

## CLINICAL PRACTICE

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## Upper Gastrointestinal Bleeding Due to a Peptic Ulcer

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**A 55-year-old woman presents to the emergency department at 11:30 p.m. with hematemesis. She is otherwise healthy and has no risk factors for liver disease. Her only medication is aspirin (at a dose of 81 mg daily), which she started to take 6 months ago after reading that it reduces the risk of heart disease. The blood pressure is 94/60 mm Hg, and the heart rate is 108 beats per minute; the physical examination is otherwise normal. The hemoglobin level is 11.0 g per deciliter, platelet count 220,000 per cubic millimeter, international normalized ratio 1.0, and blood urea nitrogen level 20 mg per deciliter (7.1 mmol per liter). How should this case be further evaluated and managed?**

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## THE CLINICAL PROBLEM

**G**ASTROINTESTINAL BLEEDING, THE MOST COMMON CAUSE OF HOSPITALIZATION due to gastrointestinal disease in the United States, accounts for more than 507,000 hospitalizations and \$4.85 billion in costs annually.<sup>1</sup> Upper gastrointestinal bleeding, defined as bleeding from the esophagus, stomach, or duodenum, is responsible for 50% or more of these hospitalizations.<sup>2</sup> The case fatality rate among hospitalized patients with upper gastrointestinal bleeding has decreased over the past 20 years and ranges from 2.1 to 2.5% in U.S. nationwide database studies<sup>3,4</sup> to 10% in large, prospective European observational studies.<sup>5,6</sup> The rate of death among patients who are already hospitalized for another condition when upper gastrointestinal bleeding develops is approximately 3 to 4 times as high as the rate among patients who are admitted to the hospital for upper gastrointestinal bleeding.<sup>5</sup>

Peptic ulcers, which are primarily due to *Helicobacter pylori* infection or the use of nonsteroidal antiinflammatory drugs (NSAIDs), occur in the stomach or duodenum and are the most frequent cause of upper gastrointestinal bleeding.<sup>4</sup> Erosions in the esophagus (which are caused by gastroesophageal reflux disease) or in the stomach or duodenum (which are frequently due to NSAIDs) are also common sources of upper gastrointestinal bleeding. Erosions are breaks confined to the mucosa (the most superficial layer of the gastrointestinal tract) and should not cause severe bleeding because veins and arteries are not normally present in the mucosa. Mallory–Weiss tears, linear tears that usually occur on the gastric side of the gastroesophageal junction, may cause severe bleeding and usually occur after retching or vomiting. Less common causes of nonvariceal upper gastrointestinal



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## KEY CLINICAL POINTS

## UPPER GASTROINTESTINAL BLEEDING

- Gastrointestinal bleeding is the most common cause of hospitalization due to gastrointestinal disease in the United States.
- Peptic ulcers, primarily due to *Helicobacter pylori* infection and the use of nonsteroidal antiinflammatory drugs (NSAIDs), are the most common cause of upper gastrointestinal bleeding.
- In patients with upper gastrointestinal bleeding, tachycardia (heart rate,  $\geq 100$  beats per minute), hypotension (systolic blood pressure,  $\leq 100$  mm Hg), age older than 60 years, and major coexisting conditions are associated with increased risks of further bleeding and death.
- Patients with bleeding ulcers due to *H. pylori* infection should receive treatment for this infection and, after eradication is confirmed, discontinue antisecretory medications.
- Patients with bleeding ulcers due to NSAIDs other than low-dose aspirin should discontinue NSAIDs; if NSAIDs must be resumed, a cyclooxygenase-2 (COX-2)-selective NSAID plus a proton-pump inhibitor should be used.
- Patients with bleeding ulcers due to low-dose aspirin taken for secondary cardiovascular prevention should resume the use of aspirin within 1 to 7 days after bleeding stops.

bleeding include neoplasms, vascular ectasias (including gastric antral vascular ectasias), Dieulafoy's lesions (aberrant vessels in the mucosa), bleeding from the bile duct or pancreatic duct, and aortoenteric fistulas. The proportion of upper gastrointestinal bleeding that is attributable to varices varies widely, from 1.9% to more than 30%,<sup>4,6</sup> depending on the characteristics of the patient population (e.g., the prevalence of injection-drug or alcohol use and the country of origin). This article, which considers only nonvariceal upper gastrointestinal bleeding, focuses on ulcer bleeding.

## STRATEGIES AND EVIDENCE

## INITIAL ASSESSMENT

At the initial encounter with a patient, risk assessment is performed to determine the severity of upper gastrointestinal bleeding according to vital signs and patient factors. Tachycardia (heart rate  $\geq 100$  beats per minute), hypotension (systolic blood pressure  $\leq 100$  mm Hg), age older than 60 years, and major coexisting conditions are associated with an increased risk of further bleeding and death.<sup>7</sup>

Risk-assessment tools are available and are useful in identifying patients at very low risk. For example, discharge from the emergency department followed by outpatient care has been suggested for patients with a Glasgow-Blatchford score of 0, 0 to 1, or, in patients who are younger than 70 years of age, 0 to 2 (on a scale of 0 to 23, with higher scores indicating higher risk) (Table 1).<sup>8-11</sup> A prospective study showed that

when hospitalized, less than 1% of such patients require intervention and less than 0.5% die.<sup>10</sup>

Hemoglobin levels should be monitored; however, unlike blood pressure and heart rate, they are a poor initial indicator of the severity of upper gastrointestinal bleeding. Because patients bleed whole blood, the hemoglobin level does not drop immediately but takes hours to equilibrate as the intravascular volume is replenished with intravenous and interstitial fluid.

