



## Pathogenesis and therapy of gastric and duodenal ulcer disease

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Despite the decreasing frequency of *Helicobacter pylori*-induced peptic ulcers, peptic ulcer disease remains a major clinical problem partly because nonsteroidal anti-inflammatory drug ulcers have increased in frequency. The reduction in nonsteroidal anti-inflammatory drug ulcers by use of selective cyclooxygenase-2 inhibitors will not eliminate the problem because of increased use of aspirin for cardiovascular prophylaxis. This article reviews current concepts of peptic ulcer pathogenesis and therapy according to ulcer etiology; discusses potential interactions between etiologies; and considers the therapy for *H pylori* infection including the effects of antimicrobial resistance, and the role of bismuth quadruple therapy or furazolidone salvage therapy.

### Epidemiology

The point prevalence of active *H pylori* ulcer is approximately 1%: about 1.5 to 2 million American adults have an active ulcer at any time. As recently as 1990 the burden of peptic ulcer disease in the United States was estimated at 4 million cases, with 500,000 new cases annually [1]. The lifetime prevalence of peptic ulcer ranges from approximately 11% to 20% for men, and 8% to 11% for women [2]. In Japan, the male to female ratio for peptic ulcer is about 2:1, with the rate of gastric ulcers being about 1.5 times greater than that of

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duodenal ulcers for either sex [3]. In Western developed countries, the ratio of duodenal ulcer to gastric ulcer is reversed, with a higher incidence of duodenal ulcers. Peptic ulcer still causes major economic losses and health care expenditures because of lost worker productivity, restricted activity, physician visits, and hospitalizations. Expenditures in the United States for peptic ulcer disease are approximately \$20 billion per year. The prevalence of *H pylori* infection and of *H pylori* peptic ulcers has steadily declined in the United States. In contrast, nonsteroidal anti-inflammatory drug (NSAID) use has remained high. In chronic NSAID users the point prevalence of gastric ulcers ranges from 9% to 31% and of duodenal ulcers ranges from 0% to 19% [4,5]. The recent introduction of the selective cyclooxygenase-2 (COX-2) inhibitors may result in a reduction in the incidence of NSAID ulcers but this may be offset in part by the increased use of aspirin for cardiovascular prophylaxis. The risk of major gastrointestinal bleeding from aspirin therapy is about 2.5% per annum, even with low-dose therapy [6].

### Pathogenesis

Peptic ulcers fundamentally result from a breakdown in the mechanisms that normally protect the gastroduodenal mucosa from the high concentrations of acid and pepsin within the lumen. *H pylori* infection and NSAID therapy are the two major causes of ulcers.

#### *H pylori and peptic ulcer*

In the early 1980s, Marshall and Warren [7] first cultured the bacterium associated with gastritis and introduced investigators to the potential role of bacterial infection in the pathogenesis of gastritis, peptic ulcer, and gastric cancer [8]. Investigators rapidly met the challenge. In 1999, *H pylori* became the first bacterial species for which the complete genome sequence was publicly available [9].

*H pylori* infection causes mucosal inflammation. The presence and severity of the inflammation is likely to underlie *H pylori*-related disease. *H pylori* strains differ in their ability to provoke inflammation and those strains that cause severe inflammation are most likely to cause symptomatic disease. Although strains vary in virulence, no strains are avirulent because any strain may cause inflammation, peptic ulcer, or gastric cancer [10]. The most virulent strains possess OipA, the outer inflammatory protein, and a functional *cag* pathogenicity island [11,12]. Low-virulent strains possess neither.

*H pylori* are trophic for gastric mucosa and can not only survive, but thrive in the hostile environment of the stomach. The bacteria produce urease, which catalyzes hydrolysis of urea into carbon dioxide and ammonia and thereby creates an alkaline microenvironment that buffers the harsh acidic gastric milieu [13]. *H pylori* also use the ammonia nitrogen produced

from urea for its own growth. Another gastric adaptation is that the bacterium is motile, and can “swim” rapidly through mucus to avoid harsh local sites and reach favored sites. *H pylori* also has several adhesins, including outer membrane proteins, that adhere to gastric mucosa at different optimal pH levels and keep *H pylori* anchored beneath the mucus layer despite periodic emptying of gastric contents [14].

