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Epidemiological and Pathophysiological Review of *Helicobacter pylori*

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ABSTRACT

Helicobacter pylori infection induces chronic gastritis, peptic ulcer disease, gastric cancer and a number of extragastric related morbidities. Hence, it is now recognized as a worldwide problem. Although clinical outcomes are dependent upon bacterial prevalence, virulence factors, host genetic diversity and environment, focus of this review is on recent findings relevant to epidemiology and gastric pathophysiology of H. pylori infection.
This article presents a review of the published literature mainly from last 15 years. The topics of main concerns were bacterial epidemiology, virulent factors and the inflammatory response of H. pylori infection. The authors used MeSH terms "Helicobacter" with "pathophysiology," "pathogenesis," or "gastric inflammation" to search PubMed database. All relevant studies identified were included and are described according to the aforementioned subheadings.

Keywords: *Helicobacter pylori*, Epidemiology, Transmission, Pathophysiology, Inflammation

INTRODUCTION

The gram-negative bacterium Helicobacter pylori persistently colonize the human stomach and also have been the focus of basic biochemical and clinical research since its introduction. The bacterium has infected almost 50% of the world's population; although most infections are asymptomatic [1]. Since the first culture of *H. pylori* the epidemiologic patterns, diagnosis and treatment strategies have changed dramatically. Although effective antimicrobial therapy is available, there is still no ideal treatment for *H. pylori*-induced gastric cancer. A comprehensive understanding of epidemiology and pathophysiology of *H. pylori* infection is very important to lead towards better management of *H. pylori*-associated diseases.

This article presents a review of the published literature from last 15 years. The topics of main concerns were current epidemiological status of *H. pylori*, bacterial virulent factors and the inflammatory response of *H. pylori* infection. The authors used MeSH terms "Helicobacter" with "epidemiology,"

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"transmission," "pathophysiology," "pathogenesis," or "gastric inflammation" to search PubMed database. All relevant studies identified were included and are described according to the aforementioned subheadings.

Prevalence

The prevalence rate of *H. pylori* and associated diseases has been highly inconsistent worldwide. In industrialized countries there is generally a low prevalence of *H. pylori* infection and yet a relatively high prevalence of gastric cancer. On the other hand, prevalence of *H. pylori* infection is high in less developed Asian countries like India, Bangladesh, Pakistan, and Thailand and is acquired at an early age than in more developed Asian countries like Japan and China. However frequency of gastric cancer is very low in India, Bangladesh, Pakistan and Thailand compared to that in Japan and China [2].

The search identified 27 population based studies reporting frequency of *Helicobacter pylori* infection primarily from Asia and the Middle East [3-26]. Several studies used stool antigen testing [3, 9, 14, 17, 24-26] others used serologic testing [5, 6, 10, 11, 13, 15, 18, 19, 21, 23] carbon-13 urea breath testing [4, 8, 12, 16, 20, 22] or urine antigen testing [7]. Prevalence of infection with *H. pylori* varied between 7% in a study conducted among asymptomatic children in the Czech Republic 24, to 92% in Pakistani population20. Prevalence in European studies 14, 24 varied between 7 and 33%, between 48 and 78% in South American studies 22, and between 37.5 and 92% in Asian studies [3, 19, 20, 26]. A study was conducted in China on children and adults in two regions of China with both a low and a high incidence of gastric cancer, reported that the prevalence of *H. pylori* was significantly lower in 2006 when compared to the early 1990s, with a decrease in prevalence of between 5 and 28%, depending on the population under study [26]. Only one study compared prevalence of *H. pylori* infection within the same population using different diagnostic tests and reported no statistically significant difference in prevalence of infection when the stool antigen test was used, compared with serologic testing [23]. In developing countries, where the majority of children are infected before the age of 10, the prevalence in adults peaks to more than 80% before 50 years of age. In developed nations, serologic evidence of *H. pylori* is rarely found before 10 years of age but increases to 10% in those between 18 and 30 years of age and to 50% in those older than age 6018. Within any age group, infection appears to be more common in Hispanics and blacks compared to the white population; these differences are probably in part related to socioeconomic factors [1]. The increased prevalence of infection with age was initially thought to represent a continuing rate of bacterial acquirement throughout one's lifetime. However, epidemiologic evidence now indicates most infections are acquired during childhood even in developed countries. Thus, the frequency of *H. pylori* infection for any age group in any locality reflects that particular cohort's rate of bacterial acquisition during childhood years [27].

