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ROLE OF *HELIOCOBACTER PYLORI* INFECTION IN PEPTIC ULCER DISEASE

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ABSTRACT

Helicobacter pylori the causative organism and has a possible role in the development of peptic ulcer disease (PUD) and gastric cancer. With medical advances and introduction of new antimicrobial agents with extended spectrum against *H.pylori*, *the* high mortality rate associated with the organism in gastric cancer continues. Gastric acid hyper secretion is still considered to be necessary factor; it is not a sufficient etiological factor. Extensive scientific research shows that two major etiological factors involved in PUD are infection with *H.pylori* and ingestion of non-inflammatory drugs (NSAIDs), a careful history of NSAIDs use is also important. Persons with serological evidence of carrying cag-positive strains are at high risk of developing both PUD and gastric carcinoma. Diagnosis of *H.pylori* infection both by invasively by endoscopy and biopsy or noninvasively by serologic analysis, and breath test. Common therapies include proton pump inhibitor, such as omeprazole and lansoprazole, and are used as parts of triple, quadruple, and sequential therapies.

KEYWORDS: *Helicobacter pylori*, Peptic Ulcer Disease, NSAIDs

INTRODUCTION

Helicobacter pylori (formerly known as *campylobacter pylori*) were first isolated from humans in 1982 [1]. *H.pylori* commonly found in the human stomach, when, as the single dominant species; essentially all persons colonized with *H.pylori* have a cellular infiltrate in the laminapropria of the gastric antrum and fundus [2]. Of special significance is that *H.pylori* is present in most persons with “idiopathic” peptic ulcer disease(PUD). The presence of *H.pylori* increases peptic ulcer disease and gastric cancer [3, 4], but decreases the risk of esophageal reflux and its consequences, and may protect against childhood asthma and related disorders [5, 6]. *H.pylori* has been isolated from persons from all parts of the world, it now appears likely that, humans are the major, if not sole, reservoir for *H.pylori* [7, 8]. The high prevalence and incidence of colonization among persons in settings where sanitary conditions are suboptimal, including institutions for the mentally retarded and orphanages, and in developing countries do not reflect modern standards, suggesting the fecal oral transmission occurs [8]. On occasion, transmission occurs from person to person via improperly cleaned endoscopes [9]. The prevalence of *H.pylori* colonization is chiefly related to age and geographic location. Males and females have essentially equal rates of colonization, with slight male predominance [10]. The incidence of *H.pylori* has been progressively declining in the United States and other developed countries [11]. Currently, extensive scientific evidence shows that two major etiological factors involved in PUD are infection with *H.pylori* and ingestion of non-steroidal anti-inflammatory drugs (NSAIDs). Although gastric acid hyper-secretion is still considered to be a necessary factor, it is not a sufficient etiological factor [12]. Each year PUD affects 4 million people worldwide with complications in 10-to 20 % of these patients, and ulcer perforation in 2-14 % of cases [13]. The annual incidence of if PUD ranges 0.10-0.19% and 0.03 -0.17% for physician diagnosed and in hospital diagnosed PUD respectively [14]. Over recent

decades, the incidence of PUD has decreased significantly, which is believed to be due to the decrease in *H.pylori* infection, particularly in developed countries [14]. Currently gastric ulcer (GU) is more commonly associated with use of NSAIDs, especially in older patients and those with comorbidities, in whom widespread prescription of NSAIDs and suboptimal adherence to gastro protective therapy is common [15].

PATHOGENESIS

H.pylori is able to survive and multiply in gastric environment, which is hostile to the growth of other bacteria [16]. When intraluminal acidity diminishes as a result of gastric atrophy, *H.pylori* is no longer able to colonize, possibly because of competing organisms. Outstanding *H.pylori* characteristics that permit gastric colonization include microerophilism for survival within mucus gel, spiral shape and flagella for motility within the viscous layer and urease activity, which generate ammonium ions that buffer gastric acidity [17]. *H.pylori* overlies only gastric–type not intestinal-type, epithelial cells. Affected gastric epithelial cells may be in the gastric antrum or fundus or may be ectopic in the duodenum or in the esophagus [18, 2,]. In contrast, *H.pylori* does not colonize intestinal epithelium, even present in the stomach [2]. The gastric tissue underneath *H.pylori* colonization virtually always has a cellular infiltrate. The lamina propria most commonly contains mononuclear cells, including lymphocytes, monocytes, and plasma cells. Neutrophils and to a lesser extend eosinophils may be present in the lamina propria and epithelium. Epithelial glands have a more complex architecture and less mucus than when *H.pylori* is absent [2]. In children, a follicular lymphoid pattern is common. The presence of *H.pylori* induces these changes and the bacterium is not just a secondary colonizer- cells responses may have systemic regulatory functions [19].

