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Clinical Manifestations, Causes and Management Strategies of Peptic Ulcer Disease

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ABSTRACT
Peptic ulcer embraces both gastric and duodenal ulcers and has been a major threat to the world's population over the past two centuries, with a high morbidity and substantial mortality. Discovery of gastric mucosa infection with *Helicobacter pylori* (*H. pylori*) and its association with chronic antral gastritis and peptic ulcer revolutionized the treatment of ulcer illness. *H. pylori* are causally related to a majority of cases of both duodenal and gastric ulcer, in the west and developing countries. Despite extensive scientific advancements, this disease remains an important clinical setback, largely because of *H. pylori* infection and widespread use of non-steroidal anti-inflammatory drugs (NSAIDs). Management of peptic ulcer disease generally involves the practice of H_2 receptor antagonists, use of proton pump inhibitors, antacids and different *H. pylori* eradication regimens. This review article outlines the epidemiology, clinical manifestations, diagnosis and treatment strategies of peptic ulcer disease.

Keywords: *Helicobacter pylori*, peptic ulcer, diagnostic tests, management strategies.

INTRODUCTION

Peptic ulcer disease is a group of disorders characterized by the presence of ulcers in any portion of gastrointestinal tract (GIT) exposed to acid in sufficient concentration and duration. Although these ulcerations most commonly occur in the stomach (gastric ulcer), or small intestine (duodenal ulcer), this disease also includes Barrett ulcer of the esophagus (Barrett's esophagus or Barrett's metaplasia) and other upper GI ulcers. [1] An ulcer is a crater like lesion in a membrane; ulcers that develop in areas of the GIT exposed to acidic gastric juice are called peptic ulcers. [2] Word '*peptic*' derives from the Greek term '*peptikos*,' meaning related to digestion. [3] Peptic ulcer is due to exposure of stomach and duodenum to pepsin and gastric acid. Imbalance occurs between aggressive factors like acid, pepsin, *H. pylori* and defensive factors such as gastric mucus, bicarbonate ions, and prostaglandins along with innate resistance of mucosal cells. [4] Gastroduodenal mucosa utilizes several defense mechanisms against the aggressive factors such as hydrochloric acid and pepsin. [5]

Danish physiologist Schierbeck in 1892 reported that food ingestion caused an increase in canine gastric CO_2. However, few years later, Pavlov investigated about the protective role of gastric alkaline mucus.

It is well established that gastric and duodenal epithelial cells in mammals actively secrete bicarbonate into the lumen. [6-7] This secretion interacting with the surface mucus gel layer comprises first line of mucosal defense. [5] Proximal duodenal mucosal bicarbonate secretion capacity in man is about five times the gastric bicarbonate secretion. [8] Mucus is secreted by mucus secreting cells that are available abundantly in the neck region of gastric glands. Mucin forms a protective layer on the gastric epithelium. It retains bicarbonate and has alkaline pH. Thus, it protects the stomach from acid peptic digestion, as it buffers hydrochloric acid. Mucus secretion is also stimulated by increased blood flow to the stomach. [9] Activation of prostaglandin receptors also inhibits gastric acid secretion. Mucosal prostaglandins are known to afford cytoprotection by various mechanisms. [10]

Natural aggressors secreted into the gastric lumen are acid and pepsin. Various studies reveal that the gastroduodenal mucosal barrier is damaged by pepsin under conditions in which it is resistant to acid alone. Pepsin has mucolytic activity and progressively digests the adherent mucus layer at its luminal surface. [11] Studies by Taylor and Roberts have identified, on the basis of charge differences, seven pepsins – 1, 2, 3, 3a, 4, 5, and 6 in human gastric juice and acidified extracts of gastric mucosa. [12-13] The most common cause of ulcer is *H. pylori*, a bacterium that colonizes the stomach of nearly half the world's population. Infection caused by *H.*

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pylori is causally linked with many GI diseases, including upto 75% of peptic ulcers. [3] Moreover, NSAIDs along with *H. pylori* combine the caustic effects of gastric acid and pepsin, which disrupts the normal defense mechanism of the GI mucosa. [14] Various protective and aggressive factors are summarized below: [15]