## INITIAL THERAPY BEFORE ENDOSCOPY

Transfusion of red cells is generally recommended when the hemoglobin level decreases below 7 g per deciliter. A randomized trial showed lower rates of death (the primary outcome), rebleeding, and adverse events with a transfusion threshold of 7 g per deciliter than with a transfusion threshold of 9 g per deciliter.<sup>12</sup> For patients in hemodynamically stable condition who have pre-existing cardiovascular disease, guidelines recommend transfusion at a hemoglobin level of less than 8 g per deciliter or in patients with symptoms. These guidelines are based on randomized trials that primarily involved patients without gastrointestinal bleeding who had undergone surgery.<sup>13</sup> In patients with hypotension due to severe upper gastrointestinal bleeding, transfusion before the hemoglobin level decreases below 7 g per deciliter is reasonable to prevent the decreases to levels well below 7 g per deciliter that will occur with fluid resuscitation alone.

A meta-analysis of six randomized trials showed that a proton-pump inhibitor administered to patients with upper gastrointestinal

bleeding soon after presentation did not significantly reduce the risks of further bleeding, surgery, or death. The use of this therapy was associated with a decrease in the frequency of high-risk endoscopic findings (active bleeding, a nonbleeding visible vessel, or an adherent clot) and the need for endoscopic therapy.<sup>14</sup> Although they are based on the same data, guidelines vary substantially regarding the use of proton-pump inhibitors before endoscopy. Some recommend high-dose intravenous proton-pump inhibitors,<sup>11,15</sup> others indicate that proton-pump inhibitors “may be considered,”<sup>8,16</sup> and still others recommend that clinicians not administer proton-pump inhibitors.<sup>17</sup>

Erythromycin (at a dose of 250 mg intravenously 30 minutes before endoscopy) increases gastric motility and improves visualization of the gastric mucosa at endoscopy. A meta-analysis of four randomized trials showed that the use of erythromycin decreased the need for blood transfusion and repeat endoscopy.<sup>18</sup>

#### USE OF A NASOGASTRIC TUBE

A nasogastric tube is not required in patients with upper gastrointestinal bleeding.<sup>8</sup> Observational evidence does not suggest a clinical benefit. Standard-bore nasogastric tubes probably do not allow sufficient clearance of clots to substantially improve visualization of the gastric mucosa at endoscopy.

#### ENDOSCOPY

Most patients who are hospitalized with upper gastrointestinal bleeding should undergo endoscopy within 24 hours, after appropriate resuscitation and transfusion, as needed, to a hemoglobin level greater than 7 g per deciliter. In some observational studies, prompt endoscopy, as compared with endoscopy after 24 hours, has been associated with reductions in the need for surgery, length of hospitalization, and mortality.<sup>8,11,16,17,19,20</sup>

Most patients with a low clinical risk (normal blood pressure and heart rate and no major coexisting conditions) should undergo endoscopy as soon as possible during routine clinical hours. Approximately 40 to 45% of patients who undergo endoscopy within 2 to 6 hours have low-risk endoscopic findings that allow discharge, thereby reducing costs.<sup>21,22</sup> An observational study and a subgroup analysis of a ran-

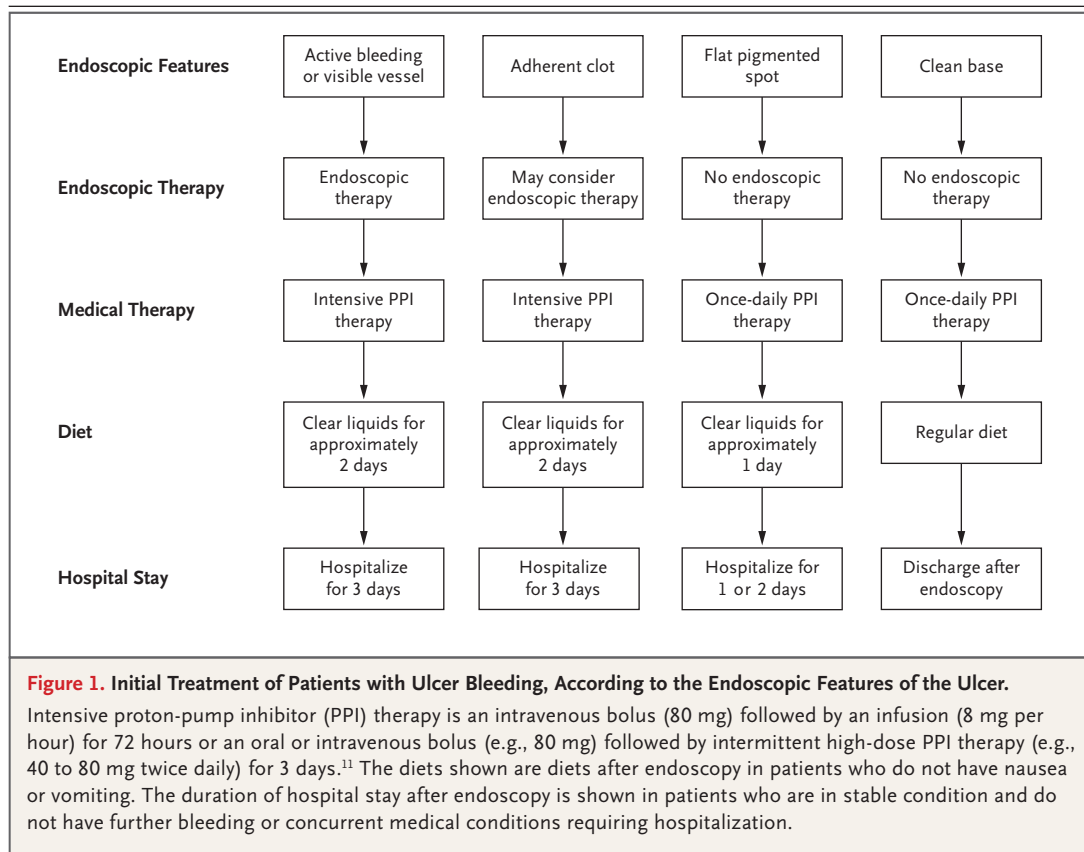
**Table 1. Glasgow–Blatchford Score.\***

