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Peptic Ulcer Disease Today

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Summary and Introduction

Summary

Over the past few decades, since the introduction of histamine H₂-receptor antagonists, proton-pump inhibitors, cyclo-oxygenase-2-selective anti-inflammatory drugs (coxibs), and eradication of *Helicobacter pylori* infection, the incidence of peptic ulcer disease and ulcer complications has decreased. There has, however, been an increase in ulcer bleeding, especially in elderly patients. At present, there are several management issues that need to be solved: how to manage *H. pylori* infection when eradication failure rates are high; how best to prevent ulcers developing and recurring in nonsteroidal anti-inflammatory drug (NSAID) and aspirin users; and how to treat non-NSAID, non-*H. pylori*-associated peptic ulcers. Looking for *H. pylori* infection, the overt or surreptitious use of NSAIDs and/or aspirin, and the possibility of an acid hypersecretory state are important diagnostic considerations that determine the therapeutic approach. Combined treatment with antisecretory therapy and antibiotics for 1-2 weeks is the first-line choice for *H. pylori* eradication therapy. For patients at risk of developing an ulcer or ulcer complications, it is important to choose carefully which anti-inflammatory drugs, nonselective NSAIDs or coxibs to use, based on a risk assessment of the patient, especially if the high-risk patient also requires aspirin. Testing for and eradicating *H. pylori* infection in patients is recommended before starting NSAID therapy, and for those currently taking NSAIDs, when there is a history of ulcers or ulcer complications. Understanding the pathophysiology and best treatment strategies for non-NSAID, non-*H. pylori*-associated peptic ulcers presents a challenge.

Introduction

For more than a century, peptic ulcer disease was most often managed surgically, with resulting high morbidity and mortality rates. Effective pharmacologic suppression of gastric acid secretion began with the introduction of histamine H₂-receptor antagonists (H₂RAs) in the 1970s, which greatly improved clinical outcomes. During the 1980s elective peptic ulcer surgery declined by 85%, which can be mainly attributed to the use of the H₂RAs cimetidine and ranitidine.^[1] The development of proton-pump inhibitors (PPIs) further improved inhibition of gastric acid secretion, and the lack of tachyphylaxis to PPI therapy ensures very high healing rates for duodenal and gastric ulcers.^[2]

It is now over 20 years since the advent of the '*H. pylori* era' and we are now at something of a plateau in our understanding, diagnosis and treatment of peptic ulcer disease. Three main issues remain to be resolved. We must find the optimal way to eradicate *H. pylori* in a time of increasing eradication failure rates, we need to find the best method to prevent ulcer development and ulcer recurrence in NSAID users, and we must discover how best to treat non-NSAID, non-*H. pylori*-associated peptic ulcers. The worldwide ulcer prevalence differs, with duodenal ulcers dominating in Western populations and gastric ulcers being more frequent in Asia, especially in Japan.^[3] Although the incidence of peptic ulcer disease in Western countries has declined over the past 100 years, around 1 in 10 Americans are still affected.^[4] The annual financial burden of peptic ulcer disease in the US, including direct and indirect costs, is estimated as US\$3.4 billion.^[5] Since peptic ulcer disease is still common, and peaks in the elderly, it is expected that its impact on human health and health economics will remain an important issue in the future.

Pathophysiology of Peptic Ulcer Disease

Historically, our understanding of the pathophysiology of peptic ulcer disease focused on abnormalities in the secretion of gastric acid and pepsin, and on the suppression of acid as a treatment strategy. Today, gastric hypersecretion—associated with gastrinoma in Zollinger-Ellison syndrome, antral G-cell hyperplasia, an increase in parietal-cell mass, and a physiological imbalance between the antagonistic gastric hormones gastrin and somatostatin—is still an important issue in peptic ulcer disease. Moreover, it is known that cholinergic hypersensitivity and parasympathetic dominance are related to the stimulation not only of hydrochloric acid but also pepsin, which is often neglected as a cofactor in the development of erosive injury to the gastric mucosa. Psychologic stress, cigarette smoking, alcohol consumption, use of nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin, oral bisphosphonates, potassium chloride, immunosuppressive medications, and an age-related decline in prostaglandin levels have all been shown to contribute to peptic ulcer disease.^[6] It was, however, the isolation of *H. pylori* and its identification as the most important cause of peptic ulcer disease that led to exploration of the role of inflammation and its associated cytokine cascade in gastric acid secretion.

