BLEEDING PEPTIC ULCER
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PEPTIC ulcer is the most common cause of acute hemorrhage in the upper gastrointestinal tract, accounting for about 50 percent of cases.1-14 There are approximately 150,000 hospitalizations per year in the United States for evaluation and treatment of bleeding ulcers (based on 1985 estimates and excluding federal hospitals).15 Although hospitalization and surgery for uncomplicated ulcers have decreased in the United States and Europe over the past 20 to 30 years, the number of hospital admissions for hemorrhage associated with ulcers has remained relatively unchanged.16-17 It is noteworthy that the incidence of bleeding ulcers appears to rise in the winter and decline in the summer.18,19

Bleeding from ulcers ceases spontaneously in at least 80 percent of patients, most of whom have an uneventful recovery without a specific intervention. However, a subgroup of patients with bleeding ulcers does not fare as well, accounting for an overall mortality rate that has remained around 6 to 7 percent for the past 30 years.1,29-34 There are at least two possible explanations for this unchanging mortality rate. First, age and the prevalence of concurrent illness, both important predictors of death, continue to rise among patients presenting with upper gastrointestinal bleeding.21 Patients with bleeding usually die not from exsanguination but from decompensation due to other diseases.21,25,26 Second, until very recently, effective nonsurgical methods for the control of bleeding from ulcers were not available.

PATHOGENESIS

Histologic Features

Histologic examination of a surgically resected gastric ulcer associated with bleeding reveals an artery eroded by the crater of the ulcer (Fig. 1).4 In most cases the diameter of the bleeding artery is small (mean, 0.7 mm; range, 0.1 to 1.8).4 A larger arterial size is probably associated with increased morbidity and mortality, as well as a decreased likelihood of success with endoscopic therapy.27 A retrospective review noted that the arterial diameter ranged from 1.5 to 3.4 mm in approximately a quarter of patients with fatal bleeding ulcers.28

Predisposing Factors

High levels of acid secretion do not appear to account for the development of bleeding in patients with peptic ulcers. Basal and stimulated acid output, as well as the sensitivity of parietal cells to pentagastrin, is similar in patients with bleeding duodenal ulcers and in those with nonbleeding ulcers.29,30 The prevalence of Helicobacter pylori in patients with bleeding ulcers may be 15 to 20 percent lower than in patients with nonbleeding ulcers.31,33 Conversely, the use of nonsteroidal antiinflammatory drugs (NSAIDs) is reported to be an important risk factor for bleeding ulcers. A number of large case-control and cohort studies suggest that the risk of upper gastrointestinal bleeding is higher for patients who use NSAIDs than for those who do not.34-40 A recent meta-analysis found that an age over 60 years, a prior "gastrointestinal event,"9 and use of NSAIDs for less than one month were associated with higher risks of complications.11

Ingestion of NSAIDs may cause both gastric and duodenal ulcers. Although gastric ulcers are more common than duodenal ulcers, in terms of the overall incidence of ulcers, the increased rates of complications associated with use of NSAIDs are similar for the two forms of ulcer.34-36 Furthermore, complications may occur soon after the initiation of NSAID therapy and appear to be more common during the first month of therapy.38,41 Thus, it appears that NSAIDs not only induce ulcers but also increase the chance of complications such as bleeding in patients whose underlying ulcer disease is not primarily due to NSAIDs.

Although the risk of an ulcer due to use of aspirin or non-aspirin NSAIDs is dependent on the dose,36 the effect of the dose on the development of bleeding from an ulcer has not been studied extensively. The risk of bleeding has been carefully assessed in a large randomized controlled trial of aspirin therapy for prophylaxis against transient ischemic attacks.42 Patients received 300 or 1200 mg of aspirin a day or placebo. Patients receiving 300 mg of aspirin a day had a significant increase in upper gastrointestinal bleeding, as compared with those receiving placebo (relative risk, 7.7; 95 percent confidence interval, 1.7 to 33.8), whereas for the patients receiving 1200 mg of aspirin a day, the relative risk of bleeding was twice that for the patients receiving 300 mg a day. Recent evidence indicates that 10 mg of aspirin a day virtually obliterates the synthesis of platelet thromboxane A2 but does not significantly decrease the output of gastric prostaglandin E2 or increase gastric injury.43 Careful clinical evaluation in large numbers of patients will be re-
required to confirm the safety of treatment with very low doses of aspirin, with respect to bleeding ulcers.