Values at Admission	Points
Blood urea nitrogen — mg/dl	
<18.2	0
18.2 to <22.4	2
22.4 to <28.0	3
28.0 to <70.0	4
≥70.0	6
Hemoglobin — g/dl	
≥13.0 (men); ≥12.0 (women)	0
12.0 to <13.0 (men); 10.0 to <12.0 (women)	1
10.0 to <12.0 (men)	3
<10.0 (men and women)	6
Systolic blood pressure — mm Hg	
≥110	0
100–109	1
90–99	2
<90	3
Heart rate — beats/min	
<100	0
≥100	1
Other variables	
Melena	1
Syncope	2
Hepatic disease according to history or clinical and laboratory evidence	2
Cardiac failure according to history or clinical and echocardiographic evidence	2

\* Glasgow–Blatchford scores range from 0 to 23, with higher scores indicating higher risk. Positive predictive values were calculated in a study by Laursen et al.<sup>10</sup> Among 2305 patients presenting to a hospital with upper gastrointestinal bleeding, 313 (14%) had a score of 0 (positive predictive value, 99.0%), 562 (24%) had a score of 0 or 1 (positive predictive value, 98.8%), and 588 (26%) had a score of 0 to 2 and were younger than 70 years of age (positive predictive value, 99.0%). To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357.

domized trial suggest that endoscopy within 12 to 13 hours in patients with high clinical risk (Glasgow–Blatchford score ≥12, bloody nasogastric aspirate, hypotension, and tachycardia) may be associated with improved outcomes.<sup>8,23,24</sup>

Endoscopic features of ulcers are key in predicting risk and determining management strategies (Fig. 1). Rates of further bleeding are highest among patients with active bleeding and nonbleeding visible vessels. If endoscopic treatment is not provided, serious further bleeding



occurs in approximately 25% of patients with actively oozing hemorrhage, approximately 35% with nonbleeding visible vessels, and more than 60% with actively spurting hemorrhage.<sup>8,25</sup> An adherent clot is also a high-risk endoscopic finding, although randomized trials show that rates of rebleeding without endoscopic therapy vary widely, from 0 to 35%.<sup>26</sup> Flat, pigmented spots and clean-base ulcers, which are detected at endoscopy in approximately 70% of patients with ulcer bleeding,<sup>27</sup> are associated with low rates of serious rebleeding (5.6% and 0.5%, respectively, in a pooled analysis).<sup>25</sup>

Endoscopic therapy with injection (e.g., of epinephrine or alcohol), thermal devices (such as bipolar electrocoagulation probes or heater probes), or clips (Fig. 2) is performed in patients who have ulcers with active bleeding or a nonbleeding visible vessel. A meta-analysis of randomized trials revealed absolute risk reductions in further bleeding of 58 percentage points among patients with active bleeding and 20 percentage points among patients with nonbleeding visible vessels.<sup>26</sup> Endoscopic therapy may be con-

sidered for ulcers with adherent clots, for which randomized trials show heterogeneous results.<sup>26</sup>

If bleeding recurs, endoscopic therapy should be repeated. A randomized trial involving patients with rebleeding after endoscopic therapy showed that surgery was avoided in 73% of cases and adverse events were significantly less common with endoscopic therapy than with surgical therapy.<sup>28</sup> Transcatheter arterial embolization or surgery is performed if repeat endoscopic therapy fails. Complications of bleeding or perforation occur in approximately 0.5% of patients who undergo endoscopic therapy.<sup>26</sup> Endoscopic therapy also may be used for vascular ectasias, Dieulafoy's lesions, neoplasms, and actively bleeding Mallory–Weiss tears.<sup>11</sup>

