PEPTIC ULCER DISEASE: A REVIEW

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Summary

Peptic ulcer is defined as disruption of the mucosal integrity of stomach and/or duodenum leading to a local defect or excavation due to active inflammation. Most common symptom of peptic ulcer is abdominal discomfort. It occurs because of an imbalance between aggressive factors (gastric acid and pepsin) and defensive factors (gastric mucus, bicarbonate, prostaglandins). About 25 percent of patients with this disease have a serious complication such as haemorrhage, perforation, or gastric outlet obstruction. Peptic ulcer can be diagnosed either by direct visualization using an endoscope or by using contrast radiography. Various class of drugs are used in the treatment of this disease like H_2 antagonists, Proton pump inhibitors, Prostaglandin analogues, Antacids, Ulcer protectives and Anti-*H.pylori* drugs. The present review summarizes the history, symptoms, complications, types, epidemiology, pathogenesis, diagnosis and therapy of Peptic Ulcer Disease.

Keywords: Peptic ulcer, pathogenesis, diagnosis, therapy.

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Peptic Ulcer

Peptic ulcer is defined as disruption of the mucosal integrity of stomach and/or duodenum leading to a local defect or excavation due to active inflammation[1]. The word 'peptic' refers to pepsin a stomach enzyme that break down proteins. Peptic ulcer located in stomach is called gastric ulcer[2].

History of Peptic Ulcer

The existence of gastric ulceration was acknowledged by Diocles of Carystos (350 B.C.), Celsus, and Galen (131–201 A.D.). In 1910, Schwartz first quoted the dictum "No Acid, No Ulcer". In 1982, Warren and Marshall provided the first insight into an important pathogenic factor in peptic ulcer disease with the discovery of *Helicobacter pylori* (*H.pylori*)[3]. The etiopathogenesis of peptic ulcer has changed from Schwartz's dictum "No acid-No ulcer" to "No mucosal damage-No ulcer" and recently to "No *Helicobacter pylori*-No ulcer"[4]. Before 16th century, Avicenna noted the relationship between gastric pain and mealtimes. Later on Stahl (1728) hypothesized that some fevers and gastric inflammation are associated with ulcerations[5]. In 1737, Morgagni described both gastric and duodenal ulcer at autopsy. In 1761, it was hypothesized that pain is associated with stomach ulcers. G. Bottcher and M.Letulle (1875) and J.Cohnheim (1880) hypothesized that ulcers are caused by bacteria and chemical factors, respectively[6].

John Lykoudis, a general practitioner in Greece, treated patients for peptic ulcer disease with antibiotics, beginning in 1958, long before it was commonly recognized that bacteria were a dominant cause for the disease.

It was a previously widely accepted misunderstanding that the use of chewing gum resulted in gastric ulcers. The medical profession believed that this was because the action of masticating on gum caused the over-stimulation of the production of hydrochloric acid (HCl) in the stomach. The low acidity (pH 2) or hyperchlorhydria was then believed to cause erosion of the stomach lining in the absence of food, thus causing the development of the gastric ulcers[7]. On the other hand, in the recent past, some believed that natural tree resin extract, mastic gum, actively eliminates the *H.pylori* bacteria[8]. However, multiple subsequent studies have found no effect of using mastic gum on reducing *H.pylori* levels[9,10].

In the year 1959, Leiber and Lefevre published a follow up study demonstrating that antibiotics prevent the conversion of urea to ammonia in the human stomach[11]. In 1962, Susser and Stein proved that stress causes peptic ulcer disease[12]. The discovery of the compound cimetidine by researchers at the UK laboratories of Smith Kline & French in the 1970s, transformed the lives of millions of people. It was sold under the trademark Tagamet, and was the first effective anti-ulcer drug that made a revolutionary impact on treatment. It decreases acid secretion, thus promoting healing of ulcers[13].

In 1982, Warren and Marshall showed that there is a relationship between *H.pylori* and Peptic Ulcer Disease (PUD). Their paper was published in June, 1984. Many reviewers disliked the paper. In order to answer his critics, he tested on himself and consumed *H.pylori*

and became ill. He then took antibiotics and got rid of his symptoms. In 2005, Warren and Marshall were awarded the Nobel prize in physiology or medicine for their work on *H.pylori* and PUD[14].

In 1990, Rauws and Tytgat described the cure of duodenal ulcer by eradication of *H.pylori* using a triple-therapy regimen consisting of bismuth and 2 antibiotics. Triple therapy, modernized to a PPI and 2 antibiotics soon became first line therapy for eradication[15].

In 1992, Covocci *et al* sequenced the CagA gene, which encodes for a cytotoxin associated surface protein, which correlated strongly with strains of *H.pylori* that caused duodenal ulcers. It was the first description of a virulence factor for *H.pylori* infection determined by molecular techniques[16].

In 1997, the Centers for Disease Control and Prevention, with other government agencies, academic institutions, and industry, launched a national education campaign to inform health care providers and consumers about the link between *H.pylori* and ulcers. This campaign reinforced the news that ulcers are a curable infection, and that health can be greatly improved and money saved by disseminating information about *H.pylori*[17]. Later in the same year, Tomb *et al* completely sequenced the entire 16,67,867 base pair *H.pylori* genome. This assisted in identifying new virulence factors for the infectivity of *H.pylori* on the molecular level[18].

In 2001, Chan *et al* showed in a randomized control trial that eradication of *H.pylori* even prevents bleeding from ulcers that are caused by aspirin and other Non-steroidal anti-inflammatory drugs (NSAID)[19].

Symptoms

Most common symptom of peptic ulcer is abdominal discomfort. This discomfort comes and goes for several days of week, generally occurs 2 to 3 hrs after a meal, in the middle of night, when stomach is empty. Other symptoms include blood loss leading to anaemia, weight loss, poor appetite, bloating, burping, nausea and vomiting. In patients with advanced stage emergency symptoms are sharp, sudden, persistent accompanied with stomach pain, bloody or black stools, blood in vomit, etc.

