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Diagnostic approach & Pharmacological treatment regimen of Peptic ulcer disease

Abstract

Peptic ulcer is an acid related disorder of gastrointestinal tract. Gastritis, erosions, and peptic ulcer of the upper gastrointestinal (GI) tract require gastric acid for their formation. Peptic ulcer disease differs from gastritis and erosions in that ulcers typically extend deeper into the muscularis mucosa. There are three common forms of peptic ulcers, *Helicobacter pylori* associated, non-steroidal anti-inflammatory drug induced, and stress ulcers. The term "stress-related mucosal damage" is preferred to stress ulcer or stress gastritis, because the mucosal lesions range from superficial gastritis and erosions to deep ulcers. Chronic peptic ulcers vary in etiology, clinical presentation, and tendency to recur. HP-associated and NSAID induced ulcers develop most often in the stomach and duodenum of ambulatory patients. Occasionally, ulcers develop in the esophagus, jejunum, ileum, or colon. Peptic ulcers are also associated with Zollinger-Ellison syndrome (ZES), radiation, chemotherapy, and vascular insufficiency. In contrast, acute ulcers (Stress related mucosal disease) occur primarily in the stomach in critically ill hospitalized patient. This chapter focuses on chronic Peptic ulcer associated with *Helicobacter pylori* and NSAIDs. A brief discussion of ZES and upper Gastrointestinal tract bleeding related to Peptic ulcer and Stress related mucosal disease is included.

Keywords: peptic ulcer, gastrointestinal tract, zollinger-ellison syndrome, non-steroidal anti-inflammatory agents, stress related mucosal damage

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Amrish Kumar,[1] Vrish Dhwaj Ashwlayan,[1] Mansi Verma,[1] Vipin Kumar Garg,[1] Avnesh Kumar Singh,[1] Anurag,[1] Sameksha Koul,[1] Anjana Sharma,[1] Satish Kumar Gupta,[1] Lubhan Singh,[2] Abhinav Agrawal,[3] Nitin Sharma[4]

[1]Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, India
[2]Kharvel Subharti College of Pharmacy, India
[3]Raj Kumar Goel Institute of Technology, India
[4]Institute of Nuclear Medicine and Allied Sciences, Defence Research & Development Organisation, India

Correspondence: Amrish Kumar, Research Scholar, Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology NH-58, Meerut, Uttar Pradesh, India, Email amrish.kumar.miet@gmail.com

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Abbreviations: PUD, peptic ulcer disease; HP, *Helicobacter pylori;* PPIs, proton pump inhibitors; NSAID, non-steroidal anti-inflammatory drug; H_2RAs, H_2-receptor antagonists; ZES, *zollinger-ellison syndrome;* MALT, muco-saassociated lymphoid tissue; NUD, nonulcer dyspepsia; COX-2, cyclooxygenase-2; PG, prostaglandin; BAO, basal acid output; MAO, maximal acid output; COX-1, cyclooxygenase-1; UBT, urea breath test

Introduction

About 60% to 100% of ulcers re-institute within one year of initial ulcer healing with conventional antiulcer medicaments. The most prominent factors through which, ulcer re-institute in the body are *Helicobacter pylori* (HP) infection and non selective use of NSAIDs. Other factors which are playing a vital role in the pathogenesis of peptic ulcer hyper-secretion of gastric acid, cigarette smoking, consumption of excessive alcohol. Table 1 revealed the comparison of common forms of peptic ulcer.

Epidemiology

According to a survey, about ten percent of Americans live with chronic peptic ulcer disease during their wholelife. The incidence depends on it's kinds like type of ulcer, age, gender, and geographic location. The prevalence of PUD in the United States has shifted from predominance in men to nearly comparable prevalence in men and women. Recent study suggest a declining rate of it's recurrence in younger men and an increasing rate for older women. This is may be due to the reduction in smoking rates among younger men and the increased non-selective use of NSAIDs in geriatrics. Since 1960, peptic ulcer-related clinician visits, hospitalizations, surgery, and deaths have declined in the United States by more than 50%, primarily because of decreased rates of PUD among men. The decline in hospitalizations has resulted from a reduction in hospital admissions for uncomplicated duodenal ulcer. However, hospitalizations of older adults for ulcer-related complications (bleeding and perforation) have increased.[1] Although the overall mortality rate from PUD has decreased, but death rates have increased in patients who are more than 75 years of age, most likely a result of increased consumption of NSAIDs and an aging population. Patients with gastric ulcer have a higher mortality rate than those with duodenal ulcer because gastric ulcer is more prevalent in older patients. Despite these trends, peptic ulcer disease remains one of the most common GI diseases, resulting in impaired quality of life, work loss, and high-cost medical care. H_2-receptor antagonists (H_2RAs), proton pump inhibitors (PPIs), and drugs that promote mucosal defense have not altered PUD complication rates (Figure 1).

Table 1 Comparison of common forms of peptic ulcer

Characteristic	*H. pylori*–induced	NSAID-induced	SRMD
Condition	Chronic	Chronic	Acute
Site of damage	Duodenum > stomach	Stomach > duodenum	Stomach > duodenum
Intragastric pH	More dependent	Less dependent	Less dependent
Symptoms	Usually epigastric pain	Often asymptomatic	Asymptomatic
Ulcer depth	Superficial	Deep	Most superficial
GI bleeding	Less severe, single vessel	More severe, single vessel	More severe, superficial mucosal capillaries

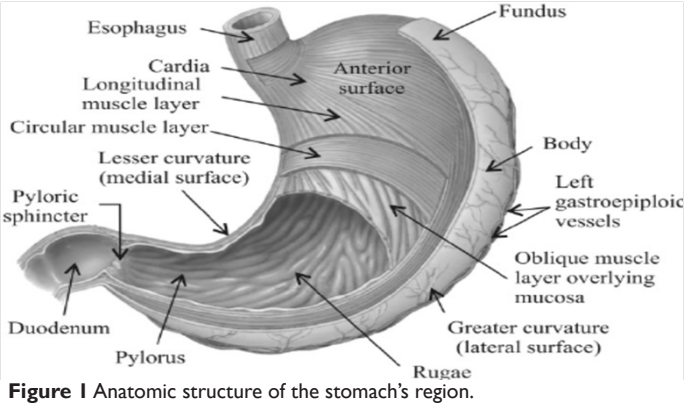

Figure 1 Anatomic structure of the stomach's region.