In patients with ulcers or erosions, biopsy specimens should be obtained from lesion-free areas of the gastric body and antral mucosa for assessment of *H. pylori* infection.<sup>8,11</sup> A pooled analysis indicated that such testing has 83% sensitivity and 100% specificity for *H. pylori*.<sup>29</sup> If this testing is negative for *H. pylori*, subsequent retesting (e.g., with a stool test or breath test)

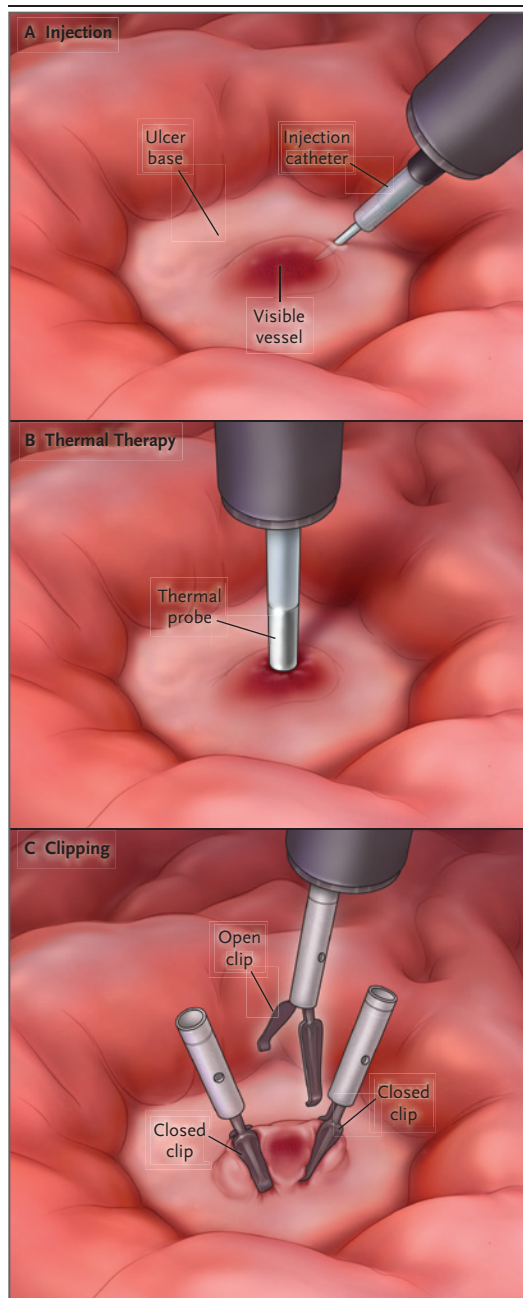
has been recommended because some observational studies suggest decreased sensitivity of testing during acute upper gastrointestinal bleeding.<sup>11,16,29</sup>

#### CARE AFTER ENDOSCOPY

Guidelines recommend that patients with ulcers and high-risk endoscopic findings receive an intravenous proton-pump inhibitor bolus (at a dose of 80 mg) followed by a continuous infusion (8 mg per hour) for 72 hours.<sup>8,11,16</sup> A meta-analysis of randomized trials showed that this strategy, as compared with endoscopic therapy alone, significantly reduced risks of further bleeding, the need for surgery, and mortality.<sup>26</sup> However, a recent meta-analysis showed that intermittent oral or intravenous proton-pump inhibitor therapy resulted in outcomes that were noninferior to those after continuous infusion<sup>30</sup>; this suggests that intermittent proton-pump inhibitor may be used in place of continuous infusion.<sup>11</sup> The most appropriate intermittent dosing is not known, but an initial oral or intravenous bolus of 80 mg followed by 40 to 80 mg twice daily for 72 hours has been suggested.<sup>11</sup>

Early studies suggested that rebleeding was uncommon more than 3 days after endoscopy, so patients who present with ulcers and high-risk endoscopic findings typically are hospitalized for 3 days after endoscopy if they have no further bleeding and no other reasons for hospitalization. However, in a systematic review of five randomized trials in which patients received endoscopic therapy and infusion of high-dose proton-pump inhibitors, among patients who had rebleeding (overall rate, 11% over 30 days), rebleeding occurred after 3 days in 44% of patients and after 7 days in 24%.<sup>31</sup> Nevertheless, anticipation that a small number of patients may have rebleeding in the coming weeks does not justify hospitalization for more than 3 days in patients who are in stable condition and do not have other medical problems. Patients should be informed about symptoms of recurrent upper gastrointestinal bleeding and the need to return to the emergency department if any occur.

After discharge, patients who presented with high-risk endoscopic findings and clinical factors (hemodynamic instability, older age, or a major coexisting condition) should receive twice-daily proton-pump inhibitor therapy for 2 weeks, followed by a proton-pump inhibitor once daily.



**Figure 2. Endoscopic Hemostatic Therapies.**

Panel A shows an injection catheter with the retractable needle extruded and the needle placed into the base of the ulcer next to the visible vessel. The visible vessel marks the site from which the ulcer bled and is associated with a high risk of recurrent bleeding. Panel B shows a thermal probe being applied to the visible vessel in the ulcer base. Panel C shows closed clips on either side of the visible vessel in the ulcer base and an open clip over the visible vessel. The open clip is about to be closed on the visible vessel.