### *Effect of H pylori infection on gastroduodenal physiology and duodenal ulcer*

Before discovery of *H pylori*, research in peptic ulcer focused on understanding alterations in gastroduodenal physiology that seemed to be responsible for ulcer disease. Numerous dysregulations were identified including elevated serum pepsinogen levels; elevated meal-stimulated gastrin secretion; and defective reflex inhibition of acid secretion induced by antral acidification, gastric distention, intraduodenal fat, or fasting [15–18]. Abnormalities in duodenal motility and bicarbonate secretion were also identified. None of these abnormalities are specific or etiologic for duodenal ulcer. Study of patients with or without *H pylori* infection and of patients before and after infection eradication allowed investigators to identify abnormalities directly attributable to the infection. Although the details of these dysregulations in gastric secretory physiology are still being elucidated at the molecular level, all of the previously described physiologic alterations, except for the abnormally increased parietal cell mass in duodenal ulcer, are reversible epiphenomena related to *H pylori* infection [19,20].

*H pylori* infection is trophic for gastric mucosa. *H pylori* can occur on ectopic gastric mucosa, such as inlet patches in the esophagus, ectopic patches in the rectum, and most importantly on metaplastic gastric epithelium in the duodenal bulb. Healing from duodenal mucosal injury also results in gastric metaplasia [17,21–25]. The extent of gastric metaplasia in the duodenum is related to gastric acid output. A high duodenal acid load promotes gastric metaplasia in the duodenal bulb and favors colonization by *H pylori*. *H pylori* colonization leads to inflammation, which in turn promotes more gastric metaplasia, resulting in more *H pylori* colonization, and the production of a vicious cycle that culminates in mucosa that becomes highly susceptible to ulceration [23]. The ulcer is thought to form at the site of the colonized and inflamed gastric metaplasia (Fig. 1), perhaps at the junction between the inflamed gastric metaplasia and the inflamed duodenal mucosa [23].

The actual scenario leading to a duodenal ulcer is unknown but the high duodenal acid load is partly related to the reduced ability of *H pylori* to interact with the corpus mucosa resulting in an antral predominant gastritis. Reducing acid secretion by any method eliminates this restriction and promotes corpus gastritis [10,23]. The lack of significant inflammation in the gastric corpus coupled with the *H pylori*-associated dysregulations of acid secretion (eg, impaired down-regulation of acid secretion when the antral

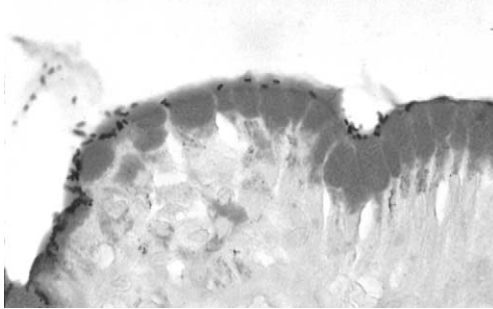


Fig. 1. Biopsy near the edge of a duodenal ulcer using the El-Zimatiy dual stain, which includes a periodic acid–Schiff stain and a silver stain [22]. The biopsy shows that the normal villus architecture has almost entirely been replaced by metaplastic gastric epithelium. *H pylori* in the area surrounding the ulcer are highlighted by the silver stain. (Courtesy of Hala El-Zimatiy, MD, Houston, TX.)

pH falls to 3 or less) results in a markedly increased duodenal acid load [19,26,27]. Both the inflammation induced by *H pylori* and the injury caused by the duodenal acid load impair bicarbonate secretion by duodenal mucosa; this impairment further augments the functional duodenal acid load. *H pylori* growth is inhibited by glycine-conjugated bile acids; this renders the normal duodenal bulb a hostile environment for *H pylori* [19,26]. The high duodenal acid load decreases the mean duodenal pH, which precipitates the glycine-conjugated bile acids and allows *H pylori* colonization within, but rarely beyond, the duodenal bulb. The duodenal acid load can be increased and *H pylori* colonization thereby promoted by several other mechanisms. For example, stress increases basal acid secretion and may also increase the amount of smoking. Smoking increases duodenal acid load by increasing gastric acid secretion and inhibiting duodenal bulb and pancreatic bicarbonate secretion [27,28]. NSAIDs increase gastric acid secretion and may injure duodenal mucosa and promote gastric metaplasia, providing new niches for *H pylori* colonization.

