IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
April 2018 Vol.:12, Issue:1

Peptic Ulcer Disease: An Overview

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submission: 20 March 2018
Accepted: 27 March 2018
Published: 30 April 2018

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: PUD, *H pylori*, PPI, H_2RA.

ABSTRACT

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 was traced back at least to 11thcentury. Peptic Ulcer a disease which can be avoidable. Although continuous exposure of different etiological factor which tries to disrupt the gastric mucosa, but gastric mucosa likely to maintain its structural integrity and functioning. Overall the PUD is a disease which is avertable or stoppable, but only due to the insignificance towards our health hygiene, the PUD becomes more lethal. But due to the development of significant therapies PUD is well countered or treated.

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.[1,2,3]

PUD is due an imbalance or variance between aggressive factors and defensive factors. Aggressive factors such as pepsin, reflexive bile, leukotrienes(LT's), reactive oxygen species(ROS) and defensive factors such as gastric mucosa, prostaglandins, nitric oxide, bicarbonate secretions, innate resistance of mucosa, mucosal blood flow, non-enzymatic antioxidants and some growth factors.[4]

PUD was traced back at least to 11thcentury[4]. But first case on perforated peptic ulcer that identified in 1670 at Princes Henrietta of England.[3] Two theories were proposed about PUD: Gunzberg (in 1852), who attributed PU to excessive acidity of gastric as a result of some disturbances in vagal control. Lester Dragsted (in 1935), suggested that gastric stasis with secondary hypergastrinemia was responsible for lesion in the gastric ulcer.[3]

Gastric ulcer is also known as stomach ulcer and it is defined as the erosion of normal gastric mucosa in submucosa or deeper. In duodenal ulcer, an ulcer is present in the duodenum or the first part of intestine. In GU, the acid secretion will be low or normal whereas in DU the acid secretion will be high in 50% of PUD patients. Peptic ulcers are mainly caused by *Helicobacter Pylori*(*H.Pylori*), NSAID's (Non-steroidal anti-inflammatory drugs), increased gastric acid secretions and other causes like stress, smoking, spicy food and nutritional deficiencies. Complications in PUD include internal bleeding, GI obstruction, perforation and refractory PU.[1,5]

Gastric acid Secretion Regulation:

Parietal cells acid secretion is triggered off by the different factors related to food ingestion and regulation is through central, peripheral and cellular mechanisms. Acid is produced by carbonic anhydrase mediated catalysis of H_2O and CO_2 to form H^+ ions and HCO_3^- ions. Then H^+ ions(hydrogen ions) will exchange with K^+ions(potassium ions) through H^+K^+ATPase pump and later coupled with Cl^- ions (chlorine ions) entering the parietal cells from blood in

exchange for HCO_3^- ions. The postganglionic neurons in the stomach contain the neurotransmitters such as gastrin releasing pepsin(GRP), acetylcholine, vasoactive intestinal peptide(VIP), nitric oxide, substance P, pituitary adenylate cyclase activating polypeptide. Through these neurotransmitters, acid secretions are regulated directly and indirectly. Directly by influencing the parietal cells and indirectly by modulation of secretions of hormonal and paracrine ligands. The principle stimulants for acid secretion are gastrin, histamine and acetylcholine are secreted from postganglionic enteric neurons. These stimulants raise intracellular levels of adenosine 3,5-cyclic monophosphate(cAMP), calcium, inositol triphosphate(IP_3) and diacylglycerol. Then sequence events induce the H^+K^+ATPase pump rich tubule vesicles to merge into apical plasma membrane helps H^+K^+ATPase pump to secrete protons(H^+ ions) directly into the lumen of the canaliculus of the parietal cells and then into the lumen of the gastric gland[1,6,7]

Prevalence

PUD is one of the major prevailing diseases throughout the world. 4% of population around world are suffering with PUD. A study in 2014 have stated that 53 million people newly begin with PUD. At some part of life minimum 10% of people around the world suffering with PUD. There were 327,000 deaths in 1990 due to PUD and it was declined to 301,000 deaths in 2013[5]. The Table No. 01 shows the pattern of PUD in India.

