Refractory Peptic Ulcer Disease

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Although the incidence of peptic ulcer disease (PUD) in Western countries has declined over the past 100 years, about 1 in 10 Americans are still affected. As the prevalence of PUD increased with advancing age, it is expected that this common disease will continue to have a significant global impact on health care delivery, health economics, and the quality of life of patients.2

PUD is the main cause for upper gastrointestinal (UGI) hemorrhage, and Helicobacter pylori infection is the main etiologic factor for PUD. Medical regimens to identify and eradicate the organism and the widespread use of proton pump inhibitor (PPI) therapy to suppress gastric acid secretion have resulted in successful medical management of PUD in the vast majority of patients.3–5 As a result, successful medical management of PUD has largely supplanted the need for gastric surgery by general surgeons.6

Surgery of PUD is now limited to treatment of more emergent complications of the disease (hemorrhage, perforation, gastric outlet obstruction), refractory disease and intractability (related to bleeding or gastrointestinal [GI] complications), or rare causes of ulcer disease, such as gastrinoma and the Zollinger-Ellison syndrome (ZES). Indications for elective peptic ulcer surgery include the following: resection of ulcers suspicious for malignancy, failure to heal despite maximal medical therapy, intolerance or noncompliance with medical therapy, and relapse while on maximal medical therapy.

In this article diagnostic and treatment issues related to refractory PUD are reviewed.7 It is most important to ensure that appropriate standard therapy for PUD is provided with subsequent confirmation of eradication of H pylori infection, because this is the best method for prevention of refractory PUD. If refractory PUD does occur, it is important to have a systematic approach for diagnosis and treatment. Refractory PUD manifests as either hemorrhagic complications (persistent or recurrent bleeding) or GI complications (perforation, stricture, obstruction). Treatment strategies for hemorrhagic complications include endoscopic therapy, surgery, and transcatheter...
angiographic embolization. Treatment strategies for GI complications include endoscopic dilation for stricture and surgery for perforation and obstruction. Potential etiologies of persistent or worsening PUD must be considered in these cases and include the following: patient risk factors and noncompliance, persistent \textit{H pylori} infection, and non-\textit{H pylori}–related infection, related to underlying idiopathic gastric hypersecretion or ZES and gastrinoma. An appropriate and meticulous diagnostic work-up for refractory PUD is mandatory.

**STANDARD THERAPY FOR PEPTIC ULCER DISEASE**

The widespread use of effective antisecretory therapies, including PPIs, and the recognition and successful eradication of \textit{H pylori} infection have made peptic ulcer a disease that can be cured by medical management in most cases.\textsuperscript{8} Surgical intervention had once been the dominant form of definitive therapy, but it is now reserved for emergent, life-threatening complications of PUD, such as bleeding, perforation, and obstruction.\textsuperscript{9} Intractability, failure to comply with or tolerate medical therapy, and rare cases of gastrinoma or ZES are indications for elective surgery for PUD.

\textit{H pylori} is associated with 95% of duodenal ulcers and 70% of gastric ulcers, and eradication of \textit{H pylori} reduces the relapse rate of ulcers. The 2004 Cochrane evidence-based review of 53 randomized controlled trials of short- and long-term treatment of PUD in \textit{H pylori}-positive adults examined the effect of this treatment. Patients received at least 1 week of \textit{H pylori} eradication therapy compared with ulcer-healing drug, placebo, or no treatment. In duodenal ulcer healing, \textit{H pylori} eradication therapy was superior to ulcer-healing drug (34 trials, 3910 patients, relative risk [RR] of ulcer persistence, 0.66; 95% confidence interval [CI], 0.58–0.76) and no treatment (two trials, 207 patients, RR, 0.37; 95% CI, 0.26–0.53). In gastric ulcer healing, no significant differences were detected between eradication therapy and ulcer-healing drug (13 trials, 1469 patients, RR, 1.32; 95% CI, 0.92–1.90). This confirmed that a 1- to 2-week course of \textit{H pylori} eradication therapy is an effective treatment for \textit{H pylori}-positive PUD.\textsuperscript{10}

There is now a worldwide consensus that the first-line treatment of \textit{H pylori} infection should be triple therapy with a PPI twice daily plus clarithromycin 500 mg twice daily and either amoxicillin 1 g twice daily or metronidazole 500 mg twice daily for 7 to 14 days.\textsuperscript{11} Treatment with PPIs twice daily is superior to treatment once daily.\textsuperscript{12} Bismuth-containing quadruple therapy, if available, is also a first choice treatment option.\textsuperscript{13} Successful eradication with first-line treatments varies from 70% to 95%, and 10- and 14-day treatments are generally 7% to 9% more effective than the most commonly used 7-day regimens.\textsuperscript{14} Rescue treatment should be based on antimicrobial susceptibility.

Eradication of \textit{H pylori} infection should be confirmed after the completion of therapy and noninvasive testing with the urea breath test is the preferred choice, 4 to 8 weeks after the completion of therapy (\textbf{Table 1}).\textsuperscript{15} If the ulcer recurs after the eradication therapy, a more careful search for reinfection or eradication failure should be performed by testing for the presence of active infection (by histologic examination and culture, together with an antibiotic-sensitivity test). The diagnosis of \textit{H pylori} infection in patients with a bleeding PUD is limited by the decreased sensitivity of standard invasive tests; usually, both the rapid urease test and histologic testing should be performed during endoscopy and then combined with the urea breath test. Infection should be considered as present when any test is positive, whereas the invasive tests and the urea breath test should be negative to establish the absence of \textit{H pylori} infection.
Furthermore, it is well accepted that in patients with uncomplicated PUD, *H pylori* eradication therapy need not be followed by antisecretory treatment. A 5-year prospective controlled study randomized 82 patients with *H pylori*-associated bleeding peptic ulcers to 1 of 4 16-week maintenance treatment groups after successful *H pylori* eradication with a 1-week PPI-based triple therapy and an additional 43-week treatment with 20 mg of omeprazole daily for ulcer healing. The four experimental groups were as follows: group A received 15 mL of an antacid suspension four times daily; group B received 300 mg of colloidal bismuth subcitrate four times daily; group C received 20 mg of famotidine twice daily; and group D, the control group, received placebo twice daily. Follow-up included a urea breath test labeled with carbon 13, biopsy-based tests, and repeated endoscopic examination. During a mean follow-up of 56 months, there was no peptic ulcer recurrence among the three treatment groups, and all the patients remained free of *H pylori* infection during the study period. This study documented that in patients with bleeding peptic ulcers, antiulcer maintenance treatment was not necessary to prevent ulcer recurrence after successful *H pylori* eradication and ulcer healing. Besides, the 1-week PPI-based triple therapy had the efficacy to ensure long-term eradication of *H pylori* in a region of high prevalence.

