

## REVIEW ARTICLE

## CURRENT CONCEPTS

# Management of Acute Bleeding from a Peptic Ulcer

Ian M. Gralnek, M.D., M.S.H.S., Alan N. Barkun, M.D., C.M., M.Sc.,  
and Marc Bardou, M.D., Ph.D.

From the Department of Gastroenterology and Gastrointestinal Outcomes Unit, Rambam Health Care Campus and Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel (I.M.G.); the Divisions of Gastroenterology and Clinical Epidemiology, McGill University Health Centre, McGill University, Montreal (A.N.B.); and INSERM Centre d'Investigations Cliniques Plurithématique, Centre Hospitalier Universitaire du Bocage and Institut Fédératif de Recherche Santé, Sciences et Techniques de l'Information et de la Communication, Université de Bourgogne — both in Dijon, France (M.B.). Address reprint requests to Dr. Gralnek at the Department of Gastroenterology and Gastrointestinal Outcomes Unit, Rambam Health Care Campus, Bat Galim, Haifa 31096, Israel, or at [i\\_gralnek@rambam.health.gov.il](mailto:i_gralnek@rambam.health.gov.il).

N Engl J Med 2008;359:928-37.  
Copyright © 2008 Massachusetts Medical Society.

**A**CU TE UPPER GASTROINTESTINAL HEMORRHAGE, WHICH IS DEFINED AS bleeding proximal to the ligament of Treitz, is a prevalent and clinically significant condition with important implications for health care costs worldwide. Negative outcomes include rebleeding and death, and many of the deaths are associated with decompensation of coexisting medical conditions precipitated by the acute bleeding event.<sup>1</sup> This review focuses specifically on the current treatment of patients with acute bleeding from a peptic ulcer.

---

## EPIDEMIOLOGY

---

The annual rate of hospitalization for acute upper gastrointestinal hemorrhage in the United States is estimated to be 160 hospital admissions per 100,000 population, which translates into more than 400,000 per year.<sup>2</sup> In most settings, the vast majority of acute episodes of upper gastrointestinal bleeding (80 to 90%) have non-variceal causes, with gastroduodenal peptic ulcer accounting for the majority of lesions.<sup>3</sup> A number of studies have suggested that the annual incidence of bleeding from a peptic ulcer may be decreasing worldwide,<sup>4</sup> yet other recent population-based estimates have suggested that the incidence is about 60 per 100,000 population,<sup>5</sup> with an increasing proportion of episodes related to the use of aspirin and nonsteroidal antiinflammatory medications. Moreover, peptic ulcer bleeding is seen predominantly among the elderly, with 68% of patients over the age of 60 years and 27% over the age of 80 years.<sup>6</sup> Mortality associated with peptic ulcer bleeding remains high at 5 to 10%.<sup>1,3</sup> Estimated direct medical costs for the in-hospital care of patients with bleeding from a peptic ulcer total more than \$2 billion annually in the United States.<sup>7</sup>

---

## CLINICAL PRESENTATION

---

### INITIAL MANAGEMENT

Hematemesis and melena are the most common presenting signs of acute upper gastrointestinal hemorrhage. Melena is sometimes seen in patients with hemorrhage in the lower gastrointestinal tract (e.g., distal small bowel and colon) and hematochezia in patients with upper gastrointestinal hemorrhage.<sup>8</sup> Appropriate hemodynamic assessment includes the careful measurement of pulse and blood pressure, including orthostatic changes, to estimate the intravascular volume status and guide resuscitative efforts. Patients who present with acute upper gastrointestinal bleeding and a substantial loss of intravascular volume have resting tachycardia (pulse,  $\geq 100$  beats per minute), hypotension (systolic blood pressure,  $< 100$  mm Hg), or postural changes (an increase in the pulse of  $\geq 20$  beats per minute or a drop in

systolic blood pressure of  $\geq 20$  mm Hg on standing).<sup>9,10</sup> Mucous membranes, neck veins, and urine output should also be evaluated as additional ways of estimating the intravascular volume status.<sup>9</sup>

The first priority in treatment is correcting fluid losses and restoring hemodynamic stability. Volume resuscitation should be initiated with crystalloid intravenous fluids with the use of large-bore intravenous-access catheters (e.g., two peripheral catheters of 16 to 18 gauge or a central catheter if peripheral access is not available). In order to maintain adequate oxygen-carrying capacity, especially in older patients with coexisting cardiac illnesses, the use of supplemental oxygen and transfusion of plasma expanders with the use of packed red cells should be considered if tachycardia or hypotension is present or if the hemoglobin level is less than 10 g per deciliter.<sup>9,11</sup> When indicated, correction of coagulopathy should be undertaken.<sup>12</sup>

The insertion of a nasogastric tube may be helpful in the initial assessment of the patient (specifically, triage), although the incremental information such a procedure provides remains controversial.<sup>10</sup> It has been suggested that the presence of red blood in the nasogastric aspirate is an adverse prognostic sign that may be useful in identifying patients who require urgent endoscopic evaluation.<sup>10,13</sup> However, the absence of bloody or coffee-ground material does not definitively rule out ongoing or recurrent bleeding, since approximately 15% of patients without bloody or coffee-ground material in nasogastric aspirates are found to have high-risk lesions on endoscopy.<sup>10</sup> The use of a large-bore orogastric tube with gastric lavage (with the use of tap water at room temperature) appears only to improve visualization of the gastric fundus on endoscopy and has not been documented to improve the outcome.<sup>14</sup> Intravenous erythromycin, through its effect as a motilin receptor agonist, has been shown to promote gastric motility and substantially improve visualization of the gastric mucosa on initial endoscopy. However, erythromycin has not been shown to improve the diagnostic yield of endoscopy substantially or to improve the outcome (Table 1).<sup>18</sup>

#### PATIENT TRIAGE AND RISK STRATIFICATION

With the use of clinical variables (i.e., before endoscopy), scoring tools have been developed to facilitate the triage of patients with acute upper

gastrointestinal hemorrhage, identify those in need of urgent endoscopic evaluation, predict the risk of an adverse outcome, and assist in guiding treatment.<sup>19,20</sup> The Blatchford score, a validated risk-stratification tool based on clinical and laboratory variables, is used to predict the need for medical intervention in patients with upper gastrointestinal hemorrhage (Fig. 1A).<sup>16</sup> The Blatchford scale ranges from 0 to 23, with higher scores indicating higher risk. The Rockall score is probably the most widely known risk-stratification tool for upper gastrointestinal hemorrhage and has been validated in numerous health care settings (Fig. 1B).<sup>17</sup> The clinical Rockall score (i.e., the score before endoscopy) is calculated solely on the basis of clinical variables at the time of presentation. The complete Rockall score makes use of both clinical and endoscopic criteria to predict the risks of rebleeding and death; the scale ranges from 0 to 11 points, with higher scores indicating higher risk. The clinical Rockall score and the Blatchford score are useful prognostic tools in patients presenting with acute upper gastrointestinal hemorrhage, since the two tools have selected common features, including a determination of the patient's hemodynamic status and coexisting illnesses, and may reduce the need for urgent endoscopic evaluation in patients who are deemed to be at low risk.<sup>21</sup> Additional risk-stratification tools have been proposed.<sup>20</sup> The use of such validated tools as adjuncts to clinical evaluation and the judgment of the medical practitioner is encouraged in clinical practice.

