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R E V I E W A R T I C L E

A Review on Peptic Ulcer Disease and Its Management

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A B S T R A C T

A peptic ulcer is a mucosal lesion of the stomach or duodenum it is a very prevalent condition, of the general population across the world. The most common etiological causes are the chronic infection with Helicobacter Pylori (Hp) and the use of Non-Steroidal Anti Inflammatory Drugs (NSAIDs). Its diagnosis is based mainly in the endoscopy, histology and serology. The eradication treatment of H.pylori (+) is essential to achieve the final cure of the PUD in chronic infected patients. Several current international guidelines recommend a standard triple therapy as first-line therapy, including a proton pump inhibitor, a combination of amoxicillin and clarithromycin with metronidazole. For the subgroup of patients with H.Pylori - negative ulcers, ceasing of NSAIDs has a clear influence in the evolution of the disease and in some cases drives to the complete healing of the peptic ulcer. In refractory or recurrent cases, continuous therapy with anti-secretory agents and/or the replacement of conventional NSAIDs by selective drugs for inhibition of Cyclooxygenase-2 (COX-2) are useful treatment options.

Keywords: Definition, Epidemiology, Etiology, Physiology of acid secretion, Pathophysiology, Diagnosis, Treatment.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Definition: A peptic ulcer is a mucosal lesion of the stomach or duodenum in which the acid and pepsin play major pathogenic roles. The major forms of peptic ulcer are gastric ulcer and duodenal ulcer, both of which are chronic

diseases often caused by Helicobacter pylori.The term peptic ulcer also encompasses gastric ulcers and duodenal ulcers associated with stress or the ingestion of drugs, most commonly aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs)[1]. The effect of peptic ulcer is shown in figure 1.

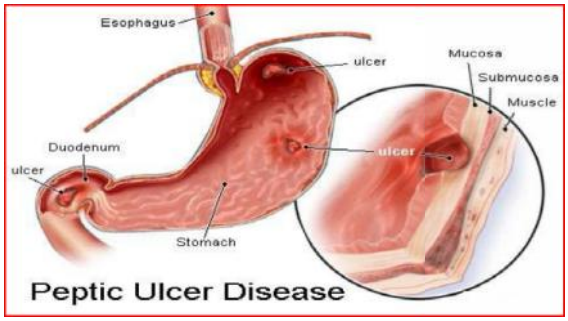

Figure 1

Epidemiology:

PUD is common condition across the world. The annual incidence ranges from 0.10% to 0.19% for physician-diagnosed PUD and from 0.03% to 0.17% for PUD diagnosed during hospitalization [2].The incidence of PUD has decreased over recent decades, due to the decrease in H. pylori infection, mainly in Western countries. But, the situation is different in Asia; a recent study in Korea revealed that the prevalence of H. pylori infection in association with GU was increasing, whereas H. pylori infection in DU was decreasing [3]. The most reliable study for physician-diagnosed PUD prevalence was from Sweden, reporting cross-sectional data representative of the general population [4]; this study include both symptomatic and asymptomatic PUD. The resulting prevalence for PUD observed in this study was 4.1% and 19.5% of all PUD cases were identified asymptomatic. In asymptomatic PUD, gastrointestinal haemorrhage is the first sign. Haemorrhage is associated with 10% of mortality and high recurrence [5]. But, in temporal trends the rate of hospitalizations for complications of PUD may vary, remain unchanged or increasing in recent decades in two studies in Finland and the Netherlands [6-7], but one study in Scotland revealed the decline[8]. The risk for peptic ulcer in infected individuals ranges from 3% in the United States to 25% in Japan [9].

Etiology:

Till the last decade 95% of duodenal ulcer and 70% of gastric ulcer is attributed to H. pylori [10]. About 14%–25% of gastric and duodenal ulcers are due to the use of NSAID [11]. The trial with NSAIDs and H. pylori eradication therapy revealed that the ulcer-inducing effects of both risk factors are cumulative [12-13]. Though, their potential interaction for theulcer disease remains undetermined. In long term NSAID usersEradication of H. pyloridoesnot reduce the rate of ulcer relapse [14]. PUD is a multisystemic disease pathway mainly due to acid imbalance and lack mucosal defence leading to inflammation. Thehyper secretion of hydrochloric acid and pepsin causes an imbalance between gastric luminal factors and degradation in the defensive function of the gastric mucosal barrier such as mucus secretion, mucosal blood flow, and epithelial cell defence. The invasion of acid and pepsin through a weakened area of the mucosal barrier releases histamine. Histamine stimulates the hyper secretion of acid from parietal cell. This results in the erosion of gastric mucosa to form the ulcer.