**REFRACTORY PEPTIC ULCER DISEASE**

Refractory PUD is defined as a disease that fails to heal after 8 to 12 weeks of therapy or one that is associated with complications. It is most challenging to evaluate and

<table>
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<tr>
<th>Diagnostic Test</th>
<th>Specific Issues</th>
<th>Can Be Used to Confirm Eradication</th>
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| Serologic ELISA | Useful only for initial testing  
Sensitivity 85%  
Specificity 79% | No |
| Urea breath test | Sensitivity 95%–100%  
Specificity 91%–98% | Yes (PPI therapy should be stopped for 2 weeks before test for eradication) |
| Stool antigen test | Inconvenient but accurate  
Sensitivity 91%–98%  
Specificity 94%–99% | Yes |
| Urine-based ELISA and rapid urine test | Sensitivity 70%–96%  
Specificity 77%–85% | No |
| Endoscopic biopsy | Culture  
Sensitivity 70%–80%  
Specificity 100%  
Histology  
Sensitivity >95%  
Specificity 100%  
Rapid urease (CLO) test  
Sensitivity 93%–97%  
Specificity 100% | Yes |

**Abbreviation:** CLO, *Campylobacter*-like organism.

treat patients with complicated and/or refractory PUD. A recent analysis regarding admission rates for PUD in the United Kingdom during 1972 to 2000 determined that emergency admission rates as a whole changed little, a decline in the young being offset by an increase in the elderly. Hemorrhage was the most common reason (approximately 115 per million population for duodenal ulcer and 87 for gastric ulcer) throughout (compared with perforation [80 and 21] and pain [90 and 68]).

**Refractory Peptic Ulcer Disease and Bleeding**

Acute UGI bleeding related to refractory PUD remains a challenging clinical problem owing to significant patient morbidity and mortality. PUD accounts for 28% to 59% of all episodes of UGI bleeding. The mortality rate associated with bleeding duodenal ulcer disease is about 10%. The first priority in treatment of bleeding due to refractory PUD is the initiation of resuscitation, critical care support, and PPI therapy (Fig. 1). A systematic review of the clinical efficacy of PPI in acute UGI bleeding concluded that PPI treatment compared with placebo or histamine-2 receptor antagonists (H2RAs) reduces mortality following PUD bleeding among patients with high-risk endoscopic findings, and reduces hemorrhage recurrence rates and surgical intervention. PPI treatment initiated before endoscopy in UGI bleeding significantly reduced the proportion of patients with stigmata of recent hemorrhage (SRH) at index endoscopy but did not reduce mortality, rebleeding, or the need for surgery in this analysis. More recently, the initiation of PPI bolus followed by continuous infusion after endoscopic therapy in patients with bleeding ulcers significantly improved outcome compared with placebo/no therapy (RR, 0.40, 95% CI, 0.28–0.59; number needed to treat [NNT], 12, 95% CI, 10–18), but not compared with H2RA. The strategy of giving PPI before and after endoscopy, with endoscopic hemostatic therapy for those with major SRH, is the most cost-effective. Treatment of *H pylori* infection was found to be more effective than antisecretory therapy in preventing recurrent bleeding from PUD. Further large randomized controlled trials are needed to address areas, such as PPI administration before endoscopic diagnosis, different doses and administration of PPIs, as well as the primary and secondary prevention of UGI bleeding.

Endoscopy is the preferred first-line management of refractory bleeding due to PUD. Current endoscopic modalities, both thermal and nonthermal, offer a wide range of choices in high-risk PUD bleeding (active arterial bleeding or nonbleeding

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**Fig. 1.** Algorithm for the treatment of refractory PUD.
visible vessel). Combinations of injection (epinephrine) along with thermal therapy or endoclips are recommended for better clinical outcomes. A recent review concluded that all endoscopic treatments are superior to pharmacotherapy alone in peptic ulcer bleeding. Optimal endoscopic therapies include thermal therapy or clips, either alone or in combination with other methods, but epinephrine injection should not be used alone.\textsuperscript{19,23} The role of endotherapy for adherent clots is controversial. A second-look endoscopy may be beneficial in high-risk patients.

Primary endoscopic hemostasis is successful in more than 90% of patients, but in 15% to 25% of the patients, either the bleeding cannot be controlled endoscopically or there is recurrence of bleeding, requiring alternative treatment. The combination of endoscopic intervention for hemostasis and PPI therapy is necessary to achieve hemostasis of active bleeding related to PUD.\textsuperscript{24} Continued bleeding after attempted endoscopic control may warrant surgical intervention. A multidisciplinary team approach should be part of all treatment protocols for the ideal management of refractory UGI hemorrhage related to PUD, and early surgical consultation is required.

