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PEPTIC ULCER: A REVIEW ON ITS ETIOLOGY, PATHOGENESIS AND PHARMACOTHERAPY

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ABSTRACT

A peptic ulcer is a sore on the coating of the stomach or duodenum. The two most regular sorts of peptic ulcer are designated "gastric ulcers" and "duodenal ulcers". Peptic ulcers are seen as because of a lopsidedness between forceful factors, for example, hydrochloric corrosive (HCL), pepsin, refluxed bile, leukotrienes (LTs), responsive oxygen species (ROS) and cautious components, which incorporate the capacity of the bodily fluid bicarbonate obstruction, prostaglandins (PGs), mucosal blood stream, cell restoration and movement, nonenzymatic and enzymatic cancer prevention agents and some development factors. H. pylori contamination and the utilization of nonsteroidal mitigating drugs (NSAIDs) are the dominating reasons for peptic ulcer ailment. Likewise, a quantities of variables are embroiled in the pathogenesis of gastric ulcer, among which main considerations included are bacterial contamination (Helicobacter pylori), certain drugs (NSAID), synthetics (Hcl/ethanol), gastric malignant growth and minor elements are pressure, smoking, fiery nourishment and dietary insufficiencies. The thought behind treating ulcers is to bring down the measure of corrosive that your stomach makes, to kill the corrosive that is made and to ensure the harmed zone so it can have the opportunity to recuperate. The principle point of this survey article needs to condense the ulcerogenic instruments of different middle people, pharmacotherapy associated with Peptic ulcer malady.

KEYWORDS: Peptic Ulcer, Types, Pathogenesis, Mediators and Pharmacotherapy.

INTRODUCTION

Ulcers are heterogeneous group of ulcerative disorder involving in upper gastrointestinal tract. An ulcer is a sore, means which cause pain or distress. Peptic Ulcer Disease (PUD) is the erosion of stomach or duodenum lining (lining consists of gastric acid secreting cells and mucosa which protect stomach cells from gastric secretions) that extends through the muscularis mucosa. PUD is mainly of 2 types (i) Gastric ulcer (ii) Duodenal ulcer.[1]

However, any disturbance between aggressive and protective factors may result in the mucosal injury and may lead to PUD.[2] 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, leading to an interruption in the mucosal integrity.[3]

Hence 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.[4] Various factors are implicated that play a pivotal role in the pathogenesis of ulcertions like, sedentary life style, alcohol intake, spicy food, drugs and various bacterial infections. Moreover, several endogenous substances have been identified and are reported to be involved in the production of gastrointestinal lesions in animals. The more important ones include some of the bacterial infection, various drugs and chemicals, gastric secretion, lipid metabolites, neuropeptides, inflammatory mediators and reactive free radicals. Oxidative stress has emerged as one of the major pathogenic factors in progression of ulcer that directly impaired the cellular functions and promotes cellular organelles damage in the cells, including mitochondria, lysosomes, and nucleus. Also, NO is accepted as vital mediator of GIT mucosal defense as decreased NO generation or synthesis contribute to the pathogenesis of ulceration.

Peptic ulcer is a broad term which includes ulcers of digestive tract in the stomach or the duodenum. Earlier it was believed that one developed this type of ulcers due to stress and spicy food. However, recent research has shown that these are just the aggravating factors. The causative agent is infection caused by the bacteria H. pylori or reaction to certain medicines like non-steroidal anti-inflammatory drugs (NSAIDs). Symptoms of peptic ulcers include abdominal discomfort and pain. Other symptoms include weight loss, poor appetite, bloating, nausea, and vomiting. Some may also experience blood in stool and vomit, and black stools that indicate gastrointestinal bleeding. The present study summarizes the

ulcerogenic mechanisms of these substances and the enable us to understand better the etiology of peptic ulcer.[5]

EPIDEMIOLOGY

Approximately 10% of Americans develop chronic PUD during their lifetime. The incidence varies with ulcer type, age, gender, and geographic location. Race, occupation, genetic predisposition, and societal factors may play a minor role in ulcer pathogenesis but are attenuated by the importance of HP infection and NSAID use. The prevalence of PUD in the United States has shifted from predominance in men to nearly comparable prevalence in men and women. Recent trends suggest a declining rate for younger men and an increasing rate for older women. Factors that have influenced these trends include the declining smoking rates in younger men and the increased use of NSAIDs in older adults. Since 1960, ulcer-related physician visits, hospitalizations, operations, 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.[6] Although the overall mortality from PUD has decreased; death rates have increased in patient older 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 individuals. Despite these trends remains one of the most common GI diseases, resulting in impaired quality of life, work loss, and high-cost medical care. To date, H2-receptor antagonists (H2RAs), proton pump inhibitors (PPIs), and drugs that promote mucosal defense have not altered PUD complication rates. Figure 1 represents the anatomical structure of the stomach regions.

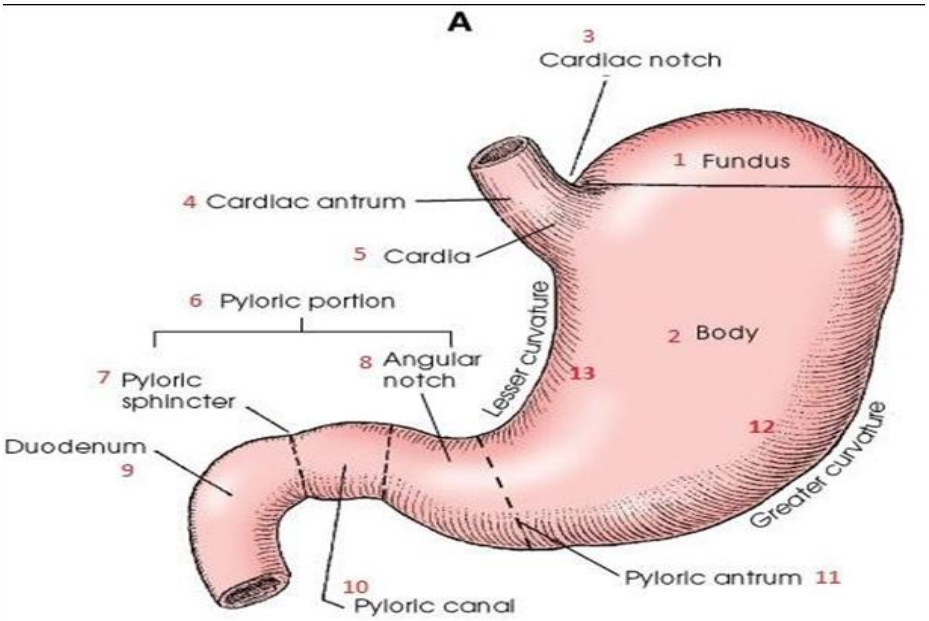

Figure 1: Anatomical structure of the stomach regions.