*H pylori* are most commonly acquired in childhood, yet duodenal ulcer typically occurs in adults. According to the aforementioned pathophysiology, duodenal ulcer pathogenesis requires a high duodenal acid load to produce duodenal alterations that favor *H pylori* colonization. Subtle changes in behavior, such as starting or stopping smoking, could affect the balance between acidity, infection, and injury versus alkalinity, infection eradication, and repair to tip the scale one way or the other. Similarly, administration of an H<sub>2</sub>-receptor antagonist reduces the duodenal acid load, thereby permitting the glycine-conjugated bile acids to remain in solution to inhibit *H pylori* growth [19,26]. Various effects may tip the balance and result in ulcer exacerbation or remission and could explain how and why agents and actions might have influenced duodenal ulcer disease in the past. A fine balance can determine whether an ulcer is present or absent.

### *Pathogenesis of H pylori–induced gastric ulcer*

Although one can now contemplate detailed scenarios regarding the pathogenesis of duodenal ulcers, the pathogenesis of gastric ulcer remains largely enigmatic. Gastric ulcers are known to occur frequently at the junction between two types of epithelium (the advancing line of damage between antral and corpus mucosa [23,29]); to require acid; and to be cured by infection eradication. Gastric ulcer patients typically have a more severe pangastritis with more impairment in acid secretion than duodenal ulcer patients. The degree of impairment is directly proportional to the ulcer location: the atrophic border gradually advances from the antrum into the corpus with more severe impairment [29]. The balance between aggressive injurious factors and defensive protective factors is important, but it is not clear which factors dominate [30]. Defensive factors seem to be mediated largely by endogenous prostaglandins, nitric oxide, and trefoil proteins. When the synthesis of these factors is diminished, gastric mucosa becomes more susceptible to injury [31,32]. *H pylori* infection may reduce the superficial mucin layer overlying gastric mucosa and thereby impair mucosal defenses [33–35].

### *Host and environmental factors in H pylori–related ulcer disease*

Peptic ulcer prevalence differs within and between countries despite a comparable prevalence of *H pylori* infection. Interactions between the bacterium, the host, and the environment must be considered in comparing different regions or countries. The virulence of *H pylori* strains may differ among regions but, as noted previously, differences in virulence only affect infection outcome by increasing the risk of a symptomatic outcome [36].

The host, the environment, and the bacterial strain all are important in determining infection outcome. The children of Japanese parents migrating from Japan to Hawaii have the same bacterial strain and the same genetic predisposition as those remaining in Japan, but experience a different risk of disease. For example, children of these immigrants have a markedly reduced risk of gastric cancer. This change associated with migration is environmental. It is paralleled by a change in the pattern of gastritis. Environmental factors important in determining the pattern of gastritis are the diet and the factors that reduce gastric acid secretory capacity (maximal acid output), such as childhood febrile illnesses. A diet rich in fresh fruits and vegetables markedly reduces the incidence, severity, and rate of progression of corpus gastritis [37]. Such a diet protects corpus mucosa and promotes duodenal ulcer rather than gastric ulcer or gastric cancer. In contrast, diets with a prolonged season without fresh vegetables, as occurs in mountainous regions, promotes rapid development of atrophic pangastritis and renders gastric ulcer and gastric cancer common and duodenal ulcer rare.

Host factors believed to be possibly pathogenic include the genetically determined parietal cell mass, polymorphisms in cytokine genes that affect the inflammatory response, and infection susceptibility [10,37,38]. A study of monozygotic and dizygotic twins reared together or reared apart,

however, found that genetic influences for peptic ulcer were independent of genetic influences important for acquiring *H pylori* infection. Host genetics are probably less important than environmental factors or strain virulence in determining outcome [39].

#### *Epidemiology of H pylori infection*

The prevalence of *H pylori* is higher in developing than developed countries. More than 80% of adults in developing countries are infected, whereas less than 15% of middle class whites in America are infected. *H pylori* is typically acquired in childhood. The decrease in incidence in developed countries is related to improved sanitation and hygiene. Inadequate sanitation, low socioeconomic class, and crowded living conditions all relate to a higher prevalence. The most likely mode of transmission is from person to person, either by the gastro-oral or fecal-oral routes [40–42]. Water-borne, food-borne, and iatrogenic transmission from contaminated endoscopes or nasogastric tubes have been rarely reported and *H pylori* DNA have been detected in vomitus, saliva, dental plaque, gastric juice, and feces [43–46]. Contaminated water, probably caused by fecal contamination, may be an important source of transmission. Improved sanitation and economic progress retard these patterns of transmission.