An emerging strategy for bleeding control in refractory PUD is angiographic embolization (see Fig. 1). In patients who are poor surgical candidates because of their high operative risk, percutaneous transcatheter angiographic arterial embolization (TAE) is a therapeutic option. A recent study evaluated the efficacy and medium-term outcomes of TAE to control massive bleeding from gastroduodenal ulcers after failed endoscopic treatment in high-operative-risk patients. This was a retrospective study of 35 consecutive emergency embolization procedures in hemodynamically unstable patients (24 men, 11 women, mean age $71 \pm 11.6$ y) referred from 1999 to 2006 for selective angiography after failed endoscopic treatment. Mean follow-up was 27 months. Endovascular treatment was feasible in 33 patients and consistently stopped the bleeding. “Sandwich” coiling of the gastroduodenal artery was performed in 11 patients and superselective occlusion of the terminal-feeding artery with glue, coils, or gelatin particles in 22 patients. Early rebleeding occurred in six patients and was managed successfully using endoscopy ($n = 2$), reembolization ($n = 1$), or surgery ($n = 3$). No major complications related to TAE occurred. Seven patients died within 30 days of TAE and three died later during the follow-up, but none of the deaths were due to rebleeding. No late bleeding recurrences were reported. These investigators concluded that selective TAE is safe and effective for controlling life-threatening bleeding from gastroduodenal ulcers, usually obviating the need for emergency surgery in critically ill patients, whose immediate survival depends on their underlying conditions.\textsuperscript{25}

Previous reports also evaluated the efficacy and safety of TAE. In a 6-year review of 40 consecutive patients with bleeding/rebleeding after endoscopic therapy and/or surgery for duodenal ulcer, superselective angiographic catheterization and coil embolization were performed by the same interventional radiologist. Lasting hemostasis was achieved in 26 of 40 patients (65%). Transfusion requirement was reduced from median 14 (range, 3–35) units of blood before TAE to two (range, 0–53) units after TAE. Ten patients died, half of them because of continuous bleeding. No adverse effects as a result of TAE were observed.\textsuperscript{26}

A recent retrospective review identified all patients admitted to Ullevål University Hospital with hematemesis and/or melena and endoscopically verified duodenal ulcer from June 2000 to 2005. The indication for TAE was endoscopically unmanageable bleeding/rebleeding or rebleeding after surgery. Technical success was defined as acute hemostasis. Clinical success was defined as technical success without rebleeding within 30 days. A total of 278 patients (mean age, 73 years) were included in the study. Primary endoscopic hemostasis failed in 13 patients (5%) and 53 patients
(20%) experienced rebleeding. An attempt was made to treat 36 patients with TAE. Technical success in the TAE group was 92% and clinical success was 72%. In total, 10 patients underwent surgery, three because of rebleeding after TAE. The 30-day mortality was 10% for all patients, 19% in the TAE group, and 20% in the surgical group. High technical and clinical success was obtained with TAE in patients with bleeding duodenal ulcer after failure of endoscopic treatment in this cohort study.\textsuperscript{27}

A retrospective review of the outcome of TAE and surgery as salvage therapy of UGI bleeding after failed endoscopic treatment was recently performed in 658 patients referred for diagnostic/therapeutic emergency endoscopy and diagnosed with UGI bleeding (January 1998–December 2005).\textsuperscript{28} Of these 658 patients, 91 (14%) had repeat bleeding or continued to bleed. Forty of those 91 patients were treated with TAE and 51 were underwent surgery. Patients treated with TAE were older (mean age, 76 years; age range, 40–94 years) and had slightly more comorbidities compared with patients who underwent surgery (mean age, 71 years; age range, 45–89 years). The 30-day mortality rate in patients treated with TAE was 1 of 40 (3%) compared with 7 of 51 (14%) in patients who underwent surgery ($P < .07$). Most repeat bleeding could be effectively treated with TAE, both in the surgical and TAE groups. The results of this study suggest that, after failure of therapeutic endoscopy for UGI bleeding, TAE should be the treatment of choice before surgery and that TAE can also be used to effectively control bleeding after failed surgery or TAE. There was a clear trend to lower 30-day mortality with the use of TAE instead of surgery.

The data from these cohort studies document that TAE is an effective and safe treatment in a significant proportion of patients with bleeding/rebleeding duodenal ulcers after therapeutic endoscopy and/or surgery and may serve as an alternative to surgery in high-risk patients (Fig. 2).

**Fig. 2.** Treatment for PUD-related UGI hemorrhage. (From Peter S, Wilcox CM. Modern endoscopic therapy of peptic ulcer bleeding. Dig Dis 2008;26:291–9; with permission.)
GI complications related to refractory PUD include perforation (duodenal or gastric perforation) and obstruction, either partial or complete gastric outlet obstruction related to stenosis and stricture at the ulcer site. These GI complications can be challenging to treat and frequently require surgical intervention.

**Perforation related to Peptic Ulcer Disease**

Perforation occurs in approximately 2% to 10% of patients with PUD. It usually involves the anterior wall of the duodenum (60%), although it may also occur in antral (20%) and lesser-curve (20%) gastric ulcers. Recent data strongly implicate *H pylori* infection as the cause of perforated duodenal ulcer, with reported *H pylori* infection rates of 70% to 92% in these patients. A randomized study in 129 patients with duodenal ulcer perforation documented that 104 (81%) were infected with *H pylori*, diagnosed by esophagogastroduodenoscopy and biopsy at the time of laparotomy. Postoperatively, patients were randomized to receive *H pylori* treatment or PPI therapy for 4 weeks. Repeat endoscopy at 1 year confirmed that the incidence of recurrent ulceration was significantly lower in the *H pylori* treatment group (5%) compared with the PPI therapy group (38%). Based on these findings, surgical treatment for perforated duodenal ulcer is simple patch closure with postoperative *H pylori* treatment, including PPI therapy and antimicrobial agents, and documentation of eradication. Some patients with complicated perforated ulcer, either with destruction of proximal duodenum and penetration into adjacent organs, giant perforations measuring more than 20 mm in diameter or with severe duodenal stenosis, may require resectional surgery.