Table No. 01: Patterns of PUD in India showing Male: Female ratio [8]

Male: Female ratio			
Year	**Duodenal ulcer**	**Gastric ulcer**	**Total cases**
1942-1945	25.8:1	21:1	1113
1962-1966	12.26:1	8.7:1	1102
1982	8.68:1	4:1	276

A retrospective analysis of endoscopic records done between years 1989-2004 resulted in 7365 patients with DU and 2834 patients with GU and 1605 patients with combined DU and GU[9]. According to the latest data published by WHO in May 2014, stated that 85,487 deaths are occurred due to PUD in India [10]

A study conducted by J.J.Y. Sung in 2009, stated that annual incidence PUD globally was 0.10 - 0.19% for PUD diagnosed physician and 0.03 - 0.17% and it is based on hospitalization data. And it was clearly stated there was a gradual reduction in PUD[11].

Around the globe, every year peptic ulcer disease (PUD) affects4 million people. 10-20% of these patients will affect with PUD complications and 2-14% of the ulcers will perforate. Perforated peptic ulcer (PPU) is relatively rare but life-threatening with the mortality rate varying from 10 to 40%. Females are the most affected with PUD when compare to males in recent years [12].

Etiopathogenesis of PUD

There are many causes for PUD.

***Helicobacter Pylori*:**

It is a gram negative microaerophilic bacteria initially named as Campylobacter pylori remains primarily in the mucus layer and the gastric antrum within aggressive environment of stomach. It is first discovered by two Australian scientists, Barry Marshall and Robin warren in 1982-1983 for which they are awarded Nobel prize in 2005[5]. It is a motile, flagellated and spiral shaped bacteria. *H pylori* abide in the antrum but in a course of time, it migrates towards the more adjacent part or segment of the stomach. The genome of *H pylori* is sequenced and encoded with 1500 proteins. It multiples with great efficiency in the hostile environment within stomach but survive poorly in the gastric lumen. Mainly found under the mucous layer and in close proximity or attached to gastric superficial epithelium cells, without substantial invasion of host tissue. PUD caused by *H. pylori* may be more potent than those without ulcers. Amongst the proteins encoded in *H. pylori* genome, there are some factors which are essential for determinants of *H. pylori* mediated colonization and pathogenesis such as the outer membrane proteins (Hop proteins), urease, cytotoxin associated gene (Cag A) and vacuolating cytotoxin A (Vac A). The initial step in *H. pylori* infection is dependent on the bacteria's motility and its potential to produce urease. Urease is first virulence factor of *H.pylori*. They can colonize the gastric mucosa and survive in the acid environment. Because of the ecological niches they are rich in urea, which they catalyses urea by hydrolysis and produce ammonium(NH_3), hydroxyl ions (H^+ ions), and carbon dioxide. By this reaction, the *H. pylori* neutralise the stomach gastric environment around it. But metabolites from the urea catalysis are toxic to the gastric epithelial cells. Thus, formed NH_3 will react with the OCl^-(hypochlorite) to give rise to monochloramine (NH_2Cl) in stomach which harm to stomach cells. Also, CO_2 reacts with environmental water and produce carbonic acid with the help of enzyme carbonic anhydrase. Then carbonic acid

converts to H^+ ions and HCO_3 ions which result in H^+ ions react with the NH_3 to form NH_4 which is toxin to epithelial cells. Major two effects of *H. pylori* are damage of gastric mucus or mucosa barrier and increase the gastric acid. Hyperacidity in duodenal ulcer may result in *H. pylori* induced gastrinemia. Persistent hypergastrinemia accelerates the production of parietal cell mass, which leads overproduction of H^+ ions or more acid production. Elevated acid content in the proximal duodenum give rise to metaplastic gastric type mucosa, which provide a niche for *H. pylori* infection then results in inflammation and ulcer formation. *H pylori* infected gastric mucosa shows infiltration lymphocytes, polymorphonuclear leukocytes and plasma cells in the lamina propriety and intraepithelial severe neutrophil infiltration. The PUD is caused 30 -40% by *H. pylori* infection only but much high in geriatrics than the other groups. 90% of DU and 70% GU are due to *H. pylori*.[4,13,16]

Non-Steroidal Anti Inflammatory Drugs (NSAID's)

Three patterns of mucosal damage are done by NSAID's. They are superficial erosions, haemorrhages and silent ulcers. NSAID's concentrated from the acidic gastric juice into the mucosal cells and produce acute superficial erosions through inhibition of cyclooxygenase (Cox) and by mediating the adherence of leucocytes to mucosal endothelial cells.

Mechanism of ulcer caused by NSAID's:

Prostaglandins (PG's) are chemicals having the role in promoting inflammation means acts as protective in nature. NSAID's inhibit certain prostaglandins which protect stomach lining from the corrosive action of gastric acids. These protective prostaglandins are produced by an enzyme called cyclooxygenase-1 or Cox-1 through arachidonic acid pathway. By blocking Cox-1 leads to disruption of production of prostaglandins in stomach, thus NSAID's cause ulcers and bleeding.