#### *NSAID ulcers*

The second major cause of peptic ulcers is NSAIDs use. NSAID ulcers are increasingly common because of the ubiquitous and increasing use by our aging population [47]. The risk of a serious, life-threatening ulcer complication ranges from 1% to 4% per annum in chronic NSAID users [47]. The fundamental mechanism for the gastrointestinal toxicity is postulated to be suppression of gastric prostaglandins [48]. Prostaglandin suppression leads to decreases in epithelial mucus, bicarbonate secretion, mucosal perfusion, epithelial proliferation, and mucosal resistance to injury [30,49]. Although *H pylori* infection stimulates mucosal prostaglandin synthesis and could theoretically provide some protection against NSAID-induced ulcers [50–52], evidence to support this hypothesis is lacking [53,54]. Recent data suggest *H pylori* infection may intensify NSAID gastrototoxicity [55,56]. For example, in a recent placebo-controlled, double-blind, randomized prospective trial, patients receiving low-dose aspirin who had *H pylori* infection had significantly worse gastric mucosal injury than uninfected patients [56]. Two other studies [57,58] suggest that *H pylori* infection may increase the risk of clinically significant gastrointestinal events, including bleeding. Eradication of *H pylori* infection may reduce the risk of gastrointestinal bleeding associated with NSAID or aspirin use. For example, Chan et al [59] reported that eradication of *H pylori* infection reduced the rate of rebleeding in patients receiving low-dose aspirin after having had a prior bleeding ulcer.

Ulcers in NSAID users often heal when the NSAID is continued, but the healing is delayed [60]. NSAID ulcers are treated by stopping the NSAID and administering antisecretory drugs to accelerate ulcer healing. If *H pylori* infection is also present, it is not possible to determine whether the ulcer is caused by NSAIDs, *H pylori*, or both. Patients with ulcers taking NSAIDs should be tested for *H pylori* infection and the infection, if present, should be eradicated. Gastric ulcers in NSAID users heal slightly more rapidly in those with active *H pylori* infection. The mechanism is unknown, but might be increased synthesis of gastric mucosal epidermal growth factor in *H pylori*-infected mucosa. Whatever the cause, the improvement is slight and clinically insignificant. Infection should be treated even in the presence of a gastric ulcer associated with NSAID use. Eradication of *H pylori* infection does not prevent NSAID ulcer complications or recurrence. If the ulcer was caused by the NSAID, it will likely recur if the NSAID is restarted. If NSAIDs are necessary, the new selective COX-2 inhibitors are preferable.

#### *Prevention of NSAID ulcers and their complications*

The pharmacology of NSAID-induced ulcer prevention has been manipulated by pharmaceutical companies. Many studies have been designed more for marketing than science. Important clinical and pharmacologic parameters have been ignored, subtherapeutic doses have been compared with therapeutic doses, and inappropriate or clinically irrelevant end points have been selected that are heavily influenced by the drug. Greenhalgh [61] provided 10 tips for the pharmaceutical industry to present their products in the best light that illustrates the approaches used in publications on NSAIDs (Table 1). This problem is compounded by the inclusion of endoscopically observed erosions as ulcers in the large prevention trials [62]. A major problem is that even though prevention of NSAID-induced ulcers differs depending on the presence or absence of *H pylori* infection, the large studies comparing omeprazole and misoprostol, or omeprazole and ranitidine, neither randomized nor stratified for the presence of *H pylori* infection [63–65]. In these studies *H pylori* infection had a large effect, and the proton pump inhibitor was not better than either misoprostol or low-dose ranitidine in patients without *H pylori* infection [63]. Indeed, very-low-dose misoprostol was superior to omeprazole (recurrence rate of 8.2% for misoprostol versus 16.6% for omeprazole,  $P < .05$ ) for prevention of gastric ulcer relapse with no significant difference between the drugs with regard to duodenal ulcer relapse [63,64] in patients without *H pylori* infection. A subsequent comparison of lansoprazole versus full-dose misoprostol confirmed that proton pump inhibitor therapy was superior to placebo but not to misoprostol in preventing gastroduodenal ulcers [66].

The risk of developing an ulcer in *H pylori*-infected individuals is about 1% to 2% per annum. The risk of an ulcer complication among those with an *H pylori* ulcer without a prior ulcer complication is about 1% to 3% per