Corticosteroids alone have not been demonstrated to increase the risk of ulcer development or bleeding. However, steroids are reported to double the NSAID-associated risk of serious gastrointestinal complications, and the concomitant use of steroids and NSAIDs may be associated with a 10-fold increase in the risk of upper gastrointestinal hemorrhage.

Although anticoagulation therapy would seem likely to increase the risk of bleeding in patients with peptic ulcers, placebo-controlled trials with warfarin (which generally exclude patients with known ulcer disease) have not documented a significant increase in bleeding ulcers.

**Clinical Presentation**

About 20 percent of patients who have bleeding ulcers present with melena, 30 percent with hematemesis, and 50 percent with both. As many as 5 percent of patients with bleeding ulcers present with hematochezia. Whether the rectal output is bright red (i.e., hematochezia) or black (i.e., melena) is determined by the volume and rapidity of blood loss. Melena can result when as little as 50 to 100 ml of blood is experimentally introduced into the upper gastrointestinal tract, whereas 1000 ml or more of blood always leads, at least initially, to hematochezia.

**Clinical Prognostic Factors**

The most widely used end points in patients with bleeding ulcers are the number of units of blood transfused, the need for urgent surgery, and death. The primary determinants of these end points are the magnitude of the initial bleeding episode, whether bleeding persists or recurs, and the patient's age and overall health. Clinical markers that indicate severe bleeding or a high risk of further hemorrhage include hemodynamic instability on presentation, bleeding manifested as repeated red hematemesis or hematochezia, and failure of the gastric aspirate to clear with lavage. Advanced age (e.g., over 60 years) and the presence of serious underlying medical illness are even more important in predicting survival after an acute episode of bleeding. A study of 701 patients with bleeding peptic ulcers reported a mortality rate of 10 percent among patients over the age of 60 years, as compared with 0.5 percent among those 60 or younger.

**Prognostic Features at Endoscopy**

Although clinical characteristics are important in predicting the outcome of a bleeding ulcer and in determining which patients should undergo urgent esophagogastroduodenoscopy (hereinafter referred to as endoscopy), the endoscopic appearance of an ulcer may provide the most helpful prognostic information. The ulcer may have a clean base or have one of several stigmata of hemorrhage: a flat pigmented spot (red, purple, brown, or black), an adherent clot, a visible vessel (a smooth-surfaced protuberance or plug in the base of the ulcer), or active bleeding (either oozing or spurting). The characteristic stigmata of hemorrhage are shown in Figure 2, with the prevalence and rate of rebleeding for each endoscopic feature shown in Table 1.

The size of an ulcer is also a prognostic indicator. Patients with ulcers larger than 1 or 2 cm in diameter have increased rates of rebleeding and death, even after endoscopic hemostatic therapy. Large ulcers are more frequently found to have stigmata of recent hemorrhage than are small ulcers.

Clinical investigators are exploring other methods to refine the prognostic usefulness of endoscopic features in patients with bleeding ulcers. The color of visible vessels has been suggested as potentially helpful in predicting rebleeding, but the available data do not support this contention. One small prospective study, however, has reported that clear or translucent vessels presage a significantly higher likelihood of rebleeding than do opaque vessels.

A Doppler ultrasound probe passed through the biopsy channel of an endoscope has been used to identify evidence of blood flow beneath the surface of the ulcer. Rebleeding is rare in the absence of a Doppler signal from the base of the ulcer, but the clinical course in patients with Doppler-positive ulcers has not been well defined. Evidence that Doppler-guided ultrasonography provides a better prediction of rebleeding than does endoscopy alone will be needed before this new technique can be recommended. The only such evidence so far comes from one small study showing that patients with Doppler-positive ulcers had rebleeding more frequently than those with Doppler-negative ulcers and the same stigmata.

**Initial Management**

Hemodynamic assessment (blood pressure, pulse, and postural changes) and, if necessary, institution of resuscitative measures are the first steps in the man-
agement of upper gastrointestinal bleeding. Clinical prognostic features and the initial response to resuscitation are used to decide whether a patient should be hospitalized and, if so, what level of care should be provided. Patients with clinical characteristics that indicate a high risk of further bleeding or death should be admitted to an intensive care unit. Patients predicted to do well may be admitted to a regular ward or may even be kept in the emergency department until diagnostic endoscopy has been performed. Healthy, young patients presenting with clinically trivial bleeding may, in some cases, be discharged home without diagnostic evaluation but with arrangements for outpatient follow-up.