The endoscopic appearance of a bleeding ulcer can be used to predict the likelihood of recurrent bleeding on the basis of the Forrest classification, which ranges from IA to III. High-risk lesions include those characterized by active spurting of blood (grade IA) or oozing blood (grade IB), a nonbleeding visible vessel described as a pigmented protuberance (grade IIA), and an adherent clot (which is defined as a lesion that is red, maroon, or black and amorphous in texture and that cannot be dislodged by suction or forceful water irrigation) (grade IIB) (Fig. 2A through 2D). Low-risk lesions include flat, pigmented spots (grade IIC) and clean-base ulcers (grade III) (Fig. 2E and 2F).<sup>8,22-24</sup> The interobserver variation in diagnosing these endoscopic stigmata is low to moderate.<sup>25</sup>

At initial endoscopy, high-risk lesions are seen in approximately one third to one half of all

**Table 1. Management of Acute Bleeding from a Peptic Ulcer, According to Clinical Status and Endoscopic Findings.\*****Clinical status**

## At presentation

- Assess hemodynamic status (pulse and blood pressure, including orthostatic changes).
- Obtain complete blood count, levels of electrolytes (including blood urea nitrogen and creatinine), international normalized ratio, blood type, and cross-match.
- Initiate resuscitation (crystalloids and blood products, if indicated) and use of supplemental oxygen.
- Consider nasogastric-tube placement and aspiration; no role for occult-blood testing of aspirate.
- Consider initiating treatment with an intravenous proton-pump inhibitor (80-mg bolus dose plus continuous infusion at 8 mg per hour) while awaiting early endoscopy; no role for H<sub>2</sub> blocker.†
- Perform early endoscopy (within 24 hours after presentation).
- Consider giving a single 250-mg intravenous dose of erythromycin 30 to 60 minutes before endoscopy.
- Perform risk stratification; consider the use of a scoring tool (e.g., Blatchford score<sup>16</sup> or clinical Rockall score<sup>17</sup>) before endoscopy.

## At early endoscopy

- Perform risk stratification; consider the use of a validated scoring tool (e.g., complete Rockall score<sup>17</sup>) after endoscopy.

**Endoscopic findings**

## High-risk — active bleeding or nonbleeding visible vessel (Forrest grade IA, IB, or IIA)

- Perform endoscopic hemostasis using contact thermal therapy alone, mechanical therapy using clips, or epinephrine injection, followed by contact thermal therapy or by injection of a second injectable agent. Epinephrine injection as definitive hemostasis therapy is not recommended.‡ The endoscopist should use the most familiar hemostasis technique that can be applied to the identified ulcer stigma.§
- Admit the patient to a monitored bed or ICU setting.
- Treat with an intravenous proton-pump inhibitor¶ (80-mg bolus dose plus continuous infusion at 8 mg per hour) for 72 hours after endoscopic hemostasis; no role for H<sub>2</sub> blocker, somatostatin, or octreotide.
- Initiate oral intake of clear liquids 6 hours after endoscopy in patients with hemodynamic stability.<sup>9</sup>
- Transition to oral proton-pump inhibitors after completion of intravenous therapy.
- Perform testing for *Helicobacter pylori*; initiate treatment if the result is positive.

## High-risk — adherent clot (Forrest grade IIB)

- Consider endoscopic removal of adherent clot,|| followed by endoscopic hemostasis (as described above) if underlying active bleeding or nonbleeding visible vessel is present.
- Admit the patient to a monitored bed or ICU setting.
- Treat with an intravenous proton-pump inhibitor¶ (80-mg bolus dose plus continuous infusion at 8 mg per hour) for 72 hours after endoscopy, regardless of whether endoscopic hemostasis was performed; no role for H<sub>2</sub> blocker, somatostatin, or octreotide.
- Initiate oral intake of clear liquids 6 hours after endoscopy in patients with hemodynamic stability.<sup>9</sup>
- Transition to an oral proton-pump inhibitor after completion of intravenous therapy.
- Perform testing for *H. pylori*; initiate treatment if the result is positive.

## Low-risk — flat, pigmented spot or clean base (Forrest grade IIC or III)

- Do not perform endoscopic hemostasis.
- Consider early hospital discharge after endoscopy if the patient has an otherwise low clinical risk and safe home environment.
- Treat with an oral proton-pump inhibitor.
- Initiate oral intake with a regular diet 6 hours after endoscopy in patients with hemodynamic stability.<sup>9</sup>
- Perform testing for *H. pylori*; initiate treatment if the result is positive.

**After endoscopy**

- If there is clinical evidence of ulcer rebleeding, repeat endoscopy with an attempt at endoscopic hemostasis,\*\* obtain surgical or interventional radiologic consultation for selected patients.
- For selected patients, discuss the need for ongoing use of NSAIDs, antiplatelet agents, and concomitant therapy with a gastroprotective agent.

\* H<sub>2</sub> blocker denotes histamine H<sub>2</sub>-receptor antagonist, ICU intensive care unit, and NSAID nonsteroidal antiinflammatory drug.

† The use of high-dose intravenous proton-pump inhibitors while awaiting endoscopy does not appear to have an effect on outcomes for patients, although it may be associated with a significant down-staging of endoscopic lesions.

‡ An epinephrine injection is defined as epinephrine mixed with normal saline at a ratio of 1:10,000.

§ The use of a large, single-channel or double-channel endoscope is recommended; if contact thermal therapy is used, a large (10 French) probe is recommended.