Complications

About 25 percent of patients with peptic ulcer disease have a serious complication such as haemorrhage, perforation, or gastric outlet obstruction. Silent ulcers and complications are more common in older patients and in patients taking NSAID.

1. **Bleeding:** It is the most frequent complication, which occurs in 15-20% patients. It accounts for 25% ulcer deaths.
2. **Perforation:** It occurs in 5% patients. It accounts for about 67% ulcer deaths.
3. **Obstruction from edema:** It occurs in 2% patients. It most often occurs due to pyloric channel ulcers. It causes crampy abdominal pain[20,21].

Types of Peptic Ulcer

On the basis of location, peptic ulcers are categorized as follows: *Gastric Ulcer*: Occurrence of ulcer in the stomach, more commonly in older age group. *Duodenal Ulcer*: Occurrence of ulcer in the duodenum. They occur commonly in younger individuals and are evenly distributed among various socioeconomic groups. These patients have higher than normal levels of acid secretion rates. Depending on severity, peptic ulcers are classified as: *Acute Peptic Ulcer*: 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 centimetres of duodenum. *Chronic Peptic Ulcer*: 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 the duodenum[22].

Epidemiology of Peptic ulcer

Peptic ulcer used to be a rare disease before 19th century. Acute perforations of gastric ulcers were first reported in young girls in the beginning of 19th century. With the progress of 19th century, peptic ulcer disease became frequent both in men and women[23].

In the West, this disease affects equally in men and women whereas, in India, men are affected 18 times more commonly than women. In a vast, developing country like India it is impossible to obtain exact figures of disease incidence and differences are bound to exist between regions.

In India, peptic ulcer is more prevalent in Jammu and Kashmir, followed by Southern India. North India comes next, and East and North East have comparatively lower prevalence[24]. Greater prevalence of peptic ulcer in southern India over northern India may be attributed to the fact that rice is the staple food in this region[25,26].

In United States approximately 4 million people have peptic ulcers, 3,50,000 new cases diagnosed, 1,80,000 hospitalized and 5000 people die each year as a result of peptic ulcer. The lifetime likelihood for developing a peptic ulcer is about 10% for males and 4% for females. Through autopsy studies and biopsy, prevalence of 6 to 14% for men and 2 to 6% for women was found. The male to female ratio for duodenal ulcers is 3:1 and for gastric ulcers is 2:1[27]. The mortality rate for duodenal ulcer in 1962 was 3.1 per 100,000 and for gastric ulcer it was 3.5 per 100,000; these rates had decreased to about 1 per 100,000 each by 1979[28,29]. In 1998, the total mortality rate due to peptic ulcer in United States was found to be 3.47 per 100,000[27]. Gastric ulcer has a higher mortality rate than duodenal ulcer because of its prevalence in older patients[30-32].

In young Norwegians, the annual incidence of duodenal ulcer was approximately 2 in 1000 men and 0.9 in 1000 women, while for gastric ulcer the annual incidence was approximately 1.5 in 1000 men and 0.9 in 1000 women[33].

In Japan, the male-to-female ratio for peptic ulcer was 2:1, but the overall gastric ulcer rate was about 1.5 times greater than that for duodenal ulcer[34]. In USA, the prevalence of duodenal ulcer is 4 times that of gastric ulcer, while in Pakistan, it is 5 times that of gastric ulcers, while in some parts of India this ratio is 32:1[35].

H.pylori infection is a major etiologic factor of peptic ulcer. Over 90% duodenal ulcers and 70% gastric ulcers occur due to *H.pylori* infection[36,37]. There are large differences in the prevalence of infection among ethnic groups in different societies. White Americans have lower infection rates than black Americans, and Australians of southern European origin have higher infection rates than Australians of Anglo-Celtic ancestry[38].

In developing countries such as India, Peru and Thailand, exposure to *H.pylori* occurs in childhood. Sero-surveys indicate a sero-prevalence of 22-57% in children under the age of five, increasing to 80-100% by the age of 20 and thereafter it remains constant. In Peru, age specific prevalence rates rise as high as 90% in persons over 60 years of age. In Thailand, 17.5% of children 5-9 years old and 75% of individuals 30-49 years of age were infected with *H.pylori*[39-41].

In developed countries such as US, serologic evidence of *H.pylori* is uncommon before the age 10, increases to 10% in those between 18 and 30 years of age and to 50% in those older than 60 years[42]. The incidence of *H.pylori* below the age 30 is dramatically decreasing in developed countries due to improved socioeconomic conditions[43].

In northern Iran, 40% children of a school were diagnosed as *H.pylori* positive and results suggested that the source of drinking water may play a role in transmission of *H.pylori*[44].

In a study by Drumm *et al*, a specific antibody was detected in 74% of the parents and 82% of the siblings of *H.pylori*-infected children. These results suggested strong person-to-person transmission of this infective organism, which occurs via oral-oral route or fecal-oral route[45,46].

Studies from India suggest that between 75%-90% of ulcers in India heal with antibiotic therapy aimed at *H.pylori* eradication[39]. Now, PUD encompassing gastric and duodenal ulcer is the most prevalent gastrointestinal disorder. Three out of 1000 individuals have peptic ulcer every year and an estimated 15,000 deaths occur each year as a result of PUD. 20% of the ulcer episodes are associated with bleeding[47,48].

Pathogenesis of Peptic Ulcer

Peptic ulcers occur because of an imbalance between aggressive factors (gastric acid and pepsin) and defensive factors (gastric mucus, bicarbonate, Prostaglandins). Gastric ulceration occurs when mucosal defences fail, as when mucosal blood flow drops, gastric emptying is delayed, or epithelial restitution is impaired[49] (Figure 1).