Studies in the early 1980s suggested that endoscopy could not alter the care of patients with acute bleeding from a peptic ulcer. Today, there is ample evidence that the endoscopic appearance of an ulcer provides an excellent complement to clinical factors in assessing the risk of further bleeding or death. Such
information dictates management in terms of therapy, level of hospital care, resumption of feeding, and length of hospitalization. Therefore, most patients with acute upper gastrointestinal bleeding should undergo endoscopic examination. Endoscopy should be performed as soon as safely possible in patients at high risk for further bleeding or death. Patients with minor bleeding who have been admitted to a medical ward can wait until the next day for endoscopy. Since the need for admission may be determined by the endoscopic findings (see below), physicians should consider placing patients at low risk in a short-stay area while they await endoscopy.

As shown in Figure 3, subsequent management of bleeding ulcers is determined by the results of endoscopy. Most studies indicate that among patients with clean-based ulcers, the rate of recurrent bleeding is 0 to 2 percent; two studies from Hong Kong in which the rates of recurrent bleeding were over 5 percent, account for the combined rate of 5 percent shown in Table 1. In addition, patients with clean-based ulcers virtually never require urgent intervention for recurrent bleeding (Table 1). Assuming that there is no other reason for hospitalization, such patients are candidates for early discharge (i.e., during the first day) after resuscitation, stabilization, and institution of therapy. Patients whose condition is stabilized in the emergency department may be sent directly home.

Among patients with ulcers characterized by flat spots or adherent clots (Fig. 2A and 2B), the incidence of rebleeding and urgent intervention is higher (Table 1). Such patients require a longer period of hospitalization, although not in an intensive care unit.

Patients with actively bleeding ulcers or nonbleeding ulcers with visible vessels, who are at the highest risk for further bleeding and death, should spend at least one day in the intensive care unit. Since most episodes of recurrent bleeding occur within three days after the initial episode, we believe that patients who have an uncomplicated hospital course may be considered for discharge after three days. Such an approach has been corroborated by a recent study in which endoscopy was performed daily in 166 patients who had bleeding ulcers with clots or visible vessels at admission. The stigmata disappeared within three days in all the patients.

The period during which food is withheld from patients with bleeding ulcers varies widely. Many physicians routinely withhold food for the first one to three days after endoscopy. On the other hand, some early studies suggested that prompt resumption of feeding was beneficial in patients with upper gastrointestinal hemorrhage. However, these conclusions were based on a comparison with historical controls who generally had been given nothing by mouth and minimal parenteral fluids. A recent randomized trial comparing immediate refeeding after endoscopy with a two-day delay in refueling found no difference in outcome among patients with clinically severe bleeding and ulcers with clean bases or flat spots. Patients with endoscopic features indicating a low risk of further bleeding or death can therefore begin eating soon after the procedure. Patients with endoscopic findings suggesting a higher risk should receive nothing by mouth or only clear liquids for the first two days of hospitalization so that food in the stomach will not interfere with an urgent endoscopic or surgical procedure, which may be necessary if rebleeding ensues.

### Table 1. Data on the Prevalence and Outcomes of Bleeding Ulcers, According to the Appearance of the Ulcer at Endoscopy.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prevalence</th>
<th>Further Bleeding</th>
<th>Surgery</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of cases</td>
<td>% (range)</td>
<td>no. of cases</td>
<td>% (range)</td>
</tr>
<tr>
<td>Clean base†</td>
<td>1211/2869</td>
<td>42 (19–52)</td>
<td>57/1159</td>
<td>5 (0–10)</td>
</tr>
<tr>
<td>Flat spot‡</td>
<td>262/2888</td>
<td>20 (0–42)</td>
<td>38/397</td>
<td>10 (0–13)</td>
</tr>
<tr>
<td>Adherent clot§</td>
<td>247/1420</td>
<td>17 (0–49)</td>
<td>102/454</td>
<td>22 (14–36)</td>
</tr>
<tr>
<td>Nonbleeding visible vessel¶</td>
<td>273/1647</td>
<td>17 (4–35)</td>
<td>248/573</td>
<td>43 (0–81)</td>
</tr>
<tr>
<td>Active bleeding¶</td>
<td>560/3194</td>
<td>18 (4–26)</td>
<td>225/411</td>
<td>55 (17–100)</td>
</tr>
</tbody>
</table>

*All data are from patients in prospective trials who did not receive endoscopic therapy.
†Data are from references 3–5, 7–9, 12, and 50–52.
‡Data are from references 2, 3, 5, 8, 12, and 51–56.
§Data are from references 2, 3, 5, 8, 10–12, 51–55, and 57–59.
¶Data are from references 2, 3, 5, 7, 8–12, 52–55, 57, and 59–68.