A trial compared once-daily with twice-daily proton-pump inhibitor dosing for 11 days (followed in both groups by 2 weeks of treatment with a proton-pump inhibitor once daily) in high-risk patients who had undergone infusion of a proton-pump inhibitor for 3 days.<sup>32</sup> This trial showed a significantly lower rate of ulcer rebleeding with twice-daily therapy than with once-daily therapy (11% vs. 29%).

Patients with low-risk clinical features (a normal heart rate and blood pressure and no major coexisting conditions), low-risk endoscopic findings (clean-base ulcers, erosions, or nonbleeding Mallory–Weiss tears), and outpatient support can be discharged home after endoscopy, and a regular diet can be resumed<sup>33</sup> (Fig. 1). Once-daily proton-pump inhibitor therapy is recommended in patients with erosions or ulcers without high-risk endoscopic features.<sup>16</sup>

#### PREVENTION OF RECURRENT ULCER BLEEDING

Rebleeding is common after ulcer healing if strategies to prevent recurrence are not used. For example, a systematic review of studies with a 12-month follow-up showed a 26% rebleeding rate among patients with *H. pylori*-associated bleeding ulcers who did not receive treatment for *H. pylori* infection.<sup>34</sup>

Strategies to prevent recurrent ulcer bleeding depend on the cause of the ulcer. The three major causes are *H. pylori* infection, the use of NSAIDs (including aspirin), and an idiopathic cause (Fig. 3).

#### H. PYLORI INFECTION

Patients with *H. pylori* infection should receive therapy to eradicate the bacteria. A meta-analysis of randomized trials of such therapy showed significantly less rebleeding in patients who received this therapy than in patients who did not receive treatment for *H. pylori* infection and in those who received maintenance antisecretory therapy.<sup>34</sup>

Eradication of *H. pylori* should be confirmed after therapy with a breath test, a stool test, or, if repeat endoscopy is performed for another reason, gastric biopsy. Patients must not receive bismuth or antibiotics for at least 4 weeks and should not receive proton-pump inhibitors for at least 2 weeks before testing to avoid false negative results; histamine H<sub>2</sub>-receptor antagonists

are permissible. In a systematic review of studies with a mean follow-up of 11 to 53 months,<sup>34</sup> the incidence of rebleeding was only 1.3% among patients with confirmed eradication of *H. pylori*.

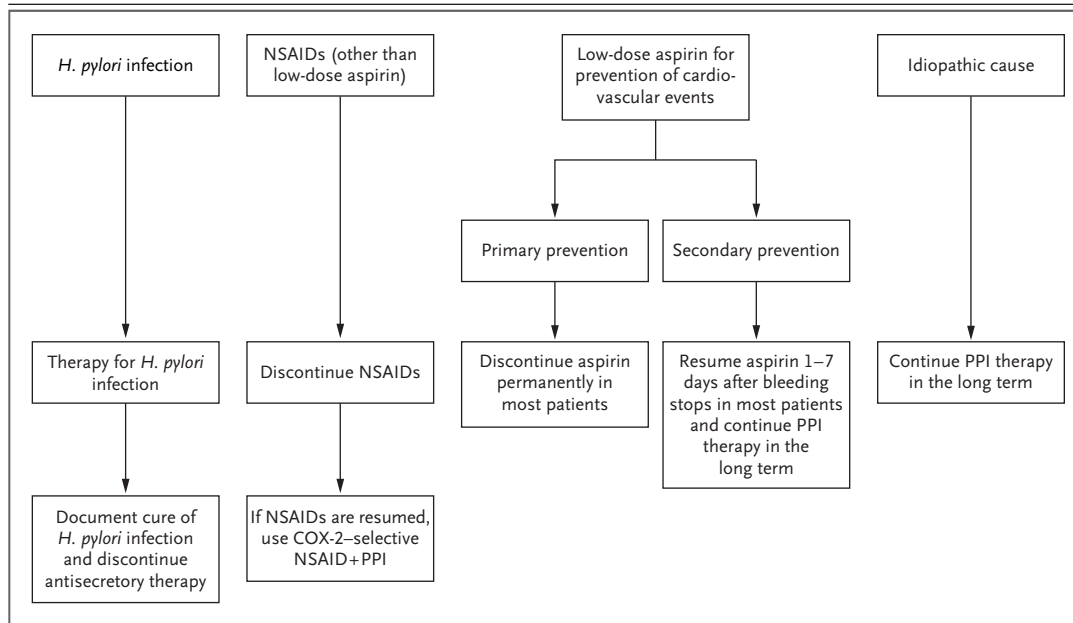
#### NSAIDS OTHER THAN LOW-DOSE ASPIRIN

Patients who have bleeding ulcers while taking NSAIDs should discontinue NSAIDs permanently if possible. If NSAIDs must be resumed, a combination of a cyclooxygenase-2 (COX-2)-selective NSAID and a proton-pump inhibitor is recommended. Studies have shown rates of rebleeding of 4 to 6% within 6 months among patients who had a bleeding ulcer and were subsequently treated with COX-2-selective NSAIDs alone or traditional NSAIDs plus a proton-pump inhibitor.<sup>36-38</sup> A 12-month double-blind trial showed significantly less ulcer rebleeding with a COX-2-selective NSAID plus a proton-pump inhibitor than with a COX-2-selective NSAID alone (0 vs. 9%).<sup>39</sup>

#### LOW-DOSE ASPIRIN

Decisions regarding continuation of low-dose aspirin (50 to 325 mg daily) for prevention of cardiovascular events should be based on whether the therapy is for primary or secondary prevention. When used for primary prevention, aspirin has been shown to result in significant but small reductions in the absolute risk of cardiovascular events; the estimated number needed to treat to prevent one myocardial infarction, stroke, or vascular death is 1745.<sup>40</sup> The risk of recurrent upper gastrointestinal bleeding probably outweighs the potential benefit of resuming primary prevention in most patients.