H. pylori evades attack by the host immune system and causes chronic, indolent inflammation by several mechanisms. *H. pylori* can damage the mucosal defense system by reducing the thickness of the mucus gel layer, diminishing mucosal blood flow, and interacting with the gastric epithelium throughout all stages of the infection. *H. pylori* infection can also increase gastric acid secretion; by producing various antigens, virulence factors, and soluble mediators, *H. pylori* induces inflammation, which increases parietal-cell mass and, therefore, the capacity to secrete acid. The *H. pylori* cytotoxin-associated gene *CagA* also has an important role: it interferes with gastric epithelial cell-signaling pathways, thereby regulating cellular responses and possibly contributing to apical junction barrier disruption, interleukin-8 secretion and phenotypic changes to gastric epithelial cells.^[7]

Understanding the pathophysiology of peptic ulcer disease is at something of a crossroads: mechanisms of injury differ distinctly between duodenal and gastric ulcers. Duodenal ulcer is essentially an *H. pylori*-related disease and is caused mainly by an increase in acid and pepsin load, and gastric metaplasia in the duodenal cap.^[8] Gastric ulcer, at least in Western countries, is most commonly associated with NSAID ingestion, although *H. pylori* infection might also be present.^[9] Chronic, superficial and atrophic gastritis predominate in patients with gastric ulcers, when even normal acid levels can be associated with mucosal ulceration.^[10] In both conditions, ulcer is associated with an imbalance between protective and aggressive factors, with inflammation being a leading cause of this imbalance.

The isolation of *H. pylori* in the early 1980s was one of the most exciting advances in the history of peptic ulcer disease.^[11] and it has dramatically changed the management of peptic ulcer. Eradication of *H. pylori* infection is now the mainstay of treatment for peptic ulcer disease, and has resulted in very high ulcer healing rates and recurrence rates that have dropped dramatically, especially for individuals with a duodenal ulcer. The greater recognition of the role of NSAIDs and aspirin in gastrointestinal-tract injury has led to the development of therapeutic and preventive strategies that rely on the use of antisecretory drugs, the prostaglandin analog misoprostol, or selective cyclo-oxygenase (COX)-2 inhibitors (coxibs).

***H. pylori*-associated Ulcer**

During the 1980s, *H. pylori* infection was found in more than 90% of patients with duodenal ulcers, and some 70% of patients with gastric ulcers.^[12, 13] The declining incidence and prevalence of peptic ulcer in developed countries has paralleled the falling prevalence of *H. pylori* infection,^[14] especially in populations with high infection rates.^[15] Only *H. pylori* eradication is an effective treatment for both duodenal and gastric ulcers. Antisecretory drugs work well for controlling symptoms and allowing ulcers to heal, and the absolute benefit of eradicating *H. pylori* infection is small with respect to healing alone. In a Cochrane meta-analysis the eradication of *H. pylori* infection combined with the use of an ulcer-healing drug significantly increased duodenal healing to 83% (intent-to-treat analysis), with the relative risk of the ulcer persisting being 0.66 (95% CI 0.58-0.76) compared with the ulcer-healing drugs alone; but eradication was not significantly superior to ulcer-healing drugs for gastric-ulcer healing (relative risk 1.32; 95% CI 0.92-1.90).^[16]

NSAID-induced Injury

Despite their well-accepted anti-inflammatory and analgesic benefits, NSAID use is probably the most common cause of gastrointestinal mucosal injury in Western countries. NSAIDs, including aspirin, significantly increase the risk of adverse gastrointestinal events, particularly those related to gastric and/or duodenal mucosal injury: erosions, ulcers and ulcer complications, especially bleeding.^[17] About 15-30% of regular NSAID users have one or more ulcers when examined endoscopically, and 3-4.5% of NSAID users have clinically significant upper gastrointestinal events, including ulcers and ulcer complications.