Etiology and risk factors

Most peptic ulcers occur in the presence of acid and pepsin when HP (*Helicobacter pylori)*, NSAIDs, or other factors (Table 2) disrupt normal mucosal defense and healing mechanisms. Hypersecretion of acid is the primary causative agent of peptic ulcer. Excessive secretion of hydrochloric acid may cause ZES. The location of peptic ulcer is related to a numbers of causative factors. Benign type of gastric ulcers may occur in any portion of the stomach, although most are located on the lesser curvature, just distal to the junction of the antral and acid-secreting mucosa. Most duodenal ulcers occur in the first part of the duodenum.

Table 2 Potential causes of peptic ulcer

Common causes
Helicobacter pylori infection
Nonsteroidal anti-inflammatory drugs
Critical illness (stress-related mucosal damage)
Uncommon causes
Hypersecretion of gastric acid (e.g., Zollinger-Ellison syndrome)
Viral infections (e.g., cytomegalovirus)
Vascular insufficiency (crack cocaine–associated)
Radiation
Chemotherapy (e.g., hepatic artery infusions)
Rare genetic subtypes

Helicobacter pylori

Helicobacter pylori infection causes chronic gastritis in all infected patients and is causally linked to PUD, gastric cancer, and muco-associated lymphoid tissue (MALT) lymphoma. However, only a minimum number of infected patients will develop symptomatic PUD (about 20%) or gastric cancer (less than 1%). The pattern and distribution of gastritis correlates strongly with the risk of a specific gastrointestinal disorder. The development of atrophic gastritis and gastric cancer is a slow processing, which occurs between 20 to 40 years of age. Host-specific cofactors and HP strain variability play an important role in the pathogenesis of PUD and gastric cancer.[2–4] Although an association between peptic ulcer and *H. Pylori* remains unclear, eradication of HP decreases recurrent bleeding. No any specific relation has been established between HP and dyspepsia, nonulcer dyspepsia (NUD), or gastroesophageal reflux disease.

Approximately 50% of the world's population is colonized by HP. The prevalence of HP varies by geographic location, socioeconomic conditions, ethnicity, and age. The prevalence of HP in the United States is thirty to fourty percent, but remains higher in African and Americans. There is a decreasing frequency of infection, especially in regions with improving sanitation and socioeconomic conditions. HP is transmitted one person-to another person by three different pathways, fecal-oral, oral-oral, and iatrogenic. Transmission of the organism is to occur by two reasons first is fecal-oral route, and second is directly from an infected person, or indirectly from fecal-contaminated water or food. People of the same house are likely to become infected when anybody in the same house is infected with *H. Pylori*. Transmission of HP can occur iatrogenically when infected instruments such as endoscopes are used.

Nonsteroidal anti-inflammatory drugs

NSAIDs are widely prescribed classes of medications through clinician in the America, particularly in those patients who are over 60 years of age and older. The chronic nonselective use of NSAID (including aspirin) responsible for a various Gastrointestinal tract injuries.[5–7] Sub-epithelial gastric-bleeding occur within 15 to 30 minutes after administration of NSAIDs. 15% to 30% of population are suffering from Gastroduodenal ulcers via the regular consumption of NSAID. NSAID-induced ulcers located either in the esophagus or colon, but are less common. The nonselective use of NSAIDs are responsible for at least 16,500 mortality and 107,000 hospitalizations in the America. The upper GI events occur may be probably in 3% to 4.5% arthritis patients who are taking NSAIDs, and 1.5% have a serious complication (major GI bleeding, perforation, or obstruction). NSAID-induced ulcers and it's complications is dose related, although it can occur with low dosages of nonselective use of aspirin, but according to the study the low dose of aspirin is taken for cardio-protective purposes (81 to 325 mg/day).[8,9] The use of corticosteroids without combination, does not increase the risk of ulcer or complications, but ulcer risk is increased two fold in corticosteroid users who are also taking concurrent NSAIDs. The use of low-dose aspirin in combination with another NSAID increases the risk of upper GI complications to a greater extent than the use of either drug alone. Gastric bleeding is markedly increased when NSAIDs are used in combination with anticoagulants. Whether HP organism is a causative factor for NSAID-induced ulcers remains controversial.[10–12] However, the non-acetylated salicylates (e.g., salsalate) and newer NSAIDs (e.g.,etodolac, nabumetone, and meloxicam) may be associated with a decreased incidence of GI toxicity. Safe dose of NSAIDs, selectively inhibit cyclooxygenase-2 (COX-2) and decrease the incidence of gastroduodenal ulcers and related GI complications when compared to the nonselective dose of NSAIDs. The use of buffered or enteric-coated aspirin confers no added protection from ulcer or GI complications (Figure 3).[13–15]

Cigarette smoking

There is an evidence that cigarette smoking is another causative agents for the pathogenesis of peptic ulcer, impaired ulcer healing, and ulcer-related GI complications. The pathogenesis of peptic ulcer is directly proportional to the number of cigarettes smoked per day by the population. The Death rates are also higher in those patients who smoked more cigarettes than non-smoking patients. Possible mechanisms behind the pathogenesis of peptic ulcer among those who smoked, is delay in gastric emptying of solids and liquids, inhibition of pancreatic bicarbonate secretion, promotion of duodenogastric reflux, and reduction in mucosal prostaglandin (PG) production.

Psychological stress

The role of psychological related problems, in the formation of Peptic ulcer remains controversial. Clinical observation suggests that the patients with ulcer are adversely affected by stressful life events. Although, results obtained from controlled trials have been failed to document a cause-and-effect relationship between psychological stress and peptic ulcer. It may be that psychological problems, may change the behavior of patients so that patients could be smoked and take the NSAIDs on regular bases.

Dietary factors

Coffee, tea, cola beverages, beer, milk, and spices may cause dyspepsia, but do not increase the risk for PUD. Although caffeine is responsible to increase gastric acid production.

Gastric acid and pepsin

Erosion of gastric mucosa is related to the hyper-secretion of gastric acid and pepsin. Gastric acid secretion done by the parietal cells, which contain receptors for histamine, gastrin, and acetylcholine. Gastric acid is most important factor that contributes in the disruption of mucosal integrity. Increase secretion of acid has been observed in patients with duodenal ulcers and may be a consequence of *H. Pylori* infection.[16,17] Those patients have hypersecretion of gastric acid, are associated with ZES and after may be probably of gastrin-producing tumor. Acid secretion is expressed as the amount of acid secreted under basal or fasting conditions, basal acid output (BAO) after maximal stimulation, maximal acid output (MAO) or in response to a meal. An increase in the BAO:MAO ratio suggests a basal hypersecretory state such as ZES. Pepsinogen, the inactive precursor of pepsin, is secreted by the chief cells located in the gastric fundus. Pepsin is activated by acid pH (optimal pH of 1.8 to 3.5), inactivated reversibly at pH 4, and irreversibly destroyed at pH 7. Pepsin appears to play a role in the proteolytic activity involved in ulcer formation.