¶ Only omeprazole and pantoprazole have been assessed in clinical trials that were designed to reduce rates of ulcer rebleeding, surgery, and death.

|| This procedure is recommended only for endoscopists who are familiar with clot removal.<sup>15</sup>

\*\* A preplanned, second-look endoscopy that is performed within 24 hours after the initial endoscopy is not recommended.

patients,<sup>3</sup> with rebleeding rates of 22 to 55% if the ulcer is left untreated endoscopically.<sup>8,22,24</sup> Additional data are needed to confirm the possible improvement risk stratification provided by endoscopic Doppler ultrasonography applied directly to the ulcer stigmata before and after endoscopic hemostasis.<sup>26</sup>

#### APPROACH TO THERAPY

A multidisciplinary approach with timely involvement of a trained endoscopist and endoscopy assistant is widely recommended.<sup>9,19,27</sup> Such involvement may entail after-hours availability, since early endoscopy (performed within 24 hours after presentation of the patient) is the cornerstone of treatment for patients with acute upper gastrointestinal hemorrhage and may improve certain outcomes (the number of units of blood transfused and the length of the hospital stay) for selected patients who are classified as being at high risk. Early endoscopy also allows for the safe and expedited discharge of patients who are classified as being at low risk and reduces the use of health care resources.<sup>19,28</sup> Goals of early endoscopy are to determine the cause of bleeding, ascertain prognosis, and administer endoscopic therapy, if indicated. Treatment recommendations have focused on the first 72 hours after presentation and endoscopic evaluation and therapy, since this is the period when the risk of rebleeding is greatest (Table 1).<sup>24,29</sup>

#### PATIENTS AT HIGH RISK

High-risk patients should be admitted to the hospital and should receive endoscopic therapy. They should then be triaged to a monitored setting or intensive care unit for the first 24 hours of what is usually at least a 3-day hospital stay.

Patients who have bleeding ulcers with high-risk stigmata as determined on endoscopy (active bleeding or a nonbleeding visible vessel) should undergo endoscopic hemostasis, a procedure that has been shown to decrease rates of rebleeding, the need for urgent surgery, and mortality.<sup>19,27,30</sup> Contemporary endoscopic treatments include injection therapy (e.g., saline, vasoconstrictors, sclerosing agents, tissue adhesives, or a combination thereof), thermal therapy (with the use of contact methods, such as multipolar electrocoagulation and heater probe, or noncontact methods, such as argon plasma coagulation), and mechanical

A Blatchford Score		
At Presentation		Points
Systolic blood pressure		
100–109 mm Hg		1
90–99 mm Hg		2
<90 mm Hg		3
Blood urea nitrogen		
6.5–7.9 mmol/liter		2
8.0–9.9 mmol/liter		3
10.0–24.9 mmol/liter		4
≥25 mmol/liter		6
Hemoglobin for men		
12.0–12.9 g/dl		1
10.0–11.9 g/dl		3
<10.0 g/dl		6
Hemoglobin for women		
10.0–11.9 g/dl		1
<10.0 g/dl		6
Other variables at presentation		
Pulse ≥100		1
Melena		1
Syncope		2
Hepatic disease		2
Cardiac failure		2

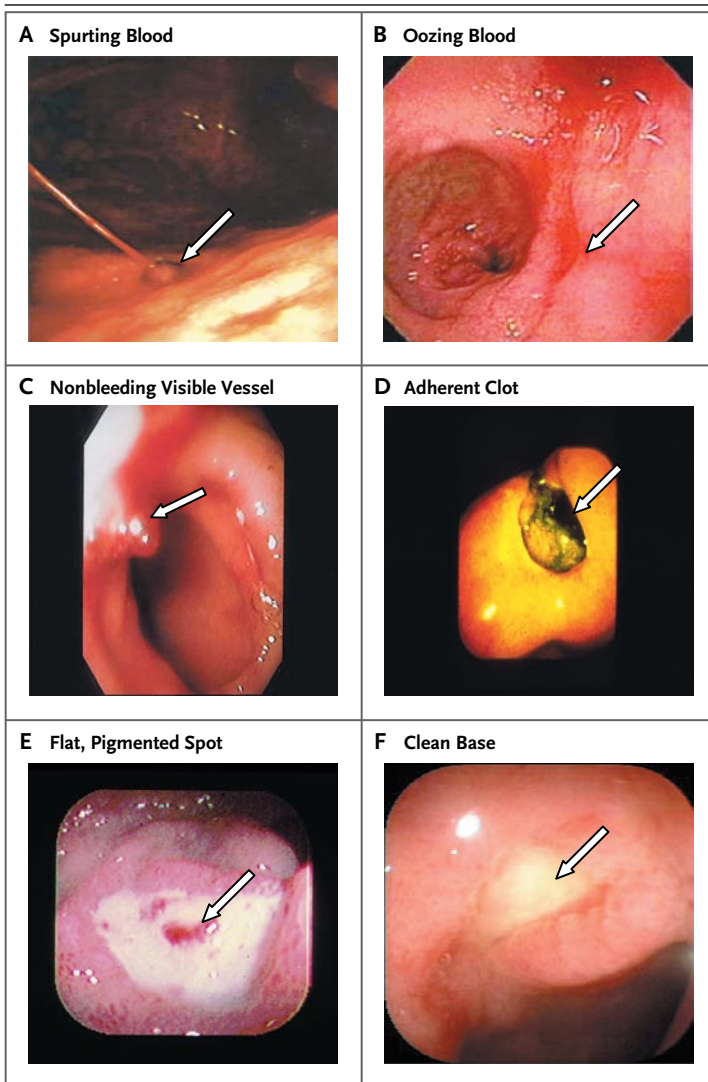
B Rockall Score		
	Variable	Points
Clinical Rockall Score	Age	
	<60 yr	0
	60–79 yr	1
	≥80 yr	2
	Shock	
	Heart rate >100 beats/min	1
	Systolic blood pressure <100 mm Hg	2
	Coexisting illness	
	Ischemic heart disease, congestive heart failure, other major illness	2
	Renal failure, hepatic failure, metastatic cancer	3
	Endoscopic diagnosis	
No lesion observed, Mallory–Weiss tear	0	
Peptic ulcer, erosive disease, esophagitis	1	
Cancer of upper GI tract	2	
Complete Rockall Score	Endoscopic stigmata of recent hemorrhage	
	Clean base ulcer, flat pigmented spot	0
	Blood in upper GI tract, active bleeding, visible vessel, clot	2

**Figure 1. Risk-Stratification Tools for Upper Gastrointestinal Hemorrhage.**

Panel A shows the values used in the Blatchford risk-stratification score, which ranges from 0 to 23, with higher scores indicating higher risk. Panel B shows the Rockall score, with point values assigned for each of three clinical variables (age and the presence of shock and coexisting illnesses) and two endoscopic variables (diagnosis and stigmata of recent hemorrhage). The complete Rockall score ranges from 0 to 11, with higher scores indicating higher risk. Patients with a clinical Rockall score of 0 or a complete Rockall score of 2 or less are considered to be at low risk for rebleeding or death. Data are from Blatchford et al.<sup>16</sup> and Rockall et al.<sup>17</sup> GI denotes gastrointestinal. To convert the values for blood urea nitrogen to milligrams per deciliter, divide by 0.357.

therapy (principally endoscopic clips). (For details, see the animation in the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org).)