The initial treatment of bleeding ulcers, which is generally the same for gastric and duodenal ulcers, is dictated by the patient's clinical condition and the endoscopic findings.

### Medical Therapy

There is no convincing evidence that gastric lavage with any fluid at any temperature will stop bleeding or prevent recurrent bleeding. If used to cleanse the stomach before endoscopy, lavage with room-temperature tap water minimizes the discomfort experienced by the patient.

Pharmacologic agents that are vasoconstrictors or...
reduce gastric acidity or both, including vasopressin, secretin, prostaglandins, somatostatin, and H₂-receptor antagonists, have been used in an attempt to staunch the flow of blood from actively bleeding ulcers. Although a few studies have reported a benefit, most have found that these agents are not effective.¹⁰⁻¹² For example, in one double-blind trial 241 patients with endoscopic documentation of actively bleeding ulcers were randomly assigned to receive an intravenous infusion of somatostatin or placebo.¹⁰ Bleeding ceased in 88 percent of the patients treated with somatostatin and in 83 percent of those receiving placebo.

Expectations have been higher that, once initial clotting occurs and bleeding has ceased, measures designed to optimize clot function may reduce the incidence of recurrent bleeding in the short term (i.e., during the first 72 hours). One potential means to this end is the reduction of gastric acidity. Data from in vitro studies suggest that clotting occurs more efficiently and the dissolution of clots by proteolytic enzymes occurs more slowly at high pH levels.¹¹,¹² Unfortunately, when randomized, placebo-controlled trials were performed with H₂-receptor antagonists in various doses, there was no reduction in the incidence of rebleeding even with the addition of antacids to achieve a sustained pH level of 7.0.²³,²⁴,²⁷,³⁶,³⁹,⁴³ A recent double-blind trial compared the most potent antisecretory agent available, omeprazole (given intravenously during the first 24 hours, then orally for 3 more days), with placebo in 503 patients with bleeding ulcers.²³ Bleeding recurred in 24 percent of the patients receiving omeprazole and in 23 percent of those receiving placebo. Similarly, neither somatostatin nor prostaglandins significantly reduce the incidence of recurrent bleeding.⁸⁸,⁹⁰,⁹⁵

Another means of enhancing clot function is through the use of tranexamic acid, which inhibits fibrinolysis. A meta-analysis of six controlled trials showed no statistically significant reduction in recurrent bleeding or the need for surgery but did find, for reasons that are unclear, a 40 percent reduction in mortality, which was significant.⁹⁶ Unfortunately, the applicability of these results to the management of bleeding ulcers is uncertain, because each of the trials included a substantial number of patients with bleeding from lesions other than peptic ulcers. Tranexamic acid is not approved by the Food and Drug Administration for the treatment of bleeding ulcers, and few U.S. physicians use it for this indication.

On the basis of the available data, institution of antisecretory therapy with standard or high-dose H₂-receptor antagonists or omeprazole to prevent recurrent bleeding of an ulcer during the first 72 hours after hospitalization is not indicated. It is reasonable, however, to initiate therapy to promote healing. For most patients, in whom feeding is resumed shortly after endoscopy, such therapy will be in oral form. Intravenous administration of H₂-receptor antagonists, which is more expensive than oral administration, can be reserved for those cases in which feeding is being delayed. The routine use of intravenous H₂-receptor antagonists is neither necessary nor cost effective.

Endoscopic Therapy

The lack of any clearly effective medical therapy for patients with bleeding ulcers has prompted a search for alternative forms of hemostatic therapy. The development of a variety of endoscopic therapies, listed in Table 2, has proved to be the most important advance in the treatment of bleeding ulcers over the past decade. Table 2 also shows the results of a recent meta-analysis of the outcomes (surgery and mortality) when various forms of endoscopic therapy are used.⁹⁷

In studies with animals, laser therapy is less effective than the other thermal devices discussed below.⁹⁷ Controlled trials of argon and neodymium:yttrium–aluminum–garnet lasers have yielded mixed results, although in the meta-analysis noted above, laser ther-
apy did significantly reduce the rates of further bleeding, urgent surgery, and mortality.97 However, laser therapy may cause transmural injury and requires a high degree of technical expertise; in addition, laser units are very expensive, bulky, and usually impossible to transport. Laser therapy therefore cannot be recommended as the treatment of choice for bleeding ulcers.