The mechanism of tissue injury are not clearly established, and both bacterial and host factors may be determinants of outcome [20]. *H.pylori* does not appear invade tissue, except as an incidental finding. Thus, the lesions are likely to reflect a response to extracellular products or to contact from organism. Ammonia, produced by urease and by deaminases, may potentiate neutrophil-induced mucosal injury [21]. Both the CagA and VacA proteins are important signaling molecules elaborated by *H.pylori*, and host mount antibody responses to both [22, 23]. Strains from patients with ulcers or stomach cancer more commonly express CagA compared with controls. Urease may be shed by *H.pylori* cells, has been observed in affected tissues, and is a chemattractant and activator of host phagocytic cells [4, 23].

The presence of *H.pylori* overlying the gastric mucosa activates epithelial cells to produce proinflammatory cytokines [24], and activaltes mononuclear and polymorphonuclear cells to produce cytokines, superoxide, tumor necrosis factor-α, and other proinflammatory molecules [25]. Because *H.pylori* persist in the stomach for many decades, these proinflammatory activities must be down regulated to permit this universally stable colonization [26]. *H.pylori* positive persons have different T-cell populations in the gastric mucosa, with increased numbers of T-reg and T_H17 cells [19]. These may be down regulating the local inflammatory responses but also may have systemic consequences [27].

Humans are polymorphic in the genetic loci involved in regulating proinflammatory cytokine production. Proinflammatory alleles regulating interleukins-1βand interleukin-10 affect risk of gastric cancer in *H.pylori* positive persons [28]. Virtually all patients with duodenal ulceration are colonized by strains possessing *cag*A (thus *cag* pathogenicity island) [29]. Thus *cag*A, the first gene described to not be conserved *among H.pylori* strains, is highly associated with both peptic ulcer disease and gastric cancer [30]. In East Asia, most *H.pylori* strains are *cag*A [27].

Patients infected with *H.pylori* the outcome of colonization is a chronic active gastritis. However, the gastric distribution of *H.pylori* and the severity of the chronic inflammatory response might differ according to the colonizing strain, host genetics and immune response, diet, and the level of acid production. While the majority of those infected develop no other complications and often are of obvious clinical symptoms, approximately 10% of those infected will develop PUD [31]. An important predisposing factor related to PUD is an individual's level of gastric acid secretion, as the determines, the location of gastritis [31]. In subjects the reduced level of gastric acid, a pangastritis results, which predisposes to GU, whereas in subjects in whom gastric acid secretion in increased, an antral-predominant gastritis develops, which predisposes to DU [31]. *H.pylori* infection impairs negative feedback of acid secretion by impairing somatostatin release and its subsequent inhibitory control of gastrin release from G cells, leading to functional disruption of antral-fundic neural connections [32]. The immunopathogenic aspect of ulcerogenesis is primarily driven by influx of neutrophils and macrophages, into the gastric mucosa in response to *H.pylori* colonization, with the release of lysosomal enzymes, leukotrienses and reactive oxygen species that impair mucosal defense [33].

H.pylori virulence factors, including adaptive enzymes, toxins and mediators of inflammation, lead to bacterial persistence in the stomach and disruption of the gastric mucosal barrier. Production of alkaline ammonia by *H.pylori* urease prevents D cells in the antral glands from sensing the true level of acidity, leading to inappropriate release of somatostatin [32]. It has been suggested that *H.pylor*i strains from ulcer patients produce higher amounts of this enzyme than those people without ulcers [34]. A wide range of *H.pylori* virulence factors have been associated with more serious disease outcome of these, the cag pathogenicity island (cagPAI), the vaculating cytotoxin A (VacA) and the duodenal ulcer promoting gene A(dupA) have received the most scrunity in relation to PUD [35].