Patients taking low-dose aspirin for the prevention of a cardiovascular event, such as myocardial infarction or thrombotic

stroke, are also at increased risk of gastrointestinal injury and complications.^[18] In asymptomatic patients taking low-dose aspirin (75-325 mg/day) for ≥ 3 months, endoscopically observed ulcers or erosions are reported in 47.83% of cases.^[19] The risk of upper gastrointestinal bleeding events is dose-dependent, with an odds ratio (OR) of 3.3 for 300 mg of aspirin (95% CI 1.2-9.0) and an OR of 6.4 for 1.2 g of aspirin (95% CI 2.5-16.5).^[20] In multivariate models adjusted for age, sex, and clinical risk, low-dose aspirin alone was independently associated with an increased risk of ulcer bleeding, with an OR of 2.4 (95% CI 1.8-3.3).^[21]

The injurious gastrointestinal effects of NSAIDs are largely caused by the inhibition of COX1 and its role in normal mucosal defense mechanisms (discussed above), and also through the inhibition of thromboxane A₂, which compromises platelet function and results in gastrointestinal bleeding. Clinical trials have repeatedly demonstrated that coxibs are associated with fewer ulcers, less gastrointestinal bleeding and fewer ulcer complications than nonselective NSAIDs,^[22, 23, 24, 25] but concurrent use of low-dose aspirin blunts this benefit.^[22] It is expected that the withdrawal of several coxibs will lead to many patients switching back to nonselective NSAIDs, with an anticipated increase in cases of gastrointestinal bleeding, especially in elderly patients.

Impact of *H. pylori* Infection on NSAID-induced Injury

H. pylori infection and NSAIDs are independent risk factors for peptic ulcer disease that have additive or synergistic effects on adverse gastrointestinal outcomes (Figure 1). In a meta-analysis, the OR for the incidence of peptic ulcer was 61.1 in patients infected with *H. pylori* and also taking NSAIDs, compared with uninfected controls not taking NSAIDs.^[26] The OR narrowed to 18.1 when comparing *H. pylori*-infected patients with *H. pylori*-uninfected patients who were not taking NSAIDs.^[26] *H. pylori* infection also potentiates the ulcer bleeding induced by low-dose aspirin.^[27] Together, *H. pylori* infection and NSAID use account for approximately 90% of peptic ulcer disease.

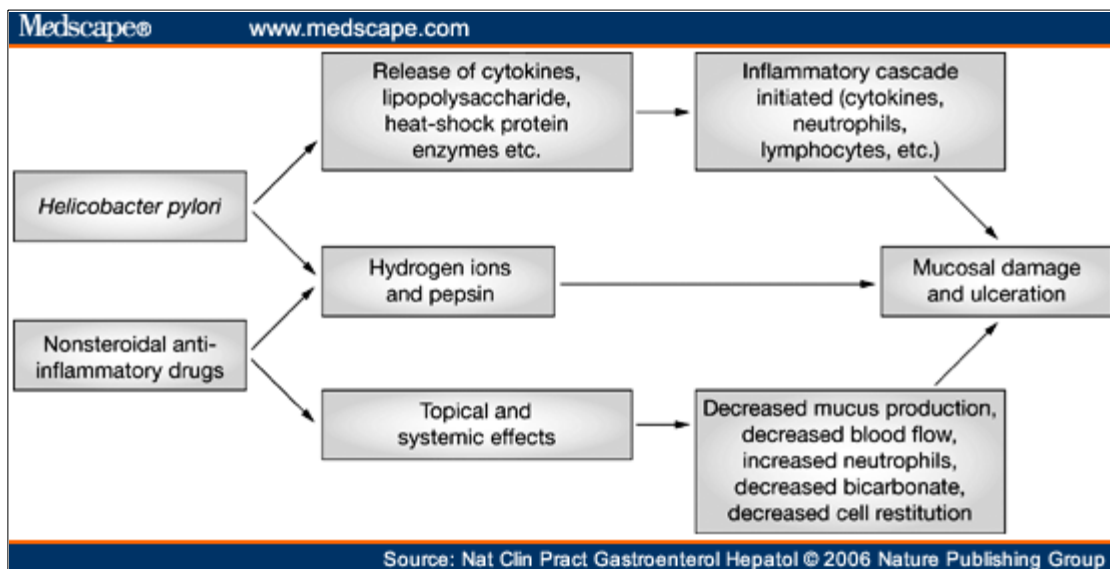


Figure 1.