ETIOLOGY AND RISK FACTORS

Most peptic ulcers occur in the presence of acid and pepsin when HP (*Helicobacter pylori)*, NSAIDs, or other factors (Table 1) disrupt normal mucosal defense and healing mechanisms. Hypersecretion of acid is the primary pathogenic mechanism in hypersecretory states such as ZES. Ulcer location is related to a number of etiologic factors. Benign gastric ulcers can occur anywhere in 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 (duodenal bbulb.[7]

Table 1: Potential causes of peptic ulcer.[7]

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 has been reported to be implicated in various gastrointestinal diseases, such as gastritis, gastric and duodenal ulcer, gastric adenocarcinoma and lymphoproliferative disorders.[8] The eradication of this organism has been found to be of great importance to minimize the complications of peptic ulcers. So, it is indisputable that *Helicobacter pylori* infection is one of the most important etiologic factor for gastroduodenal ulcer and it's discovery changed the management of patients with peptic ulcer disease.[9]

Helicobacter pylori exclusively colonizes gastric type epithelium, where it lives within or beneath the gastric mucus layer and renders the underlying mucosa more vulnerable to acid peptic damage by disrupting the mucus layer, attach to the gastric epithelium, release enzymes and toxins.[10] Finally, the host immune response to *Helicobacter pylori* with inflammatory reaction further contributes to the tissue damage.[11]

More than half of the world's population has a chronic Helicobacter pylori infection of the gastroduodenal mucosa, but only 10-15% develops ulcers. *Helicobacter pylori* can be found in 80-95% patients with duodenal ulcer, moreover eradication of *Helicobacter pylori* prevents recurrence of duodenal ulcer. Factors that determine whether the infection will lead to the disease can be observed as a complex interaction between the host and the bacterium and depend of the immunopathogenesis, pattern of histological changes, gastritis induced changes in homeostasis of gastric hormones and acid secretion, genetic factors, ulcerogenic strains, gastric metaplasia in the duodenum, interaction with the mucosal barrier.

Helicobacter pylori attaches to the gastric type epithelium with outer membrane proteins that may lead to autoimmune response cell apoptosis and tissue damage.[10]

Production of different enzymes such as urease, catalase and phospholipase can directly or indirectly damage tissue. In addition, proteolytic enzyme activity degrades mucus and makes tissue more susceptible to damage.[12]

Different strains of *Helicobacter pylori* with virulence factors, especially CagA and VacA are connected to more profound tissue inflammation, cytokine production and tissue damage. Namely, CagA+ strains can be found in 80-100% of patients with duodenal ulcer.[13]

Helicobacter pylori with it's antigenic substances induces inflammatory and immune response in gastric mucosa with polymorphonuclear leukocytes, lymphocytes, monocytes and

plasma cells infiltration. Inflammatory cells further induce release of pro-inflammatory cytokines such as interleukin IL-1, IL-6, IL-8 and necrosis factor – alpha (TNF-α) that hampers mucosal defense and stimulates the immunopathogenetic process of ulcer. In addition, immune response to *Helicobacter pylori* infection with locally and systematically production of antibodies (IgG and IgA) also contributes to tissue damage (Figure 2).[14] This inflammation resolves after eradication of the infection, and presumably the concentrations of the pro-inflammatory and antisecretory cytokines also fall.

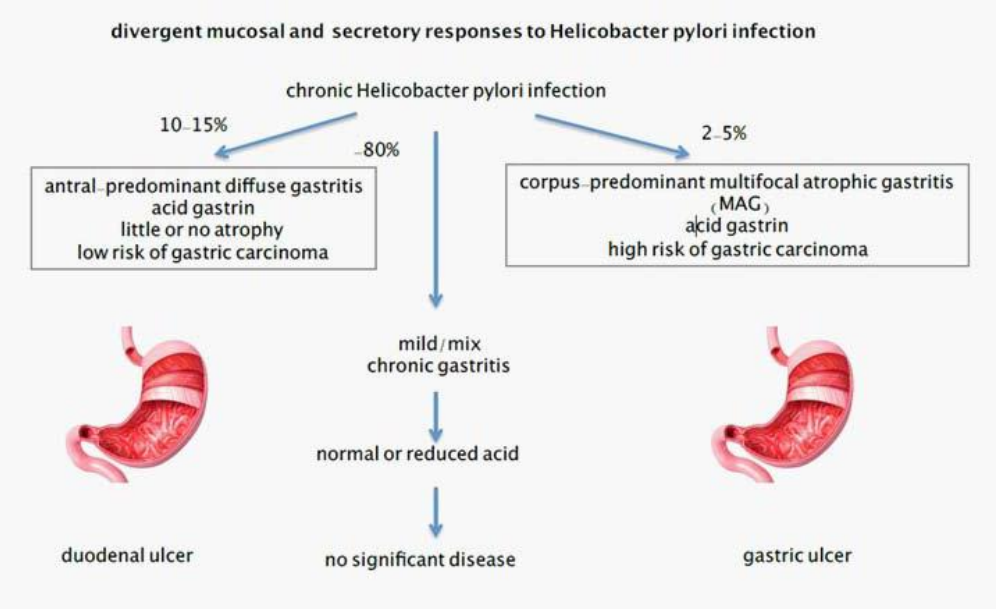

Figure 2: Helicobacter pylori induced antrum dependent gastritis with hyperchlorohydria caused by hypergastrinemia with subsequent duodenal ulcer and corpus dependent atrophic gastritis that may result in gastric ulceration.[15]

This is supported by studies which have found that gastric metaplasia increases fivefold the relative risk for ulceration, and when Helicobacter pylori present within metaplastic tissue, the risk for ulceration is 50-fold increased.[17]

Non-steroidal anti-inflammatory drugs

Although adverse effects of NSAIDs occur in only a small proportion of users, the widespread use of these drugs has resulted in a substantial overall number of affected persons who experience serious gastrointestinal complications.[18] Prevalence of peptic ulcer disease in patients receiving NSAIDs therapy ranges between 10 and 30%, what is 10- to 30-fold increase over that found in the general population. One out of 175 users of NSAIDs in the USA will be hospitalized each year for NSAIDs-induced gastrointestinal damage.