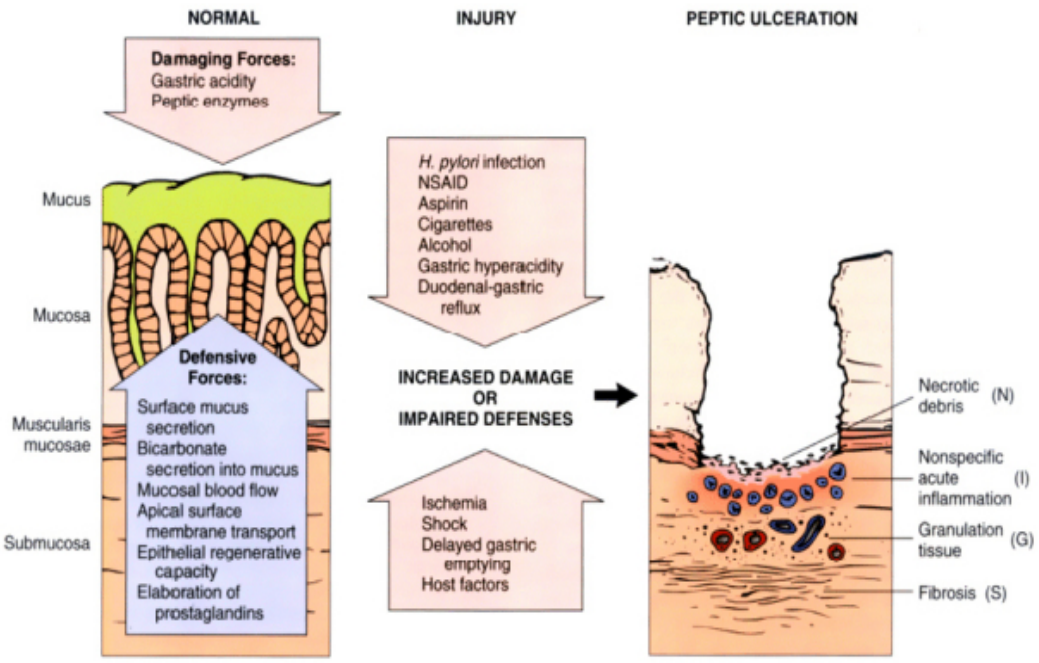

Figure 1. Role of aggressive and defences factors in the pathogenesis of peptic ulcer (Adopted from Robbin and Cotran's Pathologic Basis of Disease).

The factors that produce ulceration by aggravating gastric acid and pepsin secretion are divided into 2 categories:

a. **Endogenous factors:** These include different visceral neurotransmitters, hormones (acetylcholine, gastrin, histamine, somatostatin and cholecystokinin), second messengers (Ca^{2+}), genetic factors.
b. **Exogenous factors:** These include bacterial infection (*H.pylori*), NSAID, alcohol, psychogenic factors and dietary habits.

Endogenous Factors

1. Acetylcholine (ACh): It causes gastric acid secretion in gastric phase of acid secretion[50]. ACh exerts a considerable influence on gastric acid secretion through the direct stimulation of parietal cells, the release of gastrin from the pyloric antrum, and modifies the responsiveness of the parietal cells to gastrin and histamine[51]. It is released from vagus nerve and parasympathetic ganglion cells, which are located in gastric mucosa. It stimulates acid secretion directly by parietal cells and indirectly by stimulating release of histamine. It also stimulates secretion of pepsinogen, the inactive precursor of pepsin, which also causes peptic ulcer[52,53].

Muscarinic receptors are involved in the vagal stimulation of gastric acid secretion, mediated by ACh[54]. The muscarinic M_1 receptors appear to be more substantially involved in stress evoked gastric ulceration and mast cell degranulation. On the other hand, the muscarinic M_2 receptors may contribute to ulcer formation by increasing stomach smooth muscle motility, but not by degranulating the mast cells[55]. Muscarinic

M_3 receptors plays a significant role in ACh mediated gastrin secretion, which plays a major role in gastric acid secretion[50].

2. **Gastrin:** It is a major stimulant of acid secretion. After ingestion of food, the release of gastrin is modulated by protein content of food and accounts for acid secretory response but as the acidity of food increases or intragastric pH decreases, the gastrin secretion initiated by protein content diminishes[56]. Serum gastrin concentration in peptic ulcer patients are 120 pg/ml. Gastrenoma (Zollinger-Ellison syndrome) is a disorder which result from the oversecretion of gastrin producing adenoma of pancreas. There is a continuous stimulation of HCl secretion which cannot be turned off as with normal physiological mechanism. Fasting serum gastrin concentration in this syndrome ranges from 500 pg/ml to 7500 pg/ml. So, gastrin oversecretion is an important pathophysiologic factor for peptic ulcer development[20]. Stimuli that affect gastrin secretion are shown in Table 1.

Table 1. Summary of stimuli affecting gastrin secretion. (Adopted from Ganong)

Stimuli that increase gastrin secretion

Luminal
- Peptides and Amino acids
- Distension

Neural
- Increased vagal discharge, probably noncholinergic

Blood-borne
- Calcium
- Adrenaline

Stimuli that inhibit gastrin secretion

Luminal
- Acidic contents
- Somatostatin

Blood-borne
- Secretin, GIP, VIP, Glucagons and Calcitonin

Starvation

3. **Histamine:** It is a paracrine regulator of gastric acid secretion. It exerts its ulcerogenic effect during abnormal physiology by acting through H_2 receptors on parietal cell. It is stored in local storage site mast cells and endocrine cells. Studies on H_2 receptor antagonist suggest histamine as the final common mediator of acid secretion as these antagonists block both histamine stimulation but also block the stimulatory effect by gastrin and ACh. Release mediated by increased levels of Ca^{2+} by gastrin in the parietal cell.