Mucosal defense and repair

Mucosal defense and repair mechanisms are responsible for the protection of gastric mucosa from noxious endogenous and exogenous substances. Mucosal defense factors include such as mucus and bicarbonate secretion, intrinsic epithelial cell defense, and mucosal blood flow. Mucus-bicarbonate barrier has viscous nature and nearly neutral pH by which, protect the stomach from the acidic contents are present in the gastric lumen. The repair of gastric mucosa after injury is due to epithelial cell reinstitution, growth, and regeneration. Mucosal integrity and it's repair is successfully done by the production of endogenous prostaglandins. The term cytoprotection is often used to describe this process, but mucosal defense and mucosal protection are more accurate terms, as prostaglandins prevent deep mucosal injury and not superficial damage to individual cells. Alterations in mucosal defense that are induced by HP or NSAIDs are the most important cofactors in the formation of peptic ulcers.

Helicobacter pylori

Helicobacter pylori is a spiral-shaped, pH-sensitive, gram-negative, microaerophilic bacterium that resides between the mucus layer and surface epithelial cells in the stomach, or any location where gastric type epithelium is found. The combination of its spiral shape and flagellum permits it to move from the lumen of the stomach, where the pH is low, to the mucus layer, where the local pH is neutral. The acute infection is accompanied by transient hypochlorhydria, which permits the organism to survive in the acidic gastric juice. The exact method by which HP initially induces hypochlorhydria is unclear. According to the phenomenon HP produces large amounts of urease, which hydrolyzes urea in the gastric juice and converts it to ammonia and carbon dioxide. The local buffering effect of ammonia creates a neutral microenvironment within and surrounding the bacterium, which protects it from the lethal effect of acid. HP also produces acid-inhibitory proteins, which allows it to adapt to the low-pH environment of the stomach. HP attaches to gastric-type epithelium by adherence pedestals, which prevent the organism from being shed during cell turnover and mucus secretion. Colonization of the corpus (body) of the stomach is associated with gastric ulcer. Antral organisms are hypothesized to colonize gastric metaplastic tissue (which is thought to arise secondary to changes in acid or bicarbonate secretion, products of HP, or host inflammatory responses) in the duodenal bulb, leading to duodenal ulcer. A number of bacterial and host factors contribute to the ability of HP to cause gastroduodenal mucosal injury. Pathogenic mechanisms include: (a) direct mucosal damage, (b) alterations in the host immune/inflammatory response, and (c) hypergastrinemia leading to increased acid secretion. In addition, HP enhances the carcinogenic conversion of susceptible gastric epithelial cells. Direct mucosal damage is produced by virulence factors (vacuolating cytotoxin, cytotoxin-associated gene protein, and growth inhibitory factor), elaborating bacterial enzymes (lipases, proteases, and urease), and adherence. About 50% of HP strains produce a protein toxin (Vac A) that is responsible for cellular vacuole formation. Strains with cytotoxin-associated gene (cagA) protein are associated with duodenal ulcer, atrophic gastritis, and gastric cancer.

Nonsteroidal anti-inflammatory drugs

Nonselective dose of aspirin is a causative agents for gastric mucosal damage by two important mechanisms: (a) direct or topical irritation of the gastric epithelium and (b) systemic inhibition of endogenous mucosal prostaglandin synthesis. Two similar COX isoforms have been identified, cyclooxygenase-1 (COX-1) is found in most body tissue, including the stomach, kidney, intestine, and platelets, cyclooxygenase-2 (COX-2) is undetectable in most tissues under normal physiologic conditions, but its expression can be induced during acute inflammation and arthritis (Figure 2). COX-1 produces protective and safe prostaglandins that regulate physiologic processes such as GI mucosal integrity, platelet homeostasis, and renal function. COX-2 is induced by inflammatory stimuli such as cytokines, and produces prostaglandins involved with inflammation, fever, and pain. COX-2 is also constitutionally expressed in organs such as the brain, kidney, and reproductive tract. Adverse effects (e.g., GI toxicity or renal toxicity) of NSAIDs are associated with the inhibition of COX-1, whereas anti-inflammatory actions result from NSAID inhibition of COX-2. Nonselective NSAIDs including aspirin inhibit both COX-1 and COX-2 to varying degrees. Aspirin irreversibly inhibits platelet COX-1 for as long as 18 hours, resulting in decreased platelet aggregation and prolonged bleeding times, which may potentiate upper and lower GI bleeding. Similar effects are observed with the nonselective NSAIDs. A number of other mechanisms may contribute to the development of NSAID-induced mucosal injury. Neutrophil adherence may damage the vascular endothelium and may lead to a reduction in mucosal blood flow, or may liberate oxygen-derived free radicals and proteases. Leukotrienes, products of lipoxygenase metabolism, are inflammatory substances that may contribute to mucosal injury through stimulatory effects on neutrophil adherence (Figure 2). Topical irritant properties are predominantly associated

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with acidic NSAIDs (e.g., aspirin) and their ability to decrease the hydrophobicity of the mucous gel layer in the gastric mucosa. Most non-aspirin NSAIDs have topical irritant effects, but aspirin appears to be the most damaging. Although $NSAID_s$ are pro-drugs, enteric-coated aspirin tablets, salicylate derivatives, and parenteral or rectal preparations are associated with less-acute topical gastric mucosal injury, they can cause ulcers and related GI complications as a result of their systemic inhibition of endogenous PGs.

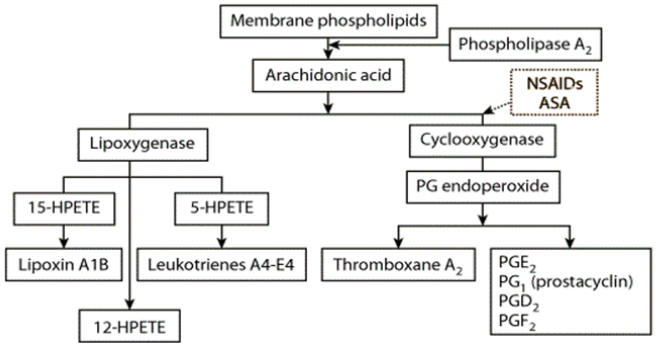

Figure 2 Metabolism of arachidonic acid after its release from membrane phospholipids. ASA, aspirin; HPETE, hydroperoxyeicosatetraenoic acid; NSAIDs, nonsteroidal anti-inflammatory drugs; PG, prostaglandin. Broken arrow indicates inhibitory effects.