In contrast, the absolute reduction in cardiovascular events is much greater when aspirin is used for secondary prevention (estimated number needed to treat, 67).<sup>41</sup> A randomized trial involving patients with bleeding ulcers and high-risk endoscopic features who were taking low-dose aspirin for secondary prevention compared resumption of aspirin use within 24 hours versus withholding aspirin for 8 weeks.<sup>42</sup> Patients assigned to prompt resumption of aspirin, as compared with those in whom aspirin was withheld, had no significant increase in the risk of rebleeding and had significantly lower mortality at 30 days (1% vs. 9%) and 8 weeks (1% vs. 13%). The risk of cardiovascular events may increase within 1 to 2 weeks after discontinuing aspirin



**Figure 3. Long-Term Treatment of Patients with Bleeding Ulcers, According to the Cause of the Ulcer.**

Patients with *Helicobacter pylori* infection who receive low-dose aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs) require interventions for both causes. Two first-line therapies (both administered for 14 days) are recommended for *H. pylori* infection if local patterns of clarithromycin resistance or eradication rates with triple therapy are not known: bismuth-containing quadruple therapy and concomitant (non-bismuth-containing quadruple) therapy.<sup>35</sup> Bismuth-containing quadruple therapy is a PPI at a dose of 20 to 40 mg twice daily, bismuth (bismuth subsalicylate at a dose of 262 mg, 2 tablets four times a day; colloidal bismuth subcitrate at a dose of 120 mg, 2 tablets twice daily or 1 tablet four times a day; bismuth bismuth citrate at a dose of 140 mg, 3 tablets four times a day; or bismuth subcitrate potassium at a dose of 140 mg as part of combination tablets, 3 tablets four times a day), metronidazole at a dose of 500 mg three times a day or 400 mg four times a day, and tetracycline 500 mg four times a day. Concomitant (non-bismuth-containing quadruple) therapy is a PPI at a dose of 20 to 40 mg twice daily, amoxicillin at a dose of 1 g twice daily, clarithromycin at a dose of 500 mg twice daily, and metronidazole at a dose of 500 mg twice daily. Triple therapy (e.g., a PPI at a dose of 20 to 40 mg twice daily, amoxicillin 1 g twice daily, and clarithromycin at a dose of 500 mg twice daily, all administered for 14 days) should only be used in geographic areas where the prevalence of clarithromycin-resistant *H. pylori* is known to be less than 15% or the eradication rate is known to be greater than 85%.

used for secondary prevention<sup>43,44</sup>; thus, aspirin should be resumed 1 to 7 days after bleeding stops.<sup>8,11,45</sup> Cotherapy with a proton-pump inhibitor also should be administered to reduce rebleeding.<sup>8,45,46</sup>

#### COMBINED *H. PYLORI* INFECTION AND NSAID USE

In patients who have received NSAIDs and who are found to have *H. pylori* infection, both eradication of *H. pylori* infection and discontinuation of NSAIDs are recommended. Randomized trials have compared outcomes of treatment for *H. pylori* infection with the use of a proton-pump inhibitor (omeprazole at a dose of 20 mg daily) in *H. pylori*-positive patients who had upper gastro-

intestinal bleeding while taking low-dose aspirin or an NSAID other than aspirin. Among patients who had bleeding while taking an NSAID and received naproxen after ulcer healing, rebleeding occurred by 6 months in 19% after treatment for *H. pylori* infection and in 4% of patients who received maintenance therapy with a proton-pump inhibitor.<sup>36</sup> In contrast, among patients who had bleeding while taking low-dose aspirin and resumed low-dose aspirin after ulcer healing, rebleeding occurred by 6 months in 2% and 1%, respectively; this suggests that eradication of *H. pylori* infection may reduce risk among patients who receive low-dose aspirin (although no placebo group was included).<sup>36</sup>

However, treatment with a proton-pump inhibitor is still recommended if aspirin is continued. A 12-month randomized trial involving *H. pylori*-positive patients with ulcer complications who were receiving low-dose aspirin showed that even after eradication of *H. pylori* infection, ulcer rebleeding was significantly less frequent with a proton-pump inhibitor than with a placebo (2% vs. 15%).<sup>46</sup>

#### IDIOPATHIC ULCER

An observational study<sup>47</sup> showed a 42% incidence of rebleeding at 7 years among patients who did not have *H. pylori* infection, use NSAIDs, or have another uncommon identified cause of an ulcer (e.g., the Zollinger–Ellison syndrome or neoplasm) and who did not receive gastroprotective therapy. Thus, these patients should continue to receive once-daily maintenance therapy with a proton-pump inhibitor.<sup>8,16</sup>