4. **Somatostatin and Cholecystokinin:** Major evidence that cholecystokinin (CCK) acts as inhibitor of gastric acid secretion is that exogenous CCK infused intravenously in a physiological dose is capable of inhibiting gastric acid secretion. Both receptor subtypes CCK A and CCK B are involved in inhibition and facilitation of gastrin action respectively. On activation of CCK A receptor, somatostatin is released which act through somatostatin receptors on gastrin G cells to inhibit gastrin secretion and CCK B receptor stimulation by CCK causes increased release gastric acid. So, it can be assumed that peptic ulcer patients are deficient in response of CCK A receptor activation by endogenous CCK, resulting in deficiency of somatostatin and increased gastric acid release[57-59].

5. **Ca^{2+} as second messengers:** Ca^{2+} play an important role in pathogenesis of gastric ulcers. The administration of calcium both orally or intravenously, stimulates acid secretion and increases circulating concentration of gastrin. Cytosolic free calcium increases the effects of ACh and gastrin on stimulation of acid secretion by parietal cells[60]. Ca^{2+} also plays an important role in the release of histamine from enterochromaffin-like (ECL) cells, a powerful chemical mediator of gastric acid secretion, which involves both mobilization of an intracellular calcium pool and influx of calcium over the ECL cell membrane[61].

6. **Genetics:** Increased familial history is found in 20-50% of patients. Ulcers are also more common in blood group O subjects and in those who do not secrete blood group antibodies into gastric secretions[62].

Exogenous Factors

1. ***H.pylori*:** *H.pylori* is a curved or S-shaped gram negative bacterium approximately 0.5 by 3 μm in size containing four to seven sheathed flagella at one pole[63,64].

Mechanism of *H.pylori* Infection

The success of a pathogen depends on both its virulence and its pathogenicity. Virulence is the ability to infect a host, whereas pathogenicity is the ability to cause a disease in the host. Sufficient number of *H.pylori* must survive the gastric acid barrier and colonize the enteric fluid or mucous layer. Examples of important virulence factors are attachment mechanisms and motility in the intestinal mucous layer. Once the organism is established in the gut, pathogenic effects on the host may be produced by one or several means; examples are physical effects, elaboration of enzymes or toxins, and competition with the host for nutrients.

(i) Binding to mucus and epithelial cells: *H.pylori* have cell wall associated lectins which allow them to bind selectively to mucus and epithelial cells. Targets of *H.pylori* lectins exist in the gastric mucus as glycoproteins and glycolipids. *H.pylori* appears to bind to all of these, including sulfated (acid) mucins, L-fucose, D-galactose and sialic acids. *H.pylori* lectins also attaches to red blood cells of various animal species[65].

(ii) Tight attachment to cells: *H.pylori* attaches tightly to the epithelial cell, and a characteristic structure called an 'attachment pedestal' forms. This attachment causes localized cell damage characterized by enhancement of microvilli and disruption of cytoskeletal elements of the cell[66]. Actin polymerization also occurs below the sites of 'attachment pedestels'[67].

(iii) Elaboration of Enzymes

(a) Urease: Most common and virulence producing enzyme produced by *H.pylori* is urease. This enzyme is highly active between the pH of 5 and 8. It hydrolyses urea into ammonia. Ammonia thus generated act as a potent cellular toxin in 3 ways[68]. Firstly, it combines with α-ketoglutarate to form glutamine, thus depleting krebs cycle of an essential intermediate substrate[69]. Secondly, it interacts with hypochlorus acid to form mono-n-chloramine, which also acts as potent cellular toxin[70]. Thirdly, its toxic effect may also be mediated by neutrophil generated oxygen radicals because it is inhibited by anti-neutrophil serum[71].

Thus, urease enzyme plays an important role in virulence of *H.pylori* and its colonization in gastric mucosa. In the course of *H.pylori* infection, accumulation of phagocytic cells in the gastric mucosa occurs through two distinct mechanisms: (i) neutrophil recruitment through Interleukin (IL) 8 production which is then released by the gastric epithelial cells, and (ii) release by the bacterium itself of substances with chemotactic activity able to attract phagocytes[72,73]. These phagocytic cells ingest the microorganism and, as in the case of other pathogens, destroy it through oxygen-dependent and oxygen independent mechanisms. The release of free oxygen radicals by the neutrophils might play a role in the genesis of chronic inflammation and in the development of peptic ulcer[74].

(b) Phospholipases A_2 and C: The epithelial cell membrane consists of a phospholipid bilayer. Phospholipids are similar to triglycerides except that one of the terminal fatty acids is replaced by a phosphate group. Phospholipase A_2 of *H.pylori* removes a long-chain fatty acid group from the second carbon. It also attacks membrane phospholipids to liberate arachidonic acid which may then be converted to leukotriene, prostaglandin or thromboxane. These compounds are known to cause mucus release, chemotaxis of inflammatory cells and altered membrane permeability. Phospholipase C removes the phosphate group from the third carbon of the phospholipids. The resultant compounds, diacyl glyceride and particularly lysolecithin, are incapable of forming the normal phospholipid bilayers and may form micellar structures instead, potentially affecting the integrity of the epithelial cell membrane[75].

(iv) Production of Toxins: *H.pylori* also produces certain chemotoxins, known as vacuolating cytotoxin (VacA) which directly act on epithelial cell surface and damage the defence system[76]. This toxin causes cell injury (characterized by vacuole formation) *in vitro* and gastric tissue damage *in vivo*[49]. VacA renders the cell membrane permeable to urea by causing formation of transmembrane pores, suggesting it can increase *H.pylori* pathogenicity by enhancing urease activity[77]. Thus, VacA plays an important role in pathogenesis of peptic ulcer.