Another two types of mechanism include:

A. Cox-1 inhibition by NSAID's

Release of endothelin-1(ET-1) (POTENT CONSTRICTOR)

Mucosal Injury

B. NSAID's

Inhibits PG's synthesis

Activation of Neutrophils

Local release of Reactive Oxygen Species (ROS)

Gastric Injury

NSAID's also cause marked reduction in mucosal blood flow, mucus bicarbonate secretion, impaired platelet aggregation, reduced epithelial cell renewal and elevated leukocyte adherence that are responsible for pathogenesis of ulceration. Gastric acid worsens the NSAID's effects by deepening superficial lesions, interfering with platelet aggregation and impairing the ulcer healing process. NSAID ulcer and GI complication risk are elevated with the use of multiple NSAIDs or the concurrent use of low-dose aspirin, anticoagulants, selective serotonin reuptake inhibitors, oral bisphosphonates, corticosteroids and anti-platelet drugs. NSAID's and *H pylori* have additive effect but act independently to elevate ulcer risk or ulcer related bleeding. PUD caused by NSAID's is more frequent cause after *H pylori*. 4%

of NSAID's users every year are affected with ulcers and ulcer complications mostly suffering group of people are geriatrics.[1,2,4,13,14]

Alcohol Consumption:

Non-distilled and fermented alcoholic beverages elevate gastrin levels and acid secretions. Alcoholic preparations containing maleic and succinic acid also stimulate gastric acid secretion. Some studies have proven that high alcohol doses reduce the gastric emptying and slow bowel movement on the other hand low alcohol doses elevate the gastric emptying. There are several mechanisms for alcohol to damage the GIT. Some of them are as follow.

Mechanism for the ethanol induced gastric lesions are deplete the gastric mucosal contents, damage the mucosal blood flow and leads to mucosal injury. Ethanol at first cause the microvascular injury that leads to increase vascular permeability, that causes oedema formation and epithelial lifting. Szabo *et al.* (1981) has described that after ingestion of ethanol through oral route in GIT, arapid and time dependent release of ET-1(endothelin-1) into the systemic circulation will happen that leads to vasoconstriction which results ultimately to development of haemorrhagic mucosal erosion and decreased production of bicarbonates and mucus, ethanol produce necrotic lesions in gastric mucosa. Alcohol also activate MTPK (Mitogen Activated Protein Kinase) and TNF alpha (Tumour Necrosis Factor) and also activate apoptosis which leads cell death. Alcohol also leads to increase in the lipid peroxidation content which leads to cell damage or death. Chari *et al.*(1993) have proposed oral, intragastric and intravenous intake of alcohol at a concentration of up to 5% elevate the acid secretion by stimulating the secretion of gastrin and to lesser extent by a direct effect on the parietal cells. On the other hand, an alcohol concentration of higher than 5% has no effect on gastric acid secretion was stated in Stermer (2002).[1,2,4,16]

Gastric acid secretions:

Major ulcerogenic factor for induction of GU and 50% of GU patients are acid and pepsin hyper secretors. Parietal cells approximate secrete hydrochloric acid at concentration of 160mmol/Lat 0.8pH. When levels of acid and pepsin overcome the mucosal defensive mechanism some common and potential serious acid related clinical conditions occur such as PUD, Barrett's oesophagus where usually squamous mucosal lining becomes replaced by columnar epithelial cells of putative specific aspect, Gastro-esophageal reflux disorder(GERD), stress related erosions. Acid gain access into the lumen through the

channels in mucus layer build by relatively colossal intra-glandular hydrostatic pressure provoked during secretions approximately 17mmHg. This luminal acid interferes with the process of restitution, resulting in the conversion of superficial injury to deeper mucosal lesion and inactivates the acid-labile growth factors important for repair of superficial injury and maintenance of mucosal integrity.[1,4,13]

Oxidative stress:

While oxidative stress, there is an imbalance between aggressive and defensive factors in stomach which plays a major role in gastric haemorrhage and ulcer formation. Excessive production of the ROS is a significant pathogenic factor that leads to oxidative damage, lipid peroxidation, protein oxidation and DNA damage which leads to cell damage.[4,13]

Other risk factors include:

a. Cigarette Smoking b. Age,

c. Physiological stress c.Dietary factors (Ex. Caffeine containing foods),

d. Radiation therapy e. Genetic factors.