All methods of endoscopic hemostasis have



**Figure 2.** Endoscopic Stigmata of Bleeding Peptic Ulcer, Classified as High Risk or Low Risk.

High-risk lesions are those that spurt blood (Forrest grade IA, Panel A), ooze blood (grade IB, Panel B), contain a nonbleeding visible vessel (grade IIA, Panel C), or have an adherent clot (grade IIB, Panel D). Low-risk lesions are those that have a flat, pigmented spot (grade IIC, Panel E) or a clean base (grade III, Panel F).

been shown to be superior to no endoscopic intervention.<sup>19,27</sup> Yet the addition of a second hemostasis approach (injectable, contact thermal therapy) to epinephrine injection (at a 1:10,000 ratio of epinephrine to normal saline) further reduces rebleeding rates, the need for surgery, and mortality,<sup>31</sup> as compared with epinephrine injection alone, which should be avoided.<sup>27,32</sup> Although the safety of injecting a sclerosant alone has been questioned, sclerosants only rarely cause serious tissue damage.<sup>33</sup>

A consensus statement recommends combination therapy (epinephrine injection to provide local vasoconstriction, volume tamponade, and facilitation of a clear view of the bleeding vessel, followed by targeted contact thermal therapy),<sup>19</sup> but the superiority of combination therapy to that of contact thermal therapy alone has been questioned.<sup>32</sup> Endoscopic therapy in the subgroup of high-risk patients who have an adherent clot has been advocated yet remains controversial (Table 1).<sup>15,19,34-36</sup>

The use of mechanical therapy, in particular endoscopic clips, has been qualified as promising.<sup>19</sup> The exact role of endoscopic clips remains incompletely defined, but emerging data and preliminary pooled analyses suggest that clips alone are similar to thermal therapy alone, a combination of injection and contact thermal therapy, and clips followed by injection.<sup>32,37</sup> These comparisons require further study. It may be that in the future, the location and appearance of a given bleeding lesion will determine the optimal method of endoscopic therapy. At present, it is probably best for endoscopists to carry out the hemostasis technique they are most comfortable using, since all methods have been shown to be efficacious. However, epinephrine injection alone should not be performed. The exact roles of newer and emerging endoscopic hemostasis techniques (including loops, cryotherapy, suturing, and stapling devices) await appropriately powered clinical trials.

Various clinical and endoscopic factors have been proposed as predictors of failure of endoscopic treatment in patients with bleeding from a peptic ulcer. These include a history of peptic ulcer disease, previous ulcer bleeding, the presence of shock at presentation, active bleeding during endoscopy, large ulcers (>2 cm in diameter), a large underlying bleeding vessel ( $\geq 2$  mm in diameter), and ulcers located on the lesser curve of the stomach or on the posterior or superior duodenal bulb.<sup>38,39</sup>

Planned, second-look endoscopy that is performed within 24 hours after initial endoscopic therapy has not been recommended.<sup>19,27</sup> Even though such a procedure was shown to be efficacious in two meta-analyses,<sup>40,41</sup> it provided only a limited reduction in the rate of rebleeding. Also, the procedure may not be cost-effective when medical therapy leading to profound acid suppression is used.<sup>42</sup> Repeat endoscopy may be considered on a case-by-case basis if there are clinical

signs of recurrent bleeding or if there is uncertainty regarding the effectiveness of hemostasis during the initial treatment.

#### PATIENTS AT LOW RISK

A significant proportion of patients who are admitted to the hospital with acute, nonvariceal upper gastrointestinal hemorrhage are at low risk for rebleeding and death.<sup>43-45</sup> Results from randomized and retrospective trials have shown that after endoscopy, low-risk patients can be discharged home, depending on when the initial endoscopy is performed.<sup>46-50</sup> A summary of selected conservative criteria for the care of low-risk patients appears in Table 2.<sup>43,44,47-51</sup> Low-risk patients who do not fulfill these clinical criteria should be admitted to the hospital for observation.

#### MEDICAL THERAPY

In the past 10 years, pharmacotherapy has focused on the use of profound acid suppression with proton-pump inhibitors in the treatment of patients with nonvariceal upper gastrointestinal hemorrhage. Experimental data have shown that gastric acid impairs clot formation, promotes platelet disaggregation, and favors fibrinolysis.<sup>52</sup> Therefore, inhibiting gastric acid and raising the intragastric pH to 6 or more and maintaining it at that level may promote clot stability, thus decreasing the likelihood of rebleeding. However, the goal of an intragastric pH of 6 or more is theoretical and has not been documented to be a reliable proxy for clinical efficacy in the treatment of peptic-ulcer bleeding. Furthermore, although data from clinical trials support the use of a bolus followed by a continuous infusion of proton-pump inhibitors, recent studies from North America show that even a high-dose, continuous infusion of proton-pump inhibitors may not sustain an intragastric pH of 6 or more.<sup>53</sup> The use of histamine H<sub>2</sub>-receptor antagonists (H<sub>2</sub> blockers) in patients with peptic-ulcer bleeding has not resulted in a significant improvement in outcomes,<sup>54</sup> probably because of early development of pharmacologic tolerance.

Potent acid-suppressing proton-pump inhibitors do not induce tachyphylaxis and have had favorable clinical results.<sup>55</sup> Recent meta-analyses showed that the use of proton-pump inhibitors significantly decreased the risk of ulcer rebleeding (odds ratio, 0.40; 95% confidence interval [CI], 0.24 to 0.67), the need for urgent surgery

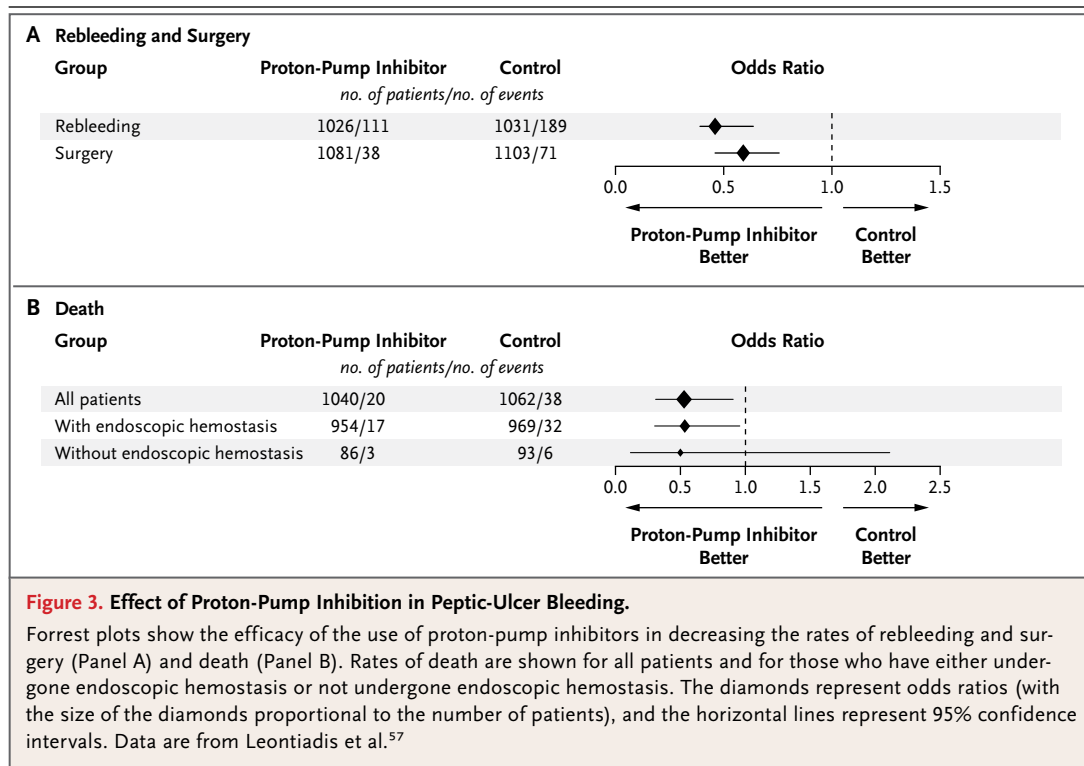
**Table 2. Proposed Selection Criteria for an Abbreviated Hospital Stay or Outpatient Treatment of Patients at Low Risk.\***

