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Etiology of Peptic Ulcer Disease

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INTRODUCTION

Peptic ulcer (PU) is defect in the gastrointestinal mucosa usually located in the stomach and duodenum, but it can develop in any portion of the gastrointestinal tract that is exposed to acid and pepsin in sufficient concentration and duration. Histologically, ulcers are defined as necrotic mucosal defects that extend through the muscularis mucosa and into submucosa, whereas superficial necrotic defects are considered as erosions [1]. PU disease is one of the main prevalent and still unresolved medical problem that faces many patients of both sexes worldwide and is an important cause of morbidity and healthcare costs.

The evolution of knowledge regarding etiology and pathogenesis from acid-driven disease to an infectious disease has opened up this topic for various studies to find the best options for management. However, no matter what ulcers related to *Helicobacter pylori* infection are becoming rarer, ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) are still a major clinical problem, even with the introduction of selective inhibitors of cyclooxygenase COX-2 [2,3].

The natural history of peptic ulcer disease ranges from resolution without intervention to the development of complications such as bleeding and perforation. The pathogenesis is considered as a combination of imbalance between defensive factors such as: prostaglandins, mucosal blood flow, mucus-bicarbonate layer, cellular regeneration and aggravating factors such as: hydrochloric acid, pepsin, bile salts, drugs and ethanol.

The etiology can be divided in three broad categories, Helicobacter pylori positive, NSAIDs associated, and third Helicobacter pylori negative and non- NSAIDs associated (Figure 1 and Figure 2). In addition, apart from Helicobacter pylori infection and NSAIDs, peptic ulcer disease may be caused by any of the following: low-dose aspirin, smoking, excessive alcohol use, emotional stress and psychosocial factors, hypersecretory states, idiopathic ulcers, Cushing's ulcer, high-dose upper abdominal radiotherapy, and genetic factors (Table 1). These factors are increasingly important causes of ulcers and their complications even in Helicobacter pylori -negative patients.

Table 1: Etiology and disease associated with peptic ulcer disease.

Infections
Helicobacter pylori
Cytomegalovirus
Herpes simplex virus
Drugs
NSAIDs and aspirine
Corticosteroids
Clopidogrel
Bisphosphonates
Spironolactone
Potassium chloride
Chemotherapy
Acid hypersecretory states
Gastrinoma
Systemic mastoctosis
Myeloproliferative diseases
Post surgical
Vascular insuffienty
Radiation therapy
Infiltrating disease
Crohn disease
Sarcoidosis
Stress ulcers
Hepatic cirrhosis
Renal failure
Chronic obstructive pulmonary disease