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.[1]

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**[1]**

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 [1,15]

Diagnosis

Normal laboratory tests are done to find Gastric acid secretory studies. Results show haematocrit and haemoglobin are low due to bleeding, and stool hemoccult tests are positive. PUD diagnosis will depend upon visualizing ulcer either by GI endoscopy or upper GI radiography.

Regular single barium contrast techniques give 30% of PUD detection. And 60-80% of ulcers are detected by optimal double contrast radiography.

Esophagogastroduodenoscopy (Fiberoptic upper endoscopy) detects 90% of PU and permits direct inspection, biopsy, visualization of superficial erosions, and sites of active bleeding. If GU is found on radiography malignancy should be excluded by direct endoscopic visualization and histology.

Upper gastrointestinal radiography with barium (Barium X-ray) has been replaced with upper GI endoscopy as the diagnostic procedure of choice for detecting PU.

Radiography with barium: A whitish liquid containing barium is orally administered and X-ray film is collected which gives the outline of ulcer.

Endoscopy: In endoscopy, a lighted tube with a special camera on its end was inserted into stomach or duodenum (initial part of small intestine). Then through camera, the inner lining of stomach is observed on monitor. Tissue can be removed during endoscopy and also used for detection of *H pylori*.

Tests to detect for *H pylori*:

Two types of tests to detect *H pylori*:

1. Invasive tests 2. Non-invasive tests.

Invasive Tests or Endoscopic tests: These methods require upper GI endoscopy with a mucosal biopsy taken for histology, culture of biopsy or detection of urease activity. For maximum diagnostic yield at least of 3 tissue samples from specific areas of stomach to be taken because *H pylori* infection can form a patchy distribution which can lead to false negative results and certain drugs or medications (PPI's, Bismuth salts, and Anti-microbial these medications should stop administering before for at least 2 to 4 weeks) may decrease the sensitivity of the rapid urease test. If it is necessary to take these medications the patient must undergo for gastric biopsy for histological diagnosis. Histological identifications have more than 95% of sensitivity and also allows for the classification of gastritis and culture gives 100% of specificity and enables susceptibility testing of antimicrobial agents to detect resistance. Rapid urease test give 90% sensitivity and specificity which detect *H pylori* urease enzyme activity. Other tests are CLO test and Pyloritek.[1,13,15,17]

Non-invasive tests or Non-endoscopic tests: These are simple and less expensive tests. Non-invasive tests are of 2 types.

1. Test that identify active infection 2. Tests that identify antibodies.

These tests include urea breath test (UBT), serologic antibody detection tests, and the fecal antigen test. Antibody tests do not have the specificity to find difference between active infection and former eradicated *H pylori*.

UBT is the most sensitive test in this category the procedure includes the patient has swallowed a capsule that containing urea made-up of both radioactive carbon(C^{14}) and non-radioactive carbon(C^{13}). Then the urea will broken-down into ammonia and labelled bicarbonate in the stomach. The labelled bicarbonate will absorb in blood and excreted in the breath by lungs. Then C^{13} will be detected by using mass spectroscopy and C^{14} with scintillation counter.

Serological antibody tests are of 2 types:

a. Antibody detection on laboratory based (Enzyme linked immune sorbent assay {ELISA} 90% sensitivity and latex agglutination techniques approved FDA) and

b. Antibody detection can be performed in office or near patient detects IgG antibodies to *H pylori* in whole blood or finger stick. But these tests are not accurate until 3 weeks of infection because up to that the *H pylori* undergo incubation.[1,13,15,17]

Treatment:

Non-pharmacological treatment:

Reduce psychological stress, cigarette smoking, use of NSAID's including aspirin. If patient who cannot discontinue NSAID's first lower the dose of NSAID's or use the less damaging agent or change the medication to Cox-2 inhibitors and can use acetaminophen or non-acetylated salicylate example salsalate. Co-administration of NSAID's along with food. Decrease spicy foods, caffeine and alcohol. Surgery of bleeding, perforation or obstruction. In past, surgical procedure was performed for medical treatment failure which includes vagotomy with pyloroplasty or vagotomy with antrectomy. And other acid reduction operations include Partial gastrectomy, gastroenterostomy and vagotomies.[13,15,16]

Pharmacological treatment:

Dictum of Karl Schwarz's, no acid no ulcer developed medical therapies that targeted on gastric acid secretions and mucosal defence mechanism. The most of successful classes of drugs are which acts by inhibiting gastric acid secretion. H_2 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 H_2RAs. 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.[13,15,17]

Glimpse of treatment:

Initial treatment for *H pylori* include:

1st line treatment- PPI + clarithromycin and either amoxicillin or metronidazole for 10-14 days and this treatment is called PPI based triple therapy or regimen. But in PPI based triple therapy or regimen amoxicillin containing regimen is preferred because bacterial resistance for amoxicillin poor or almost absent but have some adverse effects and metronidazole is used in the second line therapy as a reserved agent. If patient is penicillin allergic amoxicillin must be replaced by metronidazole in PPI based triple regimen and yields similar results when inclusion with clarithromycin.