Protective factors:
- Bicarbonate
- Mucus
- Mucosal blood flow
- Prostaglandins

Aggressive factors:
- Acid
- Pepsin
- *Helicobacter pylori*
- NSAIDs

HISTORY AND PREVALENCE

Indigestion and heartburn have been described for thousands of years, but it was only in the 16th century that the disease peptic ulcer was established by autopsy. One of the first autopsies - proven pyloric peptic ulcers was studied in 1586 by Donatus of Mantua. Bauhin, in 1679, concluded that inflammation of the stomach led to a gastric ulcer which then ruptured. The first known gastric hemorrhage was reported in 1704. [16] First classification of stomach diseases came in 1793 from Matthew Baillie, with clear descriptions of acute inflammation (arsenic), trichobezoar, ulcer, perforation, pyloric stenosis, scirrhous and ulcerated cancer. In 1817, patients with perforated gastric ulcer were reported in Dublin by Crampton and patients with perforated duodenal ulcer were reported in London by Travers, who also noted bleeding, stenosing and penetrating gastric ulcers. [17-19] The first epidemiological study on peptic ulcer in North India was conducted in 1963. [20]

Approximately 5,00,000 new cases and 4 million recurrences of peptic ulcer are reported each year, contributing to the approximately 10% of Americans developing peptic ulcer disease during their lifetime. [21-22] Complications of peptic ulcer disease, including perforation, bleeding, and obstruction, occur in up to 20 % of cases; overall, gastric outlet obstruction may affect 5% - 12% of peptic ulcer patients. [23] Johnson *et al* noted that peptic ulcer disease was the origin of obstruction in 62 % of patients from 1962 to 1975, and in 45 % of patients from 1975 to 1985. [24] Gibson *et al* investigated that only 33 % of patients in their series with peptic ulcer disease and outlet obstruction were *H. pylori* positive. [25] The annual incidence of gastric ulcers varies from approximately 1 case per 1000 population in Japan to 1.5 cases per 1000 population in Norway to 2.7 cases per 1000 population in Scotland. [26] Commonly, the ratio of duodenal ulcer to gastric ulcer varies with place and time. In most countries, duodenal ulcers are about three times more common than gastric ulcers, but gastric ulcers are more common in some locations such as Japan, Sri Lanka, the Andes and some islands off northern Norway. [27]

REGULATION OF GASTRIC ACID SECRETION

Stomach secretes about 2.5 liters of gastric juice daily. The primary exocrine secretions are pepsinogens, from the *chief* or *peptic cells*, and hydrochloric acid and intrinsic factor from the *parietal* or *oxyntic cells*. [28] Men secrete more acid than women. This can be explained partially by differences in body size. [29] Gastric acid secretion is regulated by intricate central and peripheral mechanisms. Parietal cells have receptors for several stimulants of acid secretion and these cells possess a specific Hydrogen Potassium-ATPase enzyme (proton pump), which is responsible for the exchange of H^+ for K^+ ions across the apical surface of the parietal cells. The final process of acid transport *per se* rests with this enzyme. Three distinct but interdependent pathways deliver chemical messengers that stimulate acid secretion as shown in Fig. 1 and are summarized in the following text.

- The neurocrine pathway, that acts through the transmitters such as acetylcholine.
- The paracrine pathway delivers tissue factors, such as histamine from enterochromaffin like cells.
- The endocrine pathway delivers hormones such as gastrin from antral G cells. [30]

The receptors on the surface of parietal cell include H_2 receptors responding to histamine released from specialized mast cells, receptors that are sensitive to the muscarinic effects of acetylcholine released from the vagus nerve and probably receptors responsive to endogenous circulating gastrin. A stimulated receptor modifies the activity of other receptors and at the same time releases an intracellular second messenger. Calcium ions and cyclic AMP are the principal second messengers, and these in turn activate the gastric proton pump situated near the luminal apex of the parietal cell. [31]

More data are also available on the role of GI hormones in the regulation of aggressive factors, especially gastric acid. In fact, the antral hormone gastrin was detected by its property to stimulate gastric acid secretion. [32] In 1971, McGuigan and Trudeau observed that patients with duodenal ulcer had an exaggerated gastrin release in response to meals and suggested that the trophic effect of gastrin might be responsible for the increase in parietal cell mass characteristic of duodenal ulcer disease. [33] In the late 1980s, several investigators also examined meal-stimulated gastrin release in relation to *H. pylori* infection. [34]