Perforated duodenal ulcer with perforation free into the peritoneal cavity is associated with peritonitis and warrants emergency surgical intervention. Both conventional laparotomy and laparoscopic techniques for suture closure with omental patch are acceptable surgical options for treatment in these patients. A randomized clinical trial did identify that laparoscopic repair of perforated PUD was associated with a shorter operating time, less postoperative pain, reduced pulmonary complications, shorter postoperative hospital stay, and earlier return to normal daily activities compared with the conventional open surgery, but surgeon’s laparoscopic experience and severity of illness of the patient must be considered in this decision making. A Cochrane Systematic Review concluded that laparoscopic surgery results are not clinically different from those of open surgery in patients with perforated PUD. Another systematic review concluded that laparoscopic repair seemed better than open surgery for low-risk patients, and that limited knowledge about its benefits and risks compared with open surgery suggests that the open approach may be more appropriate in high-risk studies. A more recent small prospective cohort study suggested that laparoscopic repair should be considered for all patients provided the necessary expertise is available. Specific factors have been identified that qualify as criteria for open laparotomy, including shock, delayed presentation—for more than 24 hours, confounding medical conditions, age more than 70 years, poor laparoscopic expertise, and American Society of Anesthesiologists score III to IV. However, additional studies are warranted in this area.

**Obstruction related to Peptic Ulcer Disease**

In patients presenting with gastric outlet obstruction, PUD is the underlying cause in up to 8% of patients. Many of them, however, have refractory PUD related to recurrent or persistent duodenal or pyloric channel ulcers that evolve into pyloric stenosis and obstruction as a result of acute and chronic inflammation, spasm, edema, scarring,
and fibrosis. Initial management includes nasogastric decompression, antisecretory therapy, and eradication of *H. pylori*. Endoscopic evaluation is necessary to determine the site, cause, and degree of obstruction and to evaluate for carcinoma as an etiology of the obstruction, because malignancy is the most common cause of gastric outlet obstruction in this era of antisecretory therapy.

Treatment of gastric outlet obstruction related to refractory PUD includes endoscopic pyloric balloon dilation and surgery. Endoscopic balloon dilation has been used for treatment of gastric outlet obstruction with variable results. Several large studies have demonstrated high rates of success for the relief of symptoms from pyloric stenosis using balloon dilation, which increases the diameter of the stenotic pylorus on average from 6 to 16 mm. Patients who require more than two dilations are at a high risk of endoscopic failure and the need for surgical intervention. Because many patients with benign pyloric stenosis have underlying ulcer disease, *H. pylori* infection is a common finding. Eradication of this infection at the time of balloon dilation will ensure higher long-term success rates. Endoscopic balloon dilation should therefore be the first-line therapy in appropriate patients with benign pyloric stenosis related to PUD.

Obstruction necessitates operation in about 2000 patients per year in the United States. Surgical procedures that are considered in gastric outlet obstruction related to refractory PUD include vagotomy and pyloroplasty, antrectomy, and gastroenterostomy. Minimally invasive laparoscopic techniques (truncal vagotomy, gastrojejunoscopy) have been developed for some of these surgical procedures that are associated with reduced postoperative recovery time. The largest series of laparoscopic procedures for the management of refractory PUD included 263 patients who were treated for either refractory PUD or obstruction due to PUD. Laparoscopic posterior truncal vagotomy with anterior proximal gastric vagotomy for refractory disease and laparoscopic bilateral truncal vagotomy with stapled gastrojejunoscopy for obstructive disease have become the standard surgical management at this institution.

**DIAGNOSTIC EVALUATION OF PATIENTS WITH REFRACTORY PEPTIC ULCER DISEASE**

The diagnostic evaluation of patients with refractory PUD can be challenging. Potential etiologies of persistent or worsening PUD include the following: patient risk factors and noncompliance, persistent *H. pylori* infection, and non-*H. pylori*–related infection, related to underlying idiopathic gastric hypersecretion, or ZES and gastrinoma (Fig. 3). The evaluation of the etiology of the severe PUD in any patient may require multiple
diagnostic studies. Diagnostic endoscopy in UGI series can evaluate gastric emptying. Laboratory diagnostic studies including fasting gastrin level, neuroendocrine markers, and octreotide scan may be performed for the evaluation of gastrinoma or ZES as a cause of intractable PUD. Pancreatic polypeptide and chromogranin level A are additional diagnostic laboratory studies that may be helpful. Therapy for refractory PUD involves treatment of the underlying cause. Recent data and studies regarding each of these potential etiologies of refractory PUD are reviewed in the following sections.

**Patient Risk Factors and Noncompliance**

Although curative treatment of *H pylori* infection markedly reduces the relapse of peptic ulcers, the details of the ulcers that do recur has not been well characterized until recently. A multicenter study involving 4940 PUD patients who were *H pylori* negative after successful eradication treatment were followed for up to 48 months. The crude peptic ulcer recurrence rate was 3.02% (149/4940). The annual recurrence rates of gastric, duodenal, and gastroduodenal ulcer were 2.3%, 1.6%, and 1.6%, respectively. Exclusion of patients who took nonsteroidal anti-inflammatory drugs (NSAIDs) led annual recurrence rates to 1.9%, 1.5%, and 1.3%, respectively. The recurrence rate was significantly higher in gastric ulcer. Recurrence rates of patients who smoked, consumed alcohol, and used NSAIDs were significantly higher in those with gastric ulcer recurrence compared with duodenal ulcer recurrence, and relapsed ulcers recurred at the same or adjacent sites as the previous ulcers.54

Persistent or recurrent PUD may occur because of specific patient risk factors or noncompliance with medical therapies. Patient risk factors for PUD include smoking or alcohol use, stress, and the use of NSAIDs.55 A population-based prospective cohort study (Danish adults, n = 2416) confirmed that the main risk factors for PUD were *H pylori* infection (OR, 4.3, 95% CI, 2.2–8.3), tobacco smoking (OR, 3.8, CI, 1.7–9.8), and stress due to the use of minor tranquilizers (OR, 3.0, CI, 1.4–6.6). In patients with documented *H pylori*, tobacco and alcohol use both increased the risk of PUD, whereas moderate leisure time physical activity protected against PUD in Danish adults.56

Multiple studies support a causal relationship between smoking and peptic ulcers in men and women. A Centers for Disease Control and Prevention study (the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study) used data from a nationally representative prospective study of adults in the United States, to evaluate the impact of smoking on the incidence of peptic ulcers in women (n = 2851) who had not been diagnosed as having a peptic ulcer before the baseline interview.57 Among these women, 140 (4.9%) developed PUD. During 12.5 years of follow-up, the estimated cumulative incidence of ulcers was 10.0% for current smokers, 6.4% for former smokers, and 5.4% for never smokers. After adjusting for age, education, regular aspirin use, coffee consumption, and use of alcohol, current smokers were 1.8 times more likely to develop ulcers than never smokers (95% CI, 1.2–2.6); the risk of peptic ulcer increased as the amount smoked increased.