Table 1

Ten tips for the pharmaceutical industry: how to best promote your product

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- Think of a plausible physiologic mechanism why the drug works and become slick at presenting it. Preferably, find a surrogate endpoint that is heavily influenced by the drug, even though it may not be valid.
  - When designing clinical trials, select a patient population, clinical features, and trial length to maximize the drug effect.
  - If possible, compare your product only with placebos. If you must compare it with a competitor, make sure the latter is given at a subtherapeutic dose.
  - Include the results of pilot studies in your tabulations of definitive studies (“Russian doll publication”), so more patients seem to have been randomized than actually were.
  - Omit any trial that had a fatality or serious adverse drug reaction in the treatment group. If possible, do not publish such studies.
  - Use graphics to maximize visual impact. Do not label the axes of graphs or indicate whether scales are linear or logarithmic. Do not show individual patient data or confidence intervals.
  - Master the hanging comparative (“better”, but better than what?)
  - Invert the standard hierarchy of evidence so that anecdote takes precedence over randomized trials and meta-analyses.
  - Name at least three local authorities who use the drug and offer starter packs to physicians.
  - Present a cost-effectiveness analysis that shows that your product, even if more expensive than a competitor, works out to be cheaper.
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*Adapted from* Greenhalgh T. Papers that report drug trials. In: How to read to paper. 2nd edition. BMJ publications; Zool. p. 94–104; with permission.

annum [47]. Those with a recent ulcer complication have a 1% to 3% *per month* risk of another complication, but those with a history of a remote ulcer complication have a risk of about 5% per year. The risk of new complications among NSAIDs is likely similar. If so, eradication of *H pylori* could eliminate complications from *H pylori* ulcers but have little effect on reducing the effects among those with NSAID ulcers. Large pharmacotherapeutic studies of NSAID users without *H pylori* infection, and studies in which those with *H pylori* infection are randomized and separately analyzed, are needed. Such studies are unlikely now because COX-2 inhibitors markedly reduce the risk of NSAID ulcers and their complications. Unfortunately, the COX-2 inhibitors have no effect on platelet function and are not cardioprotective. The risk of a major gastrointestinal complication even with low-dose aspirin is about 1% to 2% per annum. NSAID ulcers will remain a problem until a safe alternative for aspirin is developed.

### Stress as a factor in peptic ulcer

Stress has different connotations in relation to ulceration. Physiologic stress from sepsis, massive burn injury, head injury associated with increased intracranial pressure, severe trauma, and multiorgan failure can cause the stress-related erosive syndrome [67–69]. Although the pathophysiology is multifactorial and includes a component of ischemia that compromises gastric mucosal integrity, luminal acid also plays a role in producing the mul-

multiple erosive lesions [70]. Psychologic stress is likely to be important in traditional peptic ulcers, whether related to *H pylori* or NSAIDs. This effect is likely related to an increase in acid secretion, which enhances the aggressive factors in someone predisposed to peptic ulcer or exacerbates pre-existing peptic ulcer by increasing the duodenal acid load [71–73].

### **Clinical presentation of peptic ulcer**

Patients with ulcer disease usually present to physicians because of dyspepsia, or because of a complication, such as upper gastrointestinal hemorrhage or perforation. The classic symptoms of peptic ulcer are epigastric pain usually not present on awakening, but occurring 1 to 3 hours after meals and relieved by the ingestion of food or antacids. Pain typically occurs in clusters, or episodes, lasting weeks or months, followed by spontaneous remissions lasting for variable periods, followed by recurrence. Pain may awaken the patient from sleep. At least 10% of patients with peptic ulcer disease, particularly those with NSAID-associated ulcers, present with complications without prior pain [74]. There are no specific physical findings of peptic ulcer, but patients may present with epigastric tenderness or fecal occult blood. Likewise, the laboratory findings are typically normal, but acutely bleeding ulcers can cause anemia and chronically bleeding ulcers can cause iron deficiency anemia.

### **Diagnosis of peptic ulcer**

Most ulcers are identified by upper gastrointestinal endoscopy; barium upper gastrointestinal series are now infrequently performed. Recently, some physicians initially test patients presenting with ulcer-like dyspepsia for *H pylori*, and treat the infection if present. Endoscopy is recommended initially only when certain features suggest a more serious disease, such as gastric cancer or ulcer complications. An ulcer should be categorized by location (gastric or duodenal) and by etiology (NSAID, *H pylori*, both, or neither). Endoscopy is generally indicated to evaluate gastric ulcers because between 1% and 5% of benign-appearing chronic gastric ulcers are cancerous [75]. Gastroscopy permits directed cytologic and histologic specimens to be obtained to confirm benignity. Endoscopic ultrasound can also be used to identify the ulcer depth and fibrosis [76,77].