Helicobacter pylori and nonsteroidal anti-inflammatory drugs have synergistic effects on gastric mucosal damage. Both *H. pylori* infection and NSAID use have been found to independently and significantly increase the risk of gastric and duodenal mucosal damage and ulceration. *H. pylori* and NSAIDs act synergistically through pathways of inflammation in the development of ulcers and in ulcer bleeding.

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Diagnosis of Peptic Ulcer Disease

Symptoms of peptic ulcer disease commonly include epigastric pain, postprandial pain and nocturnal pain, pain that can wake the patient from sleep, and pain relieved by food or antacids. Less-common features include anemia caused by gastrointestinal blood loss, weight loss attributed to a reduced appetite caused by fear of pain, and vomiting associated

with a gastric ulcer or pyloric stenosis. Pain does not define an ulcer, however, and the absence of pain does not preclude the diagnosis, especially in the elderly, who can present with 'silent' ulcer complications. No specific symptom helps differentiate between *H. pylori*-associated or NSAID-associated ulcers, but a careful history can identify surreptitious NSAID users and an appropriate *H. pylori* test can detect infected individuals.

Endoscopy is essential for an accurate diagnosis and differential diagnosis of peptic ulcer disease and ulcer complications (e.g. a gastric ulcer can be biopsied to exclude malignancy or to obtain tissue for an *H. pylori* diagnostic test). Endoscopic healing is the gold standard used to evaluate ulcer healing in clinical trials. In clinical practice, many patients with dyspepsia symptoms might be tested and treated for *H. pylori* infection in primary practice without endoscopic evaluation. Guidelines have recommended this approach in young dyspepsia patients without alarm symptoms^[28] as *H. pylori* 'test and treat' is more cost-effective than endoscopy in this group of patients.^[29] A small proportion of dyspepsia patients will, therefore, have their ulcer cured without a formal diagnosis being made.

Testing for *H. Pylori* Infection

There are currently several methods to test for *H. pylori* infection. Methods that require endoscopy include culture and histologic examination, the rapid urease test (RUT), and polymerase chain reaction (PCR) of gastric biopsy specimens. PCR is very sensitive but prone to producing false-positive results. Non-endoscopic tests include the ¹³C-urea or ¹⁴C-urea breath test (UBT), serology or an *H. pylori* stool antigen test. The choice of initial test for *H. pylori* detection is also dependent on the prevalence of *H. pylori* infection in the population, because the positive and negative predictive values of a single test change according to the prevalence of the infection.^[30]

Tests can reveal active or past infection. The best test for the detection of an active infection is the UBT.^[30] In practice, however, when a patient with peptic ulcer disease undergoes endoscopy, a RUT can be used initially and a second test performed if there is a negative result. For each test there are several considerations (e.g. methodologic, technical and the impact of treatment) that must be taken into account to make the best choice for *H. pylori* testing in a particular clinical setting. For example, serology tests, which rely on the presence of anti-*H. pylori* antibody, do not identify active infection.^[30] Both the RUT and the UBT, however, are influenced by PPI or antibiotic treatment, which inhibit urease activity and directly affect test sensitivity and specificity.^[31, 32]

Eradication of infection should be confirmed after the end of therapy; noninvasive testing with the UBT is the preferred choice, 4-8 weeks after the completion of therapy.^[33] If the ulcer recurs after eradication therapy, a more careful search for reinfection or eradication failure should be carried out by testing for the presence of active infection (e.g. by histologic examination and culture, together with an antibiotic-sensitivity test). The diagnosis of *H. pylori* infection in patients with a bleeding peptic ulcer is limited by the decreased sensitivity of standard invasive tests; usually, both the RUT and histologic testing should be performed during endoscopy and then combined with the UBT test. Infection should be considered as present when any test is positive, whereas both the invasive tests and the breath test should be negative to establish the absence of infection.