#### AREAS OF UNCERTAINTY

Data from studies of new endoscopic tools such as Doppler ultrasonography (to assess bleeding risk and the adequacy of endoscopic therapy) and application of powders or cryotherapy (for hemostasis) are insufficient to establish the role of these tools in clinical practice. The appropriate dosing of proton-pump inhibitors to treat ulcers in patients with high-risk findings requires further study. In addition, more data are needed to guide the choice between interventional radiologic and surgical treatment in patients in whom endoscopic therapy has failed. Observational studies show associations between proton-pump inhibitors and adverse outcomes (e.g., dementia, chronic kidney disease, cardiovascular events, fractures, pneumonia, and enteric infections).<sup>48-50</sup> The strengths of these associations are generally modest (odds ratios or hazard ratios <2 except for enteric infections), and it is not known whether they are causal.<sup>48-50</sup> In patients with a prior bleeding ulcer, the documented benefit of proton-pump inhibitors outweighs the small and uncertain risks.

#### GUIDELINES

Guidelines for the management of upper gastrointestinal bleeding have been published by U.S.

and international professional societies.<sup>8,11,15,17</sup> The recommendations in this article are generally concordant with these guidelines. Only the European Society of Gastrointestinal Endoscopy guideline,<sup>11</sup> which was published after the meta-analysis comparing intermittent with continuous proton-pump inhibitors<sup>30</sup> became available, suggests consideration of intermittent rather than continuous proton-pump inhibitors for bleeding ulcers in patients with high-risk endoscopic findings.

#### CONCLUSIONS AND RECOMMENDATIONS

Ulcer bleeding is the most likely cause of upper gastrointestinal bleeding in the patient described in the vignette. Her aspirin use may have caused a new ulcer or may have induced bleeding from a preexisting lesion (e.g., an *H. pylori*-related ulcer).

I would initiate an intravenous normal saline infusion and recheck the patient's hemoglobin level after volume resuscitation. I would perform endoscopy the next morning, within 12 hours after presentation because of the patient's initial hypotension. If an ulcer is detected, I would perform endoscopic therapy for active bleeding or a nonbleeding visible vessel, perform biopsies of the gastric mucosa to detect *H. pylori*, initiate treatment with a proton-pump inhibitor, and discontinue aspirin given the patient's low cardiovascular risk. If *H. pylori* was not present, I would prescribe a proton-pump inhibitor for 6 to 8 weeks. If *H. pylori* was detected, I would prescribe therapy for *H. pylori* infection for 2 weeks, followed by 2 to 4 weeks of a proton-pump inhibitor. I would confirm eradication of the infection by retesting for *H. pylori* after switching the patient's treatment to a histamine H<sub>2</sub>-receptor antagonist for 2 weeks. If *H. pylori* infection was eradicated (or was never present) and the patient agreed not to use aspirin and other NSAIDs, I would discontinue antisecretory medications.

Dr. Laine reports receiving fees for serving on data and safety monitoring boards from Bayer and Pharmaceutical Product Development (a contract research organization that oversaw trials sponsored by Eisai), and providing a review for a law firm representing Mylan in a patent-litigation case regarding formulation of a pill combining an NSAID and a proton-pump inhibitor. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.