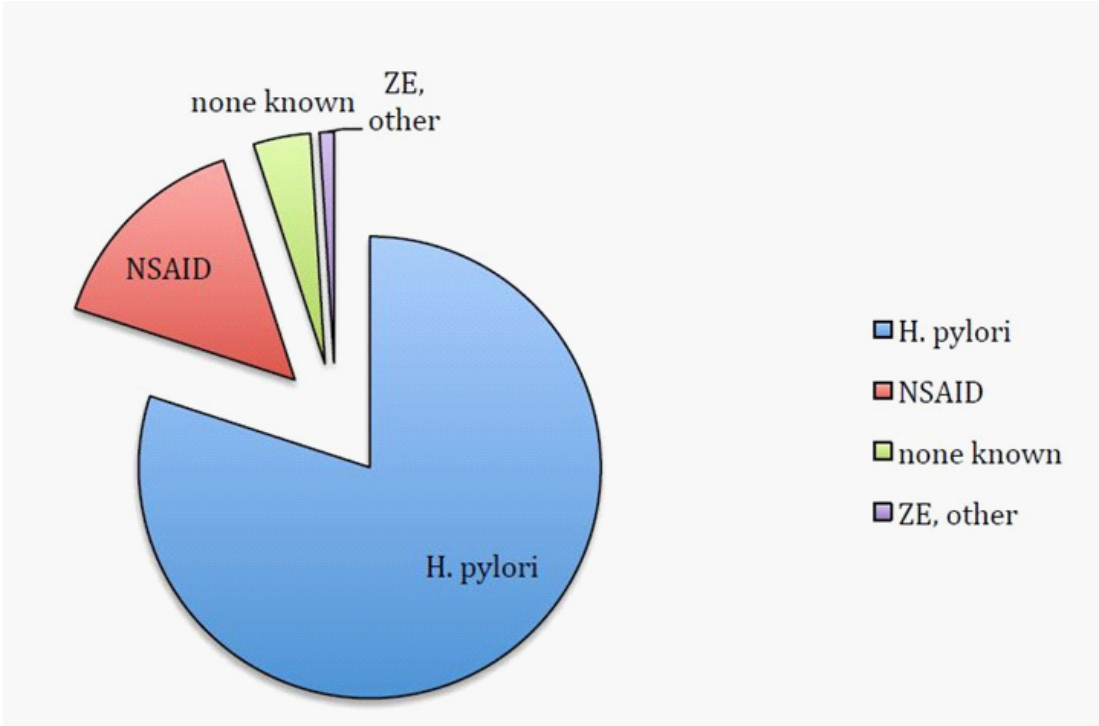

Figure 1: Pie chart represent rough percentages of conditions associated with duodenal ulcer; ZE Zollinger Elison.

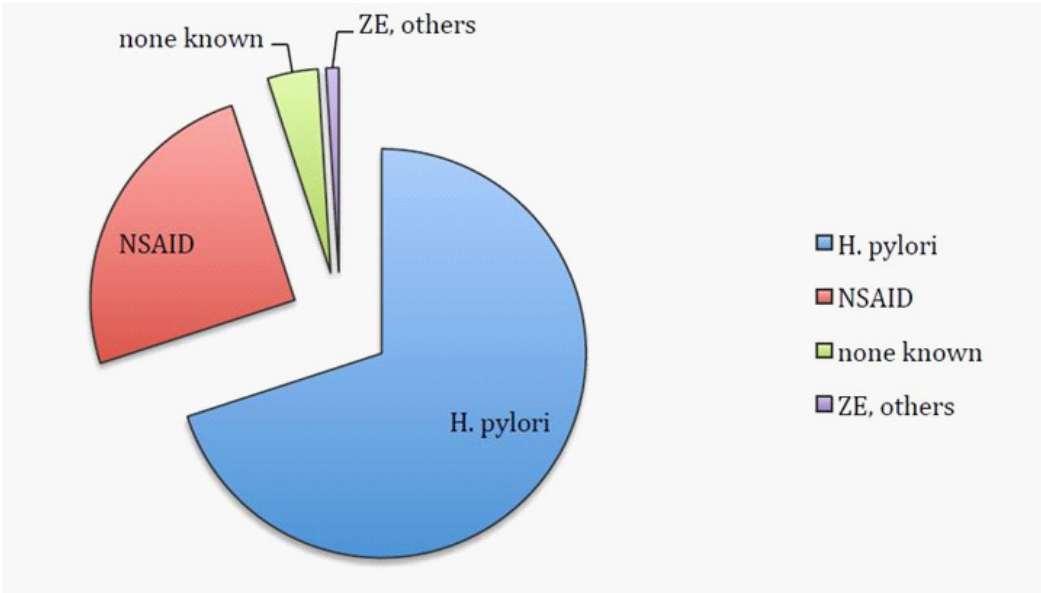

Figure 2: Pie chart represent rough percentages of conditions associated with gastric ulcer; ZE Zollinger Elison.

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 [4]. 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 [5].

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 [6]. Finally, the host immune response to *Helicobacter pylori* with inflammatory reaction further contributes to the tissue damage [7,8].

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 [6].

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 [9,10].

Different strains of *Helicobacter pylori* with virulence factors, especially CagA and VacA are connected to more profound tissue inflammation, cytokine production and tissue damage [11-13]. Namely, $CagA^+$ strains can be found in 80-100% of patients with duodenal ulcer [14].

Helicobacter pylori with it's antigenic substances induces inflammatory and immune response in gastric mucosa with polymorphonuclear leukocytes, lymphocytes, monocytes and plasma cells infiltration [15]. 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 3) [16,17]. This inflammation resolves after eradication of the infection, and presumably the concentrations of the pro-inflammatory and antisecretory cytokines also fall.