Treatment Approaches to Peptic Ulcer Disease

Eradication of *H. Pylori* Infection

Over the past 20 years, *H. pylori* eradication therapies have mainly consisted of antimicrobial agents combined with antisecretory drugs. There is now a worldwide consensus that the first-line treatment should be triple therapy with a PPI twice daily plus clarithromycin 500 mg twice daily and either amoxicillin 1 g twice daily (PPI-CA) or metronidazole 500 mg twice daily (PPI-CM) for 7-14 days.^[34] Treatment with PPIs twice daily is superior to treatment once daily.^[35] Successful eradication with first-line treatments varies from 70%-95%, and 10-day and 14-day treatments are generally 7-9% more effective than the most commonly used 7-day regimens.^[36]

Poor compliance and bacterial resistance (depending on geographic location) can lead to treatment failure, and therefore determine the choice of antibiotics used. Amoxicillin is favored over metronidazole in first-line treatments because of the greater bacterial resistance to metronidazole and the almost absent resistance to amoxicillin.^[37] PPI-CA treatment is also preferred as a first-line treatment over PPI-CM because of the concerns that treatment with PPI-CM will induce secondary resistance to both clarithromycin and metronidazole, which are the most-effective treatment options. Quadruple therapy with bismuth 120 mg four times daily, metronidazole 500 mg three times daily, tetracycline 500 mg four times daily and a PPI twice daily for a minimum of 7 days has also gained acceptance as a first-line treatment.^[38]

As a guiding principle, summarized by an international panel of experts in the Maastricht Consensus Report, second-line treatment is undertaken with a selection of antimicrobial drugs that differ to those used in the first-line treatment since

re-treatment with the initial regimen is not recommended.^[34, 39] Despite this careful approach, eradication can still fail, creating the need for additional pharmacologic intervention. Subsequently, the choice of antibiotic therapy is guided by bacterial culture and the selection of a third-line treatment prescribed according to microbial sensitivity to antibiotics.

H. pylori eradication rates are impacted by bacterial resistance and also by the pharmacogenetics associated with individual PPIs. Polymorphisms of the *CYP2C19* gene were reported to determine how effective the antisecretory properties of PPIs are, with subsequent effects on *H. pylori* eradication rates, suggesting that genotyping might be an effective tool to optimize eradication therapies.^[40] A recent meta-analysis that examined *CYP2C19* polymorphisms and *H. pylori* eradication rates with PPI first-line therapies, however, found that the eradication rates were comparable between patients with the heterozygous-extensive-metabolizer genotype and those with the poor-metabolizer genotype, thus lessening the clinical relevance of *CYP2C19* polymorphisms.^[41]

PPI-based triple therapies result in a markedly reduced ulcer recurrence rate of 12-14%, assessed from 2 weeks onwards.^[16] Earlier meta-analyses of *H. pylori* eradication reported recurrence rates of 2-3%,^[42] and similarly, in complicated bleeding ulcers the recurrence rate after *H. pylori* eradication ranged from 1.6-2.9%.^[43] These studies confirm that *H. pylori* eradication provides a very effective strategy for the management and reduction of peptic ulcer disease.

Studies indicate that eradication of infection sufficiently heals peptic ulcers in *H. pylori*-infected individuals, and significantly reduces the ulcer recurrence rate, especially in patients who are not taking NSAIDs or aspirin.^[44] In a recent meta-analysis, prolonged therapy with a PPI after a course of PPI-based 7-day triple therapy was not necessary for ulcer healing in *H. pylori*-infected patients.^[45] Some studies suggest that maintenance therapy with a PPI after eradication can significantly reduce ulcer recurrence^[46] and ulcer complications.^[47] Maintenance treatment should be continued with a PPI, following *H. pylori* eradication, in all patients who present with ulcer complications.

Management and Prevention of NSAID-associated Peptic Ulcer

In patients who continue to take NSAIDs, NSAID-associated duodenal ulcers heal after 4 weeks' treatment with a PPI, and gastric ulcers after 6-8 weeks.^[48] Co-therapy with a PPI reduces the risk of developing a peptic ulcer in both acute (OR 0.70; 95% CI 0.24-2.04) and chronic (OR 0.32; 95% CI 0.15-0.67) elderly users of NSAIDs or aspirin.^[49] Thus, it is advisable to give a PPI to symptomatic, elderly patients who need an NSAID and/or aspirin.