Incidence

A Japanese study reported a decrease in 12 month incidence with age, 0.65% among 10-year-olds, 1.3% among 7-year-olds and 2.6% among 4-year-olds7. A study from Bangladesh examined new infections from birth to 2 years of age in 258 children. They observed that children showing evidence of infection at 6 months of age increases to 49% by 2 years of age28. An Israeli study by Niv et al29 shows less than 1% of new and re-infection in adult patients. However, the small sample size in this study limits preciseness of estimating incidence rate. An Italian study investigating the source of *H. pylori* infection in the neonatal period examined 172 new-born for the onset of new infection or re-infections [30]. According to this study, at 1 month 3% of children were positive for *H. pylori*, but by 18 months all the infants had cleared the infection spontaneously. The incidence of gastric cancer varies with different geographic regions. Approximately 60 percent of gastric cancers occur in developing countries. The highest incidence rates are in Eastern Asia, the

Andean regions of South America, and Eastern Europe while the lowest rates are in North America, Northern Europe, and most countries in Africa and South Eastern Asian (figure 1).1, 2

Figure 1: Global incidence of Gastric cancer, Age-Standarized rate/100,000 population.1

Transmission

Despite extensive elaboration in literature of variety of factors delineating the causative links of *H. pylori* infection has been discussed in epidemiologic studies, the knowledge of transmission modes and reservoirs remain poor. However, some routes, such as gastro-oral, feco-oral, oral-oral and iatrogenic transmission have been described [31].

Intra-familial transmission has long been thought to be a major mode of transmission [32]. Determined the independent contribution of mothers, fathers and siblings in German population to acquirement of *H. pylori* during childhood. Chances among children for having an infected father or sibling were decreased in German population when compared to other studies. Infection status of siblings appears to matter more in populations where large families are common. Whereas compared to other family members the infection status of mother is more strongly associated with household hygiene and other risk factors [32]. A Brazilian cross-sectional study demonstrated that infected mothers were almost 20 times more likely to have an *H. pylori*-positive child, particularly mothers infected with CagA-positive strains [15]. A study in turkey by [25] screened asymptomatic children for *H. pylori* also reported a higher prevalence of infection in mothers of infected children. All of these studies concluded that spread of infection is from person-to-person which seems to occur predominantly within families and the most probable cause of intrafamilial transmission are mothers.

Iatrogenic transmission has been documented following the use of a variety of inadequately disinfected gastric devices, endoscopes, and endoscopic accessories. Adequate sterilization and disinfection of endoscopes has reduced the incidence of transmission. In addition, gastroenterologists and nurses appear to be at increased risk for acquiring H. pylori; this is most probably due to occupational exposure to infected gastric secretions [33]. Fecal/oral transmission and oral/oral transmission of bacteria is also possible. Contaminated water supplies in developing countries may serve as an environmental source of bacteria. Children who regularly swim in rivers, streams, pools, drink stream water, or eat uncooked vegetables are more likely to be infected [31]. Organisms have been identified in dental plaque and habit of feeding children with pre-masticated food commonly transmits the bacteria [34].

Bacterial Factors

Tissue injury induced by *H. pylori* depends upon bacterial attachment and the subsequent release of enzymes and other microbial products that can cause cellular damage. (Figure 2)

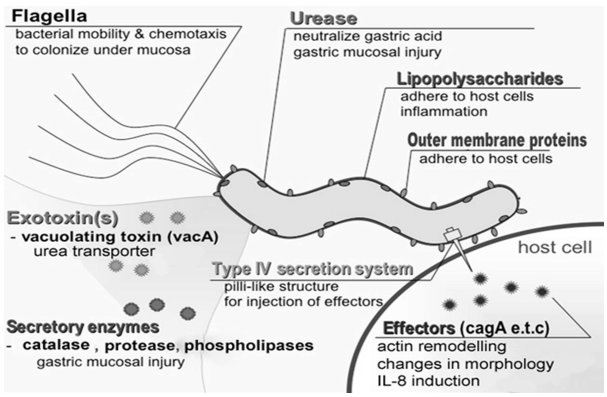

Figure 2: Bacterial factors responsible for virulence of H. pylori. (source:http://sk.wikipedia.org/wiki /Helicobacter_pylori)

Bacterial attachment

H. pylori exclusively colonize gastric type epithelium, which suggests specific recognition of cell type by the bacterium. This process requires that bacterial adhesins recognize and specifically bind to host receptors expressed on the cell surface [35]. At the site of adherence bacterial membrane proteins, coded by genes contained in the cag pathogenicity island (PAI), open channels in the epithelial cell membrane that enable a direct contact of bacterial factors with the cell cytoplasm [36].