NSAIDs can cause damage to the gastroduodenal mucosa via several mechanisms, including the topical irritant effect on the epithelium, impairment of the mucosa, suppression of gastric prostaglandin synthesis, reduction of gastric mucosal blood flow and interference with the repair of superficial injury (Figure 3). Prostaglandins are important for mucosal integrity. Cyclo-oxygenase (COX 1 and COX 2) inhibition, more so of COX 2 is supposed to cause gastric ulcer. Neutrophil liberate oxygen free radicals, release proteases and reduce capillary blood flow thus damaging gastric mucosa. NSAIDs inhibit nitric oxide (NO) and hydrogen sulphide (H_2S) whose role is to maintain integrity of gastric mucosa. For these reasons, NSAIDs are still more dangerous due to the higher base-line risk of ulcer complications. In support of this argument, the size of risk for ulcer complications in patients who have a suitability for ulceration rises to approximately 12-fold when compared to patients unexposed to NSAIDs and with no ulcer history.[19]

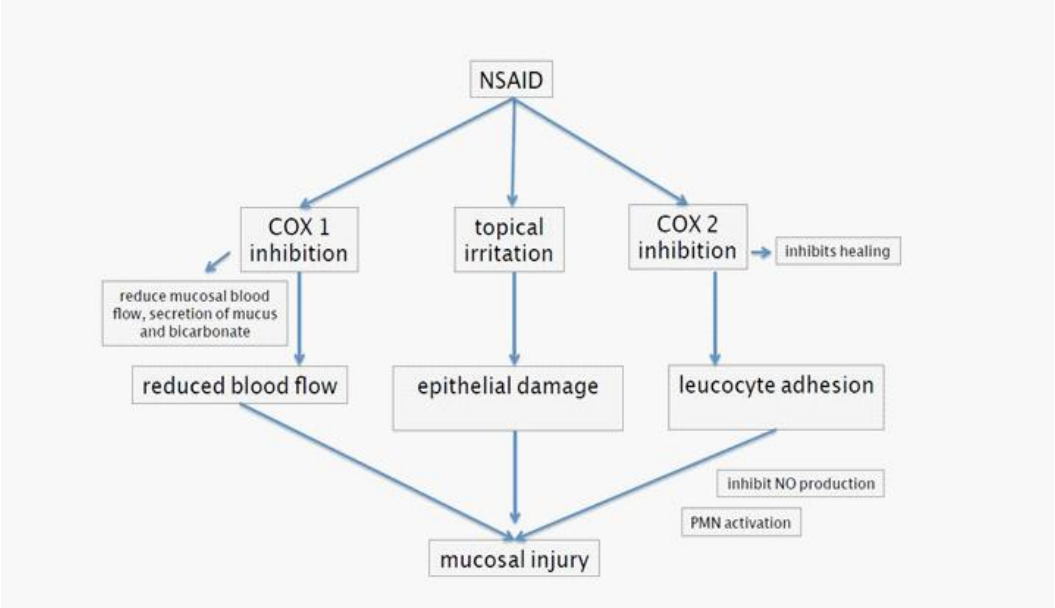

Figure 3: Nonsteroidal antiinflammatory drugs induced mucosal injury.

The presence of acid in the lumen of the stomach also contributes to the pathogenesis of NSAIDs-induced ulcers, by impairing the restitution process, interfering with haemostasis and inactivating several growth factors that are important in mucosal defense and repair. So, the prevention of NSAIDs- related gastropathy is an important clinical issue, and therapeutic strategies for both the primary and secondary prevention of adverse events are continually evolving.[20] Furthermore, NSAIDs-induced gastropathy is an intricate process involving gastric mucus depletion, increased microvascular permeability, nitric oxide imbalance, as well as free radical production.[21]

Use of proton pump inhibitors (PPI) has long been suggested to reduce the incidence of serious gastrointestinal complications during NSAIDs use. Furthermore, use of PPIs was associated with a significant reduction in the risk of ulcer in both acute and chronic users of NSAIDs.[22]

Aspirin is one of the most popular drug. At high doses in the acidic environment of gastric juice become un-ionized and freely penetrate the mucosal barrier reaching to gastric wall. Due to the weak basic nature of cytoplasm of gastric mucosal cells, aspirin could accumulate at high concentrations into mucosal cells, and yields a negatively charged anion that is unable to exit the cell. Thus, superficial or deeper erosions are produced. The combination of low-dose aspirin for cardiovascular protection, plus a PPI for gastroprotection, resulted in a low rate of ulcer bleeding.[23]

Risk factors for uncomplicated PUD of patients newly initiated on low-dose aspirin for secondary prevention of cardiovascular events include: previous history of peptic ulcer disease; current use of NSAIDs, oral steroid agents, or acid suppressive agents, tobacco use, stress, depression, anemia and social deprivation.[24]

Genetic factors

A number of observations have suggested that genetic factors predispose to development of gastric ulcer disease. The concordance for peptic ulcer among identical twins has been found to be higher than for monozygotic twins, and first-degree relatives of ulcer patients have been shown to be at high risk for developing peptic ulcer. The familial aggregation of both duodenal and gastric ulcer appear distinct: threefold increase in the prevalence of duodenal ulcer in first-degree relatives of patients with duodenal but not gastric ulcer and relatives of patients with gastric ulcer have a threefold increase in the prevalence of gastric but not duodenal ulcer. The genes responsible for this ulcer predisposition are not known.

Lifestyle factors

Evidence that tobacco use is a risk factor for duodenal ulcers is not conclusive. In the pre-Helicobacter pylori era, smokers were more likely to develop ulcers, ulcer recurrence as well as ulcers were more difficult to treat. In one prospective study of more than 47,000 men with duodenal ulcers, smoking did not emerge as a risk factor. However, in the setting of *Helicobacter pylori* infection, smoking may increase the risk of relapse of PUD. But,

smoking does not appear to be a risk factor for ulcer recurrence after eradication of *Helicobacter pylori*.