The best ulcer-preventive strategy for patients who need to continue NSAID use is still debated. Current strategies to reduce ulcer complications are not considered cost-effective in patients without risk factors, but all are cost-effective in patients with a history of ulcer bleeding.^[50] Misoprostol, a mucosa-protective analog of prostaglandin E₂, reduces the risk of ulcer complications, but only at the recommended dose of 800 µg/day. Lower doses of misoprostol are not effective.^[51] In a multicenter trial of 535 *H. pylori*-uninfected patients with a history of gastric ulcers who required chronic NSAID treatment, misoprostol 200 µg four times daily or lansoprazole 15 mg or 30 mg once daily all significantly reduced gastric-ulcer recurrence (4%, 7% and 0%, respectively) compared with placebo (65%) at 12 weeks.^[52] Adverse effects were, however, higher in the misoprostol group.

Currently, studies suggest and guidelines recommend the careful selection of the right NSAID for the right patient, based on individual risk assessment. Emphasis is placed, therefore, on the important management strategy of defining those patients at risk (Box 1).^[53] For patients with a history of NSAID-associated ulcer bleeding who continue to require an NSAID and are not infected with *H. pylori*, neither a coxib alone nor a PPI in addition to a nonselective NSAID can completely eliminate ulcer recurrence. Indeed, in one clinical trial, ulcer recurrence and ulcer bleeding combined were as high as 24% for a coxib alone and 32% for a PPI plus a nonselective NSAID.^[54] To prevent ulcer complications in a patient with a history of bleeding, a coxib combined with a PPI is, therefore, the best approach (Box 1).^[53, 55]

A new class of NSAIDs, the COX-inhibiting nitric-oxide donators, inhibit COX and simultaneously donate nitric oxide to maintain mucosal blood flow. The first COX-inhibiting nitric-oxide donator studied in a large clinical trial, AZD3582, was associated with significantly fewer erosions and ulcers than naproxen in osteoarthritis patients.^[56] A clinical trial in healthy volunteers also supports this concept, where NCX-4016, a nitric-oxide-releasing derivative of aspirin, maintains COX1 and platelet inhibitory activity while significantly decreasing gastrointestinal damage.^[57] Another new class of NSAIDs, the 5-lipoxygenase/COX inhibitors, which inhibit 5-lipoxygenase as well as COX1 and COX2, has attracted interest. The gastrointestinal tolerability of licofelone, the first-studied drug of this class, has been demonstrated in a study of healthy volunteers.^[58]

Is *H. pylori* Eradication Necessary for Everyone During or Before NSAID Therapy?

Whether users of NSAIDs or low-dose aspirin should be routinely tested and treated for *H. pylori* infection is still controversial.^[59] Factors including the patient's ulcer risk, previous history of NSAID use and their ongoing use of aspirin or NSAIDs should be considered (Box 2).^[60] In one meta-analysis of current NSAID users, the incidence of ulcer was not different between the *H. pylori* eradication and control (PPI or placebo) groups.^[61] Only two studies were included in this analysis, however, and the sample sizes were small ($n = 197$ and $n = 210$, respectively), therefore a false-negative result could not be excluded. A 'test and treat' strategy for *H. pylori* infection is not recommended for those already on long-term NSAID therapy and who have a low or absent risk of peptic ulcer.^[60] As treatment with a PPI can worsen *H. pylori*-associated corpus gastritis, testing for and eradicating *H. pylori* infection should be considered in long-term users of NSAIDs who have past or present ulcers before starting long-term prophylaxis with PPIs.^[62] Moreover, current guidelines recommend that *H. pylori* infection should be eradicated in anyone in whom it is detected.^[34, 63]

Meta-analysis suggests that eradication of *H. pylori* infection is significantly more effective for preventing recurrent ulcer bleeding than antisecretory therapy alone, either with or without long-term maintenance antisecretory therapy (1.6% versus 5.6%, and 2.9% versus 20%, respectively).^[43] In patients with ulcer bleeding related to long-term use of NSAIDs and/or low-dose aspirin, maintenance antisecretory therapy should be combined with eradication of *H. pylori* to reduce the recurrence of ulcer bleeding. As the antisecretory effect of PPIs is enhanced in the presence of *H. pylori* infection, some prefer to undertake eradication therapy after the acute ulcer bleeding episode has been successfully managed.