2. Non-steroidal Antiinflammatory Drugs (NSAID): NSAID use has been associated with development of gastric ulcers and with the major complications of ulcers i.e. gastrointestinal bleeding, perforation and can even lead to death[78,79]. The clinically important effects of NSAID – the production of ulcers with an increased risk of significant complications appear to be caused by their systemic actions[80]. NSAID reduce tissue levels of prostaglandins, especially PGE_1, PGE_2 and PGI_2, by inhibiting COX-1, which is the most important mechanism of action. By inhibition of prostaglandin synthesis, NSAID interfere with following lines of mucosal defence[81]:

1. Mucous cell secretion of mucin and surface active phospholipid.
   Both PGE and PGF induce the secretion of polysaccharide material in the stomach known as mucin, which acts as a protective agent against potential stomach ulceration induced by HCl and pepsin. This implies that NSAID cause gastric ulcers by inhibiting the secretion of this cytoprotective substance[82].
2. Basal bicarbonate secretion from gastric mucosa[83].
3. Mucosal proliferation necessary for ulcer healing[84].
4. Regulation of mucosal blood flow[85].
5. Physiological regulation of gastric acid secretion via feedback inhibition[86].

NSAID may also cause ulceration by generation of oxygen derived free radicals and products of the lipooxygenase pathway[87]. This can be explained as follows. COX inhibition by NSAID results in diversion of arachidonic acid metabolism towards lipooxygenase pathway, resulting in increased leukotriene synthesis. These leukotrienes can contribute to gastrointestinal ulceration, by two mechanisms, firstly, by a reduction in prostaglandin level and secondly, through the release of oxygen radicals mediated mucosal injury produced in this pathway[88].

3. Ethanol: Ethanol damage to the gastrointestinal mucosa starts with micro-vascular injury, namely disruption of the vascular endothelium resulting in increased vascular permeability, oedema formation and epithelial lifting. These effects are secondary to ethanol induced slowing or cessation of gastric mucosal flow. Alcohol causes the stomach cells to oversecrete both acid and histamine which make the stomach linings vulnerable to ulcer formation. Ethanol also reduces prostaglandin levels, increases the release of histamine and influx of calcium ions. Ethanol also produces a marked contraction of the circular muscles of fundic strip. Such a contraction can lead to mucosal compression at the site of the greatest mechanical stress, at the crests of mucosal folds leading to necrosis and ulceration. This reduces the secretion of bicarbonates and production of mucus and also leads to increased neutrophil infilteration into the gastric mucosa. These neutrophils adheres to endothelial cells, thereby blocking capillaries and induce damage to the endothelial cells through the release of proteases, leukotriene (LTC_4) and oxygen free radicals[89-91]. These oxygen free radicals also cause increased lipid peroxidation which causes damage to cell and cell membranes, thereby playing a major role in pathogenesis of acute mucosal injury induced by ethanol[92]. Ethanol promotes oxygen radical attack on proteins at the lipophilic side chain of amino acids[93]. Evidence for role of oxygen free radicals in the pathogenesis of ethanol induced mucosal injury is supported by the fact that administration of antioxidants reduced the ethanol-induced gastric injury in rat[94].

4. Cigarette Smoking: Continued smoking with advancing age augments the secretion of HCl and pepsin and is also expected to modify the contents of gastric juice and pepsin isoenzyme patterns. The increased gastric acid secretion is mediated through the stimulation of H_2-receptor by histamine released after mast cell degranulation and due to the increase of the functional parietal cell volume or secretory capacity in smokers. Smoking causes mucosal injury by increasing content of free oxygen radicals, PAF, pituitary vasopressin, gastric endothelin and pituitary vasopressin. Smoking and nicotine stimulate pepsinogen secretion also by increasing chief cell number or with an enhancement of their secretory capacity. Long-term nicotine treatment in rats also significantly decreases total mucus neck cell population and neck-cell mucus volume. Bile salt reflux rate and gastric bile salt concentration are increased thereby increasing duodenogastric reflux that raises the risk of gastric ulcer in smokers. Smoking and nicotine not only induce ulceration, but they also potentiate ulceration caused by *H.pylori*, alcohol, NSAID or cold restrain stress. Smoking also alter processes important in gastric and duodenal mucosal integrity or protection such as mucosal bicarbonate secretion, prostaglandin content, mucosal blood flow, or epidermal growth factor[95,96].

5. Diet: All foods are capable of stimulating gastric acid secretion through distention of the stomach, but proteins are the major stimulants. Digested protein in the form of peptides, peptones, and amino acids act primarily through the stimulation of gastrin from antral G cells. The aromatic amino acids are the most potent of the amino acids. Amino acids absorbed into the circulation stimulates acid secretion by directly stimulating parietal cells or via gastrin release in humans. Caffeinated beverages (eg. tea, coffee), cola type beverages, beer and milk are potent stimulants of gastric acid secretion. Coffee produces acid output equal to 70 percent of peak acid output as compared to pentagastrin. 5% aqueous tea and coffee beverages act by decreasing PGI_2 synthesis. A low fiber diet, high dietary consumption of salt and red/black peppers also causes peptic ulcer[97-99].

6. Psychological Factor (Stress Ulcers): There is considerable evidence that supports the role of stressful life events in the aetiology of PUD. Stress induced ulcers are due to increase in free radical generation apart from acid pepsin factors[100]. Stress causes increase in gastric motility, vagal over activity, mast cell degeneration, reduces gastric mucosal blood flow. Stress may also produce ulceration by release of histamine with enhanced acid secretion and reduced mucous production[99]. Cold restrained stress induced ulcers are result of auto digestion of gastric mucosal barrier, accumulation of HCl and generation of free radicals[101].

Diagnosis

Peptic ulcer can be diagnosed either by direct visualization using an endoscope or by using contrast radiography.