Severe physiologic stress

A number of reports have suggested that emotional stress might cause or exacerbate peptic ulcer. Stressful conditions that may cause PUD include surgery, severe medical illness, burns and CNS trauma. The risk for secondary ulceration is increased in sepsis, hypotension, respiratory failure, serious systemic illness, and multiple traumatic injuries. Stress ulceration and upper-GI hemorrhage are complications that are increasingly encountered in critically ill in the intensive care setting. Severe illness and a decreased gastric pH are related to an increased risk of gastric ulceration and hemorrhage. However, studies that investigate the influence of psychodynamic factors on the peptic ulcer disease have some limitations such as: psychological stress is difficult to measure, the pathogenesis of ulcer disease is multifactorial, psychodynamic factors need to be correlated with well-defined mechanisms in the pathogenesis of peptic ulcer disease such as *Helicobacter pylori* infections and NSAIDs use. So, the importance of psychodynamic factors in the genesis of peptic ulcer still remains controversial.[26]

PATHOGENESIS OF PEPTIC ULCER

Almost half of the world's population is colonized by H. pylori, which remains one of the most common causes of peptic ulcer disease. The prevalence of H. pylori is higher in developing countries, especially in Africa, Central America, Central Asia, and Eastern Europe. The organism is usually acquired in childhood in an environment of unsanitary conditions and crowding, mostly in countries with lower socioeconomic status. H.pylori causes epithelial cell degeneration and injury, which is usually more severe in the antrum, by the inflammatory response with neutrophils, lymphocytes, plasma cells, and macrophages. The mechanism by which H. pylori induces the development of different types of lesions in the gastroduodenal mucosa is not fully explained. H. pylori infection can result in either hypochlorhydria or hyperchlorhydria, thus determining the type of peptic ulcer. The main mediators of H. pylori infection are cytokines that inhibit parietal cell secretion, but H. pylori can directly affect the H+/K+ ATPase α-subunit, activate calcitonin gene-related peptide (CGRP) sensory neurons linked to somatostatin, or inhibit the production of gastrin.[27] Although the formation of gastric ulcers is associated with hyposecretion, 10–15% of patients with H. pylori infection have increased gastric secretion caused by hypergastrinemia and

reduced antral somatostatin content. This leads to increased histamine secretion, and subsequently the increased secretion of acid or pepsin from parietal and gastric cells. Additionally, the eradication of H. pylori leads to a decrease in gastrin mRNA expression and an increase in somatostatin mRNA expression.[28] In the remaining majority of patients, gastric ulcers are associated with hypochlorhydria and mucosal atrophy. The main mechanism of NSAID-associated damage of the gastroduodenal mucosa is the systemic inhibition of constitutively expressed cyclooxygenase-1 (COX-1), which is responsible for prostaglandin synthesis, and is associated with decreased mucosal blood flow, low mucus and bicarbonate secretion, and the inhibition of cell proliferation. NSAIDs inhibit the enzyme reversibly in a concentration-dependent manner. The co-administration of exogenous prostaglandins and cyclooxygenase-2 (COX-2)-selective NSAIDs use reduces mucosal damage and the risk of ulcers.[29] However, the different physicochemical properties of NSAIDs cause differences in their toxicity. NSAIDs disrupt mucus phospholipids and lead to the uncoupling of mitochondrial oxidative phosphorylation, thus initiating mucosal damage. When exposed to acidic gastric juice (pH 2), NSAIDs become protonated and cross lipid membranes to enter epithelial cells (pH 7.4), where they ionize and release H+. In that form, NSAIDs cannot cross the lipid membrane, and are trapped in epithelial cells, leading to the uncoupling of oxidative phosphorylation, decreased mitochondrial energy production, increased cellular permeability, and reduced cellular integrity. Patients who have a history of peptic ulcers or hemorrhage, are over the age of 65, also use steroids or anticoagulants, and take high doses or combinations of NSAIDs are at the highest risk for acquiring NSAID-induced ulcers.[30]

Main pathophysiological mechanisms and the sites of action of antiulcer treatment are shown in the Figure 4.

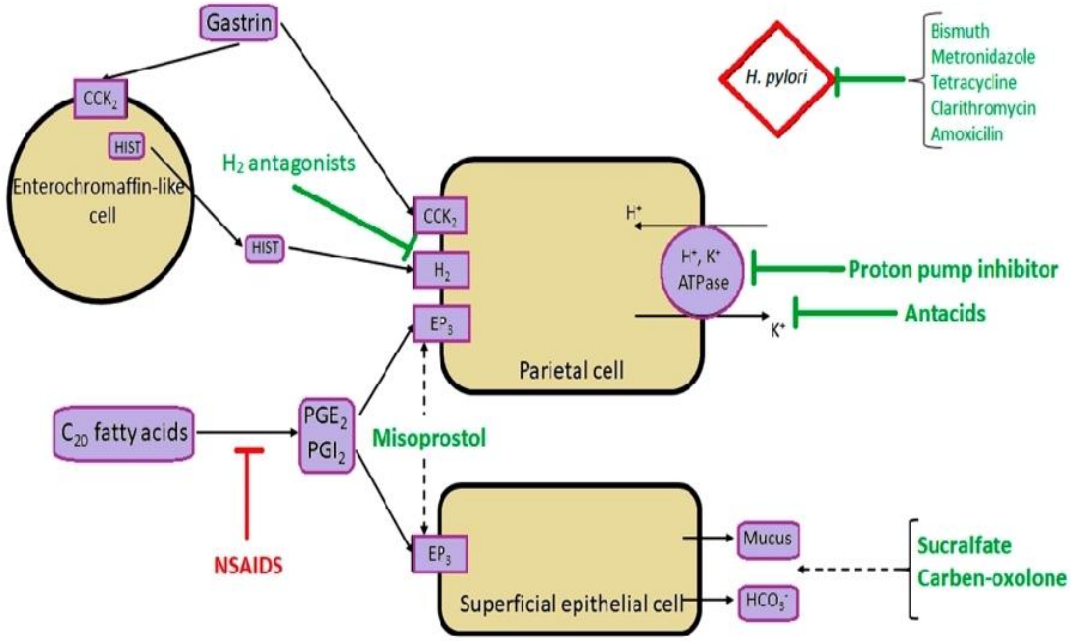

Figure 4: Schematic presentation of main pathophysiological mechanisms involved in the development of peptic ulcer disease, and the sites of action of the most commonly used pharmacological options in the treatment of peptic ulcer disease. CCK2 = Cholecystokinin Receptor; PGE2 = Prostaglandin E2; PGI2 = Prostaglandin I2; EP3 = Prostaglandin E receptor 3; HIST = Histamine.