Use of low-dose aspirin in patients with *H. pylori* infection is a complex issue, because aspirin can provoke bleeding from a pre-existing *H. pylori*-related ulcer by its topical injurious effects on the gastric mucosa and its systemic antiplatelet effects. In patients starting aspirin, *H. pylori* eradication prevents gastroduodenal mucosal injury.^[64] Among *H. pylori*-infected patients with a history of ulcer bleeding who were taking low-dose aspirin, eradication of *H. pylori* infection was comparable to PPI treatment for preventing recurrent bleeding.^[65] Eradication alone does not guarantee complete protection: antisecretory therapy with a PPI in addition to confirmed *H. pylori* eradication significantly reduced recurrent aspirin-related ulcer complications in long-term low-dose aspirin users.^[47] Eradication of *H. pylori* infection followed by antisecretory maintenance therapy can, therefore, reduce ulcer rebleeding in long-term aspirin users, but more clinical trials are needed to explore the effect of eradication on ulcer bleeding and rebleeding.

Ulcers and ulcer complications occur in former users of NSAIDs, and their risk remains higher than baseline even after 1 year of non-exposure.^[66] *H. pylori* infection is a known risk factor for ulcers in both NSAID users and nonusers.^[26] Switching from a nonselective NSAID to a coxib, therefore, does not eliminate the risk of developing an ulcer and ulcer complications in patients with *H. pylori* infection, although the risk is decreased in both infected and uninfected coxib users.^[25]

Non-NSAID, Non-*H. Pylori* Ulcers

With the declining prevalence of *H. pylori* infection, some studies report an increased proportion of non-NSAID, non-*H. pylori* ulcers, especially in the US.^[67] In studies of more than 100 patients, up to 35% of duodenal-ulcer patients^[68] and up to 34% of gastric-ulcer patients^[69] had idiopathic ulcers. By contrast, non-NSAID, non-*H. pylori* ulcers are rare in Asia, where *H. pylori* prevalence is high.^[70] The true prevalence of non-NSAID, non-*H. pylori* ulcers is unclear because it is not known whether the prevalence is truly increasing or merely overestimated as a result of undetected NSAID use and/or inaccurate diagnosis of *H. pylori* infection; similarly, the reported increase might be associated with decreasing incidence or prevalence of *H. pylori* infection or a lower background ulcer rate.^[6, 67] The diagnosis of non-*H. pylori*, non-NSAID ulcers should be made only after careful exclusion of surreptitious NSAID use and/or misdiagnosis of *H. pylori* infection. This process is aided by obtaining a careful history, taking biopsies from several sites, use of more than one *H. pylori* diagnostic test, testing after stopping PPIs and antibiotic treatments, and by delaying tests in the case of a bleeding ulcer.^[67] Investigations should also exclude other uncommon causes of peptic ulcers.^[6]

Much remains to be learned about non-*H. pylori*, non-NSAID ulcers. While the mechanism underlying the development of non-*H. pylori*, non-NSAID ulcers is uncertain, acid hypersecretion, weakened mucosal defense after *H. pylori* eradication, or other etiologic factors (e.g. diet and smoking status) might play a role.^[6] There are no randomized, controlled trials, but antisecretory therapy remains the cornerstone of treatment to promote ulcer healing. Standard-dose PPI treatment should be prescribed for 4 weeks in patients with duodenal ulcers and for 8 weeks in patients with gastric ulcers.^[6] Generally, patients respond well to these therapies, and no established evidence supports the need for a longer duration or higher dose of antisecretory therapy in uncomplicated idiopathic ulcer alone, although it might be required in a subset of patients. Nonresponders should, however, be investigated for any possible underlying pathophysiology, such as a pathological

acid hypersecretory state.^[6]

Complicated Ulcer and Refractory Ulcer

For patients with a history of ulcer bleeding, treatment with a PPI significantly reduces the risk of rebleeding and surgery.^[71] Patients who have a history of bleeding or frequent ulcer recurrence should be considered for maintenance PPI therapy. All patients with a history of ulcer bleeding should be tested, and treated if infected with *H. pylori*.