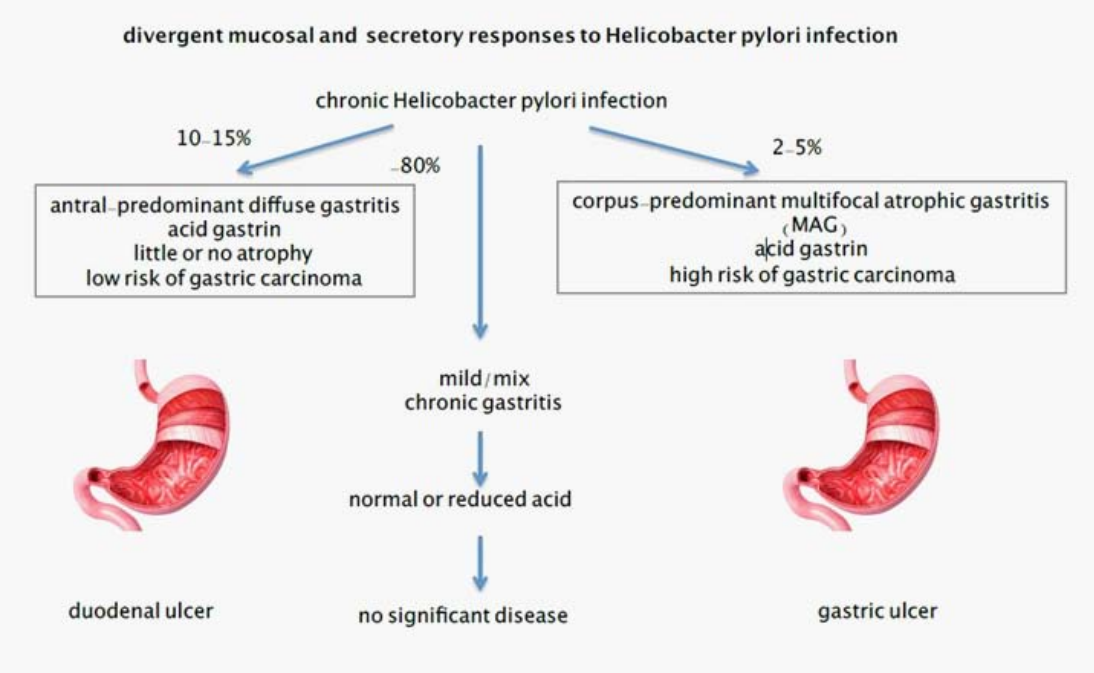

Figure 3: Helicobacter pylori induced antrum dependent gastritis with hyperchlorohydria caused by hypergastrinemia with subsequent duodenal ulcer and corpus dependent atrophic gastritis that may result in gastric ulceration. (adapted from Rembiasz K, Konturek PC, Karcz D, et al. Biomarkers in various types of atrophic gastritis and their diagnostic usefulness. Dig Dis Sci 2005; 50: 474-482.)

In addition, it has been reported that Helicobacter pylori infection induces a three-fold increase in the serum gastrin concentration [18]. *Helicobacter pylori* infection is associated with low acid secretion in gastric cancer patients and with high gastric acid secretion in patients with duodenal ulcers [19]. Certain cytokines such as tumor necrosis factor alpha and specific products of Helicobacter pylori, such as ammonia, release gastrin from G cells and might be responsible. The infection also diminishes mucosal expression of somatostatin. These changes in gastrin and somatostatin increase acid secretion and lead to duodenal ulceration. But the acid response depends on the state of the gastric corpus mucosa.

The net effect of corpus gastritis is to decrease acid secretion. Specific products of *Helicobacter pylori* inhibit parietal cells. Also, interleukin 1 beta, inhibits both parietal cells and histamine release from enterochromaffin-like cells. *Helicobacter pylori* also promotes gastric atrophy, leading to loss of parietal cells. Factors such as a high-salt diet and a lack of dietary antioxidants, which also increase corpus gastritis and atrophy, may protect against duodenal ulcers by decreasing acid output. However, the resulting increase of intragastric pH may predispose to gastric cancer by allowing other bacteria to persist and produce carcinogens in the stomach [19].

Presence of gastric epithelium in the duodenum is adoptive mechanism of the mucosa to excessive acid exposure, and is an essential prerequisite for *Helicobacter pylori* colonization of duodenal epithelium, because colonization is specific and exclusive to gastric epithelial cells. After colonization of islands of duodenal gastric metaplasia, the inflamed duodenal mucosa becomes more susceptible to peptic acid attack and ulceration. 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 [20].

NONSTEROIDAL 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 [21]. 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 4). 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 [22].