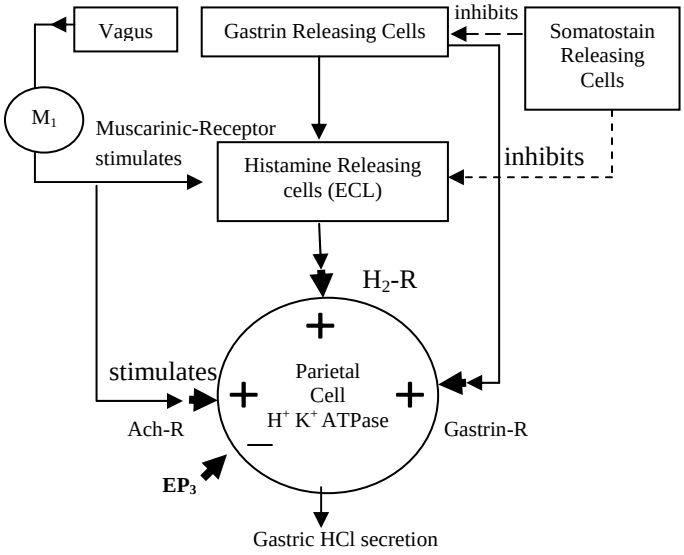

Fig. 1: Mechanism involved in regulation of gastric acid secretion by the parietal cells

R= Receptors, EP_3= PG receptor for PGE_2, M_1= Muscarinic receptor, ECL= Enterochromaffin like cells, Ach = Acetylcholine, H_2 = Histamine

TYPES OF PEPTIC ULCER

Ulceration of the gastrointestinal mucosa is caused by disruption of normal balance of the corrosive effect of gastric juice and the protective effect of mucus on gastric epithelial cells. On the basis of location, peptic ulcers are categorized as follows - *Gastric ulcer*: means occurrence of ulcer in stomach. These ulcers occur more generally in the older age group.

Duodenal ulcer: Occurrence of ulcer in the duodenum is referred as duodenal ulcer. These ulcers are more common than gastric ulcers. They occur commonly in younger individuals and are evenly distributed among various socio-economic groups. Duodenal ulcer patients have higher than normal levels of acid secretion rates. [35, 29, 30] Depending on severity, peptic ulcers are also classified as: *Acute peptic ulcers*: These ulcers involve tissues to the depth of the submucosa. They may arise in the form of single or multiple lesions. They are found in many sites of stomach and in the first few centimeters of duodenum. *Chronic peptic ulcers*: These ulcers penetrate through the epithelial and muscle layers of stomach wall and may include the adjacent pancreas or liver. In majority of cases, they occur singly in the pyloric antrum of the stomach and in duodenum. [36]

H. PYLORI INFECTION

H. pylori infection plays a crucial role in the pathogenesis of peptic ulcer disease. More than 95 % of patients suffering from the duodenal ulcers and about 70 % - 80 % of patients with gastric ulcers are *H. pylori* positive. [37] *H. pylori* is a gram-negative, motile, microaerophilic, curved bacillus that is found in the mucus layer overlying the gastric epithelium. [38] In 1981, Marshall and Warren conducted a prospective study of 100 consecutive patients undergoing endoscopy to correlate gastric mucosal biopsy findings with clinical and endoscopy data. In this investigation, they isolated microaerophilic, catalase-positive bacterium. [39] *H. pylori* infection has been recognized as the primary cause of chronic gastritis and peptic ulcer disease. [38] In 1994, United States (U.S.) National Institutes of Health Consensus Development Panel concluded that infection appears to play an important contributory role in the pathogenesis of peptic ulcers. [40] The role of *H. pylori* infection is well explained in peptic ulcer disease by O'connor. [41]

Currently, 70 % of all gastric ulcers occurring in the U.S. can be attributed to *H. Pylori* infection. In addition to an increase in acid secretion, bacterial infection also predisposes patients to ulcer disease by disrupting mucosal integrity. [26] In developed countries, however, infection with *H. pylori* is uncommon before age 10 and increases to 10 % in 18 - 30 years old, compared with 50 % in those older than 60. [42] In developing nations, 60 % - 70 % of children are infected with the bacteria by age 10, probably because of overcrowding and poor sanitation. [43] Chronic gastritis associated with *H. pylori* infection is often observed in children with primary duodenal ulcer. Colonization of the gastric mucosa by *H. pylori* is currently uncommon among children who live in industrialized countries, compared to those who live in developing countries, with prevalence upto the tenth year of life of 5 % - 10 % and up to 80 %, respectively. [44]