Because tobacco and alcohol use are independent risk factors for PUD, and interfere with patient compliance and rate of ulcer healing, cessation should be considered in patients with refractory or severe PUD.58

NSAIDs are widely used for their anti-inflammatory, analgesic, and antipyretic effects, and low-dose aspirin (also an NSAID) is used for cardiovascular prophylaxis. The main concern limiting the use of these drugs is their GI toxicity. GI side effects include the following: ulcers (found at endoscopy in 15%–30% of patients using NSAIDs regularly); complications, such as upper GI bleeding (annual incidence of
1.0%–1.5%); and the development of upper GI symptoms, such as dyspepsia (occurring in up to 60% of patients taking NSAIDs). H2RAs are not effective at preventing NSAID-induced gastric ulcers when used at standard doses, although they can decrease upper GI symptoms. Misoprostol effectively decreases NSAID-induced ulcers and GI complications but is used infrequently in the United States—perhaps because of issues of compliance (multiple daily doses) and side effects (eg, diarrhea, dyspepsia). Once-daily PPI therapy also decreases the development of NSAID-associated ulcers and recurrent NSAID-related ulcer complications; it also decreases upper GI symptoms in NSAID users. In patients using aspirin, the addition of a cyclooxygenase-2-specific inhibitor seems to significantly increase GI risk to the level of a nonselective NSAID; aspirin plus a nonselective NSAID seems to increase GI risk still higher. Patients taking low-dose aspirin who have risk factors for GI complications (including concomitant nonselective NSAID therapy) should therefore receive medical co-therapy, such as a PPI.59

Clinical trials have reproducibly demonstrated that the healing of NSAID-associated gastric and duodenal ulcers is accelerated with the use of acid suppressive agents, such as H2RAs and PPIs, even with the continued use of the NSAIDs. The risk of developing gastroduodenal ulcers or ulcer complications with the continued and long-term use of NSAIDs is now well recognized as an important problem commonly encountered in daily clinical practice. Clinical trials have shown that co-prescription of misoprostol, high-dose H2RAs or PPIs can effectively prevent or reduce the rate of gastroduodenal mucosal damage associated with the use of nonselective NSAIDs.60

Multiple studies have examined whether PPI prophylaxis could prevent ulcer relapse in patients with NSAID-related peptic ulcers. In one study, patients who presented with PUD and infected with H pylori while receiving NSAIDs were recruited. Patients with healed ulcers and H pylori eradication were given naproxen 750 mg daily and randomly assigned to receive lansoprazole 30 mg daily or no treatment for 8 weeks. At the end of the 8-week treatment period, significantly fewer patients (1/22, 4.5%, 95% CI, 0–23) in the lansoprazole group compared with the group that received H pylori eradication alone (9/21, 42.9%, 95% CI, 22–66) developed recurrence of symptomatic and complicated ulcers (log rank test, P = .0025). Lansoprazole significantly reduced the cumulative relapse of symptomatic and complicated ulcers in patients requiring NSAIDs after eradication of H pylori.61 This and other studies confirmed that PPI treatment is more effective than H pylori eradication in preventing ulcer recurrence in long term NSAID users.

Although a tremendous amount of research supports the use of preventative therapies and interventions to reduce and/or avoid NSAID- or aspirin-associated ulcers and ulcer complications in the UGI tract, these strategies are often not applied sufficiently, not optimally dosed, and/or associated with poor patient compliance. This reinforces the need for continued clinician and patient education to improve the outcomes of care.

**Persistent H pylori Infection**

H pylori is the primary cause of PUD.62 H pylori infection is curable with regimens of multiple antimicrobial agents, but antimicrobial resistance is a leading cause of treatment failure.63 Current treatment for H pylori infections generally includes two or more antimicrobial agents (eg, amoxicillin, clarithromycin, metronidazole), but treatment fails in 10% to 20% of all cases, often because of drug resistance. The eradication rates
of *H pylori* with standard treatments are decreasing worldwide (Fig. 4). The choice of antibiotic treatment for refractory *H pylori* infections should be based on in vitro susceptibility data, and physicians should consider local resistance patterns when treating these infections empirically.

The efficacy of a culture-guided treatment approach for the eradication of persistent *H pylori* infection was analyzed in 94 consecutive patients in whom *H pylori* infection persisted after two eradication attempts. Susceptibility analysis was performed for amoxicillin, clarithromycin, metronidazole, tetracycline, and levofloxacin. Patients were then treated with a culture-guided, third-line regimen: 89 patients with a 1-week quadruple regimen, including omeprazole, bismuth, doxycycline, and amoxicillin and five patients with a 1-week triple regimen containing omeprazole, amoxicillin, and levofloxacin or clarithromycin. Ninety-four subjects (100%) were resistant to metronidazole, 89 (95%) to clarithromycin, 29 (31%) to levofloxacin, and five (5%) to tetracycline. No resistance to amoxicillin was found in any patient. Overall, *H pylori* eradication was obtained in 90% of subjects. The quadruple regimen was effective in 81 patients (92% by per protocol and 91% by intention-to-treat [ITT] analysis). Four patients (80%, both per protocol and ITT analysis) were *H pylori* negative after the triple regimen. This study confirmed that the culture-guided, third-line therapeutic approach is effective for the eradication of *H pylori*. Furthermore, the 1-week doxycycline- and amoxicillin-based quadruple regimen is a good third-line ‘rescue’ treatment option.

The *H pylori* Antimicrobial Resistance Monitoring Program is a prospective, multicenter United States network that tracks national incidence rates of *H pylori* antimicrobial resistance. Of 347 clinical *H pylori* isolates collected from December 1998 to 2002, 101 (29.1%) were resistant to 1 antimicrobial agent and 17 (5%) were resistant to two or more antimicrobial agents. Eighty-seven (25.1%) isolates were resistant to metronidazole, 45 (12.9%) to clarithromycin, and three (0.9%) to amoxicillin. On multivariate analysis, black race was the only significant risk factor (*P*<.01, hazard ratio, 2.04) for infection with a resistant *H pylori* strain.