Monopolar electrocoagulation, bipolar electrocoagulation, and heater-probe therapy use thermal contact — that is, local tamponade and heat — to effect hemostasis (Fig. 4). Monopolar electrocoagulation has been replaced by the other two methods primarily because of the concern that monopolar electrocoagulation causes a greater degree of tissue injury. In studies with animals, both bipolar electrocoagulation and heater probes are highly effective in stopping bleeding and coagulating mesenteric arteries up to 2 mm in diameter.27,96 As mentioned above, most ulcers bleed from vessels that are smaller than 2 mm.5

Both bipolar electrocoagulation and heater-probe therapy require a portable generator as well as a probe, which is passed through the biopsy channel of the endoscope and placed firmly on the bleeding lesion. Heat generated by electrical energy (with bipolar electrocoagulation) or thermal energy (with the heater probe) leads to coagulation and hemostasis. Maximal temperatures are 100°C with bipolar electrocoagulation100 and 250°C with the heater probe.101 Prospective, randomized trials have demonstrated that these approaches result in a significant reduction in further bleeding, blood transfusions, the length of the hospital stay, and the need for urgent surgery in patients with clinical evidence of major bleeding and endoscopic evidence of actively bleeding ulcers or nonbleeding ulcers with visible vessels.64,73,97,102,103 In 1989 a National Institutes of Health consensus conference concluded that bipolar electrocoagulation and heater-probe therapy are the two most promising approaches to endoscopic hemostasis.20

Injection therapy is a nonthermal method of achieving hemostasis. One of a variety of solutions is injected into the base of the ulcer with a catheter that has a retractable needle (the type of catheter used for esophageal variceal sclerotherapy). Solutions documented in controlled trials to provide effective hemo-

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>SURGERY</th>
<th>MORTALITY</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>odds ratio (95% confidence interval)</td>
<td></td>
</tr>
<tr>
<td>Laser</td>
<td>0.55 (0.36–0.80)</td>
<td>0.57 (0.40–0.79)</td>
</tr>
<tr>
<td>Thermal contact</td>
<td>0.28 (0.15–0.42)</td>
<td>0.32 (0.22–0.44)</td>
</tr>
<tr>
<td>Injection</td>
<td>0.22 (0.11–0.41)</td>
<td>0.24 (0.13–0.42)</td>
</tr>
<tr>
<td>All therapies</td>
<td>0.37 (0.27–0.46)</td>
<td>0.40 (0.31–0.48)</td>
</tr>
</tbody>
</table>

*Data are from a meta-analysis of prospective controlled trials of endoscopic treatment versus no endoscopic treatment, by Cook et al.10
†Neodymium:yttrium–aluminum–garnet or argon laser.
‡Monopolar or bipolar electrocoagulation or heater probe.

The two major complications of endoscopic therapy, perforation and induction of uncontrollable bleeding, are rare. A compilation of data from prospective controlled trials of bipolar electrocoagulation, heater-probe therapy, and injection therapy reveals induction of bleeding requiring surgery in 5 of 1684 cases (0.3 percent) and perforation in 8 (0.5 percent).11–13,59,64–67,73,75,102,107,110,111,113–120 Although endoscopic hemostatic therapy can enlarge the area of ulceration, the rate of healing with standard medical therapy among patients who have undergone endoscopic therapy for bleeding is similar to that among patients who have not been treated endoscopically.74,104,106–108

Endoscopic therapy is not required in most patients with bleeding ulcers, only in those with clinical evidence of substantial bleeding (e.g., hemodynamic instability with tachycardia, hypotension, or postural changes in blood pressure or pulse; a dropping hematocrit; or the need for transfusions) and endoscopic evidence of active bleeding or a nonbleeding visible vessel.20 In ulcers with a flat
Surgical Therapy

Surgery is generally performed if endoscopic therapy has failed or is unavailable. The same clinical and endoscopic criteria used to determine whether a patient requires urgent endoscopic therapy (features associated with a high risk of further bleeding and death) are used to determine whether a patient should have urgent surgery.