There are several strains of *H. pylori* along with two phenotypes of the bacterium. Both make a vacuolating cytotoxin Vac A. Type I also has a cytotoxin-associated gene (cag A) that may be necessary for transcription, function, or excretion of Vac A cytotoxin. This type I phenotype is associated with ulcer formation. Type II organisms lack cag A and do not produce as much of an inflammatory response. This bacterium also makes mucolytic enzymes, platelet activating factor, and lipopolysaccharide. Each of these can cause cellular injury. [45] Covacci *et al* have suggested that only bacteria expressing the cag A antigen are associated with ulcer disease. These findings explain the link between *H. pylori* cytotoxin expression and ulcer disease. [46-47]

INDISCRIMINATE USE OF NSAIDs

NSAID including aspirin use is the second most common etiologic factor for this disease and a major factor for peptic ulcer complications. [48] The function of long term NSAIDs use in various GI tract injuries has been well documented in commendable number of scientific publications. [49] Patients with rheumatoid arthritis and osteoarthritis who take NSAIDs have 15-20 % annual incidence of peptic ulcer. More than half of patients who present with peptic ulcer hemorrhage or perforation report the recurrent use of NSAIDs, including aspirin. [50] Aspirin has been indisputably correlated with this complication. [51] NSAIDs induce GI mucosal injury by direct toxic effects and reduce mucosal prostaglandins which play a critical role in defense mechanisms and repair processes. NSAIDs inhibit cyclooxygenase (COX), which is the rate-limiting enzyme required for the conversion of arachidonic acid to prostaglandins. [52]

H. pylori infection is a prevailing risk factor for peptic ulcer disease along with the widespread use of NSAIDs, grounds for evidence of ulcer development. Overall, the risk of developing an ulcer is at least 15 times higher in subjects infected with *H. pylori* than in those not infected with the bacterium. [53]

OTHER CAUSES

Numerous other factors causing this disease include smoking habits, alcohol consumption, coffee drinking and familial occurrences of peptic ulcers in patients with gastric or duodenal ulcer. [54] Epidemiologic studies suggest that smokers are about twice as likely to develop peptic ulcer disease as non-smokers. Smoking increase gastric acid secretion and duodenogastric reflux and decreases both gastroduodenal prostaglandin production and pancreatic duodenal bicarbonate production. [50] Lam *et al* have also documented that an unfavorable trend in duodenal ulcer healing exists for cigarette smokers as compared with non-smokers who receive H_2-blockers. [55]

Conventionally, peptic ulcer disease has also been considered to be a stress-associated psychosomatic disease. Importance of emotional disturbances due to stress has long been shown to be a consideration in the pathogenesis of this disease. [56] There is evidence that psychological stress induces many ulcers and impairs response to treatment. This stress probably functions most often as a cofactor with *H. pylori*. It may act by stimulating the production of gastric acid or by promoting behavior that causes a risk to health. [57] Bleich *et al* in 1996 and Sullivan *et al* in 1999 along with other researchers signify the relevance of emotional disturbance due to stress in the pathogenesis of peptic ulcer disease which cannot be ignored. [58-59] It has also been well reported that people who work the night shift have a frequently higher incidence of ulcers than day workers. [60]

DIETARY ASPECTS

Various types of food stimulate mucosal defense factors in experimental models. [61] Incidence of peptic ulcer disease has decreased due to increase in the use of dietary essential fatty acids since the beginning of 20th century. [62] Intake and handling of rice in various areas of the world may also explain peptic ulceration, as fresh rice oil in animal experiments protect against gastric ulceration, but stored oil is ulcerogenic. [63] Salt increases mortality from gastric but not duodenal ulcer. [64] Dietary fibre may be protective, as found in Swedish-Norwegian study, in which duodenal ulcers relapsed more quickly on a low fibre diet than on a bran

supplemented diet. [65] Milk, on the other hand, seems to have an adverse effect on the healing rate of duodenal ulcers. [66] Duodenal ulceration is generally rare in areas of the world where the intake of dietary fibre in the form of unrefined wheat is the staple carbohydrate food eaten. [67] In 1978, Malhotra found that the rate of recurrence of duodenal ulceration was significantly lower in patients eating unrefined wheat compared to when they were on their previous more refined rice diet. [68] Consequently, both animal studies as well as studies in human beings show that a diet rich in fibre protects the GIT against the development of peptic ulceration.