Endoscopy: Endoscopy is the preferred diagnostic test in most cases because of its superior sensitivity and specificity for significant organic disease and the ability to obtain biopsies. It is particularly helpful in identifying lesions too small to be detected by radiographic examination. It is recommended in patients with over 50 years of age. With modern wide-angle endoscopic television chip and endoscopic instruments, visualization of the stomach and duodenum should be complete in almost all patients.

Radiology: A double contrast barium study is a radiological technique which can easily detect ulcers both in the stomach and duodenum, but it is only used where endoscopy is either technically difficult or where the patient prefers it to endoscopy. It is indicated when endoscopy is unsuitable or not feasible or complications such as gastric outlet obstruction is present.

Since, these endoscopic and radiographic procedures are highly expensive, attempts have been made to develop a surrogate marker for ulcer diagnosis, such as the response to an empirical trial with antisecretory agents or the evaluation of *H.pylori* status with serologic markers[23,102] (Table 2).

Table 2. Diagnosis of *H.pylori* (Adopted from Harrison's Principle of Internal Medicine).

Test	Description	Comments
Invasive (Endoscopic/Biopsy Required)		
Culture	Culture of Biopsy	100% specific, time consuming, expensive, requires experience, allows determination of antibiotic susceptibility results are not immediate, not recommended for initial diagnosis; antibiotics, bismuth, and PPIs may cause false negative results
Histology	Microbiological examination using various stains	> 95% sensitive & specific, Requires pathologic processing and staining; provides histologic information, results are not immediate, not recommended for initial diagnosis; antibiotics, bismuth, and PPIs may cause false negative results
Rapid urease	HP urease generates ammonia, which causes a color change	Test of choice at endoscopy,> 90% sensitive & specific, easily performed, rapid results(within 24 hrs); antibiotics, bismuth, and PPIs may cause false negative results
Noninvasive (Nonendoscopic tests)		
Antibody detection(laboratory based)	Detects antibodies to *H.pylori* in serum	Quantitative, less sensitive, Inexpensive, convenient, not useful for early follow up.

Urea breath test	HP urease breaks down ingested labelled C-urea, patient exhales labelled CO_2	95% sensitive and specific, tests for active HP infection, results take about 2 days, false negatives with antibiotics, bismuth, PPIs; may be used posttreatment to confirm eradication
Stool antigen test	Identifies HP antigen in stool, leading to color change that can be detected visually or by spectrophotometer	Inexpensive, convenient; tests for active HP infection, sensitivity and specificity same as urea breath test when used for initial diagnosis, false negative results to lesser extent than with the urea breath test, may be used posttreatment to confirm eradication.

HP = *H.pylori*

A. Endoscopic Tests

The critical role of endoscopy for the diagnosis of *H.pylori* is to obtain gastric mucosal biopsies that are used for both direct tests (culture and histology) and indirect tests (urease testing). The biopsy based tests are dependent on the actual bacterial load and identify only patients with active *H.pylori* infection. Medications that affect the density or viability of *H.pylori* organisms within the stomach decrease the sensitivity of these tests by increasing the possibility of sampling error. Therefore, bismuth compounds and antibiotics should be withheld for 4 weeks, and PPIs should be withheld for 1 to 2 weeks before endoscopic *H.pylori* testing.

1. **Culture:** Culture has the advantage of allowing for the determination of antibiotic sensitivity. Stuart medium or glycerol containing media will be more appropriate if culture is to be kept for long time. The later one is useful for storage of biopsy specimens at -70˚C.

   Various selective and nonselective media are suitable for culture, such as brain-heart infusion agar plates with other supplements and media used for *Campylobacter*. Culture intubation is performed under microaerophilic conditions at 37˚C, with positive cultures usually detected after 3 to 5 days. Identification of *H.pylori* is made on the basis of colony morphology that contain gram-negative, curved rods that test positive for urease, catalase and, oxidase[103,104].

2. **Histological assessment:** This is done using a variety of histological stains. Multiple biopsies should be obtained to achieve 100% sensitivity and specificity. Haematoxylin and Eosin are the commonly used stains. Although *H.pylori* is readily seen on hematoxylin and eosin (HE) stained slides of biopsy specimens, for better identification of the organism, special staining methods have been used, such as Warthin-Starry, Giemsa and Steiner silver stain, Genta stain, toluidine blue stain, carbol fuchsin stain, Modified Mcmullen's method, HpSS, methylene blue, modified Geimsa and immunohistochemical staining method. Among these, Geimsa stain is the method of choice. However, Methylene blue staining can be substituted for Giemsa stain to

visualize *H.pylori*. Fluorescence in situ hybridization is a complementary technique to histology, which is used to detect the presence of *H.pylori*[105,106].

3. **Rapid urease tests:** The CLOtest was the first of the commercially available biopsy urease tests designed for *H.pylori* detection. *H.pylori* urease hydrolyzes the urea contained in the agar gel of the test packet and leads to production of ammonia, pH rise and a color change of the phenol red indicator. The test is interpreted up to 24 hours after insertion of the gastric biopsy sample into the well containing the agar gel. Specificity of the CLOtest is uniformly excellent (95% to 100%), but when read at 24 hours, false positive results may be encountered. **Hpfast** is another gel test, similar to the CLO test, but it uses a different pH indicator. It is interpreted up to 24 hours. **PyloriTek** is a strip test. In the presence of urease, ammonia is produced from urea impregnated into a reaction strip. An overlying pH indicator detects the diffusion of ammonia through a membrane. A potential advantage of this test is that interpretation may be performed only 1 hour after tissue inoculation. Simultaneous studies of the three tests have been performed, and the results have been comparable[107,108].