A prospective comparison of immediate surgery, selective surgery (based on the patient’s age and response to transfusion), and no surgery among patients with massive upper gastrointestinal bleeding was carried out between 1953 and 1963 at Kings County Hospital in Brooklyn. There was no difference in mortality among the patients with confirmed ulcer disease who were assigned to the following groups: immediate surgery, 13 of 99 patients (13 percent); selective surgery, 10 of 86 (12 percent); and no surgery, 7 of 51 (14 percent).

A more recent prospective, randomized trial compared early surgery, which was performed on the basis of minimal criteria, such as the presence of any stigmata of hemorrhage or a history of prior bleeding, with delayed surgery, which was performed only if there was clinical evidence of severe persistent or recurrent bleeding. Three of 71 patients in the early-surgery group (4 percent) died, as compared with 7 of 71 patients in the delayed-surgery group (10 percent), a difference of 6 percentage points (95 percent confidence interval, −3 to 14 percentage points). All the patients who died were over 60 years of age. Thus, the more recent trial does suggest the possibility of a benefit with early surgery, primarily for patients over 60 years old. However, these studies did not assess the impact of early endoscopic therapy and are therefore not strictly applicable to current practice. A recent review of surgical therapy for bleeding ulcers provides a more thorough discussion of this approach to treatment.

Angiographic Therapy

Angiographic therapy is rarely used to treat patients with bleeding ulcers and should be considered only for severe, persistent bleeding if surgery poses an extremely high risk and endoscopic therapy has been unsuccessful or is unavailable. Ulcers may stop bleeding with an intraarterial infusion of vasopressin in up to 50 percent of cases. Uncontrolled studies suggest that arterial embolization with an absorbable gelatin sponge (Gelfoam), an autologous clot, tissue adhesives, or mechanical occlusion devices may control bleeding identified angiographically in approximately 75 to 80 percent of cases, although recurrent bleeding may occur in over half these cases. Complica-
tions of embolization include ischemia with stenosis, infarction, perforation, or abscess formation in target and nontarget organs.\textsuperscript{128,130-132}

**Prevention of Recurrent Bleeding**

The first goal in preventing recurrent bleeding is successful healing of the ulcer. Bleeding and nonbleeding ulcers have similar rates of healing with standard therapy.\textsuperscript{133} Follow-up endoscopy may be warranted to document healing and rule out cancer in patients with bleeding from gastric ulcers. We believe that for most patients with duodenal ulcers, follow-up endoscopy to document healing is neither necessary nor cost effective. However, it seems prudent to maximize the chance of healing by prescribing more potent antisecretory therapy than that routinely used (e.g., 20 mg of omeprazole daily for six to eight weeks) or longer-than-usual courses of standard therapy (e.g., an H\(_2\)-receptor antagonist for three months), especially with large ulcers. Such an approach is still far less expensive than repeated endoscopy.

Most patients with peptic ulcer disease have a recurrence. Moreover, patients who have had one episode of bleeding from an ulcer may have another episode. In a recent study of patients who had bleeding duodenal ulcers, there was a 36 percent incidence of reblooding over a mean period of 61 weeks.\textsuperscript{134} It is therefore important to develop a long-term strategy to prevent recurrent bleeding. This is accomplished by eliminating as many risk factors for recurrence as possible for an individual patient. These risk factors, which are generally the same for gastric and duodenal ulcers, include the use of NSAIDs, infection with *H. pylori*, and gastric acid.

**Medical Therapy**

Our approach to the long-term care of patients who have had bleeding from peptic ulcers is based on whether NSAIDs were used before the bleeding occurred and whether they must be continued.

Gastric acid and *H. pylori* infection are the two factors that must be considered among patients who were not using NSAIDs when the bleeding occurred. Maintenance therapy with H\(_2\)-receptor antagonists is widely used to prevent recurrent peptic ulceration. However, only two published randomized studies have examined such therapy specifically in patients with bleeding from peptic ulcers. One study found no significant difference in the rate of recurrent bleeding from duodenal ulcers over a two-year period when patients took placebo or ranitidine (150 mg) at bedtime. However, the patients who took placebo had no episodes of recurrent bleeding, an extraordinarily low rate.\textsuperscript{135} A more recent study reported significantly fewer episodes of recurrent bleeding among patients taking ranitidine (150 mg) at bedtime (3 of 32 [9 percent]) than among those taking placebo (12 of 33 [36 percent]) during a period of up to three years.\textsuperscript{136} Further studies are required before the role of maintenance therapy in the prevention of recurrent bleeding from ulcers is clear.