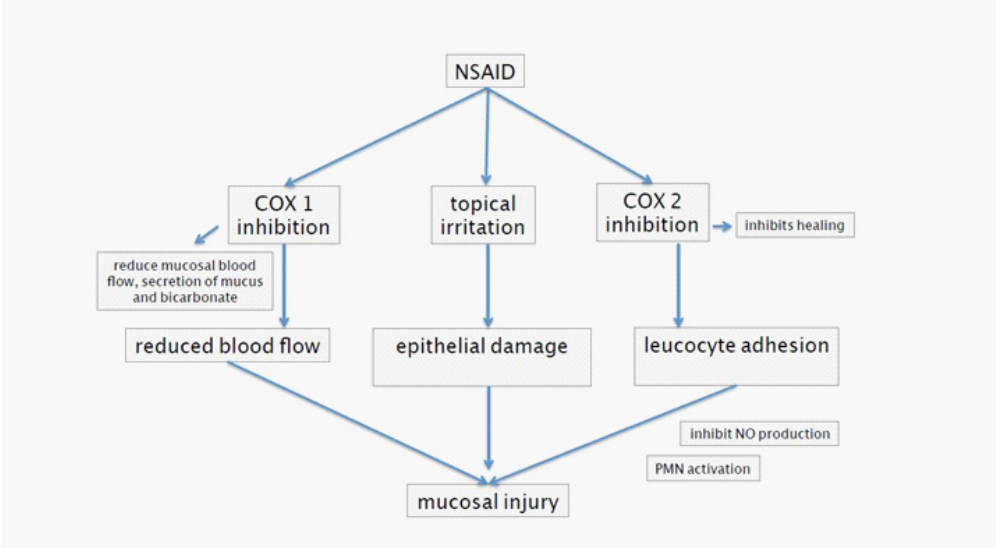

Figure 4: Nonsteroidal antiinflammatory drugs induced mucosal injury.

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 [23]. 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 [24]. Furthermore, NSAIDs-induced gastropathy is an intricate process involving gastric mucus depletion, increased microvascular permeability, nitric oxide imbalance, as well as free radical production [25].

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 [26].

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 [2].

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 [27].

The selective COX-2 inhibitors consistently show comparable efficacy to that of conventional NSAIDs, but have a reduced propensity to cause gastrointestinal toxicity [28]. These findings warrant the consideration of COX-2 inhibitors as first-line therapy in patients requiring long-term pain control [21]. The risk of peptic ulcer disease in patients taking NSAIDs is influenced with many factors such as age of patients above 75 years, dose, duration of therapy and action of NSAIDs and polymorphism of cytochrome P450 2C9 that can delay the metabolism of NSAIDs with a prolonged duration of drug thus enhancing the ulcerogenic effect [29]. The most important factors are prior history of ulcer disease or ulcer complications. In addition, other drugs such as steroids, anticoagulants, alendronate, and selective serotonin reuptake inhibitors can potentiate ulcerogenic effect of NSAIDs.

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 [30]. 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 [31]. The genes responsible for this ulcer predisposition are not known. An elevated level of serum pepsinogen I, appears to be reversible consequence of Helicobacter pylori infection [32]. However, Italian investigators identified a family in which peptic ulcer was linked to elevated serum pepsinogen A in the absence of *Helicobacter pylori* infection [33]. The association of certain blood group antigens with peptic ulcer disease has been reported. Blood groups 0 and A, the Lewis phenotype Le(a^+b^-), and non-secretors of ABH have been associated for increased risk of peptic ulcers [34]. However, other studies have not found the association between blood group 0 with *Helicobacter pylori* infection or with ulcer disease [35,36]. The role of Lewis blood group antigens in *Helicobacter pylori* adherence has been disputed.

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 [37,38]. In one prospective study of more than 47,000 men with duodenal ulcers, smoking did not emerge as a risk factor [39]. However, in the setting of *Helicobacter pylori* infection, smoking may increase the risk of relapse of PUD [40]. But, smoking does not appear to be a risk factor for ulcer recurrence after eradication of *Helicobacter pylori* [41].

Ethanol is known to cause gastric mucosal irritation, nonspecific gastritis and increases gastric secretion [42]. Despite these effects, evidence that consumption of alcohol is a risk factor

for duodenal ulcer is inconclusive. A prospective study of more than 47,000 men with duodenal ulcer did not find an association between alcohol intake and duodenal ulcer [39].

Little evidence suggests that coffeine intake is associated with an increased risk of duodenal ulcers, although increase consumption may be associated with a higher rate of infection with *Helicobacter pylori* [39].

Ulcer patients often describe dyspepsia associated with the ingestion of certain foods, but no study has established a convicting link between diet and peptic ulcer disease. However, some data implicated that dietary factors may influence peptic ulcer pathogenesis. For instance, freshly milled and unmilled rice were protective against damaging effects of alcohol whereas stored rice exacerbated mucosal damage [43].

Insufficiency in essential fatty acids has been proposed as a pathogenic factor in duodenal ulcer and polyunsaturated fatty acids were protective against Helicobacter pylori infection [44]. There is also no evidence that dietary manipulations can enhance healing of peptic ulcer as previously stated [45].

SEVERE PHYSIOLOGIC STRESS

A number of reports have suggested that emotional stress might cause or exacerbate peptic ulcer [46,47]. 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.

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