidence led to a change from the 2012 ACG Guidelines, which stated that either surgery or TAE is generally used (1).

FUTURE DIRECTIONS

Much of the evidence supporting these guideline statements is low or very low quality, suggesting many opportunities exist for further investigation to enhance the management of patients with UGIB. Topics to explore in the future may include the following. **(i) Improvements in the performance of risk assessment instruments and implementation in electronic health records to allow timely decision support.** Further studies should seek to increase specificity in identifying very-low-risk patients, improve performance in identifying high-risk patients (e.g., those likely to require blood transfusion, hemostatic intervention, or intensive care), and document that implementation can improve outcomes. **(ii) Enhancement of initial, pre-endoscopic management.** Uncertainty remains regarding initial resuscitation: Should the target be normal blood pressure levels or are more limited fluid administration and lower blood pressure targets appropriate, at least in a subset of patients with more severe bleeding? Similarly, are there criteria (e.g., hemodynamic status and response to initial resuscitation) that identify a subgroup of patients who benefit from very-early endoscopy? Although pre-endoscopic PPIs are widely used with marked variability in guideline recommendations, a study properly designed to identify any potential small clinical benefit not previously shown will be large and complex. **(iii) Refinements in hemostatic therapy.** Areas for investigation include determining whether ulcers treated with hemostatic powder spray require endoscopic treatment with a second modality—at least in selected cases (e.g., spurting), better defining situations for use of different modalities (e.g., over-the-scope clips), appropriately assessing new hemostatic interventions, role of Doppler probe in guiding endoscopic therapy, and developing economic models to help guide the choice of therapy among multiple effective techniques.

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CONFLICTS OF INTEREST

Guarantor of the article: Loren Laine, MD.

Specific author contributions: L.L.: study concept and design; literature review; data extraction; analysis and interpretation of data; and initial drafting of manuscript. A.N.B. and J.R.S.: study concept and design; literature review; data extraction; interpretation of data; and critical revision of manuscript. M.M.: literature review; data extraction; analysis and interpretation of data; and critical revision of manuscript. G.I.L.: study concept and design; literature review; data extraction; analysis and interpretation of data; and critical revision of manuscript. All authors approved the final draft submitted.

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