Studies have demonstrated that the recurrence of peptic ulcers is rare if *H. pylori* is eradicated,\textsuperscript{136-138} but most studies have not specifically examined recurrence among patients with bleeding ulcers. Two small studies with median follow-up periods of 9 and 17 months reported no recurrent bleeding after the eradication of *H. pylori*.\textsuperscript{139,140} Although larger, controlled trials are required to confirm this finding, it appears reasonable to attempt to eradicate *H. pylori* in infected patients and thereby remove an important risk factor for recurrent bleeding. This is best accomplished with combination therapy, such as a two-week course of bismuth subsalicylate (two tablets four times daily) plus metronidazole (250 mg four times daily) and tetracycline (500 mg four times daily).

Because up to 25 percent of patients with bleeding ulcers who are not taking NSAIDs may not be infected with *H. pylori*,\textsuperscript{133} the presence of infection should be documented before eradication is attempted. This may be accomplished at the time of diagnostic endoscopy by means of a rapid urea slide test (e.g., CLO-test; Delta West, Bentley, Australia) or by histologic examination of an antral-biopsy specimen. If specimens were not obtained at the time of the initial endoscopy, it is neither necessary nor cost effective to repeat the procedure just to diagnose *H. pylori*. If a patient has never undergone a course of therapy designed to eradicate *H. pylori*, currently available serologic tests, which are quite accurate, can be used. The urea breath test may also be used when it becomes commercially available.

Although it is an expensive procedure, endoscopic biopsy is currently the only means of confirming the eradication of *H. pylori*. Serologic tests are unsatisfactory because titers drop very slowly.\textsuperscript{141} When commercially available, the less expensive and noninvasive urea breath test should become the standard method to document the eradication of *H. pylori*.

Although support from randomized, controlled trials is scant, our recommendations for patients who were not taking NSAIDs at the time of bleeding is to test for the presence of *H. pylori* and attempt eradication in those who are infected. We recommend long-term therapy with H\(_2\)-receptor antagonists for patients who are not infected with *H. pylori*, for infected patients in whom eradication has failed, and for individual patients in whom *H. pylori* has been eradicated but another bleeding episode might be devastating.

Among patients who have bleeding ulcers associated with the ingestion of NSAIDs, the most important intervention is discontinuation of the drugs. If this is possible, ulcers should heal with standard therapy. The available evidence does not suggest that the presence of *H. pylori* increases the risk of ulceration in patients taking NSAIDs.\textsuperscript{142-144} However, in an individual patient with both risk factors, one cannot determine whether the ulcer was caused primarily by the NSAIDs or by *H. pylori* infection. For this reason, we would attempt to eradicate *H. pylori*, if present. Similarly, even if NSAIDs are discontinued, one might consider, on a case-by-case basis, the use of mainte-
nance therapy with H₂-receptor antagonists for patients at very high risk.

Bleeding ulcers in patients who must continue to take NSAIDs or aspirin represent a difficult management problem. Misoprostol significantly decreases the development of new gastric and duodenal ulcers in patients taking non-aspirin NSAIDs. H₂-receptor antagonists, on the other hand, are effective in preventing duodenal, but not gastric, ulcers. Although the evidence is sparse, potent antisecretory therapy with proton-pump inhibitors such as omeprazole may also prevent both gastric and duodenal ulceration caused by NSAIDs. Unfortunately, there is no published evidence that any agent will prevent the development of bleeding ulcers in patients who continue to take aspirin or non-aspirin NSAIDs. Although the use of NSAIDs does not appear to increase the risk of ulceration in patients with *H. pylori* infection, it does seem to increase the risk of complications in patients with underlying ulcer disease (which is usually related to *H. pylori* infection). Therefore, we would attempt to eradicate *H. pylori* in infected patients who need to continue taking NSAIDs.

**Surgical Therapy**

Patients who have recurrences of bleeding from ulcers despite medical therapy are candidates for surgical therapy; the available operations include proximal gastric vagotomy, truncal vagotomy and drainage (e.g., pyloroplasty), or vagotomy and antrectomy. Surgery is often an important part of the care of patients with the Zollinger–Ellison syndrome, although the advent of proton-pump inhibitors has changed the primary purpose of surgery from control of acid secretion to resection of tumors.

**References**