CLINICAL MANIFESTATIONS

Duodenal Ulcer, located in first part of the small intestine (Duodenum). Severe pain in lower abdomen or chest area along with the burning sensation at upper abdomen. Usually, the DU patients awakens with pain from sleep. Pain occurs when stomach is empty usually 2 hours after meal or during night and relieve after eating. DU are also called as Kissing ulcers. Gastric Ulcers, located in the stomach with pain, higher in abdomen. In GU unlike DU eating may increase pain rather than relieve pain. Nausea, emesis and weight loss are some symptoms of GU. Diminished acid production is normal in GU patients, ulcers may occur even in absence of acid.

Other symptoms include for PU are

a) Abdominal pain (epigastric pain and described as burning may present abdominal fullness or cramps and vague discomfort)

b) Heartburn

c) Belching

d) Anorexia

e) Weight loss

f) Bloating

g) Mild epigastric pain

h) Typical nocturnal pain that awakens the patient from sleep between 12-3am

i) Burning, Gnawing and aching

j) Dyspepsia (postprandial abdominal bloating, distension and nausea).

In some cases, PU can be life threatening with some complications like bloody stools may be red, black or tarry texture, severe abdominal pain and cramps along with vomiting blood which resembles coffee grounds.[31]

DIAGNOSIS

It is mandatory to perform a good clinical history and a complete physical examination, in order to make a complete data collection of all the symptoms and signs of PUD. Also, it is extremely important to register all the past medical antecedents, and the duration of alcohol intake, history of NSAIDs and smoking consumption, and also for the possible existence of previous episodes of peptic ulcer.

There are two major considerations in the diagnosis of peptic ulcer. One is to assess if the referred symptoms are or not related to functional dyspepsia and the second is to determine the specific etiology of the ulcer.

Radiology

Barium gastro duodenal studies have been almost completely relegated and happily substituted by the endoscopic explorations in the routine diagnostic protocols, although they can still be useful in few patients who refuse to perform it, or in the cases that endoscopy is inaccessible by narrowing of the esophagus. The sensitivity and specificity of barium radiographic studies, depends on the radiologist experience, the technique used, the size of the lesion (if they are <0, 5 cm in diameter, it can be difficult to detect) and ulcer depth. Radiologic signs suggesting on benign nature are regular margins and symmetrical mucosal folds, a smooth translucent band or collar, surrounding the ulcer crater suggesting edema and indentation of the opposite wall (Figure 5). The signs that suggest malignancy by contrary are a big size of the ulcer, irregular mucosal folds, contrast absence or irregular filling (Figure 6).

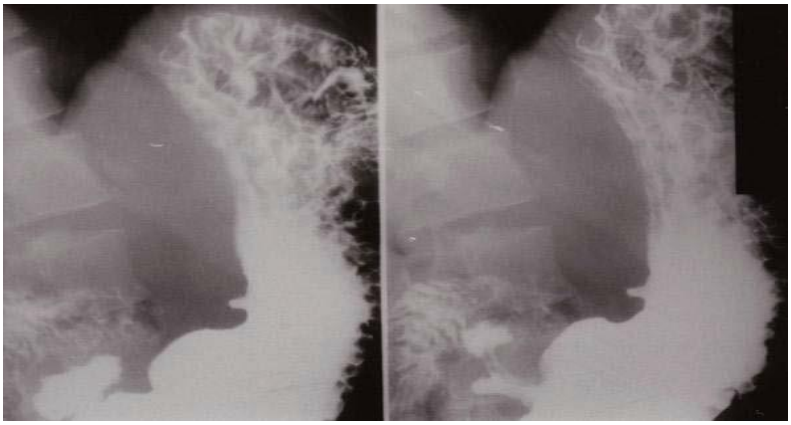

Figure 5: A benign gastric ulcer at the lesser curve.

Figure 6: Malignant lesion in the gastric body.

Endoscopic Findings

Upper GI endoscopy is the most accurate diagnostic test for PUD. It gives information about the size and the location of the lesion. In addition, mucosal biopsies can be performed, in order to do a differential diagnosis and to carry out endoscopic treatments in case of bleeding peptic ulcer.

The signs suggesting benign origin are the presence of regular mucosal folds surrounding the ulcer base and the fibrin deposit at the crater base (Figure 7). The feature that suggests malignancy, are the finding of overhanging margins, irregular or thickened borders and/ or the presence of an ulcerated mass, that protrudes into the lumen (Figure 8).

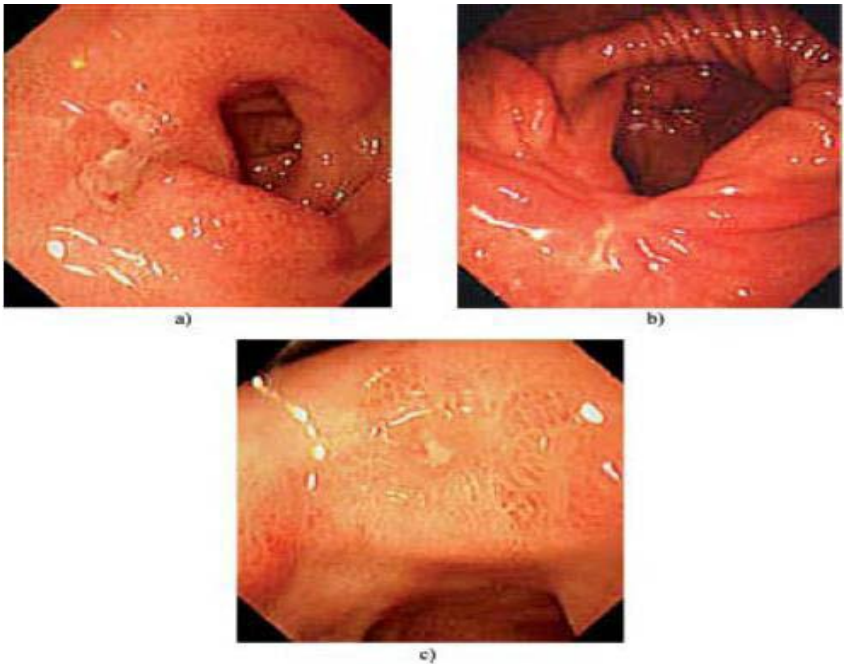

Figure 7: Endoscopic images a) Active ulcer. b) Ulcer scar c) Last stage of the mucosal healing, in benign peptic gastric ulcers.