### **Diagnosis of *H pylori* infection**

Several techniques are available to diagnose *H pylori* infection [78]. Non-invasive methods include serology, urea breath testing, and fecal assay for *H pylori* antigens. The breath test and the fecal antigen test provide direct evidence of active infection. Serologic testing has become less popular because test interpretation is markedly influenced by pretest probability. For

example, the predictive value of a serologic test with 95% specificity and 95% sensitivity is critically influenced by the prevalence of infection in the population (Fig. 2). When infection is highly likely (eg, patients with duodenal ulcers), false-positive results should occur rarely, but false-negative results should occur at an appreciable rate. The clinician should treat for *H pylori* based on a positive result, but should proceed with a more specific test, such as the urea breath test (UBT), if the result is negative. In contrast, a patient with dyspepsia, thought likely from gastroesophageal reflux disease, has a low pretest probability for *H pylori* infection. In this case, false-negative tests should occur rarely but false-positive results should occur at an appreciable rate. In this case, positive tests should be confirmed by a more specific test before embarking on therapy. Most office-based serologic tests are less than 90% sensitive and specific. Unless the pretest probability is very high (eg, a patient with a duodenal ulcer) serologic tests results should usually be confirmed by a more specific test.

Antibody titers, even using paired sera, do not reliably demonstrate successful therapy because antibody titers decrease very slowly after successful therapy. Seroconversion from positive to negative correlates with cure but rarely occurs less than 1 to 2 years after therapy.

The UBT is commercially available for office use and is the test of choice for the routine diagnosis of the infection. *H pylori* contain abundant urease; in the UBT infection is detected by identification of isotopically labeled CO<sub>2</sub> in the breath following ingestion of labeled urea [79,80]. The <sup>13</sup>C-UBT using the naturally occurring, nonradioactive isotope <sup>13</sup>C has advantages over tests using radioactive <sup>14</sup>C because it can be repeated as necessary and is safe in all patients, including pregnant women and children. Urea breath testing is particularly useful to demonstrate infection eradication by antimicrobial therapy.

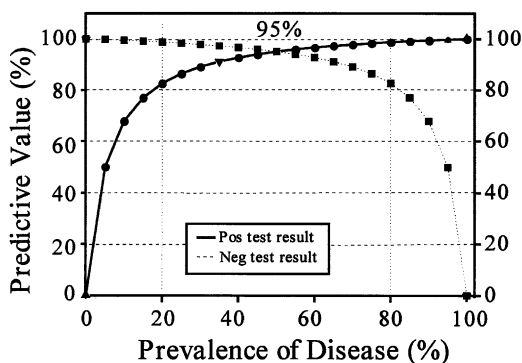


Fig. 2. Effect of prevalence of *H pylori* in a population on the predictive value of a positive or negative test result, for a test with 95% specificity and 95% sensitivity. A decreasing prevalence of *H pylori* results in an increasing proportion of false-positive tests with a high accuracy of negative tests. In contrast, when the prevalence of *H pylori* is expected to be high (eg, in duodenal ulcer) false-negative tests become common.

The urine-based ELISA and rapid urine test, which detects anti-*H pylori* antibody excreted in urine, recently have been validated and have accuracy comparable with that of serum ELISA [81–83]. In the stool antigen test, *H pylori* antigens are assayed for by an ELISA test in stool [78,84]. Stool antigen testing is simple and reliable, but has a slightly higher false-positive rate than the UBT for confirmation of cure and takes longer to become negative after infection eradication (6 to 8 weeks versus 4 weeks) [78]. Both the UBT and the stool antigen test may yield false-negative results when the bacterial load is low. This most commonly occurs when the patient takes antibiotics, bismuth, or a proton pump inhibitor. H<sub>2</sub>-receptor antagonists hardly affect the <sup>13</sup>C-UBT, but may adversely affect the <sup>14</sup>C-UBT.

At endoscopy, gastric mucosal biopsies can be performed for culture, rapid urease tests, and histology. Isolation by culture or identification by histology is definitive. For histology, the authors recommend obtaining a biopsy from at least three sites (the distal antrum, angularis, and mid to upper body); embedding the biopsy specimens on edge; and staining the slides with a special stain, preferably one of the new triple stains. Although the bacteria can be detected on hematoxylin-eosin-stained sections, a special stain, such as the Genta stain, the El-Zimaity stain, or the combination of hematoxylin and eosin plus another slide stained with Diff-Quik, is more accurate [85]. The triple stains have the advantage of highlighting the bacteria, while providing excellent histology of the gastritis [85,86].