4. **Polymerase chain reaction (PCR):** PCR assays, which have been shown to be sensitive and specific, have been developed for the detection of *H.pylori* in gastric mucosal biopsies. However, the diverse genetic organization of *H.pylori* may affect the sensitivity of the assay. Currently, PCR assays should be restricted to the research setting for identification of different *H.pylori* strains.

Nonendoscopic Tests

1. **Antibody test:** Antibody tests both under diagnose (false negative results) and over diagnose (false positive results) *H.pylori* infection with some frequency. Antibody testing offers numerous advantages: it is non-invasive, relatively inexpensive, and overcomes some of the limitations that identify patients with active infection such as urea breath test or stool antigen test. Ingested bismuth compounds, PPIs, or antibiotics do not cause false negative serologic test results[109]. In addition to laboratory antibody tests, rapid qualitative antibody tests (in-office or near patient tests) using either serum or finger stick whole blood are commercially available. They are inexpensive, results are available in 5 to 15 minutes and they are simple to use[110].

2. **Urea breath test:** The urea breath test (UBT) is one of the most important non-invasive methods for detecting *H.pylori* infection. The examination is simple, innocuous when ^{13}C is used, easy to repeat, highly accurate, and requires a low number of precautions in order to obtain reliable results[111]. The diagnostic accuracy of UBT is >95%[112].

Patients ingest ^{13}C or ^{14}C-labelled urea. If *H.pylori* is present in the stomach, urease hydrolyzes the labelled urea and releases labelled HCO_3^-, which is transported by the bloodstream to the lungs and is exhaled as labelled carbon dioxide. Breath or blood is collected, and either the radioactive ^{14}C isotype is detected using a scintillation counter or mass spectroscopy or infrared spectroscopy is used to detect nonradioactive ^{13}C[111]. The performance characteristics of both the ^{13}C and ^{14}C tests are similar. False negative results can occur in patients taking certain drugs, such as PPIs, that decrease the density of *H.pylori* organisms or its metabolic activity[113].

3. **Stool antigen test:** The stool antigen test is considered as a valuable non-invasive alternative to diagnose *H.pylori* when UBT is not available. This test identifies *H.pylori* antigens in stool. This test utilizes polyclonal anti-*H.pylori* capture antibody adsorbed to microwells. Diluted stool and a peroxidase conjugated polyclonal antibody are added, followed by substrate 1 hour later. In infected patients, enzyme-substrate binding leads to a color change, which can be detected visually or spectrophotometrically. After collection, stool samples can be stored at 2 to 8˚C for 3 days and at -20˚C indefinitely[114]. Sensitivity and specificity for the faecal antigen test is more than 90%[115]. The sensitivity of the stool test is decreased by the recent use of antibiotics, bismuth or PPIs[116].

Therapy for Peptic Ulcer

Overall treatment is aimed at relieving ulcer pain, healing the ulcer, preventing ulcer recurrence, and reducing ulcer-related complications. Over 99% of peptic ulcers are caused by infection with the bacterium *H.pylori* or by use of NSAID. The goal of therapy in *H.pylori*-positive ulcer patients is to eradicate this bacterium. Successful eradication heals ulcers and reduces risk of recurrence to less than 10% at 1 year. The goal of therapy in a patient with 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 cotherapy to reduce ulcer risk and ulcer related complications. PPIs, H_2RAs, and sucralfate are used to heal *H.pylori*-negative NSAID-induced ulcers. Prophylactic cotherapy with a PPI or misoprostol is used to decrease the risk of an ulcer and upper GI complications in patients taking nonselective NSAID[109,117].

Non Pharmacological Treatment of PUD

- Identify and instruct patients to avoid foods that cause excess HCl secretion; doing so improves symptoms for some individuals.
- Educate patients that avoidance of alcohol and caffeine improves symptoms and increases healing of a pre-existing ulcer.
- Fiber rich diet can reduce the risk of developing an ulcer and can also speed the recovery if it already exists.
- Flavonoid rich foods like apples, celery, cranberries, onions, garlic and tea may inhibit the growth of *H.pylori*.
- Discontinue, reduce NSAID ingestion or switch to selective COX-2 inhibitor therapy; this often relieves symptoms in mild cases.
- Strongly urge individuals who smoke to quit because tobacco both irritates the gut and delays healing.
- Stress management with relaxation techniques such as yoga, or sedatives can be used to relieve psychological influences.