![Fig. 4. Results of recent comparative studies on more than 100 patients tested for the combined effect of a PPI plus amoxicillin and clarithromycin. The dotted line signifies the threshold for an acceptable result. The results are shown as mean cure rates (ITT) and upper limits of 95% CIs. The number of patients in the studies and the country where the study was performed are shown within each column. (From Graham DY, Lu H, Yamaoka Y. A report card to grade *Helicobacter pylori* therapy. Helicobacter 2007;12(4):275–8; with permission from Blackwell Publishers Ltd.)](image-url)
Owing to rising drug-resistant *H pylori* infections, currently recommended PPI-based triple therapies are losing their efficacy, and regimens efficacious in the presence of drug resistance are needed. A recent meta-analysis examined the efficacy, safety, and adherence of first-line quadruple *H pylori* therapies in adults. Quadruple therapy containing a gastric acid inhibitor, bismuth, metronidazole, and tetracycline was enhanced when omeprazole was included, treatment duration lasted 10 to 14 days, and when therapy took place in the Netherlands, Hong Kong, and Australia. Treatment efficacy decreased as the prevalence of metronidazole resistance increased. Even in areas with a high prevalence of metronidazole resistance, this quadruple regimen eradicated more than 85% of *H pylori* infections when it contained omeprazole and was given for 10 to 14 days. Furthermore, in the presence of clarithromycin resistance, this quadruple regimen eradicated 90% to 100% of *H pylori* infections, whereas the currently recommended triple therapy containing clarithromycin, amoxicillin, and a PPI eradicated only 25% to 61% ($P < .001$). Adherence and adverse events for quadruple therapy were similar to currently recommended triple therapies. This study questions whether quadruple therapy with a PPI, a bismuth compound, metronidazole and tetracycline should be recommended as first-line anti-*H pylori* therapy.69

In patients who present with persistent or worsening PUD, it is important to assess for active *H pylori* infection, and to determine whether antimicrobial resistance is present.70,71 Bacteriologic methods are necessary for detection of the putative antimicrobial resistance of *H pylori*. The main cause for failure of *H pylori* eradication therapy is resistance to clarithromycin, which is due to point mutations. In these patients with resistant isolates, the provision of alternative therapeutic regimens for the successful eradication of *H pylori* infection is mandatory.

High-dose PPI/amoxicillin therapy can also be used as an alternative strategy for retreatment of *H pylori* after failure to eradicate the infection. High-dose dual therapy with rabeprazole (10 mg four times a day) and amoxicillin (500 mg four times a day) for 2 weeks was a useful treatment strategy after failure of eradication of *H pylori* by the usual triple PPI/amoxicillin/clarithromycin therapy.72 *H pylori* infections are difficult to cure and successful treatment generally requires the administration of several antibacterial agents simultaneously. Duration of therapy is also important and depends on whether resistance is present; 14 days is often best. With few exceptions, worldwide increasing macrolide resistance now undermines the effectiveness of the legacy triple therapy (PPI, clarithromycin, and amoxicillin) and, in many areas, cure rates have declined to unacceptable levels. The development of sequential therapy was one response to this problem. Sequential therapy has repeatedly been shown in head-to-head studies to be superior to legacy triple therapy. Sequential therapy, as originally described, is the sequential administration of a dual therapy (PPI plus amoxicillin) followed by a Bazzoli-type triple therapy (PPI plus clarithromycin and tinidazole) and has been shown to be especially useful where there is clarithromycin resistance. However, the cure rates of the original sequential treatment can probably be further improved by changes in dose, duration, or administration, such as by continuing the amoxicillin into the triple therapy arm. The sequential approach may also be more complicated than necessary, based on the fact that the same four drugs have also been given concomitantly (at least nine publications with >700 patients) as a quadruple therapy with excellent success.73

The future development of new anti-*H pylori* therapies presents enormous challenges to clinical pharmacologists, not only in the identification of novel targets but also in ensuring adequate drug delivery to the unique gastric mucus niche of *H pylori*.74 It is now recognized that *H pylori* infects about half of the world’s population.
and is a major cause of diseases in the UGI tract. Based on results of clinical studies, the World Health Organization has assigned *H pylori* as a class I carcinogen. The prevention of the initial infection by a suitable vaccination might be the new therapeutic strategy for the future. Several lines of evidence from experimental animal models of infection have clearly demonstrated the feasibility of a prophylactic and therapeutic vaccine against *H pylori*. However, comparatively few clinical studies have been performed to evaluate whether the positive results obtained in animals can be reproduced in humans. These studies are also needed for deciphering those aspects of the effector immune responses that correlate with protection against *H pylori* infection and disease. The recent report of a phase I study of an intramuscular *H pylori* vaccine in noninfected volunteers documented satisfactory safety and immunogenicity, produced antigen-specific T-cell memory, and warrants further clinical study.

### Non–*H pylori*–Related Ulcer

The proportion of ulcers that are not associated with *H pylori* infection is increasing, especially in the United States and Australia. The increase in this type of ulcer warrants an analysis of the diagnostic and treatment approaches to *H pylori*-negative ulcers. Review of the medical literature documents show that up to 52% of duodenal ulcers and 47% of gastric ulcers are not caused by *H pylori* infection. The cause of *H pylori*-negative ulceration seems to be multifactorial. Contributing factors include covert NSAID use, false-negative *H pylori* tests, genetic predisposition, and in rare cases, Crohn’s disease or ZES. *H pylori*-negative ulcers tend to be associated with hypersecretion and can have serious clinical sequelae.

*H pylori*-negative ulcers are often refractory to treatment, and may have an aggressive clinical course, possibly because they lack the beneficial effect of *H pylori* infection on antisecretory therapy. PPIs appear to effectively treat both *H pylori*-positive and *H pylori*-negative ulcers. Furthermore, the recent availability of intravenous PPIs has simplified therapy in patients who cannot receive enteral therapy, such as in patients with partial gastric outlet obstruction, and when there is a question or concern for adequate absorption of enteral PPIs.