## REFERENCES

- Peery AF, Crockett SD, Barritt AS, et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. *Gastroenterology* 2015;149(7):1731-1741.e3.
- Lanas A, García-Rodríguez LA, Polo-Tomás M, et al. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. *Am J Gastroenterol* 2009;104:1633-41.
- Abougergi MS, Travis AC, Saltzman JR. The in-hospital mortality rate for upper GI hemorrhage has decreased over 2 decades in the United States: a nationwide analysis. *Gastrointest Endosc* 2015; 81(4):882-888.e1.
- Laine L, Yang H, Chang SC, Datto C. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. *Am J Gastroenterol* 2012;107:1190-5.
- Hearnshaw SA, Logan RFA, Lowe D, Travis SPL, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut* 2011;60: 1327-35.
- Nahon S, Hagège H, Latrive JP, et al. Epidemiological and prognostic factors involved in upper gastrointestinal bleeding: results of a French prospective multicenter study. *Endoscopy* 2012;44:998-1008.
- Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996;38:316-21.
- Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012;107:345-60.
- Stanley AJ, Ashley D, Dalton HR, et al. Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation. *Lancet* 2009;373: 42-7.
- Laursen SB, Dalton HR, Murray IA, et al. Performance of new thresholds of the Glasgow Blatchford score in managing patients with upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2015; 13(1):115-121.e2.
- Gralnek IM, Dumonceau JM, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015;47(10):a1-46.
- Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013;368:11-21.
- Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: a clinical practice guideline from the AABB. *Ann Intern Med* 2012;157:49-58.
- Sreedharan A, Martin J, Leontiadis GI, et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2010;7:CD005415.
- Hwang JH, Fisher DA, Ben-Menachem T, et al. The role of endoscopy in the management of acute non-variceal upper GI bleeding. *Gastrointest Endosc* 2012;75: 1132-8.
- Barkun AN, Bardou M, Kuipers EJ, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2010;152:101-13.
- National Institute for Health and Clinical Excellence. Acute upper gastrointestinal bleeding: management. London: National Clinical Guideline Centre at the Royal College of Physicians, 2012.
- Bai Y, Guo JF, Li ZS. Meta-analysis: erythromycin before endoscopy for acute upper gastrointestinal bleeding. *Aliment Pharmacol Ther* 2011;34:166-71.
- Cooper GS, Chak A, Connors AF Jr, Harper DL, Rosenthal GE. The effectiveness of early endoscopy for upper gastrointestinal hemorrhage: a community-based analysis. *Med Care* 1998;36:462-74.
- Wysocki JD, Srivastav S, Winstead NS. A nationwide analysis of risk factors for mortality and time to endoscopy in upper gastrointestinal haemorrhage. *Aliment Pharmacol Ther* 2012;36:30-6.
- 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.
- 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.
- Lim LG, Ho KY, Chan YH, et al. Urgent endoscopy is associated with lower mortality in high-risk but not low-risk nonvariceal upper gastrointestinal bleeding. *Endoscopy* 2011;43:300-6.
- Lin HJ, Wang K, Perng CL, et al. Early or delayed endoscopy for patients with peptic ulcer bleeding: a prospective randomized study. *J Clin Gastroenterol* 1996; 22:267-71.
- Laine L, Peterson WL. Bleeding peptic ulcer. *N Engl J Med* 1994;331:717-27.
- Laine L, McQuaid KR. Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analyses of randomized controlled trials. *Clin Gastroenterol Hepatol* 2009;7:33-47.
- Enestvedt BK, Gralnek IM, Mattek N, Lieberman DA, Eisen G. An evaluation of endoscopic indications and findings related to nonvariceal upper-GI hemorrhage in a large multicenter consortium. *Gastrointest Endosc* 2008;67:422-9.
- 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.
- Gisbert JP, Abaira V. Accuracy of *Helicobacter pylori* diagnostic tests in patients with bleeding peptic ulcer: a systematic review and meta-analysis. *Am J Gastroenterol* 2006;101:848-63.
- Sachar H, Vaidya K, Laine L. Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis. *JAMA Intern Med* 2014;174:1755-62.
- El Ouali S, Barkun A, Martel M, Maggioro D. Timing of rebleeding in high-risk peptic ulcer bleeding after successful hemostasis: a systematic review. *Can J Gastroenterol Hepatol* 2014;28:543-8.
- Cheng HC, Wu CT, Chang WL, Cheng WC, Chen WY, Sheu BS. Double oral esomeprazole after a 3-day intravenous esomeprazole infusion reduces recurrent peptic ulcer bleeding in high-risk patients: a randomised controlled study. *Gut* 2014;63:1864-72.
- Laine L, Cohen H, Brodhead J, Cantor D, Garcia F, Mosquera M. Prospective evaluation of immediate versus delayed refeeding and prognostic value of endoscopy in patients with upper gastrointestinal hemorrhage. *Gastroenterology* 1992;102:314-6.
- Gisbert JP, Khorrami S, Carballo F, Calvet X, Gene E, Dominguez-Muñoz E. Meta-analysis: *Helicobacter pylori* eradication therapy vs. antisecretory non-eradication therapy for the prevention of recurrent bleeding from peptic ulcer. *Aliment Pharmacol Ther* 2004;19:617-29.
- Fallone CA, Chiba N, van Zanten SV, et al. The Toronto consensus for the treatment of *Helicobacter pylori* infection in adults. *Gastroenterology* 2016 April 18 (Epub ahead of print).
- Chan FKL, Chung SCS, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med* 2001; 344:967-73.
- Chan FKL, Hung LCT, Suen BY, et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *N Engl J Med* 2002;347:2104-10.
- Lai KC, Chu KM, Hui WM, et al. Celecoxib compared with lansoprazole and naproxen to prevent gastrointestinal ulcer complications. *Am J Med* 2005;118:1271-8.
- Chan FK, Wong VW, Suen BY, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. *Lancet* 2007;369:1621-6.
- Berger JS, Lala A, Krantz MJ, Baker GS, Hiatt WR. Aspirin for the prevention

of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials. *Am Heart J* 2011;162(1):115-124.e2.

41. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849-60.

42. Sung JJ, Lau JY, Ching JY, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann Intern Med* 2010;152:1-9.

43. Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J* 2006;27:2667-74.

44. Burger W, Chemnitz JM, Kneissl GD, Rücker G. Low-dose aspirin for secondary cardiovascular prevention — cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation — review and meta-analysis. *J Intern Med* 2005;257:399-414.

45. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2008;118:1894-909.

46. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med* 2002;346:2033-8.

47. Wong GL, Wong VW, Chan Y, et al. High incidence of mortality and recurrent bleeding in patients with *Helicobacter pylori*-negative idiopathic bleeding ulcers. *Gastroenterology* 2009;137:525-31.

48. Abraham NS. Proton pump inhibitors: potential adverse effects. *Curr Opin Gastroenterol* 2012;28:615-20.

49. Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Intern Med* 2016;176:238-46.

50. Gomm W, von Holt K, Thomé F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurol* 2016;73:410-6.

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