Lu *et al* [36], in 2005 identified the first disease specific *H.pylori* factor and named *dupA*, and showed *dupA* to increase the risk of DU (odds ratio (OR):3.1, 95% confidence intervals (CI):1.7-5, 7) but protect against gastric atrophy, intestinal metaplasia and GC. Although the association of between *dupA* and DU has been supported by number of subsequent reports [37, 38, 39,], many studies have failed to show an association between dupA and DU [40]. However, two recent global meta-analysis by Hussein et al [41], and Shiota*et al* [42], which included 2358 and2466 individuals respectively, concluded that worldwide *dupA*-positive subjects had indeed an increased risk of DU (OR:1.4,95% CI:1.1-1,7 and OR1.41,95% CI:1.12-1,76, respectively). However in both studies distinct geographical variations in the prevalence of *dupA* gene, and the association between *dupA* and DU were observed. Given this, a recent study by Jung et al [43], investigated if genetic differences in the makeup of dupA *g*ene may explain this disparity. In this study, the presence of a complet*e dupA*cluste*r* rather than *dupA* alone was found to be associated with the development of DU and increased IL-8 production, suggesting that the complete *dupA* cluster is required for full expression of this virulence factor [43].

ROLE OF NSAIDs IN PUD

NSAIDs have been shown to inhibit the synthesis of protective prostanoid in gastric and duodenal mucosa leaving the mucosa susceptible for subsequent ulceration by gastric acid [44]. While animal; studies have shown that neutrophil adherence to gastric microcirculation plays a critical role in initiation of NSAIDs damage [45]. NSAID related gastropathy in humans is characterized by an absence of inflammatory cells unless there is concomitant *H.pylori* infection [34]. However it is not known if neutrophils can initiate NSAID damage in humans [46]. NASIDs have also been shown to increase the risk of PUD complications. For example the use of low- dose acetylsalicylic acid(ASA) increases the risk of

ulcer bleeding by 2-3 fold compared with non-users [47]. This has been mainly attributed to ASA antiplatelet action on preexisting *H.pylori* related ulcer, rather its ulcerogenic effects as a NASIDs [48].

CONTRIBUTORY FACTORS IN PUD

There are several contributory factors in PUD in addition to *H.pylori* infection and the use of NSAIDs. Researchers have confirmed that mucosal resistance to the effect of acid might be a key factor in PUD pathogenesis. Forexample, the presence or absence of protective substances in staple diet including certain phospholipids sterols, and ester fractions in lipids, which protect the gastric mucosa, has been related to geographical differences in the prevalence of duodenal ulceration [49]. These substances have been shown to exert protective activities against both gastric and duodenal ulceration, including NSAIDs-associated ulceration, and also promote healing of ulceration [49]. Although smoking is not the primary cause of PUD it has been reported to regulate aggressive and protective factors in the gastric mucosa, and therefore, it might be still considered an important contributor to the pathogenesis of PUD [50]. Studies examining the possible role of host genetic factors in ulcerogenesis have been reported genetic polymorphisms in the nucleotide-binding oligomerization domain-containing protein (NOID) the metabolizing enzyme cytochrome P450 2C19(CYP2C19) and IL-8 to be associated with an increased risk of PUD [51]. In contrast, specific polymorphisms in IL-1β toll like receptor(PLR) 4 and TLR 1 have been negatively correlated with the disease [51].

CLINICAL SYMPTOMS

Acute Presentation

Natural, voluntary, or accidental *H.pylori* acquisition may cause an acute upper gastrointestinal illness with nausea and upper abdominal pain [52]. Vomiting, burping, and fever may be present. Symptoms last from 3 to 14 days, with most illnesses persisting less than 1 week. A diagnosis of food poisoning may be made in persons seeking medical attention. For many individuals, the acquisition of *H.pylori* is clinically silent [52]. One adult volunteer who ingested *H.pylori* seemed to have had an acute self-limiting infection [52].