Recent studies document that NSAID/aspirin use is the most common cause of *H pylori*-negative duodenal ulcer disease. The priority, therefore, is cessation of NSAID/aspirin use if possible in these patients with refractory PUD. In patients with hypersecretion as the etiology of the non-*H pylori*–related ulcer, the potential etiologies include idiopathic gastric hypersecretion or ZES and/or gastrinoma. The most frequent conditions of hypergastrinemia in humans are the ZES with autonomous gastrin hypersecretion by the tumor cell and reactive hypergastrinemia in type A autoimmune chronic atrophic gastritis with achlorhydria causing unrestrained gastrin release from the gastrin-producing antral G cells. Both entities differ with respect to the pH in the gastric fluid, which is less than two in patients with ZES and neutral in patients with type A gastritis. Other conditions with moderate hypergastrinemia are treatment with PPIs, gastric outlet obstruction, previous vagotomy, chronic renal failure, or short bowel syndrome.

The diagnostic evaluation in these patients, however, is difficult, because most of these patients have hypergastrinemia due to chronic treatment with acid suppressive therapy and medical regimens for eradication of *H pylori*. PPIs are potent acid suppressants which, at normal doses, can result in hypergastrinemia. In fact, there is a significant inverse correlation between the fasting serum gastrin concentration and gastric acid profile in patients with gastroesophageal reflux and PUD. An elevated fasting serum gastrin concentration while on PPI therapy suggests that gastric acid
secretion is adequately suppressed.\textsuperscript{85} Additionally, gastric outlet obstruction may be a contributing etiology of elevated serum gastrin.

Therefore, the use of PPIs could delay or mask the diagnosis of gastrinoma.\textsuperscript{86} In patients receiving PPI therapy, an attempt should be made to eliminate PPI therapy as a possible cause of hypergastrinemia. It is critical to determine the etiology of the refractory PUD and hypergastrinemia in these patients. A short course of high-dose H2RA therapy can be initiated with PPI discontinuation and before repeat gastrin measurements. However, this strategy is not recommended in the treatment of acute PUD, because it has been well established that ulcer-healing rates are superior with PPI therapy.\textsuperscript{87}

Because PPIs have been released and come into widespread use, the diagnosis of gastrinoma has been masked and will probably be delayed, with the result that patients with gastrinoma will be diagnosed at more advanced stages in the course of the disease.\textsuperscript{88} Physicians must therefore maintain a high index of suspicion for this disease and not mask a potential malignancy with prolonged control of acid-related symptoms without taking steps to diagnose gastrinoma.

Furthermore, differentiation of idiopathic gastric hypersecretion versus gastrinoma or ZES can be difficult, and frequently requires multiple diagnostic studies. This work-up is necessary, however, because the medical and surgical therapy of these patients differs. Patients with “idiopathic” ulcers are characterized by postprandial hypersecretion of acid and hypergastrinemia with accelerated gastric emptying. Any patient with intractable or recurrent PUD requires diagnostic evaluation for the ZES or gastrinoma.

ZES is characterized by severe PUD due to gastric acid hypersecretion that results from gastrin-secreting tumors (gastrinomas) of the GI tract. Gastrin stimulates the parietal cell to secrete acid directly and indirectly by releasing histamine from enterochromaffin-like cells, and induces hyperplasia of parietal and enterochromaffin-like cells. ZES should be suspected in patients with severe erosive or ulcerative esophagitis, multiple peptic ulcers, peptic ulcers in unusual locations, refractory peptic ulcers, complicated peptic ulcers, peptic ulcers associated with diarrhea, and a family history of multiple endocrine neoplasia type 1 (MEN-1) or any of the endocrinopathies associated with MEN-1. In about 75% of patients the tumors are sporadic, and 25% of patients have MEN-1. Patients with ZES have two problems that require treatment—the hypersecretion of gastric acid and the gastrinoma itself. Although most gastrinomas grow slowly, 60% to 90% are malignant and 25% show rapid growth.

The clinical signs and symptoms of patients presenting with ZES can be myriad. The classic triad of abdominal pain, weight loss, and diarrhea in the presence of ulcer disease suggests gastrinoma and should prompt investigation. A prospective evaluation of the initial presenting symptoms in 261 patients with ZES was performed over a 25-year period at the National Institutes of Health (NIH). A mean delay to diagnosis of 5.2±0.4 years occurred in all patients. Abdominal pain and diarrhea were the most common symptoms, present in 75% and 73% of patients, respectively. Heartburn and weight loss, which were reported uncommonly in early series, were present in 44% and 17% of patients, respectively. GI bleeding was the initial presentation in a quarter of the patients. Patients rarely presented with only one symptom (11%); pain and diarrhea was the most frequent combination, occurring in 55% of patients. An important presenting sign that should suggest ZES is prominent gastric body folds, which were noted on endoscopy in 94% of patients; however, esophageal stricture and duodenal or pyloric scarring, reported in numerous case reports, were noted in only 4% to 10%. A correct diagnosis of ZES was made by the referring physician initially in only 3% of the patients. The most common misdiagnoses made were idiopathic PUD (71%),
idiopathic gastroesophageal reflux disease (7%), and chronic idiopathic diarrhea (7%). The introduction of successful antisecretory therapy has probably led to patients presenting with less severe symptoms and fewer complications.89

Despite numerous publications and widespread awareness of ZES, delay in diagnosis persists. Analysis of reported series indicates several features that should lead the physician to suspect ZES and shorten the delay in diagnosis including the following: (1) the combination of abdominal pain, diarrhea, and weight loss; (2) recurrent or refractory ulcers; (3) prominent gastric rugal folds (secondary to the trophic effect of gastrin) seen on endoscopy (94% in NIH series), and (4) GI symptoms with or without ulcers occurring in an MEN-1 patient. It is recommended that patients in these groups have a fasting serum gastrin determination off PPIs for a minimum of 72 hours and possibly up to 7 days.