Biopsy specimens can also be used for a rapid urease test in which the biopsy is put into a medium that contains urea and a pH indicator. In this test hydrolysis of urea to ammonia by the urease of *H pylori* raises the pH and produces a color change [87]. The urease test is significantly less sensitive (up to 25% false-negative rate) in patients with bleeding as compared with patients with nonbleeding peptic ulcer [88]. Rapid urease testing often provides a positive result while the patient is in the recovery room after endoscopy and provides a check on the reliability of the pathologist. Frequent discrepancies between rapid urease testing and histologic results suggest a problem with histologic interpretation, often from failure to use a special stain. A practical strategy in the United States, where histology is expensive, is to retain biopsy samples for histology taken from normal-appearing mucosa until after rapid urease test determination. If the urease test is positive the patient should be treated for *H pylori*, so the histologic samples can be discarded. If the urease test is negative the retained biopsy samples should be submitted for histologic confirmation. Biopsies from endoscopically abnormal tissue or from an ulcer edge should always be submitted for histologic analysis.

Culture is not routinely performed because *H pylori* is fastidious and difficult to culture. Nevertheless, as resistance to antibiotics increases, culture may eventually become required to select nonresistant antibiotic therapy [89,90]. Confirmation of successful therapy should be performed, typically by a noninvasive test. Testing by either the UBT or the stool antigen test

should be delayed at least 2 and preferably 4 weeks after antibiotic cessation to ensure that residual *H pylori*, if present, have multiplied to detectable levels. If infection remains despite two courses of therapy including different antibiotics, culture with susceptibility testing is indicated. Recent novel polymerase chain reaction hybridization assays, using Light Cycler or fluorescent in situ hybridization, can detect point mutations in the 23 S ribosomal RNA, can thereby demonstrate clarithromycin resistance within a few hours, and can be used directly on biopsy specimens when culture is unavailable [91,92].

### **Diseases associated with peptic ulcer**

Duodenal ulcer seems to occur more commonly in patients with chronic pulmonary diseases, cystic fibrosis,  $\alpha_1$ -antitrypsin deficiency, chronic renal failure, and cirrhosis [93–96]. The mechanisms of these associations, however, are mostly unknown. It is difficult to control for the effect of cigarette smoking in ulcerogenesis among patients with chronic pulmonary diseases. Most of these associations may relate to duodenal acid load. Cystic fibrosis may cause decreased gastroduodenal or pancreatic bicarbonate secretion [95], and cirrhosis or chronic pancreatitis may cause decreased bile or bicarbonate secretion into the duodenum [93]. The absence of protease inhibitors may underlie the increased risk of duodenal ulcer disease in  $\alpha_1$ -antitrypsin deficiency [96].

### **Ulcer disease therapy**

Ulcer therapy has two goals: ulcer healing and cause elimination. Other important considerations are relief of symptoms and prevention of complications. Antisecretory therapy both accelerates ulcer healing and provides rapid symptomatic improvement. Even though an  $H_2$ -receptor antagonist is cheaper, most clinicians now use a proton pump inhibitor [97]. Proton pump inhibitor therapy is particularly preferred to treat ulcers causing complications, unusual ulcers, such as giant ulcers, and patients with major comorbidity because it produces more rapid ulcer healing.

Therapy is predicated on ulcer etiology. Previously, therapy was directed initially at accelerating ulcer healing and after healing, antisecretory therapy was maintained using a lower daily dosage [98,99]. Even today antisecretory therapy for a complicated ulcer is not discontinued until the cause of the ulcer has been eliminated.

### *Treatment of H pylori infection*

Treatment of *H pylori* infection accelerates ulcer healing, prevents ulcer relapse, and prevents ulcer complications. Successful eradication dramatically reduces ulcer recurrence [100]. Reinfection after eradication is rare

in developed countries. Table 2 presents treatment regimes for *H pylori* infection.

Combination therapies, including traditional bismuth triple therapies, proton pump inhibitor triple therapies, ranitidine bismuth citrate triple therapies, and bismuth quadruple therapies, are preferred because monotherapy is unreliable. The proton pump inhibitor or ranitidine bismuth citrate is recommended twice a day with clarithromycin, 500 mg twice daily, metronidazole, 500 mg twice daily, or amoxicillin, 1 g twice daily. The therapeutic efficacy of a proton pump inhibitor or ranitidine bismuth citrate is comparable [101–103]. When these combination therapies are administered for 10 or 14 days and the bacterial strain is susceptible to the administered antibiotic, 95% to 99% of duodenal ulcers are cured in clinical trials, but the typical cure rate in routine clinical practice is only 65% to 80%.