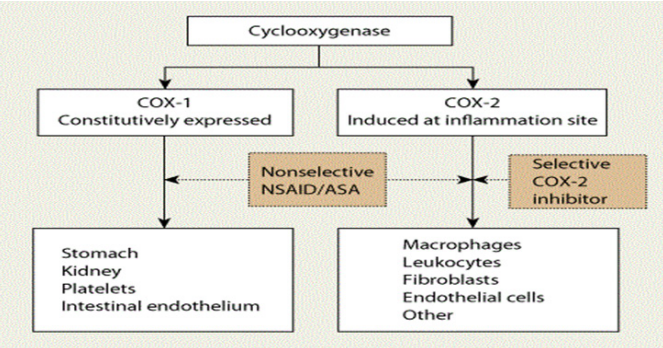

Figure 3 Tissue distribution and actions of cyclooxygenase (COX) isoenzymes. Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin (ASA) inhibit COX-1 and COX-2 to varying degrees; COX-2 inhibitors inhibit only COX-2. Broken arrow indicates inhibitory effects.

Diagnosis

Tests for Helicobacter pylori infection

The diagnosis of HP infection can be possible by two tests, using endoscopic or non-endoscopic tests (Table 3).[18] The non-endoscopic tests- include serologic antibody detection tests, the urea breath test (UBT), and the stool antigen test. These tests are more convenient and less expensive than the endoscopic tests. The stool antigen test is approved by the Food and Drug Administration (FDA), but availability in the United States is limited. It is less expensive and easier to perform than the UBT, and may be useful in children. Although comparable to the UBT in the initial detection of HP, the stool antigen test is less accurate when used to confirm HP eradication post-treatment.[19] Post-treatment evaluation to confirm eradication is unnecessary in most patients with PUD unless they have recurrent symptoms, complicated ulcer, MALT lymphoma, or gastric cancer. The UBT is the preferred non-endoscopic method to verify HP eradication after treatment. To avoid confusing bacterial suppression with eradication, the UBT must be delayed at least 4 weeks after the completion of treatment. The term "eradication" or "cure" is used when post-treatment tests conducted 4 weeks after the end of treatment do not detect the organism.

Imaging and endoscopy

The diagnosis of PUD depends on visualizing the ulcer crater either by upper GI radiography or endoscopy. Because of its lower cost, greater availability, and greater safety, many physicians believe that radiography should be the initial diagnostic procedure in patients with suspected uncomplicated PUD. If complications are thought to exist, or if an accurate diagnosis is warranted, upper endoscopy is the diagnostic procedure of choice. If a gastric ulcer is found on radiography, malignancy should be excluded by direct endoscopic visualization and histology.

Treatment

The treatment of chronic PUD varies depending on the etiology of the ulcer (HP or NSAID), Overall treatment is aimed to relieving ulcer pain, healing the ulcer, and prevent the re-institution of ulcer. The goal of therapy in HP-positive patients is successful eradication heals ulcers and reduces the risk of recurrence to less than 10% at 1 year. The goal of therapy in a patient with a NSAID-induced ulcer is to heal the ulcer as rapidly as possible. Patients at high risk of developing NSAID ulcers should be switched to a COX-2 inhibitor or receive prophylactic drug co-therapy to reduce ulcer risk and ulcer related complications. When possible, the most cost-effective drug regimen should be utilized.

General approach to treatment

The treatment of PUD is the eradication of HP in HP-positive patients and reducing the risk of NSAID-induced ulcers and ulcer related complications. Drug regimens containing antimicrobials agent such as clarithromycin, metronidazole, amoxicillin, and bismuth salts and anti-secretory drugs such as the PPIs or H_2RAs are used to relieve ulcer symptoms, heal the ulcer, and eradicate HP infection. PPIs, H_2RAs, and sucralfate are used to heal HP-negative NSAID-induced ulcers, but ulcer recurrence is likely in high-risk patients if the NSAID is initiate on regular bases. Prophylactic co-therapy with a PPI or misoprostol is used to decrease the risk of an ulcer and upper GI in patients taking nonselective NSAIDs. COX-2 inhibitors are often used in place of a nonselective NSAID to reduce the risk of ulcers and complications. Dietary modifications may be important for some patients, especially those who are unable to tolerate certain foods and beverages. Lifestyle modifications such as reducing stress and stopping cigarette smoking is often encouraged. Some patients may require radiographic or endoscopic procedures for a definitive diagnosis or for complications such as bleeding. Surgery may be necessary in patients with ulcer-related bleeding or other complications such as perforation.

Non-pharmacologic therapy

Patients with PUD should eliminate or reduce psychological stress, cigarette smoking, and the use of nonselective NSAIDs (including aspirin). Although there is no "antiulcer diet," the patient should avoid foods and beverages (e.g., spicy foods, caffeine, and alcohol) that cause dyspepsia or that exacerbate ulcer symptoms. If possible, alternative agents such as acetaminophen, nonacetylated salicylate (e.g., salsalate), or COX-2 inhibitors should be used for relief of pain (Figure 4).

Table 3 Tests for Detection of *Helicobacter pylori*

Test	Description	Comments
Endoscopic tests Histology	Microbiologic examination using various stains	Gold standard; >95% sensitive and specific; permits classification of gastritis; results are not immediate; not recommended for initial diagnosis; tests for active HP infection; antibiotics, bismuth, and PPIs may cause false-negative results
Culture	Culture of biopsy	Enables sensitivity testing to determine appropriate treatment or antibiotic resistance; 100% specific; results are not immediate; not recommended for initial diagnosis, but may be used after failure of second-line treatment; tests for active HP infection; antibiotics, bismuth, and PPIs may cause false-negative results
Biopsy (rapid) urease	HP urease generates ammonia, which causes a color change	Test of choice at endoscopy; >90% sensitive and specific; easily performed; rapid results (usually within 24 hours); tests for active HP infection; antibiotics, bismuth, and PPIs may cause false-negative results; test may yield false-negatives in active ulcer bleeding; available as gel tests, paper tests, and tablets
Nonendoscopic tests Antibody detection (laboratory-based)	Detects antibodies to HP in serum; in the U.S., only FDA-approved anti-HP lgG antibody should be used	Quantitative; less sensitive and specific than endoscopic tests; more accurate than in-office or near-patient tests; unable to determine if antibody is related to active or cured infection; antibody titers vary markedly between individuals and take 6 months to 1 year to return to the uninfected range; not affected by PPIs or bismuth; antibiotics given for unrelated indications may cure the infection but antibody test will remain positive
Antibody detection (can be performed in office or near patient)	Detects lgG antibodies to HP in whole blood or fingerstick	Qualitative; quick (within 15 minutes); unable to determine if antibody is related to active or cured infection; most patients remain seropositive for at least 6 months to 1 year post HP eradication; not affected by PPIs, bismuth, or antibiotics
Urea breath test	HP urease breaks down ingested labeled C-urea, patient exhales labeled CO2	Tests for active HP infection; 95% sensitive and specific; results take about 2 days; antibiotics, bismuth, PPIs, and H2RAs may cause false-negative results; withhold PPIs or H2RAs (1 to 2 weeks) and bismuth or antibiotics (2 to 4 weeks) before testing; may be used posttreatment to confirm eradication
Stool antigen	Identifies HP antigen in stool, leading to color change that can be detected visually or by spectrophotometer	Tests for active HP infection; sensitivity and specificity comparable to urea breath test when used for initial diagnosis; antibiotics, bismuth, and PPIs may cause false-negative results, but to a lesser extent than with the urea breath test; may be used post treatment to confirm eradication