Alternative or 2nd line treatment includes bismuth based quadruple regimen, drugs include are H_2RA, bismuth salts, tetracyclines and metronidazole for 10-14 days.

Sequential therapy- PPI+amoxicillin for5 days followed by PPI+Clarithromycin and metronidazole for 5 days. This therapy is alternative for PPI based triple therapy and bismuth based quadruple regimen.

For eradication of H pylori; avoid antibiotics which are used in the initial treatment.

Bismuth based quadruple regimen- Bismuth salts+tetracycline+metronidazole and PPI or H_2RA for 10-14 days.

PPI based triple regimen-Levofloxacin+ amoxicillin+PPI for 10 days.

In detail explanation of treatment:

Treatment for H pylori positive ulcers:

It must be effective, well tolerated, good compliance and economic. Successful eradication of Hp depends upon the good drug regimen. The effective action of drug regimen depends upon the following factors:

1. Duration of therapy,
2. Resistance to antibiotics used,
3. Medication adherence or compliance and
4. Genetic Polymorphism.

Minimum eradication rates must be 80-90%. Two drug regimen consists of PPI+amoxicillin or clarithromycin have less effect in eradication of *H pylori* infection in United States. But use of one antibiotic leads to higher antimicrobial resistance. Drugs like clarithromycin, amoxicillin, metronidazole and tetracycline showed an effective eradication rates against *H pylori* in various combinations. Due to the insufficient data till now these drugs were, not substituted with other or regular drugs like:

a. Ampicillin for amoxicillin

b. Doxycycline for tetracycline

c. Erythromycin or azithromycin for clarithromycin.

Duration of eradication treatment or therapy is controversial in Europe it is 1 week triple regimen is suggested on other hand United states follows triple regimen for 10-14 days. But a meta-analysis proved that increasing the duration of triple regimen therapy from 7 days to 10 days, increase the eradication rate by 4% and 7 days to 14 days showed 5% eradication rate. Quadruple regimen therapy is a substitute for 1st line therapy in high prevalence areas with antibiotic resistance. Several studies done in Italy has confirmed that 1st line 10 days' sequential therapy was better than triple therapy. Most effective treatment regimen will fail in 10-20% cases. Bismuth based quadruple therapy is the best 2nd line therapy if these compounds not used as 1st line therapy with eradication rates of 57-95%. Levofloxacin or rifabutin as 3rd component besides PPI and amoxicillin can be used for treatment of Hp infection after failure. Triple regimen containing levofloxacin range eradication rates of 63-94%. Use of rifabutin+PPI+amoxicillin for more than 7 days is well tolerated and highly

effective against double resistant *H pylori* after failure of 1st line triple therapy. In high metronidazole resistance condition furazolidone is used as alternative. Drug regimen that contains an antisecretory drug+2 antibiotics and bismuth salt has high eradication rate and reduce risk of resistance. Clarithromycin is the only single most effective antibiotic in treating *H pylori* infection.[13,14,15,16,17,18]

Important points about drug regimens:

PPI based triple drug regimen:

This regimen is decreased in North America and Europe because increased clarithromycin resistant *H pylori* strain. PPI is the integral part of this regimen and should be taken 30-60 minutes before meal.

Bismuth based quadruple therapy:

Substitution of amoxicillin for tetracycline decrease the eradication rate and is not recommended. Substitution of Clarithromycin 250to 500mg QID yields similar results but have more adverse effect. Bismuth salts are used as topical antimicrobial effect. Antisecretory drugs have the tends for ulcer healing and relieves pain in patient with an active ulcer. PPI is replaced by H_2RA in this regimen, but a recent meta-analysis indicated that quadruple therapy with PPI provides greater efficacy and permits a shorter treatment duration (7days) when compared with H2RA based regimen (10-14 days) in with higher eradication.