Criteria
Age, <60 yr
Absence of hemodynamic instability, which is defined as resting tachycardia (pulse, $\geq 100$ beats per minute), hypotension (systolic blood pressure, <100 mm Hg), or postural changes (increase in pulse of $\geq 20$ beats per minute or a drop in systolic blood pressure of $\geq 20$ mm Hg on standing), or hemodynamic stability within 3 hours after initial evaluation
Absence of a severe coexisting illness (e.g., heart failure, chronic obstructive pulmonary disease, hepatic cirrhosis, hematologic cancer, chronic renal failure, and cerebrovascular accident)
A hemoglobin level of more than 8 to 10 g per deciliter after adequate intravascular volume expansion and no need for blood transfusion
Normal coagulation studies
Onset of bleeding outside the hospital
Presence of a clean-base ulcer or no obvious endoscopic finding on early endoscopy (performed within 24 hours after presentation)
Adequate social support at home with the ability to return promptly to a hospital

\* Data are from Rockall et al.,<sup>43</sup> Longstreth and Feitelberg,<sup>44</sup> Lai et al.,<sup>47</sup> Moreno et al.,<sup>48</sup> Lee et al.,<sup>49</sup> Cipolletta et al.,<sup>50</sup> and Bjorkman et al.<sup>51</sup> Some of the criteria were used in published studies that involved only adults with bleeding from ulcers or other nonvariceal lesions, such as Mallory-Weiss tears, excluding those with esophageal or gastric varices, portal hypertensive gastropathy, and tumors of the upper gastrointestinal tract.

(odds ratio, 0.50; 95% CI, 0.33 to 0.76), and the risk of death (odds ratio, 0.53; 95% CI, 0.31 to 0.91) (Fig. 3A and 3B),<sup>56,57</sup> findings that have also been confirmed in a “real-world” setting.<sup>3</sup> However, the reduction in mortality appears to occur only among patients with high-risk stigmata who have first undergone endoscopic therapy, a finding that supports the use of medical therapy as an adjunct to but not a replacement for endoscopic hemostasis in such patients.<sup>34,57</sup>

There are only limited data from randomized clinical trials in the United States that have evaluated therapy with intravenous proton-pump inhibitors for acute bleeding from a peptic ulcer. A recent study comparing the use of high-dose intravenous proton-pump inhibitors with that of H<sub>2</sub> blockers was halted prematurely because of slow recruitment of subjects, and although there was a trend favoring therapy with high-dose intravenous proton-pump inhibitors, the study was underpowered to show any statistical difference between the two treatments.<sup>58</sup> In addition, the dosing method for treatment with proton-pump inhibitors appears to be important. A pooled analysis of 16 randomized, controlled trials that enrolled more than 3800 patients suggested that intravenous bolus loading followed by continuous



infusion of proton-pump inhibitors is more effective than bolus dosing alone in decreasing the rates of rebleeding and the need for surgery.<sup>59</sup> Therefore, it is reasonable to recommend the use of an intravenous bolus of proton-pump inhibitors followed by a continuous infusion for 72 hours after endoscopic hemostasis, although controversy persists as to optimal dosing (Table 1). The use of high-dose intravenous proton-pump inhibitors after endoscopic therapy has also been shown to be more effective and less costly than alternative approaches in a variety of clinical settings.<sup>60,61</sup>

The administration of high-dose intravenous proton-pump inhibitors while the patient is awaiting endoscopy does not appear to have an effect on the outcome, even though its use may be associated with a significant down-staging of endoscopic lesions — in other words, patients who receive such treatment are less likely to have endoscopic evidence of high-risk stigmata than are patients who receive placebo (odds ratio, 0.67; 95% CI, 0.54 to 0.84).<sup>62</sup> Therefore, such patients are less likely to need endoscopic hemostasis therapy (19.1% vs. 28.4%,  $P=0.007$ ).<sup>63</sup> The cost-effectiveness of proton-pump inhibitors for this indication remains somewhat controversial.<sup>64,65</sup>

The use of high-dose oral proton-pump in-

hibitors in peptic-ulcer bleeding has been shown in Asian populations to lead to reductions in the risk of rebleeding (odds ratio, 0.24; 95% CI, 0.16 to 0.36), the need for surgery (odds ratio, 0.29; 95% CI, 0.16 to 0.53), and the risk of death (odds ratio, 0.35; 95% CI, 0.16 to 0.74).<sup>66</sup> However, these results may not be completely generalizable to North American or European populations because of underlying differences in physiological measures, pharmacodynamic profiles (metabolism of proton-pump inhibitors through the cytochrome P-450 2C19 genetic polymorphism), and prevalence rates of *Helicobacter pylori* infection, factors that may favor the acid-suppressive effect of a given dose of a proton-pump inhibitor in Asian patients.<sup>66</sup> Additional data from randomized clinical trials comparing the use of intravenous proton-pump inhibitors with that of oral proton-pump inhibitors are required in Western patient populations, since high oral doses could result in significant savings in health care resources.<sup>61</sup>

Somatostatin and its analogue, octreotide, inhibit both acid and pepsin secretion while also reducing gastroduodenal mucosal blood flow. However, these drugs are not routinely recommended in patients with peptic-ulcer bleeding, since contemporary randomized, controlled trials

have shown little or no benefit attributable to them, either alone or in combination with an H<sub>2</sub> blocker.<sup>67</sup> Furthermore, there are no strong data to support the adjunctive use of these drugs after endoscopic therapy for ulcer bleeding.