SIGNS AND SYMPTOMS

Moynihan, an Irish surgeon was the first to relate the clinical symptoms of peptic ulcer disease with the pathological findings. [69-70] It has been reported that small ulcers may not cause any symptoms and large ulcer can cause serious bleeding. [71] The most common symptom is burning pain, especially just below the breast bone. [72] Gastric ulcer pain may be less severe than duodenal ulcer pain and is noticeably higher in abdomen. Eating may increase pain in subjects rather than relieving pain. Other symptoms may include nausea, vomiting and weight loss. Vomiting might be related to partial or complete gastric outlet obstruction. Duodenal ulcer pain may awaken the patients from sleep and also involve burning or gnawing sensation in upper abdomen. Pain in back, lower abdomen or chest area may occasionally arise and occurs when the stomach is empty about two hours after a meal or during the night. Relief frequently occurs after eating. [73] Epigastric tenderness, melena resulting from acute or sub acute gastrointestinal bleeding and complete gastric outlet obstruction may also occur in ulcer disease. [74]

DIAGNOSTIC TESTS

Until early 20th century, the diagnosis of peptic ulcer was made on clinical grounds. In 1950's various flexible endoscopies revolutionized the direct visualization of ulcer disease. [75] Various diagnostic tests which are frequently employed by gastroenterologists depending upon patient's symptoms are summarized in the following text.

Esophagogastroduodenoscopy

This is a special test performed by gastroenterologists in which a thin tube with a camera on the end is inserted through mouth into the GI tract to see stomach and small intestine. During this examination, the doctor may take a biopsy from the wall of stomach for detection of *H. pylori*. [71]

X-ray

In this, patient is made to swallow a white chalky substance called barium that is visible on X-ray and then patient is made to lie down on a tilted examining table. The tilting distributes the barium evenly around upper digestive tract and X-ray can capture images at different angles. This allows the doctor to locate the ulcer and determine its type and severity. [75]

Computed tomography

It is a rapid way to confirm an uncertain diagnosis of perforation and penetration associated with peptic ulcer disease. This study is carried out retrospectively to review the abdominal computed tomography findings in patients with peptic ulcer disease and correlated them with the clinical history, endoscopic and upper GIT series findings, and surgery when it is performed. [76-77]

DIAGNOSIS OF *H. PYLORI*

Diagnosis of *H. pylori* in peptic ulcer needs to be established before treatment is initiated. This can be done via noninvasive and/or invasive testing. The noninvasive tests include urea breath test, stool antigen test, and serology testing. [78]

Urea breath test involves radioisotopes ^{13}C or ^{14}C, which help in identifying the production of urease by *H. pylori.* Patients ingest ^{13}C or ^{14}C labeled urea and then exhales labeled carbon dioxide. If *H. pylori* are present, since the bacterium produces urease this splits urea thereby, detecting the presence of the organism. False negative tests can occur if *H. pylori* is suppressed but not completely eliminated after treatment. [79] Several commercial stool antigen tests are also available. This test checks whether substances that trigger the immune system to fight an *H. pylori* infection are present in the feces of the patients infected with the bacterium. [80-81] Serology testing includes presence of human IgG antibodies against *H. pylori.* Antibody levels decline after treatment for infection and hence the positive antibody levels may indicate current or past infection. Antibodies for *H. pylori* can be measured in serum, plasma or whole blood. [82-83]

Invasive testing includes endoscopy with subsequent histology, urease production testing and cultures allowing the clinician to identify the organism. Hematoxylin-eosin, Giemsa, or Warthin-Starry stains can be used in the detection and easier visualization of bacterium. Thus, many gastroenterologists utilizes urease test first, followed by histology, if the urease test is negative or if confirmation of the urease is desired. Culture is difficult to perform but it is helpful in evaluating treatment failure since antibiotic sensitivity can be evaluated. [84-85] The diagnostic tests for *H. pylori* are represented in table 1 along with their advantages. [86]

Table 1: Methods for diagnosis of *H. pylori* infection

Test	Advantages
NON-INVASIVE	
Urea breath tests	High sensitivity and specificity
Stool antigen test	Cheap, accurate
Serology	Rapid office kits available good for population studies
INVASIVE (ANTRAL BIOPSY)	
Histology	Sensitivity and specificity
Rapid urease tests	Cheap, quick specificity
Microbiological culture	'Gold standard' defines antibiotic sensitivity

COMPLICATIONS

As the epidemiology of peptic ulcer has led to decreased incidence of this disease, it remains an important surgical problem because of the severity of its complications.