Sequential therapy:

It is a new therapy and drugs are administered in a sequence. Initial treatment with antibiotics that poorly permits resistance for example amoxicillin and that decrease the bacterial load and latent bacterial resistant organism. Then it is followed by various antibiotics that eradicate remaining bacteria. Example: Clarithromycin and metronidazole.

Treatment consists of PPI and amoxicillin for 5 days and followed by PPI, clarithromycin and metronidazole for 5 days. Treatment require change in medication in middle which may contribute to non-adherence in sequential therapy.[13,15,19]

Eradication of *H pylori* after initial treatment failure(13):

Initially patient should concern gastroenterologist for further diagnostic evaluation. After a failure of initial treatment, these are recommendations for the second line treatment.

a) Use antibiotics which were not used in the initial therapy'

b) Use antibiotics that are that are not prone to resistance'

c) Use medicaments which have topical effects like bismuth'

d) 14 days of duration should be strictly followed.

Treatment includes:

PPI+amoxicillin+clarithromycin regimen is used. Levofloxacin may be act as a substitute in penicillin allergic patients.

Probiotic like strains of Bifidobacterium and lactobacillus and foodstuffs like cranberry juice and some milk proteins with bioactive components are used to control *H pylori* colonization. But these alone cannot eradicate *H pylori* infection.

Treatment of NSAID's or aspirin (low dose) induced ulcers(13,14,15,16)**:**

Uncomplicated peptic ulcers: 90% of GU or DU heal within 8weeks of standard dose H_2RA like Ranitidine 150mg twice a day and NSAID's should be discontinued. If NSAID's are still continued treatment may impair. If NSAID's are not discontinued reduce the dose of NSAID's or switch to acetaminophen or non-acetylated salicylate or move to selective Cox-2 inhibitors. These ulcers must be treated with H_2RA, PPI and sucralfate. PPI are preferred because they show more symptomatic relief and ulcer healing. A recent review has proved that PPI's showed better in healing GU than standard dose of ranitidine who continuously using NSAID's. A recent study has proved that there is no any difference in GU healing between patients receiving esomeprazole 140 mg (85·7%), esomeprazole20 mg (84·8%), and ranitidine (76·3%).Some of recent studies proved that there is no difference in healing GU who continuously using NSAID's. When NSAID's are continued, the PPI's are the drugs of choice because potent acid suppression is required to accelerate ulcer healing. If ulcer is *H pylori* positive, the treatment should be initiated with regimen that contains PPI. PPI's show better results in healing ulcers than H_2RA and misoprostol for prevention of DU. Misoprostol

shows good results in treating GU but not DU when compared with H_2Ras. But PPI have no advantage over misoprostol in reducing the risk of GU. Misoprostol 200mg 4 times a day prevent NSAID's induced ulcer complications.

Treatment Non-H pylori and Non-NSAID ulcers (13,20)**:**

These are also called idiopathic peptic ulcer. Very rare case of PUD. Should be properly re-diagnose once after first diagnosis and verify that the ulcer are H pylori negative and they are not taking any ulcerogenic medication.

Some of the possible causes are:

a) Gastric hypersecretions,

b) Gastric outlet obstruction,

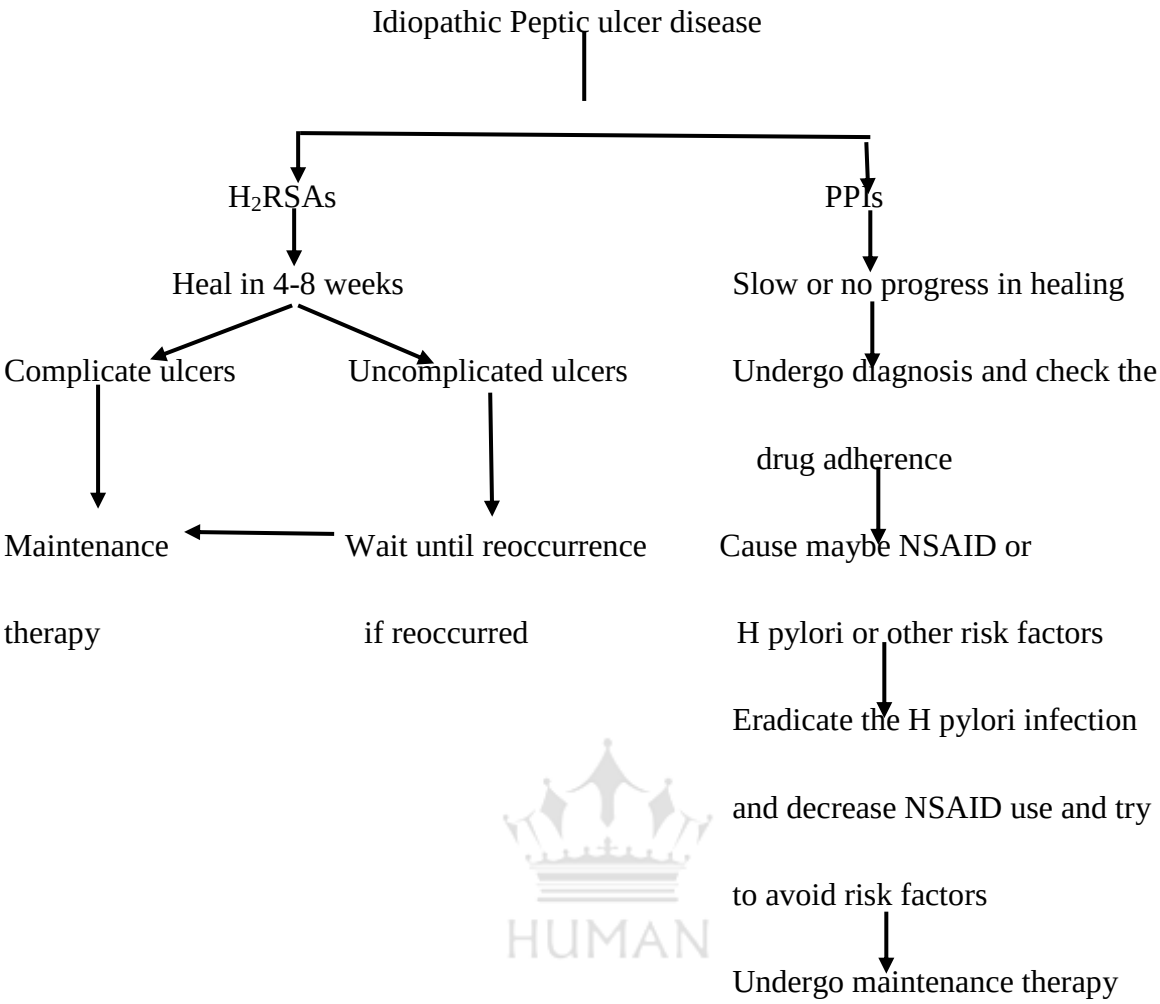
c) Genetic predisposition,

d) Concomitant diseases and

e) Heavy tobacco use.

Initiate with conventional ulcer healing therapy. Standard H_2RA and sucralfate dosage regimens heal the majority of GU and DU in 6-8 weeks and PPI heals ulcer within 4 weeks. Higher dose and longer treatment duration required to heal larger gastric ulcers. Antacids doesn't have capability to heal ulcers and should not be used as single agents to treat. If antiulcer therapy was discontinued a recurrent ulcer may occur within 1 year.

Flowchart for treatment of Idiopathic peptic ulcer:



Treatment of Refractory ulcer(13,21)**:**

Refractory ulcers are defined as when symptoms of ulcer are persistent beyond 8-12 weeks despite conventional treatment when several courses of Hp eradication treatment fails.

Factors contribute to refractory PUD:

a) Poor patient compliance

b) Antimicrobial resistance,

c) Cigarette smoking,

d) NSAID's use,

e) Gastric acid hypersecretion and

f) Tolerance to anti-secretory effects of H_2RA.

Diagnosis includes upper endoscopy to confirm non-healing ulcer, assess H pylori status.If *H pylori* positive- Eradication therapy same as in *H pylori* induced PUD whereas if *H pylori* negative – Higher PPI dosages heal majority of ulcers. Eg: Omeprazole 40mg/day

Regular treatment with PPI is essential to maintain healing and Refractory ulcer reoccur when therapy is discontinued or dose is reduced. Sometimes may require surgery because of possibility of malignancies.

Minimal cost treatment:

A recent study on rats done in Spain have shown that Manuka honey has antiulcer property by keeping enzymatic(GPx and SOD) and non-enzymatic(GSH and NO) antioxidants as well as inflammatory cytokines(TNF-α, IL-1β, and IL-6) in a reduced form, inhibited lipid peroxidation (MDA), and preserved mucous glycoproteins levels.[22]

A recent review has published that many plants from Cucurbitaceae family have showed potential antiulcer effect. Ex: *Wilbrandia ebreacteata, Gynostemma pentaphyllum*[1]

Home remedies to treat PUD are cabbage+carrot juice, bananas, cayenne pepper+water, coconut water, licorice tea, boiled fenugreek water+honey, honey, garlic, powder of inner bark of slippery elm+warm water, wood apple leaves.[23]

DISCUSSION AND 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 H_2RA'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.