---

SURGERY AND INTERVENTIONAL  
RADIOLOGY

---

The drop in surgical rates to 6.5 to 7.5% has been suggested by meta-analyses<sup>31</sup> and national registry data,<sup>3</sup> whereas epidemiologic studies have suggested an increase in the population-based annual incidence of emergency surgery from 5.2 to 7.0 operations per 100,000 population between 1987 and 1999.<sup>68</sup> Because of a new understanding of peptic ulcer disease, the role of surgery has changed markedly within the past two decades and now obviates the need for routine early surgical consultation in all patients presenting with acute upper gastrointestinal hemorrhage. The aim of emergency surgery is no longer to cure the disease but rather to stop the hemorrhage when endoscopic therapy is unavailable or has failed. The role of early elective surgery is less clear, as is the optimal surgical approach in patients with acute disease.<sup>69,70</sup> A recent cohort analysis comparing vagotomy and drainage with vagotomy and resection procedures suggested equivalent outcomes.<sup>71</sup> Surgery remains an effective and safe approach for treating selected patients with uncontrolled bleeding (i.e., those in whom hemodynamic stabilization cannot be achieved through intravascular volume replacement using crystalloid fluids or blood products) or patients who may not tolerate recurrent or worsening bleeding.<sup>72</sup> For most patients with evidence of persistent ulcer bleeding or rebleeding, a second attempt at endoscopic hemostasis is often effective, may result in fewer complications than surgery, and is the recommended management approach.<sup>3,73</sup> Exceptions may include patients with ulcers that are more than 2 cm in diameter and those who have hypotension associated with a rebleeding episode, since such patients may be at increased risk for the failure of repeat endoscopic hemostasis.<sup>27,73</sup>

Angiography with transcatheter embolization provides a nonoperative option for patients in whom a locus of acute bleeding has not been identified or controlled by endoscopy. Agents such as

Gelfoam, polyvinyl alcohol, cyanoacrylic glues, and coils are used to embolize bleeding lesions.<sup>74</sup> Primary rates of technical success range from 52 to 94%, with recurrent bleeding requiring repeated embolization procedures in approximately 10% of patients.<sup>75</sup> In uncontrolled trials, successful transcatheter embolization has been shown to significantly reduce mortality in patients with upper gastrointestinal hemorrhage,<sup>74</sup> although uncommon complications include bowel ischemia, secondary duodenal stenosis, and gastric, hepatic, and splenic infarction.<sup>75</sup> In most institutions, radiologic intervention is reserved for patients in whom endoscopic therapy has failed, especially if such patients are high-risk surgical candidates. A retrospective analysis showed no significant differences between embolization therapy and surgery in the incidence of recurrent bleeding (29.0% and 23.1%, respectively), the need for additional surgery (16.1% and 30.8%), and mortality (25.8% and 20.5%), despite a more advanced age and higher prevalence of heart disease in the group receiving embolization therapy.<sup>76</sup> Although radiologic embolization may not always be a permanent cure, it may allow for the stabilization of the patient's condition until more definitive therapy is performed, depending on available expertise.<sup>74</sup>

Although a discussion of the long-term treatment of patients after acute peptic ulcer bleeding falls outside the focus of this review, testing for and treatment of *H. pylori* infection are critical considerations to be addressed.<sup>77</sup> In addition, in selected patients, evaluation for any ongoing need for a nonsteroidal antiinflammatory or antiplatelet agent and, if such treatment is indicated, appropriate coadministration of a gastroprotective agent are important.<sup>78</sup>

Supported by an Advanced Research Career Development Award and a grant (01-191-1) from the Department of Veterans Affairs (to Dr. Gralnek) and a research scholarship from Fonds de la Recherche en Santé du Québec (to Dr. Barkun).

Dr. Barkun reports receiving consulting fees from AstraZeneca and Abbott; and Dr. Bardou, lecture fees from AstraZeneca. No other potential conflict of interest relevant to this article was reported.



*An animation showing endoscopic management of acute bleeding from a peptic ulcer is available with the full text of this article at [www.nejm.org](http://www.nejm.org).*