Refractory ulcer—generally accepted to be a symptomatic, endoscopically proven ulcer greater than 5 mm in diameter that does not heal after treatment with a PPI (duration of PPI therapy is 6 weeks for duodenal ulcers or 8 weeks for gastric ulcer), or does not heal after a full dose of H₂RA (within 8 weeks for duodenal ulcers or 12 weeks for gastric ulcers)—is now rare.^[72, 73] For patients with a refractory ulcer, a careful search should be made for *H. pylori* infection, surreptitious use of NSAIDs or an acid hypersecretory state such as Zollinger-Ellison syndrome. Most ulcers will heal with 4-8 weeks of a standard-course PPI; in patients whose ulcers are refractory to a standard dose of PPI, twice-daily dosing of the PPI treatment should be prescribed for an additional 6-8 weeks.

Future Directions

In the past, *H. pylori* infection and the use of NSAIDs have dominated research into peptic ulcer disease and have shaped its diagnosis and treatment. Even though *H. pylori* infection can be successfully controlled with currently available pharmacologic approaches, there is still a serious need for novel eradication monotherapies that will simplify treatment regimens, while improving eradication rates.

Molecular techniques will continue to help us identify genetic factors that predict the development of idiopathic ulcers. The identification of an *H. pylori* gene that promotes the development of duodenal ulcers has introduced a novel marker that can identify patients at increased risk of duodenal ulcer development and reduced risk for gastric atrophy and cancer.^[74] The array of predisposing factors is, however, predominantly host-oriented; that is, based on the genetic characteristics of the patient. The existence of host-related differences in the physiology of acid secretion might lead to the identification of genetic markers associated with peptic ulcer disease. Such markers might, in the future, help to identify patients at high risk of or with susceptibility to peptic ulcer disease.

Conclusions

A search for *H. pylori* infection, the overt or surreptitious use of NSAIDs and the possibility of an acid hypersecretory state are important considerations in the diagnosis of peptic ulcer and determine the therapeutic approach. *H. pylori* eradication and/or antisecretory therapies are the mainstay of today's treatment strategies. In the future, it is anticipated that advances in the fields of molecular biology and genetic engineering will assist in the management of peptic ulcer disease. As the prevalence of peptic ulcer disease increases 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.

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Sidebar: Box 1. Selecting the Right Nonsteroidal Anti-Inflammatory Drug for Patients with Peptic Ulcer Disease.

No history of gastrointestinal events

- For patients not on aspirin who are aged <65 years old, use an NSAID alone
- For patients on aspirin, use a COX2 inhibitor or an NSAID plus a PPI

History of gastrointestinal events

- For patients not on aspirin, use a COX2 inhibitor or an NSAID plus a PPI
- For patients on aspirin, use a PPI plus either a COX2 inhibitor or an NSAID

COX2, cyclo-oxygenase-2; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor.

Sidebar: Box 2. Using Peptic Ulcer History and NSAID Status to Guide the Approach to *Helicobacter pylori* Infection.

Patients with low risk of peptic ulcer disease

- For NSAID-naive patients, use the test-and-treat strategy
- For chronic users of NSAIDs or aspirin, routine test-and-treat strategy is not recommended

Patients with a history of or active peptic ulcer disease

- For NSAID-naive patients, use the test-and-treat strategy
- For chronic users of NSAIDs or aspirin, use the test-and-treat strategy; prescribe a PPI to patients with active peptic ulcer disease to heal the ulcer before eradicating *H. pylori* infection

Patients with ulcerated upper gastrointestinal bleeding

- For all patients with upper gastrointestinal bleeding, this should be managed first; testing for *H. pylori* should be undertaken and treated if positive
- For patients who continue to require anti-inflammatory drugs, PPI co-therapy is recommended

NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor.

Sidebar: Key Points.

- When diagnosing peptic ulcer disease, important considerations are detecting *H. pylori* infection, NSAID and/or

aspirin use, and an acid hypersecretory state

- The first-line choice for *H. pylori* eradication is combination treatment with antisecretory drugs and antibiotics for 1-2 weeks
- For patients at risk of developing an ulcer or ulcer complications, the choice of anti-inflammatory drugs, nonselective or COX2-selective NSAIDs should be carefully made
- Testing for and eradicating *H. pylori* infection is recommended before starting NSAIDs, in those taking NSAIDs who have a history of ulcers or ulcer complications
- Understanding the pathophysiology and optimal treatment of non-NSAID, non-*H. pylori* associated peptic ulcers is an important focus for future research

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