Pharmacological Treatment of PUD

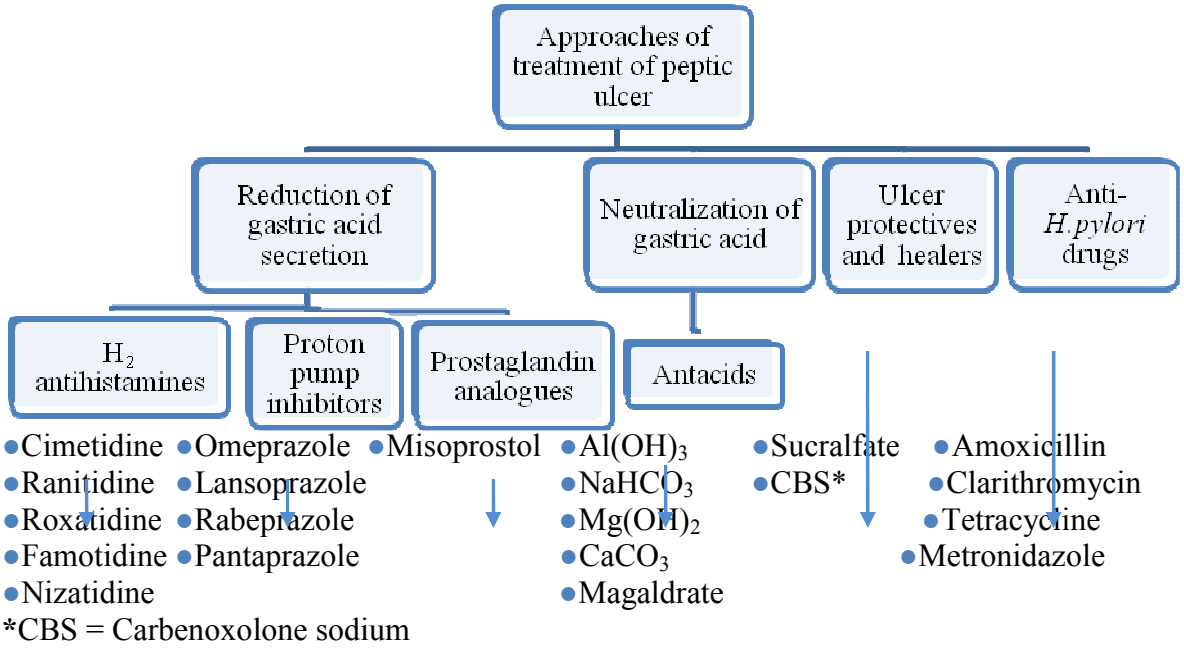

Figure 2. Classification of various class of drugs used in the treatment of Peptic ulcer (Adopted from Tripathi KD. Essentials of Medical Pharmacology).

Mechanism of Action

1. **H_2 antagonists:** They exhibit competitive inhibition at the parietal cell H_2 receptor. The volume of gastric secretion and concentration of pepsin are also reduced. H_2 antihistamines reduce acid secretion stimulated by histamine as well as by gastrin and cholinomimetic agents through two mechanisms:

   - Histamine release from ECL cells by gastrin or vagal stimulation is blocked by binding to the parietal cell H_2 receptor.
   - Direct stimulation of the parietal cells by gastrin or ACh results in diminished acid secretion in the presence of H_2 receptor blockade. It appears that reduced parietal cell cAMP levels attenuate the intracellular activation of protein kinases by gastrin and ACh[117].

2. **Proton pump inhibitors:** PPIs act by inhibiting the action of H^+K^+-ATPase, an enzyme that occurs almost exclusively in the gastric parietal cell. The enzyme catalyses the exchange of protons (H^+) for potassium ions at the cell membrane, i.e. the final step in the acid secretory process, sometimes called the proton pump. Therefore they antagonise all stimulants of gastric secretion[118].

3. **Anticholinergics:** Antimuscarinic drugs inhibit the basal and maximum gastric acid secretion by upto 40%. It prolongs the gastric emptying time, which increase the stay of an antacid in the stomach and increases its effectiveness[119]. The ACh receptor on the parietal cell itself is of the M_3 subtype, and these drugs are believed to suppress neural stimulation of acid production *via* actions on M_1 receptors of intramural ganglia. Because

of their relatively poor efficacy, significant and undesirable anticholinergic side effects, and risk of blood disorders (pirenzepine), they rarely are used today[120].

4. **Prostaglandin analogues:** Misoprostol has both acid inhibitory and mucosal protective properties. They enhance mucous bicarbonate secretion, stimulate mucosal blood flow, and decrease mucosal cell turnover. In addition, it binds to a prostaglandin receptor on parietal receptor, reducing histamine stimulated cAMP production and causing modest acid inhibition[117].

5. **Antacids:** These are basic substances which neutralize gastric acid and raise pH of gastric contents to > 4. Peptic activity is indirectly reduced if the pH rises above 4, because pepsin is secreted as a complex with an inhibitory terminal moiety that dissociates below pH 5; optimum peptic activity is exerted between pH 2 to 4[57]. They also increase tone of oesophageal sphincter and reduce the reflux of the acid and gastric contents in to the oesophagus. Hence, they are also useful in the treatment of gastroesophageal reflux disease (GERD)[118].

6. **Ulcer protectives:** Sucralfate is a complex sucrose salt in which hydroxyl groups have been substituted by aluminium hydroxide and sulphate. Sucralfate may act by 2 mechanisms:

   - In the gastric environment, aluminium hydroxide dissociates, leaving the polar sulphate anion, which can bind to positively charged tissue proteins found within the ulcer bed, and providing a physicochemical barrier impeding further tissue injury by acid and pepsin.
   - It may induce a trophic effect by binding growth factors such as EGF, enhance prostaglandin synthesis, stimulate mucous and bicarbonate secretion, and mucosal defence and repair[1].

7. **Ulcer healers:** Carbenoxolone sodium (CBS) is derived from liquorice, and is a synthetic derivative of glycyrrhizinic acid. It can be used orally for the treatment of gastric ulcers because it acts as cytoprotective and promotes healing[121]. It acts by stimulating mucus secretion which protects ulcer site from gastric acid. But, it has aldosterone like side effects with fluid retention and hypokalemia, making it an undesirable therapeutic option[122] (Figure 2).

8. **Anti *H.pylori* drugs:** Antimicrobial agents that are clinically effective against *H.pylori* are: amoxicillin, clarithromycin, tetracycline and metronidazole. However, any single drug is relatively ineffective because resistance develops rapidly, especially to metronidazole. Earlier, bismuth was used in the combination regimens for eradication of *H.pylori* but due to poor patient acceptability is infrequently used now. In 1994, NIH Consensus Development Conference on *H.pylori* concluded that ulcer patients with *H.pylori* infection require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation with the illness or on recurrence[123].

   (i) Triple therapy: A number of 3-drug regimens of 1 or 2 weeks duration have been tested reporting 60-96% eradication. However, the 2 week treatment is considered

more appropriate, because higher relapse rate after one week regimen indicates incomplete eradication leading to recrudescence.

(ii) Quadruple therapy: A 4 drug regimen consisting of PPI, metronidazole, tetracycline, and bismuth subcitrate has been reported to be highly efficacious against metronidazole resistant strains[124].

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