Physiology of Acid Secretion:

When gastrin or acetylcholine or histamines binds to their receptors on parietal cells, increases thecytosolic calcium, which in turn stimulates protein kinases that stimulates acid secretion from an H+/ K+ATPase (proton pump). The parietal cells are gut endocrine cells known asEnterochromaffin like cells (ECL cells). Histamine binds with H2 receptor on the parietal cells, activates the adenylcyclase, which elevates intracellular cyclic Adenosine Mono Phosphate (cAMP). cAMP activates protein kinase which stimulates acid secretionby the proton pump. In human, the major effect of gastrin on acidsecretion is mediated indirectly through the release of histamine from ECL cells rather than directly through parietal cell stimulation [15].

The oxyntic cells of fundus secrets hydrochloric acid. From various experimental data, it appears that the mechanism of secretion of hydrochloric acid as follows.

- ✓ The hydrogen ions (H+) and chloride ions (Cl-) are secretedseparately into stomach lumen, the net effect is secretion of hydrochloric acid.
- ✓ The transport H+into the lumen is facilitated by powering proton pump with H+/ K+ATPaseswhile bringing potassium ions into the cell.
- ✓ SimultaneouslyCl- and K+ diffuse out through Cl- and K+channels in the apical membrane.
- ✓ The enzyme carbonic anhydrasecatalysesthe formation of carbonic acid (H2CO3) from water (H2O) and carbon dioxide (CO2).
- ✓ The dissociation of carbonic acid provides a ready source of H+for the proton pumps but it also generates bicarbonate ions (HCO3-).
- ✓ As a result HCO3- builds up in the cytosol; It exit the parietal cell for the exchange ofCl-via Cl-/ HCO3- antiporters. HCO3-diffuses into nearby blood capillaries. This is “alkaline tide” of bicarbonate ions entering the blood stream.
- ✓ As a result, one molecule of NaHCO3 is formed in the blood against one molecule of HCl formed and excreted into the stomach.
- ✓ The H+ ions developed as stated in step (5) join with OH- ions as described in step (1) to form water [16]. The normal physiology of acid secretion is shown in figure 2.

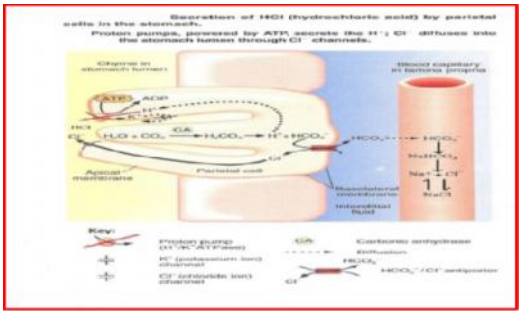

Fig 2: Normal physiology of acid secretion

2. Pathophysiology

Helicobacter pylori:

There has been a great interest in the contribution of *H. pylori* to the mechanism of gastric mucosal injury. Due to the unique adaptation features, such as urease production, allow it to survive in the acidic, unfavourable environment of the stomach, there it causes inflammation and triggers peptic ulcer disease.*H. pylori* initially colonize in the antrum, where parietal cells, which produce gastric acid, are absent, and thus acid secretion is not affected. The mechanism for cause of disease can be described in a multistage process. In the first step, the bacteria break the antimicrobial activity of gastric acid barrier and enter the mucous layer. It adapt to environmental conditions of gastric mucus. In the next step, *H. pylori* adhere to the gastric mucosa of host, and this triggers the expression of several bacterial genes, which permits *H. pylori* to persist to the environment and avoid clearance caused by peristaltic movements or shedding of the mucous layer. Theenzyme urease is the important factors in *H. pylori* growth, this convert urea into ammonia and carbon dioxide in order to elevate the pH to neutral thus protecting the bacterial cell from gastric acid. *H. pylori* colonization is facilitated by an abundant inflammatory response and gastric epithelial cell injury. *H. pylori* gastritis is characterized by infiltration of the gastric mucosa with inflammatory cells. Protease and lipase produced by *H. pylori* is responsible for degradation of gastric mucus and cell injury from back infusion of gastric acid. Moreover, ammonia produced through urease activity may be toxic to gastric epithelial cells. The mechanism of *H. p*ylori is shown in Figure 3.

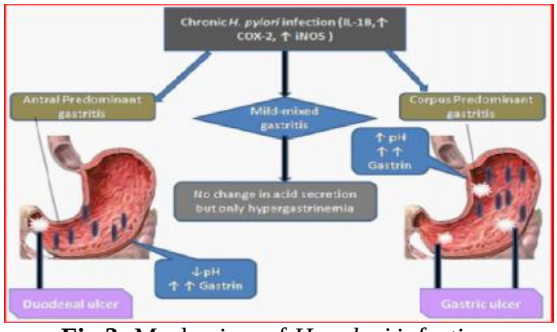

Fig 3: Mechanism of *H. pylori* infection

NSAIDs

Prostaglandins are produced from arachidonic acid in the presence of cyclooxygenases(COX-1 and COX-2) and prostaglandin synthases. NSAIDs block the cyclooxygenases; thereby, gastric injury related to their administration is closely associated with inhibition of prostaglandin production. For instance, prostaglandins reduce the activation of mast cells as well as inhibit leukocyte adhesion to vascular endothelium. Furthermore, prostaglandins play a role in maintaining adequate blood flow in mucosal microcirculation. Administration of NSAIDs results in cyclooxygenase-dependent inhibition of bicarbonate secretion, which also inevitably impairs mucosal defence mechanism[17]. The pathogenesis of NSAIDs induced GI injury is shown in figure 4.