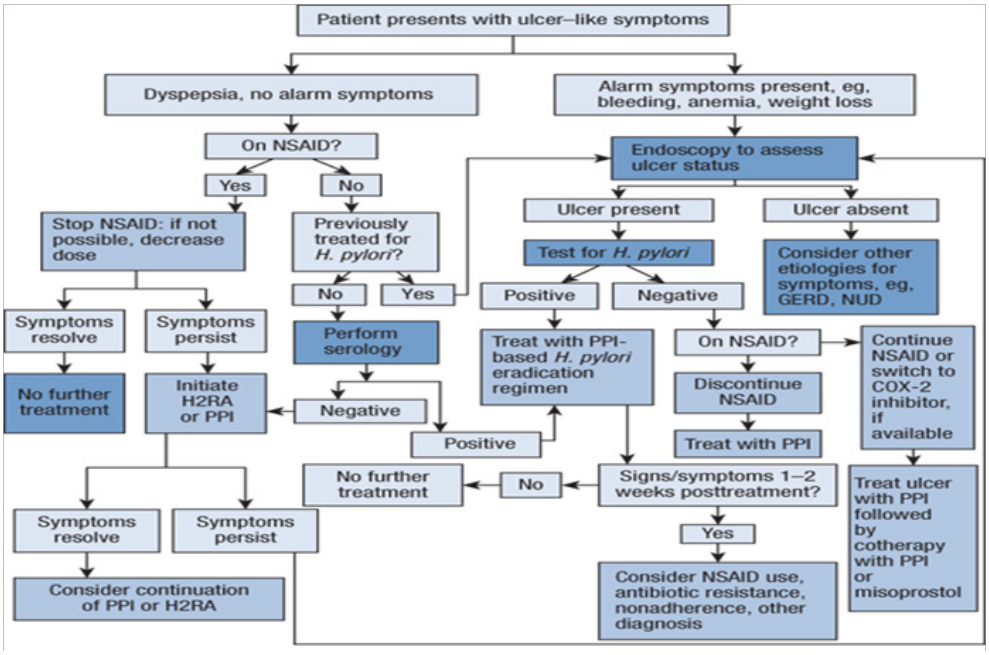

Figure 4 Algorithm: Guidelines for the evaluation and management of a patient who presents with dyspeptic or ulcer-like symptoms. COX-2, cyclooxygenase-2; GERD, gastroesophageal reflux disease; HP, *Helicobacter pylori*; H_2-RA, H2-receptor antagonist; PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug; NUD, nonulcer dyspepsia.

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Elective surgery for PUD is rarely performed today because of highly effective medical management such as the eradication of HP and the use of potent acid inhibitors.[20] A subset of patients, however, may require emergency surgery for bleeding, perforation, or obstruction. In the past, surgical procedures were performed for medical treatment failures and included vagotomy with pyloroplasty or vagotomy with antrectomy. Vagotomy (truncal, selective, or parietal cell) inhibits vagal stimulation of gastric acid. A truncal or selective vagotomy frequently results in postoperative gastric dysfunction and requires a pyloroplasty or antrectomy to facilitate gastric drainage. When an antrectomy is performed, the remaining stomach is anastomosed with the duodenum (Billroth I) or with the jejunum (Billroth II). A vagotomy is unnecessary when an antrectomy is performed for gastric ulcer. The postoperative consequences associated with these procedures include postvagotomy diarrhea, dumping syndrome, anemia, and recurrent ulceration.

Pharmacologic therapy

The goal of drug therapy is eradication of the organism. The dosage regimens should minimize the potential for antimicrobial resistance.[21,22] Alone antibiotic, bismuth salt, or antiulcer drug are not fulfill to achieve the goal. However, clarithromycin is one of the single most potent antibiotic. Two-combination of dosage form, PPIs and either amoxicillin or clarithromycin have yielded marginal eradication rates in the America but are not recommeded. In addition, the use of only one antibiotic is associated with a higher rate of antimicrobial resistance. Eradication regimens that combine two antibiotics and one anti-secretory drug (triple therapy) or a bismuth salt, two antibiotics, and an anti-secretory drug (quadruple therapy) increase eradication rates to an acceptable level and reduce the risk of antimicrobial resistance. The antibiotics that have been most extensively studied and found to be effective in various combinations include clarithromycin, amoxicillin, metronidazole, and tetracycline. Although other antibiotics may be effective, they should not be used as part of the initial HP regimen. Because of insufficient data, ampicillin should not be substituted for amoxicillin, doxycycline should not be substituted for tetracycline, and azithromycin or erythromycin should not be substituted for clarithromycin. Amoxicillin should not be used in penicillin-allergic patients and metronidazole should be avoided if alcohol is consumed by the patients. Bismuth salts have a topical antimicrobial effect.