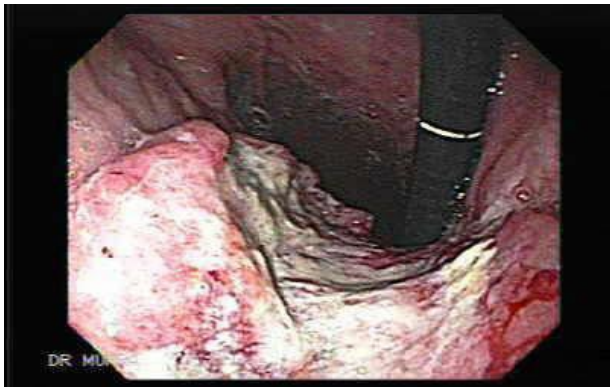

Figure 8: Endoscopic picture of malignant gastric fundus ulcerated lesion (view by retroflexion).

Malignancy of the duodenal ulcers is exceptional. Therefore, it is rutinary biopsy is not recommended. However, it is mandatoryto take several mucosal biopsies form the margins at any gastric ulcer, despite it is benign appearance. A follow-up endoscopy will be performed until the healing is completed.[32]

The presence of Helicobacter pylori infection must be investigated in every patient presenting peptic ulcer. Since it is discovery in 1983, the management has changed a lot. It is known that the prevalence of the infection increases with the age, and there is no difference between women and men.

Diagnostic tests for helicobacter pylori are divided into direct (based upon the need for endoscopy) and indirect tests, and several are used not only for diagnosis, but also in the follow-up after the eradication treatment in order to confirm this one (Tables 2 and 3).[33]

Table 2: Diagnostic methods for Helicobacter pylori infection.

	Sensitivity (%)	Specificity (%)
A.- Direct methods		
Rapid urease test	85-95	95-100
Histology	85-95	95-100
Gram	90	90-100
Culture	75-90	100
B.- Indirect methods		
Serology	85-95	80-95
Urea breath test	90-100	>95
Stool antigen test	90-100	90-100

Table 3: Selection of diagnostic method for the Hp infection in different situations.

1.-While performing an endoscopy in which we find a duodenal or gastric ulcer
•Rapid urease test + histology
2.- Medical history of peptic ulcer (gastric or duodenal), asymptomatic patient
•Urea breath test (^{13}C-UBT)
•Validated serology
3.- While performing an endoscopy for gastrointestinal bleeding due to peptic ulcer
•If not active bleeding is detected: Rapid urease test + histology
•If active bleeding is detected or the rapid urease testing was negative: Urea breath test (^{13}C-UBT)

TREATMENT

The treatment of chronic PUD varies depending on the etiology of the ulcer (HP or NSAID), whether the ulcer is initial or recurrent, and whether complications have occurred. Overall treatments aimed at relieving ulcer pain, healing the ulcer, preventing ulcer recurrence, and reducing ulcer-related complications. The goal of therapy in HP-positive patients with an active ulcer, a previously documented ulcer, or a history of an ulcer-related complication, is to eradicate HP, heal the ulcer, and cure the disease. 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 centers on the eradication of HP in HP-positive patients and reducing the risk of NSAID-induced ulcers and ulcer related complications. Drug regimens containing antimicrobials such as clarithromycin, metronidazole, amoxicillin, and bismuth salts and anti-secretory drugs such as the PPIs or H2RAs are used to relieve ulcer symptoms, heal the ulcer, and eradicate HP infection. Successful eradication will alter the natural history of PUD and cure the disease. PPIs, H2RAs, and sucralfate are used to heal HP-negative NSAID-induced ulcers, but ulcer recurrence is likely in high-risk patients if the NSAID is continued. 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 decreasing or 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 inpatients with ulcer-related bleeding or other complications such as perforation.

Nonpharmacologic 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, non-acetylated salicylate (e.g., salsalate), or COX-2 inhibitors should be used for relief of pain. Figure 9 shows an algorithm for guidelines for the evaluation and management of a patient who presents with dyspeptic or ulcer-like symptoms.

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. 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 post vagotomy diarrhea, dumping syndrome, anemia, and recurrent ulceration.[7]

Pharmacologic therapy

The most of successful classes of drugs are which acts by inhibiting gastric acid secretion. H2 receptor antagonists has revolutionized the treatment of PUD, healing ulcers and keeping the remission when given as a maintenance therapy. In 1989 introduction of proton pump inhibitors(PPI's), are totally replaced H2RAs. PPI's block selectively H+K+ATPase of the parietal cells. Second group of drugs are useful for reinforcement of mucosal barrier and has the significant application in protection against NSAID's and aspirin. Misoprostol is a prostaglandin analogue, widely used but is limited by abdominal side effects, especially at higher dose. Sucralfate and bismuth salts also promote ulcer healing by improving mucosal repair. Bismuth salts have some intrinsic anti *H pylori* activity and given only in combination with antibiotics. Nowadays cytoprotective drugs are outdated with effective therapy.[34]