An algorithm for the diagnosis and localization of gastrinoma is helpful (Fig. 5).80 The initial diagnostic test for ZES should be a fasting serum gastrin level when antisecretory medications are discontinued. Patients with ZES have significantly increased serum gastrin concentrations, frequently between 150 and 1000 pg/mL and higher. Fasting gastrin levels tend to be higher in patients with extensive disease. If the gastrin level is elevated, gastric acidity should be assessed through pH or gastric analysis. It should be noted that hypochlorhydria causes feedback stimulation of antral gastrin secretion. In suspected cases of ZES with mild hypergastrinemia, the secretin stimulation test may be useful.

An elevation of fasting gastrin is not diagnostic of ZES; provocative testing is necessary. The most commonly used tests are secretin, calcium, and meal stimulation. The release of gastrin from gastrinoma tissue is sensitive to alterations in the serum

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**Fig. 5.** Algorithm for the diagnosis and localization of gastrinoma. (From Ellison EC. Zollinger-Ellison syndrome: a personal perspective. Am Surg 2008;74:563–71; with permission.)
calcium level, and the calcium infusion test is recommended in ZES when the results of the secretin stimulation test are equivocal or if secretin is not available.90

Serologic markers helpful in reaching a diagnosis of gastrinoma are also available, as serum chromogranin A has been shown to be a general marker for neuroendocrine tumors. It is elevated in gastrinoma, and the elevation has been reported to correlate with tumor volume.91 It is less sensitive and specific than fasting serum gastrin for the diagnosis of ZES, but can be a confirmatory test. Chromogranin A is considered the most accurate marker in the diagnosis of gastro-entero-pancreatic (GEP) endocrine tumors. Pancreatic polypeptide has also been proposed to play this role, but then not used because of its low sensitivity. The combined assessment of pancreatic polypeptide and Chromogranin A leads to a significant increase in sensitivity in the diagnosis of GEP tumors.92

Imaging for gastrinoma localization can be accomplished using computed tomography or magnetic resonance imaging, but perhaps the best modality with highest sensitivity and specificity for localization is by means of somatostatin-receptor scintigraphy with 111-In-pentetreotide and spectroscopy.93 Somatostatin-receptor scintigraphy, which images the entire body at one time, is more sensitive for detecting gastrinomas than any conventional imaging study.93 Since this test became available, all liver metastases detected at exploration have been detected by the test, and it is therefore the initial localization study of choice. This study, however, has limited sensitivity for detection of the primary gastrinoma. Somatostatin-receptor scintigraphy is superior to computed tomography and ultrasonography for determining the extent of the disease in patients with gastrinomas. However, the problem of detecting primary tumors in these patients is not solved by somatostatin-receptor scintigraphy.94 Endoscopic ultrasound may have a similar sensitivity for identifying primary tumors. A combination of somatostatin-receptor scintigraphy and endoscopic ultrasound detects more than 90% of gastrinomas.

Initial treatment for ZES should be oral high-dose PPIs. Maintenance per os pantoprazole therapy at a dose of 80 to 240 mg/d in divided doses was both effective and generally well tolerated for patients with ZES and idiopathic hypersecretion in a recent study.95 If parenteral therapy is needed, intermittent bolus injection of pantoprazole is recommended.96 The dose and duration of therapy depends on the response of the patient, based on symptoms and documented ulcer healing.

The role of surgery in patients with the ZES is controversial.97 Because the use of PPIs, the number of acid-reducing procedures has decreased substantially. Total gastrectomy and antisecretory surgery is rarely required. In patients without metastasis and without MEN-1, surgical cure is possible in 30%. It has been suggested that patients with gastrinomas larger than 2.5 cm, irrespective of whether they have MEN-1, should undergo surgical resection in an effort to decrease the risk for metastasis.98 A recent study examined the outcomes of 151 ZES patients who underwent surgical intervention. Of these patients, 123 had sporadic gastrinomas and 28 had MEN-1 with an imaged tumor of at least 3 cm in diameter. Among the patients with sporadic gastrinomas, 34% were free of disease at 10 years, as compared with none of the patients with MEN-1. The overall 10-year survival rate was 94%. This study concluded that all patients with the ZES who do not have MEN-1 or metastatic disease should be offered surgical exploration for possible cure.99 The role of surgery in the ZES MEN-1 patients may be determined by imaging: (1) image-negative patients should be observed and not undergo surgery given the low cure rates; and (2) image-positive patients with no distant metastases (liver, bone) should undergo exploration for surgical resection because resection has been shown to improve survival, independent of a biochemical cure.80
SURGERY FOR REFRACTORY PUD

Surgery is indicated in patients who are intolerant of medications or do not comply with medication regimes, and those at high risk for complications (eg, transplant recipients, patients dependent on steroids or NSAIDs, those with giant gastric or duodenal ulcer, and those with ulcers that fail to heal with adequate medical treatment). Surgery should also be considered for patients who have a relapse during maintenance treatment or who have had multiple courses of medications. Surgical options for duodenal ulcers include truncal vagotomy and drainage (pyloroplasty or gastrojejunostomy), selective vagotomy (preserving the hepatic and celiac branches of the vagus) and drainage, highly selective vagotomy (division of only the gastric branches of the vagus, preserving Latarjet’s nerve to the pylorus), or partial gastrectomy. Surgery for gastric ulcers usually involves a partial gastrectomy. Procedures other than highly selective vagotomy may be complicated by postprocedure dumping and diarrhea.53,100,101

SUMMARY

Refractory PUD is a diagnostic and therapeutic challenge. Optimal management of severe or refractory PUD requires a multidisciplinary team approach, using primary care providers, gastroenterologists, and general surgeons. Medical management has become the cornerstone of therapy. Identification and eradication of H pylori infection combined with acid reduction regimens can heal ulceration and also prevent recurrence. Severe, intractable or recurrent PUD and associated complications mandates a careful and methodical evaluation and management strategy to determine the potential etiologies and necessary treatment (medical or surgical) required.

REFERENCES