Proton pump inhibitor–based three-drug regimens

Three-drug regimens in which, two antibiotics and one PPIs constitute first-line therapy for eradication of HP. Ameta-analysis of 666 studies indicates that PPI-based regimens that combine clarithromycin and amoxicillin, clarithromycin and metronidazole, or amoxicillin and metronidazole yield similar eradication rates (78.9% to 82.8%) using intent-to-treat analysis; however, other studies suggest that the amoxicillin-metronidazole combination is less effective. Eradication rates were improved when the clarithromycin dose was increased to 1.5 g/day, but increasing the dosage of the other antibiotics did not increase eradication rates.[23] Most clinicians prefer to initiate triple therapy with clarithromycin and amoxicillin rather than clarithromycin and metronidazole. Reserving metronidazole as an alternative or second-line agent leaves an effective back-up agent and reduces exposure and adverse effects from metronidazole. Alternatively, the PPI-clarithromycin-metronidazole regimen is an excellent alternative in penicillin-allergic patients. An initial 7-day course of therapy provides minimally acceptable eradication rates and has been approved by the FDA and is recommended in Europe. One meta-analysis reports a 7% to 9% increase in eradication rates with a 14-day treatment regimen when compared to a 7-day regimen. A number of other antibiotics and antibiotic combinations have been evaluated as part of the PPI-based three-drug regimen with varying degrees of success. The PPI is an integral part of the three-drug regimen and should be taken 15 to 30 minutes before a meal (see section on PPIs) along with the two antibiotics. Although gastric acid inhibition is necessary to influence HP eradication rates, the specific level of inhibition remains unknown. Substitution of one PPI for another is acceptable and does not appear to enhance or diminish HP eradication. An H_2RA should not be substituted for a PPI, as better eradication rates have been demonstrated with a PPI.[24]

Bismuth-based four-drug regimens

The bismuth-based four-drug combination were originally used as first-line therapy to eradicate HP. Substitution of clarithromycin 250 to 500 mg four times a day for tetracycline yields similar results, but increases adverse effects. Although the original bismuth-based four-drug combination is effective and inexpensive, it is associated with frequent adverse effects and poor compliance. A capsule containing bismuth, metronidazole, and tetracycline is under investigation. First-line treatment with quadruple therapy using a PPI (with bismuth, metronidazole, and tetracycline) in place of the H_2RA achieves similar eradication rates as those of PPI-based triple therapy and permits a shorter treatment duration (7 days).[25] Although evidence supports the efficacy of bismuth-based quadruple therapy as first-line treatment, it is often recommended as second-line treatment when a clarithromycin-amoxicillin regimen is used initially. All medications except the PPI (see section on PPIs) should be taken with meals and at bedtime.

Eradication regimens after initial treatment failure

HP eradication is often more difficult when initial treatment approach becomes result-less and eradication rates are extremely variable. Because there are limited data on second attempts to eradicate HP, treatment failures should be handled on a case-by-case basis. Failure of first- and second-line regimens in primary care requires referral to a specialist. Second-line empiric treatment should: utilize antibiotics that were not previously used during initial therapy; use antibiotics that do not have resistance problems; use a drug that has a topical effect such as bismuth; and the duration of treatment should be extended 10 to 14 days. Thus after unsuccessful initial treatment with a PPI-amoxicillin-clarithromycin regimen, empiric second-line therapy should be instituted with bismuth subsalicylate, metronidazole, tetracycline, and a PPI for 10 to 14 days When metronidazole resistance is suspected, metronidazole may be replaced by furazolidone (100 mg four times a day) in either the proton pump inhibitor-based three-drug regimen or the bismuth-based four-drug regimen. When furazolidone is used, patients should be counseled not to ingest alcohol or monoamine oxidase inhibitors.1 Other successful second-line regimens are discussed elsewhere.[26,27]

Factors that contribute to unsuccessful eradication

Factors that contribute to unsuccessful eradication include poor patient compliance, resistant organisms, low intra-gastric pH, and a high bacterial load. Poor patient compliance is an important factor influencing successful therapy. Although a longer treatment duration may contribute to noncompliance, missed doses in a 7-day regimen may also lead to failed eradication. Tolerability varies with different

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regimens. Metronidazole-containing dosage combination increase the frequency of adverse effects (especially when the dose is >1 gm/day). Metronidazole resistance is most common in 10% to 60% patients, but varies depending on prior antibiotic exposure and geographic region. The clinical importance of metronidazole resistance in eradicating HP remains uncertain, as the synergistic effect of combining metronidazole with other antibiotics appears to render resistance to metronidazole less important. Primary resistance to clarithromycin is lower in10% to 15% patients than with metronidazole, but it is more likely to affect the clinical outcome. Secondary resistance occurs in up to two thirds of treatment failures. Resistance to tetracycline and amoxicillin is uncommon. Resistance to bismuth has not been reported. The role of antibiotic sensitivity testing before initiating HP treatment has not been established. Table 4 revealed the oral drug regimens to cure peptic ulcer.

Table 4 Oral drug regimens used to heal peptic ulcers or maintain ulcer healing

Drug	Duodenal or Gastric ulcer healing (mg/dose)	Maintenance of duodenal or Gastric ulcer healing (mg/dose)
Proton pump inhibitors		
Omeprazole	20–40 daily	20–40 daily
Lansoprazole	15–30 daily	15–30 daily
Rabeprazole	20 daily	20 daily
Pantoprazole	40 daily	40 daily
Esomeprazole	20–40 daily	20–40 daily
H_2-receptor antagonists		
Cimetidine	300 four times daily 400 twice daily 800 at bedtime	400–800 at bedtime
Famotidine	20 twice daily 40 at bedtime	20–40 at bedtime
Nizatidine	150 twice daily 300 at bedtime	150–300 at bedtime
Ranitidine	150 twice daily 300 at bedtime	150–300 at bedtime
Promote mucosal defense		
Sucralfate (g/dose)	1 four times daily 2 twice daily	1–2 twice daily 1 four times daily

Treatment of NSAID-induced ulcers

Nonselective use of NSAIDs should be discontinued if an active ulcer is confirmed after diagnosis. If the NSAID is stopped, most uncomplicated ulcers will heal with standard regimens of ranitidine, PPI, or sucralfate (Table 4). PPIs are usually considered first because they provide more rapid ulcer healing rather than H_2RAs or sucralfate. If the NSAID must be continued in a patient despite ulceration, consideration should be given to reducing the NSAID dose, or switching to acetaminophen, a nonacetylated salicylate, a partially selective COX-2 inhibitor, or a selective COX-2 inhibitor. The PPIs are the drugs of choice when the NSAID must be continued, as potent acid suppression is required to accelerate ulcer healing. H_2RAs are less effective in the presence of continued NSAID use; sucralfate does not appear to be effective. If HP is present, treatment should be initiated with an eradication regimen that contains a PPI.