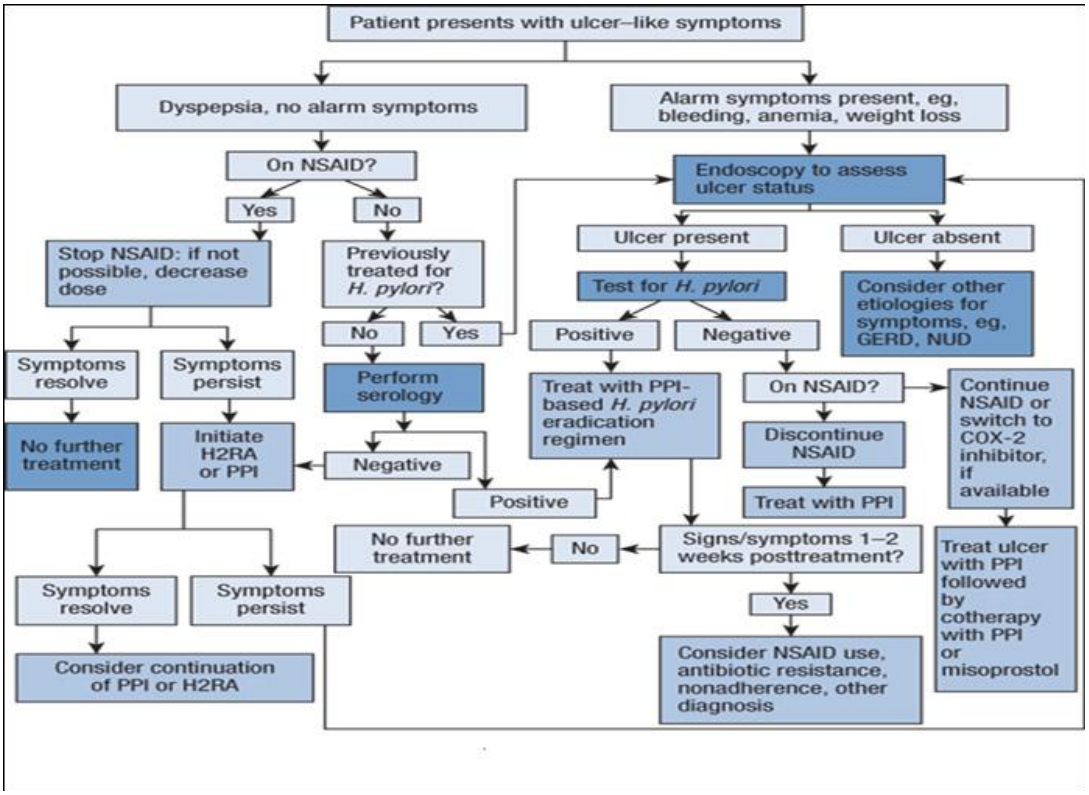

Figure 9: Algorithm: Guidelines for the evaluation and management of a patient who presents with dyspeptic or ulcer-like symptoms. COX-2, cyclooxygenase-2; GERD, gastroesophageal reflux disease; HP, *Helicobacter pylori*; H2-RA, H2-receptorantagonist;

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

Approaches for the treatment of peptic ulcer are

1. *Reduction of gastric acid secretion*

(a) *H_2 antihistamines*: Cimetidine, Ranitidine, Famotidine, Roxatidine

(b) *Proton pump inhibitors*: Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Dexrabeprazole

(c) *Anticholinergic drugs*: Pirenzepine, Propantheline, Oxyphenonium

(d) *Prostaglandin analogue:* Misoprostol

2. *Neutralization of gastric acid (Antacids)*

(a) *Systemic:* Sodium bicarbonate, Sod. citrate

(b) *Nonsystemic:* Magnesium hydroxide, Mag. trisilicate, Aluminium hydroxide gel, Magaldrate, Calcium carbonate

3. *Ulcer protectives*

Sucralfate, Colloidal bismuth subcitrate (CBS)

4. *Anti-H. pylori drugs:* Amoxicillin,

Clarithromycin, Metronidazole, Tinidazole, Tetracycline.[35]

An overview of conventional antiulcer treatment options is summarized in Tables 4 and 5.[36]

Table 4: Mechanisms of action and adverse effects of the most commonly used antiulcer treatment options.

Medicine		Mechanism of Action	Adverse Effects
Proton Pump Inhibitors (PPIs)	Omeprazole Lansoprazole Rabeprazole Esomeprazole Pantoprazole	Inhibition of the gastric H+/K+-ATPase (proton pump) enzyme system	Headache Abdominal pain Diarrhea Nausea Vomiting Constipation Flatulence Vitamin B12 deficiency Osteoporosis

H2 Receptor Blockers	Cimetidine Famotidine Nizatidine Ranitidine	Blocking the action of histamine at the histamine H2 receptors of parietal cells	Headache Anxiety Depression Dizziness Cardiovascular events Thrombocytopenia
Antacids	Aluminum hydroxide Magnesium hydroxide	Increases gastric pH to greater than four, and inhibits the proteolytic activity of pepsin Causes osmotic retention of fluid	Frequency not defined: Nausea Vomiting Hypophosphatemia Chalky taste Constipation Abdominal cramping Diarrhea Electrolyte imbalance
Potassium-Competitive Acid Blocker **Cytoprotective Agents**	Vonoprazan Misoprostol Sucralfate	Inhibits H+, K+-ATPase in gastric parietal cells at the final stage of the acid secretory pathway Stimulate mucus production and enhance blood flow throughout the lining of the gastrointestinal tract	Nasopharyngitis Fall Contusion Diarrhea Upper respiratory tract inflammation Eczema Constipation Back pain Diarrhea Abdominal pain Headache Constipation

Table 5: Types and efficiency of Helicobacter pylori (H. pylori) eradication treatment options.

Type	Duration	Efficiency
First line Standard triple therapy: PPI + two antibiotics (clarithromycin + metronidazile or amoxicilin	7–14 days	70–85%
Second line Bismuth-containing quadruple therapy: PPI + bismuth salt + tetracycline + metronidazole	14 days	77–93%
Non-bismuth based concomitant therapy: PPI + clarithromycin + amoxicillin + metronidazole	14 days	75–90%
Levofloxacin triple therapy: PPI + amoxicillin + levofloxacin	14 days	74–81%

Salvage regimens Rifabutin-based triple therapy: PPI + rifabutin + amoxicillin	10 days	66–70%

***Helicobacter Pylori* Eradication**

The eradication therapies of *H. pylori* infection are based on the scientific evidence, collected in the most recent consensus reports. In settings with a high prevalence of *H. pylori* infection and in the absence of NSAID use, is reasonable to consider the empiric eradication treatment. Drugs that have demonstrated efficacy include amoxicillin, clarithromycin, metronidazol, tetracycline and bismuth (Table 5).

The most recent data show that classic triple therapy containing PPI clarithromycin and amoxicillin or metronidazol has lost some efficacy, mainly due to the increase resistance to clarithromycin observed in the latest years. For this reason, this standard regimen is currently recommended for first-line treatment, only in areas of low resistance rate. Double doses of PPI (twice daily) and extend treatment to 14 days improve the eradication rates. In regions with high clarithromycin resistance, quadruple therapy (the so called "concomitant" treatment) which includes the combination of PPIs, amoxicillin, clarithromycin and metronidazol, is recommended as first-line empirical treatment. If these combinations fail to achieve the eradication, either a bismuth-containing quadruple therapy, or a rescue treatment with levofloxacin, are recommended. After the failure with three different regimens, it is better to refer the patient to a center with greater expertise in the management of multi-drug resistant *H. Pylori*.