Quadruple therapies consisting of a bismuth, tetracycline, 500 mg, metronidazole, 250 or 500 mg administered four times a day and an antisecretory drug, produce excellent cure rates. A high dose of metronidazole (500 mg thrice daily) and the addition of a proton pump inhibitor provide the best results and are effective even in the presence of metronidazole resistance. Quadruple therapy is an excellent choice for initial therapy or for second-line therapy after treatment failure. An alternate approach is to replace metronidazole with furazolidone (100 mg) in quadruple therapy.

Complications occur in about 15% to 20% of those treated but tend to be minor. Common side effects include diarrhea; taste disturbance; and nausea

Table 2  
Treatment regimens for *H pylori* infection

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PPI, or ranitidine bismuth citrate, triple therapies for 10 to 14 d
PPI or ranitidine bismuth citrate bid and clarithromycin, 500 mg bid, and amoxicillin, 1 g bid or
Clarithromycin, 500 mg bid, and metronidazole, 500 mg bid
Traditional bismuth quadruple therapy for 14 d
A bismuth (two tablets) qid
Tetracycline HCl, 500 mg qid
Metronidazole, 250 mg tid or qid
An H <sub>2</sub> -receptor antagonist or PPI once daily
Alternative bismuth quadruple therapy for 10 to 14 d
A bismuth (two tablets) qid
Tetracycline HCl, 500 mg qid
Metronidazole, 500 mg tid
A PPI once or twice daily
Furazolidone salvage therapy for 14 d
A bismuth (two tablets) qid
Tetracycline HCl, 500 mg qid
Furazolidone, 100 mg tid
A PPI once or twice daily

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*Abbreviations:* bid, twice daily; PPI, proton pump inhibitor; qid, four times daily; tid, thrice daily.

or side effects of antibiotics, including a rash for any antibiotic, dysgeusia for clarithromycin, black stools for bismuth, reactions to alcohol for metronidazole, and monilial vaginitis for tetracycline. Furazolidone, a monamine oxidase inhibitor, interacts with many drugs and foods. Adverse effects of furazolidone include nausea, vomiting, headache, tachycardia, and hypertension [104,105].

The patient must be advised of the importance of following prescription instructions, no matter how complicated, because poor compliance is the most important preventable cause of treatment failure. Bismuth triple therapy (Helidac) and proton pump inhibitor triple therapy (PREVPAC) packs are convenient and simplify patient compliance.

Antimicrobial resistance, especially to metronidazole and clarithromycin, is becoming a problem. Currently in the United States, clarithromycin resistance averages about 11% and metronidazole resistance about 25%. Pretreatment with metronidazole increases metronidazole resistance by 37%, and pretreatment with clarithromycin increases clarithromycin resistance by 55% [90]. Although clarithromycin resistance effectively disqualifies clarithromycin for therapy, metronidazole resistance can be overcome partially by increasing the dosage. Resistance to antibiotics often develops during the course of unsuccessful eradication therapy. If the original regimen used clarithromycin, replacement by metronidazole is recommended, and vice versa. If both antibiotics were previously used, bismuth quadruple therapy or furazolidone salvage therapy are the preferred alternatives.

### *Complications of peptic ulcer*

Approximately 25% of patients with peptic ulcer experience a major complication, such as hemorrhage, perforation, penetration, or obstruction. About 15,000 die each year as a result of these complications. As noted previously, approximately 1% of chronic ulcer patients experience a complication per year. In patients suffering one complication, the risk of a second subsequent complication may be greater than 1% per month. Hemorrhage is the most common complication, occurs in approximately 15% of ulcer patients, and has a mortality rate of about 10% [106,107]. Patients with active hemorrhage from peptic ulcer disease should undergo endoscopic hemostasis. This hemostasis is usually attempted before surgery because emergency surgery is associated with an increased mortality rate. Routine follow-up endoscopy and prophylactic retreatment and high-dose oral or intravenous proton pump inhibitor therapy theoretically reduces the risk of rebleeding [108,109].

Approximately 7% of peptic ulcers cause perforation. Duodenal ulcers tend to perforate anteriorly, and gastric ulcers tend to perforate along the anterior wall toward the gastric lesser curvature. With increased NSAID administration, the incidence of perforation is increasing, particularly in elderly women. For treatment of the perforation, laparoscopic repair is starting to replace laparotomy because it is a safe and efficient therapy [110,111].

### Role of surgery

Potent antisecretory therapy and infection eradication have decreased the frequency of refractory ulcers that require surgery. Surgery is now reserved for patients presenting with ulcer complications, such as major hemorrhage or perforation.

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