Strategies to reduce the risk of NSAID-induced ulcers and ulcer-related Upper gi complication

A number of strategies are used to reduce the risk of NSAID-related ulcers and GI complications. Strategies aimed at reducing the topical irritant effects of nonselective NSAIDs. Medical co-therapy with misoprostol or a PPI decreases the risk of ulcers and GI complications in high-risk patients Switching to a selective COX-2 inhibitor also decreases ulcer risk and complications.[28–30]

Misoprostol co-therapy with a nonselective NSAIDs

Misoprostol, 200 mcg four times a day, markedly reduces the risk of NSAID-induced gastric ulceration, duodenal ulcer, but diarrhea and abdominal cramping may be occur during regimen. Because of misoprostol 200 mcg three times a day provides a comparable results than misoprostol 800 mcg/day, the lower dosage should be considered in patients unable to tolerate the higher dose. Reducing the misoprostol dosage to 400 mcg/day or less to minimize diarrhea may compromise its prophylactic effects. A fixed combination of misoprostol 200 mcg and diclofenac (50 mg or 75 mg) is available and may enhance compliance, but the flexibility to individualize drug dosage is lost. A large double-blind clinical trial in rheumatoid arthritis patients who are receiving misoprostol 200 mcg four times a day provides the most compelling evidence that serious upper GI complications can be prevented, especially in high-risk patients.

H_2-receptor antagonist co-therapy with a nonselective NSAIDs

H_2-receptor antagonist (e.g., famotidine 40 mg/day) are effective in reducing the risk of NSAID-induced duodenal ulcer, but not gastric ulcer (the most frequent type of ulcer associated with NSAIDs). Therefore standard H_2RA dosages should not be used as co-therapy with a nonselective NSAID for prophylaxis. The evidence that higher dosages (e.g., famotidine 40 mg twice daily, ranitidine 300 mg twice

daily) reduce the risk for gastric ulcer and duodenal ulcer. However, there are no studies that have evaluated whether higher H_2RA dosages reduce the risk of ulcer-related upper GI complications. The H_2RAs may be used when necessary to relieve NSAID-related dyspepsia.

Proton pump inhibitor co-therapy with a nonselective NSAIDs

Standard PPI dosages (e.g., omeprazole 20 mg/day and lansoprazole 30 mg/day) reduce the risk of NSAID-induced gastric ulcer and duodenal Ulcer. In a large comparative multicenter trial, omeprazole 20 mg/day was superior to ranitidine 150 mg twice daily in preventing NSAID-induced gastro-duodenal ulcers. Two randomized Controlled trials have compared with misoprostol and placebo. In the first study, omeprazole 20 mg/day was as effective as Misoprostol 400 mcg/day in reducing the incidence of gastric ulcer; However, if a higher dosage of misoprostol had been used it might have been more effective. In the second study of HP-negative NSAID users with a history of gastric ulcer, misoprostol 800 mcg/day was More effective than lansoprazole (15 mg or 30 mg/day) and placebo. When withdrawals from the study (primarily related to the side effects of misoprostol) were regarded as "treatment failures," lansoprazole And full-dose misoprostol were considered clinically equivalent. Although there are no large clinical studies to prove that decrease the risk for NSAID-related upper GI complications, two Small studies have reported a reduction in serious upper GI complications In patients with a history of upper GI bleeding.[31,32] Proton Pump inhibitor co-therapy is considered an alternative to misoprostol In high-risk patients taking nonselective NSAID (including low-dose Aspirin).

Selective cox-2 inhibitors

Of the oral selective COX-2 inhibitors now available in the U.S. only celecoxib was investigated in arthritic patients, in a large, long-term, randomized controlled trial (named CLASS), that was specifically designed to evaluate upper gastrointestinal complications versus nonselective NSAIDs.[33,34] Patients in the CLASS trial, were permitted to take low-dose aspirin for cardioprotection. The initial analysis of the CLASS trial indicated that, when compared to nonselective NSAIDs, celecoxib had 50% fewer symptomatic ulcers and serious upper GI complications in patients not taking concomitant low-dose aspirin. However, in the CLASS trial, these benefits were negated in the aspirin users. Although a systematic review of celecoxib found that it is safer than nonselective NSAIDs, a re-evaluation of the CLASS data by the FDA concluded that celecoxib does not provide a GI safety results over nonselective use of NSAIDs. The manufacturer of celecoxib argued (and the FDA acknowledged) that confounding factors in study design, including the use of low-dose aspirin, account for these discrepant results. Concerns about the cardiovascular safety of selective COX-2 inhibitors (e.g., thrombotic events and myocardial infarction) have arisen. GI effects such as dyspepsia and abdominal pain, fluid retention, hypertension, and renal toxicity can also occur with the COX-2 inhibitors. Two small comparative trials in HP-negative patients with histories of NSAID-related ulcer complications suggested that a standard dosage of a PPI and a nonselective NSAID have a GI safety profile similar to that observed with a selective COX-2 inhibitor. However, the comparative benefits and cost effectiveness of these regimens remain controversial. Co-therapy with a PPI and a selective COX-2 inhibitor should be considered in patients with multiple or life-threatening risk factors.

Conventional treatment of active duodenal and gastric ulcers and long-term Maintenance of ulcer healing

Treatment with standard drug ranitidine or sucralfate relieves ulcer symptoms and heals the majority of gastric and duodenal ulcers in 6 to 8 weeks.[35] Proton pump inhibitors provide comparable and valuable ulcer healing rates just in 4 weeks. When conventional antiulcer therapy is discontinued after ulcer healing, most HP-positive patients develop a recurrent ulcer within 1 year. Continuous antiulcer therapy is aimed at the long-term maintenance of ulcer healing and at preventing ulcer-related complications. Because HP eradication dramatically decreases ulcer recurrence (<10% at 1 year), continuous maintenance therapy has become largely obsolete. Long-term maintenance therapy with an H_2RA, PPI, or sucralfate is safe, but sucralfate should be avoided in renal impairment.

Treatment of refractory ulcers

Ulcers are considered refractory to therapy when symptoms, ulcers, or both persist beyond 8 weeks (duodenal ulcer) or 12 weeks (gastric ulcer) despite conventional treatment, or when several courses of HP eradication fail. Poor patient compliance, antimicrobial resistance, cigarette smoking, NSAID use, gastric acid hypersecretion, or tolerance to the antisecretory effects of an H_2RA (see section on antiulcer agents) may contribute to refractory PUD. Patients with refractory ulcers should undergo upper endoscopy to confirm a nonhealing ulcer, exclude malignancy, and assess HP status. HP-positive patients should receive eradication therapy (see section on treatment of HP associated ulcers). In HP-negative patients, higher PPI dosages (e.g., omeprazole 40 mg/day) heal the majority of ulcers. Continuous treatment with a PPI is often necessary to maintain healing, as refractory ulcers typically recur when therapy is discontinued or the dose is reduced. Switching from one PPI to another is not beneficial. Patients with refractory gastric ulcer may require surgery because of the fear of malignancy.