## REFERENCES

- Lim CH, Vani D, Shah SG, Everett SM, Rembacken BJ. The outcome of suspected upper gastrointestinal bleeding with 24-hour access to upper gastrointestinal endoscopy: a prospective cohort study. *Endoscopy* 2006;38:581-5.
- Lewis JD, Bilker WB, Brensinger C, Farrar JT, Strom BL. Hospitalization and mortality rates from peptic ulcer disease and GI bleeding in the 1990s: relationship to sales of nonsteroidal anti-inflammatory drugs and acid suppression medications. *Am J Gastroenterol* 2002;97:2540-9.
- Barkun A, Sabbah S, Enns R, et al. The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE): endoscopic hemostasis and proton pump inhibition are associated with improved outcomes in a real-life setting. *Am J Gastroenterol* 2004;99:1238-46.
- Targownik LE, Nabalamba A. Trends in management and outcomes of acute nonvariceal upper gastrointestinal bleeding: 1993-2003. *Clin Gastroenterol Hepatol* 2006;4:1459-66. [Erratum, *Clin Gastroenterol Hepatol* 2007;5:403.]
- Lassen A, Hallas J, Schaffalitzky de Muckadell OB. Complicated and uncomplicated peptic ulcers in a Danish county 1993-2002: a population-based cohort study. *Am J Gastroenterol* 2006;101:945-53.
- Ohmann C, Imhof M, Ruppert C, et al. Time-trends in the epidemiology of peptic ulcer bleeding. *Scand J Gastroenterol* 2005;40:914-20.
- Viviane A, Alan BN. Estimates of costs of hospital stay for variceal and nonvariceal upper gastrointestinal bleeding in the United States. *Value Health* 2008;11:1-3.
- Laine L, Peterson WL. Bleeding peptic ulcer. *N Engl J Med* 1994;331:717-27.
- British Society of Gastroenterology Endoscopy Committee. Non-variceal upper gastrointestinal haemorrhage: guidelines. *Gut* 2002;51:Suppl 4:iv1-iv6.
- Aljebreen AM, Fallone CA, Barkun AN. Nasogastric aspirate predicts high-risk endoscopic lesions in patients with acute upper-GI bleeding. *Gastrointest Endosc* 2004;59:172-8.
- Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;340:409-17. [Erratum, *N Engl J Med* 1999;340:1056.]
- Baradaran R, Ramdhany S, Chapalamadugu R, et al. Early intensive resuscitation of patients with upper gastrointestinal bleeding decreases mortality. *Am J Gastroenterol* 2004;99:619-22.
- Corley DA, Stefan AM, Wolf M, Cook EF, Lee TH. Early indicators of prognosis in upper gastrointestinal hemorrhage. *Am J Gastroenterol* 1998;93:336-40.
- Lee SD, Kearney DJ. A randomized controlled trial of gastric lavage prior to endoscopy for acute upper gastrointestinal bleeding. *J Clin Gastroenterol* 2004;38:861-5.
- Jensen DM, Kovacs TO, Jutabha R, et al. Randomized trial of medical or endoscopic therapy to prevent recurrent ulcer hemorrhage in patients with adherent clots. *Gastroenterology* 2002;123:407-13.
- Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. *Lancet* 2000;356:1318-21.
- Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996;38:316-21.
- Carbonell N, Pauwels A, Serfaty L, Boelle PY, Becquemont L, Poupon R. Erythromycin infusion prior to endoscopy for acute upper gastrointestinal bleeding: a randomized, controlled, double-blind trial. *Am J Gastroenterol* 2006;101:1211-5.
- Barkun A, Bardou M, Marshall JK. Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2003;139:843-57.
- Das A, Wong RC. Prediction of outcome of acute GI hemorrhage: a review of risk scores and predictive models. *Gastrointest Endosc* 2004;60:85-93.
- Romagnuolo J, Barkun AN, Enns R, Armstrong D, Gregor J. Simple clinical predictors may obviate urgent endoscopy in selected patients with nonvariceal upper gastrointestinal tract bleeding. *Arch Intern Med* 2007;167:265-70.
- Forrest JA, Finlayson ND, Shearman DJ. Endoscopy in gastrointestinal bleeding. *Lancet* 1974;2:394-7.
- Consensus conference: therapeutic endoscopy and bleeding ulcers. *JAMA* 1989;262:1369-72.
- Freeman ML, Cass OW, Peine CJ, Onstad GR. The non-bleeding visible vessel versus the sentinel clot: natural history and risk of rebleeding. *Gastrointest Endosc* 1993;39:359-66.
- Lau JY, Sung JJ, Chan AC, et al. Stigmata of hemorrhage in bleeding peptic ulcers: an interobserver agreement study among international experts. *Gastrointest Endosc* 1997;46:33-6.
- Wong RC. Endoscopic Doppler US probe for acute peptic ulcer hemorrhage. *Gastrointest Endosc* 2004;60:804-12.
- Adler DG, Leighton JA, Davila RE, et al. ASGE guideline: the role of endoscopy in acute non-variceal upper-GI hemorrhage. *Gastrointest Endosc* 2004;60:497-504. [Erratum, *Gastrointest Endosc* 2005;61:356.]
- Spiegel BM, Vakili NB, Ofman JJ. Endoscopy for acute nonvariceal upper gastrointestinal tract hemorrhage: is sooner better? A systematic review. *Arch Intern Med* 2001;161:1393-404.
- Lau JY, Chung SC, Leung JW, Lo KK, Yung MY, Li AK. The evolution of stigmata of hemorrhage in bleeding peptic ulcers: a sequential endoscopic study. *Endoscopy* 1998;30:513-8.
- Cook DJ, Guyatt GH, Salena BJ, Laine LA. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. *Gastroenterology* 1992;102:139-48.
- Calvet X, Vergara M, Brullet E, Gisbert JP, Campo R. Addition of a second endoscopic treatment following epinephrine injection improves outcome in high-risk bleeding ulcers. *Gastroenterology* 2004;126:441-50.
- Marmo R, Rotondano G, Piscopo R, Bianco MA, D'Angella R, Cipolletta L. Dual therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers: a meta-analysis of controlled trials. *Am J Gastroenterol* 2007;102:279-89, 469.
- Park WG, Yeh RW, Triadafilopoulos G. Injection therapies for nonvariceal bleeding disorders of the GI tract. *Gastrointest Endosc* 2007;66:343-54.
- Sung JJ, Chan FK, Lau JY, et al. The effect of endoscopic therapy in patients receiving omeprazole for bleeding ulcers with nonbleeding visible vessels or adherent clots: a randomized comparison. *Ann Intern Med* 2003;139:237-43.
- Kahi CJ, Jensen DM, Sung JJ, et al. Endoscopic therapy versus medical therapy for bleeding peptic ulcer with adherent clot: a meta-analysis. *Gastroenterology* 2005;129:855-62. [Erratum, *Gastroenterology* 2006;131:980-1.]
- Laine L. Systematic review of endoscopic therapy for ulcers with clots: can a meta-analysis be misleading? *Gastroenterology* 2005;129:2127-8.
- Sung JJ, Tsoi KK, Lai LH, Wu JC, Lau JY. Endoscopic clipping versus injection and thermo-coagulation in the treatment of non-variceal upper gastrointestinal bleeding: a meta-analysis. *Gut* 2007;56:1364-73.
- Chung IK, Kim EJ, Lee MS, et al. Endoscopic factors predisposing to rebleeding following endoscopic hemostasis in bleeding peptic ulcers. *Endoscopy* 2001;33:969-75.
- Thomopoulos KC, Theocharis GJ, Vagenas KA, Danikas DD, Vagianos CE, Nikolopoulou VN. Predictors of hemostatic failure after adrenaline injection in patients with peptic ulcers with nonbleeding visible vessel. *Scand J Gastroenterol* 2004;39:600-4.
- Marmo R, Rotondano G, Bianco MA, Piscopo R, Prisco A, Cipolletta L. Outcome of endoscopic treatment for peptic ulcer bleeding: is a second look necessary? A meta-analysis. *Gastrointest Endosc* 2003;57:62-7.
- Chiu PW-Y, Lau T-S, Kwong K-H, Suen DT-K, Kwok SP-Y. Impact of programmed