Overall the PUD is a disease which is avertable or stoppable, but only due to the insignificance towards our health hygiene, the PUD becomes more lethal. But due to the development of significant therapies PUD is well countered or treated.

REFERENCES

1. KaushikAvinash et al, Peptic ulcer: A Review with Emphasis on Plants from Cucurbitaceae Family with Antiulcer Potential IJRAP 2011, 2(6) 1714-1716.
2. Kumar Sunil et al, Peptic Ulcer: A Review on a etiology and pathogenesis, IRJP 2012 3(6)
3. Dr. Avijeet Mukherjee1, Dr. Naveen. N2*,A Clinical Study of Peptic Ulcer Disease and its Complications in RuralPopulationSch. J. App. Med. Sci., 2014; 2(4E):1484-1490.
4. Jianyuan Chai, Peptic Ulcer Disease, Book · November 2011Published by InTechJanezaTrdine 9, 51000 Rijeka, Croatia
5. Subrata Roy, Clinical Study of Peptic Ulcer Disease, Asian Journal of Biomedical and Pharmaceutical Sciences, 2016.
6. Alex Mejia, MD; Walter K Kraft, MD, MS, FACP, Acid peptic disease: Pharmacological approach to treatment, Expert Rev Clin Pharmacol. 2009;2(3):295-31.
7. BS Anand, Peptic Ulcer Disease, www.emedicine.medscape.com, Jan 29, 2017.
8. N. Madanagopalan, Epidemiology of peptic disease in India, Indian J gastroenterol, 1986 vol 5(suppl).
9. JijoVelliyapallil Cherian, AravindhSomasundaram, SivaramanRamalingam, VenkataramanJayanthi, Peptic ulcer disease in India- A 16-year trend analysis
10. www.worldlifeexpectency.com
11. J.J.Y. Sung, Systematic review: The global incidence and prevalence of peptic ulcer disease, Aliment Pharmacol Ther. 2009;29, 938–946.
12. Dr. K. Anand Goud, Prevalence, Risk Factors of Chronic Peptic Ulcer Disease in Khammam, Telangana State, Sch J App. Med.Sci, 2017(2D):600-603.
13. RosemaryR.Berardi and LyndaS. Welage, Peptic ulcer disease, Pharmacotherapeutics- A Pathophysiologic Approach, 6th Edition, The McGraw-Hill Companies, Inc. United States, 2005; 1089-1104.
14. Peter Malfertheiner, Francis K L Chan, Kenneth E L McColl, Peptic ulcer disease Published Online, August 14, 2009.http://www.thelancet.com
15. Randolph V.Fugit, Rosemary R.Berardi, Upper gastrointestinal disorders, Koda-Kimble & Young's, Applied therapeutics the clinical use of drugs, 10th edition,
16. Yuhong Yuan, Ireneusz T Padol and Richard H HuntPeptic ulcer disease today, Nature clinical practice gastroenterology &hepatology, Feb 2006; 3 (2).
17. Joshita Sabbineni, A Note on Peptic Ulcers, Research and Reviews Journal of Pharmacognosy and PhytochemistryJanuary – 2016.
18. D.J.Colin jones, There is more to healing ulcers than suppressing acid, Gut, 1986, 27;475-480.
19. BB Subudhi*et al* Updates in Drug development stratagies against peptic ulcer, Journal of gastrointest Dig sus 2016,6:2
20. Chen-Shuan Chung1, Tsung-Hsien Chiang2, and Yi-Chia Lee2A systematic approach for the diagnosis and treatment of idiopathic peptic ulcers Korean J Intern Med 2015;30:559-570http://dx.doi.org/10.3904/kjim.2015.30.5.559
21. PrangthipCharoenpong*et al*, Refractory Peptic Ulcer Disease: Listen for the cause, The American Journal Of Medicine, 2014; 127(2).
22. Steve Harakeh, SaadAlmasaudi, Nagla El-Shitany, Aymn Abbas, Umama Abdel-dayem, Soad Ali and Soad Al Jaouni, Effects of manuka honey on gastric ulcers in rats, J Gastrointest Dig Syst 2016,6:7(suppl)
23. www.top10homeremedies.com