Gastrointestinal bleeding

Peptic ulcer disease is an important cause of upper-GI bleeding in 50 % of cases. [87] Upper GI bleeding is a common clinical problem, resulting in about 2,50,000 hospitalizations in the U.S. annually. This disease is recognized the most common origin of upper-GI bleeding, accounting for 45 %-78 % of bleeding episodes. [88] The most frequent and severe complication of peptic ulcer is bleeding, which is reported 50 - 170 per 1, 00,000 with highest risk in people aged older than 60 years. [89] Bleeding is the deadliest complication of duodenal and gastric ulcer, accounting for almost all mortality in the surgical treatment of this disease. [90] Patients whose ulcer reveals a flat dot or clean base (forrest class 3) rarely re-bleed or need hospitalization. However, actively bleeding ulcers or those with evidence of

recent hemorrhage (forrest class 1 and 2) are likely to re-bleed and may need intensive care. [91]

Gastric outlet obstruction

Other complication includes gastric outlet obstruction that is the obstruction at the pylorus from severe duodenal ulcer disease. This can occur because of extensive disease and subsequent scarring in the area, resulting in a mechanical blockage. Propulsive element of stomach, the antrum, becomes ineffective in efforts to evacuate the stomach because of the chronic impairment of normal emptying process from inflammation. [90] On the other hand, some authors have also concluded that gastric outlet obstruction is associated with high *H. pylori* infection rate. Taskin *et al* studied 10 consecutive patients presenting with clinically and endoscopically significant gastric outlet obstruction. During each endoscopy, seven gastric biopsy specimens were obtained (from the antrum, corpus and fundus) and analysed for *H. pylori* colonization by both rapid urease test and histological methods. The antral mucosal biopsy specimens were *H. pylori* positive in nine patients, that is, in 90 % of patients. [92-93]

Perforation

Another complication is perforation of the gastric or duodenal ulcer. Survival is lower in ulcer perforation patients than in general population. [94] Perforation is less frequent than bleeding, with an incidence of around 7-10 per 1,00,000. [89]

MANAGEMENT STRATEGIES

Management of peptic ulcer disease continues to evolve because of the emergence of various novel therapeutic agents, advancements in several operative techniques and pharmacological oriented strategies. With the development of various therapies, as well as recognition and understanding of *H. pylori* infection along with mechanism, the medical management of ulcer has been largely successful. [95] Several drugs are extensively used for the reduction of acidity in peptic ulcer, gastroesophageal reflux disease and in many form of gastritis. Enormous drugs are also employed in the regimens for treating *H. pylori* infection. Various therapeutic agents utilized in management of ulcer and in the regimens for treating *H. pylori* infection includes H_2 blockers, proton pump inhibitors, antacids, prostaglandins etc. [96]

H_2 receptor antagonists

Until the mid-1970s, there was no really effective medical treatment for duodenal ulcer. The outlook changed in November 1976, with the emergence of cimetidine, the first histamine H_2 receptor antagonist which dramatically transformed management resulting in swift symptom relief, ulcer healing and marked reduction in relapse. [97] Various other H_2 antagonists which are available in India; includes cimetidine, ranitidine, famotidine and roxatidine etc., others are also marketed in several countries. [98] These drugs are competitive inhibitors of histamine at the H_2 receptor, thus suppressing gastrin stimulated acid secretion and proportionately reducing gastric juice volume. Histamine-mediated pepsin secretion is also decreased. [96] Long-term continuous maintenance treatment with H_2 receptor antagonists for five or more years effectively prevents ulcer recurrence in the majority of patients and significantly reduces the risk of ulcer complications. In addition, maintenance treatment has proved to be safe and is well tolerated by patients. [99]