- second endoscopy with appropriate retreatment on peptic ulcer re-bleeding: a systematic review. *Ann Coll Surg Hong Kong* 2003;7:106-15.
42. Spiegel BM, Ofman JJ, Woods K, Vakil NB. Minimizing recurrent peptic ulcer hemorrhage after endoscopic hemostasis: the cost-effectiveness of competing strategies. *Am J Gastroenterol* 2003;98:86-97.
43. Rockall TA, Logan RF, Devlin HB, Northfield TC. Selection of patients for early discharge or outpatient care after acute upper gastrointestinal haemorrhage: National Audit of Acute Upper Gastrointestinal Haemorrhage. *Lancet* 1996;347:1138-40.
44. Longstreth GF, Feitelberg SP. Successful outpatient management of acute upper gastrointestinal hemorrhage: use of practice guidelines in a large patient series. *Gastrointest Endosc* 1998;47:219-22.
45. Dulai GS, Gralnek IM, Oei TT, et al. Utilization of health care resources for low-risk patients with acute, nonvariceal upper GI hemorrhage: an historical cohort study. *Gastrointest Endosc* 2002;55:321-7.
46. Hay JA, Maldonado L, Weingarten SR, Ellrodt AG. Prospective evaluation of a clinical guideline recommending hospital length of stay in upper gastrointestinal tract hemorrhage. *JAMA* 1997;278:2151-6.
47. Lai KC, Hui WM, Wong BC, Ching CK, Lam SK. A retrospective and prospective study on the safety of discharging selected patients with duodenal ulcer bleeding on the same day as endoscopy. *Gastrointest Endosc* 1997;45:26-30.
48. Moreno P, Jaurrieta E, Aranda H, et al. Efficacy and safety of an early discharge protocol in low-risk patients with upper gastrointestinal bleeding. *Am J Med* 1998;105:176-81.
49. Lee JG, Turnipseed S, Romano PS, et al. Endoscopy-based triage significantly reduces hospitalization rates and costs of treating upper GI bleeding: a randomized controlled trial. *Gastrointest Endosc* 1999;50:755-61.
50. Cipolletta L, Bianco MA, Rotondano G, Marmo R, Piscopo R. Outpatient management for low-risk nonvariceal upper GI bleeding: a randomized controlled trial. *Gastrointest Endosc* 2002;55:1-5.
51. Bjorkman DJ, Zaman A, Fennerty MB, Lieberman D, Disario JA, Guest-Warnick G. Urgent vs. elective endoscopy for acute non-variceal upper-GI bleeding: an effectiveness study. *Gastrointest Endosc* 2004;60:1-8.
52. Barkun AN, Cockram AW, Plourde V, Fedorak RN. Review article: acid suppression in non-variceal acute upper gastrointestinal bleeding. *Aliment Pharmacol Ther* 1999;13:1565-84.
53. Metz DC, Am F, Hunt B, Vakily M, Kukulka MJ, Samra N. Lansoprazole regimens that sustain intragastric pH >6.0: an evaluation of intermittent oral and continuous intravenous infusion dosages. *Aliment Pharmacol Ther* 2006;23:985-95.
54. Levine JE, Leontiadis GI, Sharma VK, Howden CW. Meta-analysis: the efficacy of intravenous H2-receptor antagonists in bleeding peptic ulcer. *Aliment Pharmacol Ther* 2002;16:1137-42.
55. Lau JYW, Sung JYJ, Lee KKC, et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med* 2000;343:310-6.
56. Bardou M, Toubouti Y, Benhaberou-Brun D, Rahme E, Barkun AN. Meta-analysis: proton-pump inhibition in high-risk patients with acute peptic ulcer bleeding. *Aliment Pharmacol Ther* 2005;21:677-86.
57. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database Syst Rev* 2006;1:CD002094.
58. Jensen DM, Pace SC, Soffer E, Comer GM. Continuous infusion of pantoprazole versus ranitidine for prevention of ulcer rebleeding: a U.S. multicenter randomized, double-blind study. *Am J Gastroenterol* 2006;101:1991-9, 2170.
59. Morgan D. Intravenous proton pump inhibitors in the critical care setting. *Crit Care Med* 2002;30:Suppl:S369-S372.
60. Barkun AN, Herba K, Adam V, Kennedy W, Fallone CA, Bardou M. High-dose intravenous proton pump inhibition following endoscopic therapy in the acute management of patients with bleeding peptic ulcers in the U S A and Canada: a cost-effectiveness analysis. *Aliment Pharmacol Ther* 2004;19:591-600.
61. Spiegel BM, Dulai GS, Lim BS, Mann N, Kanwal F, Gralnek IM. The cost-effectiveness and budget impact of intravenous versus oral proton pump inhibitors in peptic ulcer hemorrhage. *Clin Gastroenterol Hepatol* 2006;4:988-97.
62. Dorward S, Sreedharan A, Leontiadis G, Howden C, Moayyedi P, Forman D. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2006;4:CD005415.
63. Lau JY, Leung WK, Wu JCY, et al. Omeprazole before endoscopy in patients with gastrointestinal bleeding. *N Engl J Med* 2007;356:1631-40.
64. Al-Sabah S, Barkun AN, Herba K, et al. Cost-effectiveness of proton-pump inhibition before endoscopy in upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2008;6:418-25.
65. Tsoi KK, Lau JY, Sung JJ. Cost-effectiveness analysis of high-dose omeprazole infusion prior to endoscopy for patients presenting with upper-GI bleeding. *Gastrointest Endosc* 2008;67:1056-63.
66. Leontiadis GI, Sharma VK, Howden CW. Systematic review and meta-analysis: enhanced efficacy of proton-pump inhibitor therapy for peptic ulcer bleeding in Asia — a post hoc analysis from the Cochrane Collaboration. *Aliment Pharmacol Ther* 2005;21:1055-61.
67. Arabi Y, Al Knawy B, Barkun AN, Bardou M. Pro/con debate: octreotide has an important role in the treatment of gastrointestinal bleeding of unknown origin? *Crit Care* 2006;10:218.
68. Paimela H, Oksala NK, Kivilaakso E. Surgery for peptic ulcer today: a study on the incidence, methods and mortality in surgery for peptic ulcer in Finland between 1987 and 1999. *Dig Surg* 2004;21:185-91.
69. Poxon VA, Keighley MR, Dykes PW, Heppinstall K, Jaderberg M. Comparison of minimal and conventional surgery in patients with bleeding peptic ulcer: a multicentre trial. *Br J Surg* 1991;78:1344-5.
70. Millat B, Hay JM, Valleur P, Fingerhut A, Fagniez PL. Emergency surgical treatment for bleeding duodenal ulcer: over-sewing plus vagotomy versus gastric resection, a controlled randomized trial. *World J Surg* 1993;17:568-73.
71. de la Fuente SG, Khuri SF, Schiffner T, Henderson WG, Mantyh CR, Pappas TN. Comparative analysis of vagotomy and drainage versus vagotomy and resection procedures for bleeding peptic ulcer disease: results of 907 patients from the Department of Veterans Affairs National Surgical Quality Improvement Program database. *J Am Coll Surg* 2006;202:78-86.
72. Imhof M, Ohmann C, Röher HD, Glutig H. Endoscopic versus operative treatment in high-risk ulcer bleeding patients — results of a randomised study. *Langenbecks Arch Surg* 2003;387:327-36.
73. Lau JYW, Sung JYJ, Lam Y, et al. Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. *N Engl J Med* 1999;340:751-6.
74. Kim SK, Duddalwar V. Failed endoscopic therapy and the interventional radiologist: non-variceal upper gastrointestinal bleeding. *Tech Gastrointest Endosc* 2005;7:148-55.
75. Ljungdahl M, Eriksson LG, Nyman R, Gustavsson S. Arterial embolisation in management of massive bleeding from gastric and duodenal ulcers. *Eur J Surg* 2002;168:384-90.
76. Ripoll C, Bañares R, Beceiro I, et al. Comparison of transcatheter arterial embolization and surgery for treatment of bleeding peptic ulcer after endoscopic treatment failure. *J Vasc Interv Radiol* 2004;15:447-50.
77. Suerbaum S, Michetti P. *Helicobacter pylori* infection. *N Engl J Med* 2002;347:1175-86.
78. Lanas A, Hunt R. Prevention of anti-inflammatory drug-induced gastrointestinal damage: benefits and risks of therapeutic strategies. *Ann Med* 2006;38:415-28.

Copyright © 2008 Massachusetts Medical Society.