Conclusion

The eradication of *Helicobacter pylori* infection has dramatically changed the way in which chronic PUD is treated. Although substantial progress has been made, there is still no ideal treatment, and much of what has been learned has not yet been instilled into clinical practice. The widespread use of NSAIDs and their associated GI complications remains a major concern, especially in older adults. Co-therapy with misoprostol or a PPI reduces NSAID-related GI events, but studies are needed to determine their comparative cost effective dosage regimen.

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None.

Conflicts of interest

Authors declare no conflicts of interest.

References

1. Del Valle J, Chey WD, Scheiman JM, et al. Acid peptic disorders. In: Yamada T, Aplers DH, Kaplowitz N, et al. eds. *Textbook of Gastroenterology.* 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2003:1321–1376.
2. Suerbaum S, Michetti P. *Helicobacter pylori* infection. *N Engl J Med*. 2002;347(15):1175–1186.

3. Go MF. Review article: Natural history and epidemiology of *Helicobacter pylori* infection. *Aliment Pharmacol Ther*. 2002;16(Suppl 1):3–15.

4. Peterson WL. Review article: *Helicobacter pylori* and gastric adenocarcinoma. *Aliment Pharmacol Ther*. 2002;16:(Suppl 1):40–46.

5. Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology*. 2001;120(3):594–606.

6. Hawkey CJ. Nonsteroidal anti-inflammatory drug gastropathy. *Gastroenterology*. 2000;119(2):521–535.

7. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1999;340(24):1888–1899.

8. Derry S, Loke YK. Risk of gastrointestinal hemorrhage with long-term use of aspirin: Meta-analysis. *BMJ*. 2000;321(7270):1183–1187.

9. Sorensen HT, Mellemkjaer L, Blot WJ, et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol*. 2000;95(9):2218–2224.

10. Laine L. Review article: The effect of *Helicobacter pylori* infection on nonsteroidal anti-inflammatory drug-induced upper gastrointestinal tract injury. *Aliment Phamacol Ther*. 2002;16(Suppl 1):34–39.

11. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drugs in peptic ulcer disease. *Lancet*. 2002;359(9300):14–22.

12. Lanas A, Fuentes J, Benito R, et al. *Helicobacter pylori* increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. *Aliment Phamacol Ther*. 2002;16(4):779–786.

13. Micklewright R, Lane S, Linley W, et al. Review article: NSAIDs, gastroprotection and cyclo-oxygenase-II-selective inhibitors. *Aliment Pharmacol Ther*. 2003;17(3):321–332.

14. Warner TD, Giuliano F, Vojnovic I, et al. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: A full in vitro analysis. *Proc Natl Acad Sci USA*. 1999;96(13):7563–7568.

15. Kelly JP, Kaufman DW, Jurgelon JM, et al. Risk of aspirin-associated major upper gastrointestinal bleeding with enteric-coated or buffered product. *Lancet*. 1996;348(9039):1413–1416.

16. Del Valle J, Todisco A. Gastric secretion. In: Yamada T, Aplers DH, Kaplowitz N, et al, eds. *Textbook of Gastroenterology*, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2003:266–307.

17. Sachs G, Shin M, Munson K, et al. The control of gastric acid and *Helicobacter pylori* eradication. *Aliment Pharmacol Ther*. 2000;14(11):1383– 1401.

18. Vaira D, Gatta L, Ricci C, et al. Review article: Diagnosis of *Helicobacter pylori* infection. *Aliment Pharmacol Ther*. 2002;16(Suppl 1):16–23.

19. Bilardi C, Biagini R, Dulbecco P, et al. Stool antigen assay (HpSA) is less reliable than urea breath test for post-treatment diagnosis of *Helicobacter pylori* infection. *Aliment Pharmacol Ther*. 2002;16(10):1733–1738.

20. Seymour NE, Andersen DK. Surgery for peptic ulcer disease and postgastrectomy syndromes. In: Yamada T, Aplers DH, Kaplowitz N, et al. eds. *Textbook of Gastroenterology*. 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2003:1441–1454.

21. Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of *Helicobacter pylori* infection—The Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther*. 2002;16(2):167–180.

22. Qasim A, O'Morain CA. Review article: Treatment of *Helicobacter pylori* infection and factors influencing eradication. *Aliment Pharmacol Ther*. 2002;16(Suppl 1):24–30.

23. Laheij RJ, Rossum LG, Janser JB, et al. Evaluation of treatment regimens to cure *Helicobacter pylori* infection-a meta-analysis. .*Aliment Pharmacol Ther*. 1999;13(7):857–864.

24. Gisbert JP, Khorrami S, Calvet X, et al. Meta-analysis: Proton pump inhibitors vs. H2-receptor antagonists—their efficacy with antibiotics in *Helicobacter pylori* eradication. *Aliment Pharmacol Ther*. 2002;18(8):757– 766.

25. Gene E, Calvet X, Azagra R, et al. Triple vs quadruple therapy for treating *Helicobacter pylori* infection:Ameta-analysis. *Aliment Pharmacol Ther*. 2003;17(9):1137–1143.

26. Megraud F, Lamouliatte H. Review article: The treatment of refractory *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2003;17(11):1333– 1343.

27. Gisbert JP, Pajares JM. Review article: *Helicobacter pylori* "rescue" regimen when proton pump inhibitor-based triple therapies fail. *Aliment Pharmacol Ther*. 2002;16(6):1047–1057.

28. Chan FKL, Leung WK. Peptic ulcer disease. *Lancet*. 2002;360(9337):933–941.

29. Fennerty MB. NSAID-related gastrointestinal injury: Evidence-based approach to a preventable complication. *Postgrad Med*. 2001;110(3):87–94.

30. Fitzgerald GA, Patrono C. Coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med*. 2002;345(6):433–442.

31. Chan PK, Chung SCS, Suen BY, et al. Preventing recurrence of upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med*. 2001;344(13): 967–973.

32. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of upper gastrointestinal complications from long-term lowdose aspirin use. *N Engl J Med*. 2002;346(26):2033–2038.

33. Silverstein F, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal antiinflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: A randomized controlled trial. *JAMA*. 2000;284(10):1247–1255.

34. Bombardier C, Laine L, Reicin A, et al. Comparison of upper intestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med*. 2000;343(21):1520–1528.

35. Welage LS, Berardi RR. Evaluation of omeprazole, lansoprazole, pantoprazole, and rabeprazole in the treatment of acid-related diseases. *J Am Pharm Assoc*. 2000;40(1):52–62.