Proton pump inhibitors

The first proton pump inhibitor (PPI) on the US market, omeprazole, appeared in 1988.This approval paved the way for the sequential introduction of other PPI congeners such as pantoprazole, lansoprazole rabeprazole, esomeprazole magnesium, the S-isomer of omeprazole etc. These are most potent suppressors of gastric acid secretion and inhibit gastric H^+K^+-ATPase enzyme (proton pump). [100] In typical doses, these drugs diminish the daily production of acid (basal and stimulated) by 80 % to 95 %. PPI are prodrugs that require activation in an acid environment. After absorption into the systemic circulation, the prodrug diffuses into parietal cells of the stomach and accumulates in the acidic secretory canaliculi. The activated form then binds covalently with sulfhydryl groups of cysteines in the H^+ K^+-ATPase, irreversibly inactivating the pump molecule. [101]

Pantoprazole was first approved for use in the treatment of gastritis and duodenal ulcer in Germany in early 1994. [102] A single intravenous bolus of 80 mg of pantoprazole inhibits acid production by 80 % to 90 % within an hour, and this inhibition persists for up to 21 hours, permitting once-daily dosing to achieve the desired degree of hypochlorhydria. The FDA-approved dose of intravenous pantoprazole for gastroesophageal reflux disease is 40 mg daily for upto 10 days. [101] The comparison of currently available proton pump inhibitors are described in table 2. [100]

Table 2: Pharmacological comparison of currently available proton pump inhibitors

PPI	Bioavailability	Half-life	Renal/Hepatic dosing
Omeprazole	30-40%	0.1-1 h	Reduce in hepatic impairment
Esomeprazole	64%	1-1.5 h	Max. dose - 20 mg in severe hepatic impairment
Pantoprazole	77%	3.5-10 h	None
Lansoprazole	>80%	2 h	Reduce in severe hepatic impairment
Rabeprazole	52%	1-2 h	Use caution in severe hepatic impairment

Antacids

Antacids neutralize gastric acid and reduce pepsin activity. These agents relieve symptoms, promote ulcer healing, and decrease recurrence. They are relatively inexpensive. The optimal antacid regimen for ulcer healing generally includes 10 to 30 ml of liquid or 2 to 4 tablets 1 h and 3 h after each meal and at bedtime. The total daily dosage of antacids should provide 200 - 400 mEq neutralizing capacity. However, antacids have been superseded by acid suppressive therapy in the treatment of peptic ulcer and are used only for short-term symptomatic relief. [96]

Anticholinergics

Although anticholinergic medications inhibit basal and meal-stimulated gastric acid secretion, they do so at a substantially lower rate than do other antisecretory agents. Also, significant adverse effects of nonselective anticholinergic agents limit their use in ulcer disease. [103]

Misoprostol, Sucralfate, Carbenoxolone and Colloidal bisumth

Naturally occurring prostaglandins have been shown to heal peptic ulcer in almost non-antisecretory doses. [104] However, these compounds are rapidly metabolized when given orally, and they also cause abdominal cramps, diarrhea, and uterine contractions. Therefore, in order to develop therapeutically effective prostaglandins, chemical and structural modifications are required. Significant number of

prostaglandins analogues has been synthesized in search for a longer duration of action, increased potency, and greater pharmacological specificity. [105]

Prostaglandins especially misoprostol which is a synthetic prostaglandin E1 analogue protects against peptic ulcers by reducing gastric acid secretion, increasing bicarbonate production, and boost production of gastric mucus, a natural defense against peptic ulcers. Sucralfate is a sucrose-aluminium complex that dissociates in the stomach, rapidly reacting with hydrochloric acid to form a thick, pasty substance that adheres to the gastric mucosa, especially to ulcer. By binding to the ulcer, sucralfate protects the ulcer from damaging effects of acid, pepsin and promoting healing. [106] Carbenoxolone is a derivative of glycyrrhizic acid, a constituent of liquorice. [107] It exerts minimum inhibitory effect on gastric acid secretion. [108] It inhibits pepsin activity, stimulates mucus secretion and reduces gastric epithelial cell loss. [109] Tripotassium dicitrate bismuthate is colloidal bismuth. At low pH it binds to ulcerated mucosa and forms a protective layer lasting for about 6 h. It should therefore, be given before meals and at bedtime. [110]