The combined treatments are generally well tolerated and the rates of adverse effects depend on the antibiotics used in the different treatment regimens. The most frequently registered are diarrhea, rash and candidiasis (amoxicillin); nausea, metallic taste, peripheral neuropathy and anta bus-like effect with alcohol intake (metronidazol); prolongation of QT interval and seizures can appears in predisposed patients for other reasons (fluoroquinolones) and in few cases transient pigmentation of the tongue and dark stools (bismuth).[37]

Treatment of NSAID-induced ulcers

Nonselective NSAIDs should be discontinued (when possible) if an active ulcer is confirmed. If the NSAID is stopped, most uncomplicated ulcers will heal with standard regimens of an H2- receptor antagonist, PPI, or sucralfate. PPIs are usually preferred because they provide

more rapid ulcer healing than H2RAs or sucralfate. If the NSAID must be continued in a patient despite ulceration, consideration should be given to reducing the NSAID dose, or acetaminophen, a nonacetylated salicylate, a partially selectiveCOX-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. H2RAs 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.[7]

Potassium-Competitive Acid Blockers

Since up to 13% of patients treated with lansoprazole still experience ulcer recurrence, the search for alternative treatment is ongoing. Vonoprazan is a potassium-competitive acid blocker that inhibits H+, K+-ATPase in gastric parietal cells at the final stage of the acid secretory pathway. The difference in the mechanism of action between vonoprazan and PPIs is that vonoprazan inhibits the enzyme in a K+-competitive and reversible manner, and does not require an acidic environment for activation. Additionally, vonoprazan shows a rapid onset of action and prolonged control of intragastric acidity.[38] Vonoprazan at doses of 10 mg and 20 mg was non-inferior to lansoprazole for the prevention of peptic ulcer recurrence in Japanese patients during NSAID therapy, or those who required aspirin therapy for cardiovascular or cerebrovascular protection[39], with good tolerance, a similar safety profile, and no new safety issues. Also, five weeks of treatment with vonoprazan significantly reduced post-endoscopic submucosal dissection bleeding, compared to eight weeks of treatment with PPIs. Similarly, it was shown to be superior to esomeprazole and rabeprazole[38] for scarring artificial ulcers, which could help make an endoscopic submucosal dissection a safer treatment.

Alternative Therapy for Peptic Ulcer

The usage of medicinal plants in healing numerous diseases is as old as human beings, and well-known as phytotherapy. Moreover, in the past few years, there has been a rising interest in alternative therapies and the usage of herbal products, in particular, those produced from medicinal plants. Also, due to appearance of various side effects by usage of conventional drugs for numerous diseases, medicinal plants are considered the major reservoir of potentially new drugs. Plant extracts and their crude are the most significant sources of new drugs, and have been shown to cause promising results in the treatment of gastric ulcer as well. It is known that numerous pharmaceutical agents such as proton pump inhibitors,

anticholinergics, antacids, antimicrobial agents, H2-receptor antagonists, sucralfate, and bismuth are not fully effective, and produce numerous adverse effects such as impotence, arrhythmia, hematopoietic alterations, hypersensitivity, and gynecomastia. Due to that, investigations of the new pharmacologically active agents through the screening of different plant extracts led to the discovery of effective and safe drugs with gastroprotective activity. Especially, plants with antioxidant capability as the main mechanism are used as the herbal reservoir for the treatment of ulcer disease.[36]

Certain herbs are recommended by herbal specialist for peptic ulcers. They are:

- Astragalus (Astragalus membranaceus): Used traditionally to treat stomach ulcers.
- Barberry (Berberis vulgaris): This herbs contains active substances called berberine alkaloids. These substances have been shown to combat infection and bacteria. For this reason barberry is used to ease inflammation and infection of the gastro intestinal tract. Barberry has also been used traditionally to improve apetite.
- Bilberry (Vaccinium myrtillus): Bilberry fruits helps to prevent stomach ulcer related to a variety of factors including stress, medications and alcohol.
- Cat's claw (Uncaria tomentosa): The back and root of this herb have been used among indigenous people of the rainforest for centuries to treat a variety of health problems including ulcers and other gastro intestinal disorders. The benefits of this herb may be due to its ability to reduce inflammation.
- Cranberry (Vaccinium spp): May have properties that help to prevent H pylori infection.
- Dong Quai (Angelica sinensis): Animal studies with dong quai, soothe ulcers, but studies in needed before a definitive conclusion can be drawn.
- Garlic (Allium sativum): Some studies suggest that high amounts of garlic may protect against stomach cancer, which is a potential complication of H pylori peptic ulcers. This is controversial, however and high amounts of garlic may infact cause gastro intestinal distress.
- Licorice (glycyrrhiza glabra): This herb is a demulcent (soothing, coating agent) that has long been valued for its use in food and medicinal remedies, including treatment of ulcers. Some licorice root extracts, known as deglycyrrhizenated licorice (DGL), still have the healing properties of licorice without the harmful effects. DGL may be better for stomach or duodenal ulcers than Glycyrrhia glabra and may even prove as effective as some prescription drugs for stomach ulcers.

- Slippery elm (ulmus fulva): Although there has been little scientific research on slippery elm, it has along history of use based on clinical experience. Gastritis (stomach inflammation) and peptic ulcer are among the conditions that seem to respond well to slippery elm.
- Turmeric (curcuma longa): Turmeric has long been used in both Ayurvedic and Chinese medicine to treat digestive disorders. In an animal study, for example, extracts of turmeric root reduced the release of acid from the stomach and protect intestinal walls and ulsers from injuries such as gastritis or inflammation. Further studies are needed to know to what extend these protective effects apply to human volunteer as well (Note: at very high doses, turmeric may induce ulcers). It is very important to stick with the dose recommended by an herbal specialist.

1. Angelica (Angelica archangelica)
2. German chamomile (Matricaria recutita)
3. Lemon balm (Melissa officinalis)
4. Milk thistle (Silybum marianum)
5. Peppermint (Mentha piperita)[40]

CONCLUSION

Peptic Ulcer a disease which can be avoidable. Although continuous exposure of different etiological factor which try to disrupt the gastric mucosa, but gastric mucosa likely to maintain its structural integrity and functioning. However, mucosal defence were loss to different etiological factors leads to gastric mucosal injuries. The action of etiological factors on gastric mucosa were lead to the development of potential therapies to treat PUD. *H. Pylori* and NSAIDs are the leading cause for the gastric mucosal damage which is eventually countered by magical drugs for PUD are PPI's and H2RA's. Both the class of drugs play a mainstay in treatment of PUD. Even the refractory PUD can be effectively treated with the well developed treatment regimen. Not only the drug regimen but also some home remedies have prove to be control PUD.

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