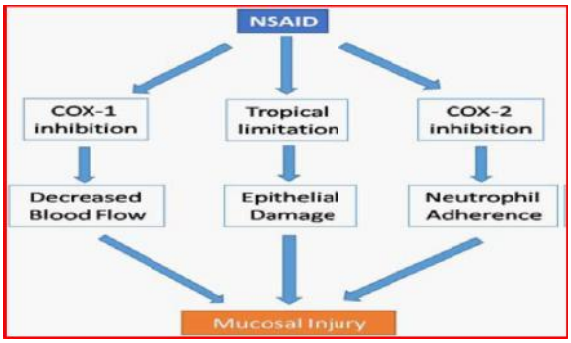

Figure4

3. Diagnosis

Currently numerous validated methods to diagnose patients with H. pylori infection are in practice. The diagnostics methods are broadly classified as:

- Invasive method
- Non-invasive method

Invasive Tests

Endoscopy: Thisincludes gastric biopsy taken at endoscopy for Rapid Urease Test (RUT), bacterial culture, histology or the polymerase chain reaction. Biopsy specimen taken from angularis mucosa of the stomach is reported with 100% sensitivity by Genta and Graham (1994).

Histology: Histological detection of H. pylori is facilitated by using stains like conventional Haematoxylin & Eosin (H&E) and special stains such as the Warthin-Starry and modified Giemsa stains are also used. Histology provides useful information concerning the severity of gastritis and the possible presence of premalignant and malignant changes .

Non-invasive method

Urea breath test: The 13C-Urea Breath Test (UBT) relies on the principle that 13C-labeled urea is hydrolyse the bacterial urease with the formation of 13CO2, that can be detected in the exhaled breath. UBT is able to detect active infection, but the performance of the test in young children has been debated.

Serology:

Infection with H. pylori elicits the production of IgG antibody and its response that can be detected for diagnostic purposes. Anti-H.pylori antibodies can be assessed using ELISA or western blot which has the advantage of characterizing the immune response towards different bacterial antigens. Serologic methods are valuable in screening large number of individuals in epidemiologic studies. These tests are relatively rapid and simple to perform, and much less expensive than other tests. It is more accurate than the biopsy based assays. The patient with gastric atrophy in whom the number of H. pylori organisms is so small as to be undetectable by biopsy or breath test-based methods can be detected by serological tests.

4. Treatment

Dyspepsia:

- ✓ Magnesium trisilicate, oral 15 ml 8 hourly (in between meals and at bedtime to control dyspepsia).

- ✓ Avoid taking antacids within 2 hours of proton pump inhibitors (PPIs).
- ✓ NSAID-associated duodenal or gastric ulcer and gastro-duodenal erosions
- ✓ Esomeprazole, oral, Adults20 mg daily for 4 weeks. Repeat course if ulcer is not fully healed. Or Omeprazole, oral, Adults20 mg daily for 4 weeks. Repeat course if ulcer is not fully healed. Or Rabeprazole, oral, Adults20 mg daily for 4 weeks. Repeat course if ulcer is not fully healed.
- ✓ Bleeding peptic ulcer- Esomeprazole, IV,Adults40 mg daily Or Omeprazole, IV, Adults40 mg 12 hourly for up to 5 days

Helicobacter pylori Eradication:

Majority of patients presenting with duodenal ulcer are infected with Helicobacter pylori. Eradication of H. pylori should therefore be done using a 7-day course of treatment consisting of a PPI plus a combination of two of the antibiotics indicated in the table 1.

Table 1: Treatment for eradication of H. pylori

PPI	ANTIBIOTICS		
	Amoxicillin, Oral	**Clarithromycin, Oral**	**Metronidazole, Oral**
Esomeprazole, oral, 20 mg 12 hourly	1 g 12 hourly	500 mg 12 hourly	-----
	-----	500 mg 12 hourly	400 mg 12 hourly
Or Omeprazole, oral, 20 mg 12 hourly	1 g 12 hourly	500 mg 12 hourly	-----
	500 mg 8 hourly	-----	400 mg 8 hourly
	-----	500 mg 12 hourly	400 mg 12 hourly
Or Rabeprazole, oral 20 mg, 12 hourly	1 g 12 hourly	500 mg 12 hourly	-----
	------	500 mg 12 hourly	400 mg 12 hourly

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