Table 3: Some of recommended anti-*Helicobacter* regimens

Triple antibiotics	Half life	Dose	Duration
Bismuth subcitrate	-	120mg 4 times/day	
Tetracycline	9 h	500mg 4 times/day	1 week
Metronidazole	8 h	400 mg 4 times/day	
Two antibiotics with an antisecretory agent			
Amoxicillin	1 h	500 mg 3 times/day	
Metronidazole	8 h	400 mg 3 times/day	1 week
Omeprazole	0.5-3 h	40 mg/day	
Amoxicillin	1 h	1gm 2 times/day	
Clarithomycin	3-4 h	500 mg 2 times/day	1 week
Omeprazole	0.5-3 h	20 mg 2 times/day	
Amoxicillin	1 h	750 mg 3 times/day	
Metronidazole	8 h	500 mg 3 times/day	2 weeks
Ranitidine	2-3 h	300 mg at bedtime	

TREATMENT OF *H. PYLORI*

H. pylori peptic ulcers are treated with various therapeutic agents that kill the bacteria, reduce stomach acid, and protect the stomach lining. Acid-suppressing drugs may also be used which includes H2 blockers, proton pump inhibitors etc. [111] The National Institute of Health Consensus Conference recommends combination of antimicrobial regimens for treatment of *H. pylori.* [112] In *H. pylori* related ulcers, combination of triple drug therapy have been necessary to eradicate this organism. [113] Original triple therapy, which combines bismuth subcitrate with metronidazole and tetracycline for a period of one to two weeks, is most widely used regimen for the treatment of *H. pylori* infection as depicted in Table 3. [114] Extensive efforts have been undertaken for the eradication of *H. pylori* with the administration of several drugs using dual or triple therapy. Various antimicrobial drugs employed to eradicate the bacterium, including amoxicillin, tetracycline, clarithromycin and metronidazole results in an effective treatment scheme in patients with *H. pylori* infection [115] Earlier it was a strong conviction according to Schwratz dictum that *'No acid, No ulcer'* but in future, with the continuous efforts of scientific community worldwide, it will recognize that "No *Helicobacter*, No (or very few ulcer) ulcer". [116]

Several studies have also documented a significant decrease in number and change in type of surgery starting in the mid 1970s. Multiple factors have been implicated in our changing surgical management of patients. Introduction of novel pharmacotherapy has made significant impact on the frequency and presentation of peptic ulcer disease to surgeons. [117] This trend started, however already before the H2-antagonist era, thus perhaps rather reflecting changes in the incidence or severity of the disease. [118]

FUTURE PERSPECTIVES

Despite the remarkable achievements in various management strategies, few issues associated with this disease still remain unaddressed or partially defined. Exciting opportunities along with advanced pharmacotherapeutic approaches must be developed, and the mechanism involved in regulation of gastric acid secretion and *H. pylori* pathogenicity should be elucidated more evidently which holds great potential for the treatment in the future. Furthermore, innovative research should also attempt to solve the enigma related with various factors and causes on the prevalence of this disease. Extensive experiments must be carried out to establish the mechanisms and for development of new and safe drugs with advanced therapeutic interventions. Moreover, explorations in this field have to address the different etiologies of gastric and duodenal ulcer and other acid-peptic conditions as well as attempting to cure the disease rather than simply heal the ulcer. Advanced research on various novel gastroretentive dosage forms with several new antimicrobial agents for eradication of *H. pylori* infection would lead to management of complicated ulcer cases; thereby creating an exciting revolution in treatment strategies. Understanding and further study of complete genome of the bacterium should also aid in the development of most effective genetically engineered therapeutic regimens in times to come. Such knowledge might facilitate the design of specific vaccination regimens, allowing exclusive tissue-specific targeting drug delivery. New medical and pharmaceutical developments should also be conducted in close collaboration with gastroenterologist surgeons utilizing innovative surgical approaches.

Peptic ulcers result from an imbalance between factors that maintain mucosal integrity with high concentration of acid and the proteolytic enzyme pepsin. Patients with peptic ulcer frequently have symptoms of indigestion and bowel dysfunction or acid related symptoms of pain and dyspepsia. *H. pylori* colonization of gastric mucosa is also recognized to be strongly associated with both chronic active gastritis and peptic ulcer disease. Enormous potential benefits of *H. pylori* eradication in the management of peptic ulcer disease will provide the necessary stimulus for continued research into the treatment of this infection. It is emphasized that suitable management and treatment strategies along with proper diagnosis of peptic ulcer are imperative considerations in decreasing patient morbidity and efficient eradication of the bacterium.

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