Chronic Colonization

In most persons after acquisition *H.pylori* persists for years, if not for decades [52]. Not every exposure to *H.pylori* leads to persistent colonization, either due to lack adaptation to the particular host or to coincident or proximate use of antibiotic [53]. The acute *H.pylori*-induced upper gastrointestinal symptoms do not return in most persons; most with persistent *H.pylori* colonization are asymptomatic. However, studies of patients with nonulcer dyspepsia indicate that *H.pylori* may be slightly more common in cases than in age-matched models, and that *H.pylori* colonization may be one of the causes of this common but poorly defined heterogeneous group of disorders [54]. Supporting this hypothesis are the results of some studies indicating that some patients with nonulcer dyspepsia who are colonized with *H.pylori* show better responses to antimicrobial therapy than to placebo, an effect not seen in patients with nonulcer dyspepsia who do not have *H.pylori* colonization [55, 56].

Peptic Ulcer Disease

Gastric Ulceration: A smaller -50% to 80% proportion of patients with benign gastric ulcer than with duodenal ulceration are colonized by *H.pylori*. The major reason is that a much higher proportion of gastric are due to NSAIDs or aspirin use, when such use is excluded most the remaining patients with benign gastric ulcer are colonized with

H.pylori, which significantly more common than age-matched controls [57]. The results of treatment of gastric ulceration with antimicrobial agents parallel the results of treatment of duodenal ulceration, changing its natural history [58].

Duodenal Ulceration: In the absence of medication-associated ulceration, more than 90% of patients with duodenal ulceration carry *H.pylori*, an occurrence that is significantly more common than in age-matched controls [59, 57]. Conversely, duodenal ulceration in the absence of aspirin or NSAIDs use or Zollinger-Ellison syndrome is usually associated with *H.pylori* colonization. *H.pylori* may colonize the duodenum but only overliesmetaplastic islands of gastric–type epithelium (gastric metaplasia) [2]. The occurrence of *H.pylori* colonization gastric metaplasia is highly associated with active dudinitis, a precursor lesion to ulceration, and the presence of *H.pylori* in the duodenum is associated with a markedly increased risk of duodenal ulceration [60, 61]. Previous *H.pylori* colonization is associated with three to four fold increased risk of development of either gastric or duodenal ulceration and the risk of *cagA*$^+$ strains [59, 3]. In total a significant body of evidence association *H.pylori* colonization with idiopathic duodenal ulceration has accumulated. A causative role of *H.pylori* in ulcer disease is unproven; none of the experimental human studies have shown progression to ulceration and why peptic ulcer has a remitting and relapsing course in the face of persistent colonization has never been resolved [62].

DIAGNOSIS

The demonstration of *H.pylori* colonization can be made either by invasively by endoscopy and biopsy or noninvasively by serologic analysis, breath test or fecal antigen detection [4]

THERAPY

The most commonly used therapies include proton pump inhibitor, such as omeprazole and lansoprazole, and used as parts of triple, quadruple and sequential [63, 64, 65] therapies:

Proton pump inhibitor (PPI) triple Therapy: PPI (standard dose twice daily) + amoxicillin (I g daily) + clarithromycin (500mg twice daily) for 7 to 10 days.

Quadruple Therapy: PPI (standard dose twice daily) + metronidazole (500mg 3 times daily) + tetracycline (500 mg 3 times daily) + bismuth (dose depends on preparation) for 10 days.

Sequential therapy: PPI(standard dose twice daily) + amoxicillin (I g twice daily) for 5 days followed by PPI(standard dose twice daily) + clarithromycin (500mg twice daily) + tindazole (500mg twice daily) for 5 days

Levofloxacin triple therapy: PPI (standard dose twice daily) + amoxicillin (Ig twice daily) + levofloxacine (500mg twice daily) for 10 days.

Rifabutin triple therapy: PPI(standard dose twice daily) + amoxicillin (I g twice daily) + rifabutin (150-300 mg/day) for 10 days.

CONCLUSIONS

In PUD, *H.pylori* infection and history of NSAIDs are important factors, persons with serological evidence of *H.pylori* virulence factors cagA, vacA and newly discovered *dupaA* are at increased risk of developing PUD. A successful eradication of *H.pylori* is the main goal.

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