Three Hop proteins have been implicated in the pathogenesis of H. pylori infection, BabA (HopS), OipA (HopH), and SabA (HopP) [37]. BabA, the best characterized of the three adhesin proteins, mediates binding to fucosylated Lewis b (Le (b)) blood group antigens on host cells. OipA may serve as an adhesin but it also promotes inflammation by increasing IL-8 expression [38]. SabA mediates binding to glycoconjugates containing sialic acid. Replacement of non-sialylated Lewis antigens by sialylated Le (x) or Le (a) has been associated with *H. pylori* induced gastric inflammation and cancer [39]. Thus, the role of Lewis antigen expression in bacterial attachment is unclear. Nevertheless, the homologous structures of *H. pylori* lipopolysaccharide and host Lewis antigen may lead to an autoimmune response with subsequent cell injury [40]. *H. pylori* can also bind to class II MHC molecules on the surface of gastric epithelial cells and induce apoptosis. In fact, binding of the organism's urease to surface class II MHC is itself sufficient to induce apoptosis [41].

Release of enzymes

H. pylori elaborate several enzymes that can cause cellular damage by direct or indirect mechanisms. Urease accounts for over 5% of the organism's total protein weight. Urea, when hydrolyzed by bacterial urease, can form compounds such as ammonium chloride and monochloramine that can directly damage epithelial cells. In addition, the urease enzyme itself is antigenic, activates the host immune system, and indirectly produces injury by stimulating inflammatory cells [41].

Bacterial phospholipases can alter the phospholipid content of the gastric mucosal barrier, changing its surface tension, hydrophobicity, and permeability. The conversion of lecithin to lysolecithin (a toxic compound) by phospholipase A2 can lead to cell injury, while lipolysis can disrupt the structure and integrity of gastric mucus [42].

H. pylori produce more catalase enzyme than most other bacteria. This enzyme, an antioxidant, may protect the organism from toxic oxygen metabolites liberated by activated neutrophils and allow it to survive and proliferate in an inflamed and damaged gastric mucosa. Hence, bacterial proteolytic enzyme activity can further degrade the mucus layer. However, the importance of proteolysis remains controversial [42].

Bacterial strain differences

Functional differences exist between strains of *H. pylori* that may relate to virulence and tissue damage. VacA behaves as a passive urea transporter that is potentially capable of increasing the permeability of the gastric epithelium to urea, thereby creating a favorable environment for *H. pylori* infectivity [43]. Virulence of VacA appears to depend upon the function of a tyrosine phosphatase receptor in gastric epithelial cells [44]. *H pylori* strains with different VacA alleles have differing toxicity [45]. CagA is not cytotoxic but is antigenic and can be detected serologically. Its function is unknown but, since it is necessary for VacA expression, it may play a role in transcription, excretion, or function of the VacA cytotoxin. *H. pylori* can translocate its CagA protein into gastric epithelial cells via a type IV secretory apparatus. There it is tyrosine phosphorylated and possibly plays a role in host cell responses such as hummingbird morphology, actin remodeling and impaired cell adhesion [46-48]. Virulent strains of *H. pylori* encode cag PAI, which expresses a type IV secretion system (T4SS). This T4SS forms a syringe-like pilus structure for the injection of virulence factors such as the CagA

effector protein into host target cells. This is achieved by a number of T4SS proteins, including CagI, CagL, CagY and CagA, which by itself binds the host cell integrin member ß(1) followed by delivery of CagA across the host cell membrane. A role of CagA interaction with phosphatidylserine has also been shown to be important for the injection process. After delivery, CagA becomes phosphorylated by oncogenic tyrosine kinases (e.g., Src Kinase) and mimics a host cell factor for the activation or inactivation of some specific intracellular signaling pathways i.e. protein tyrosine phosphatase pathway [46-49]. (Figure 2)

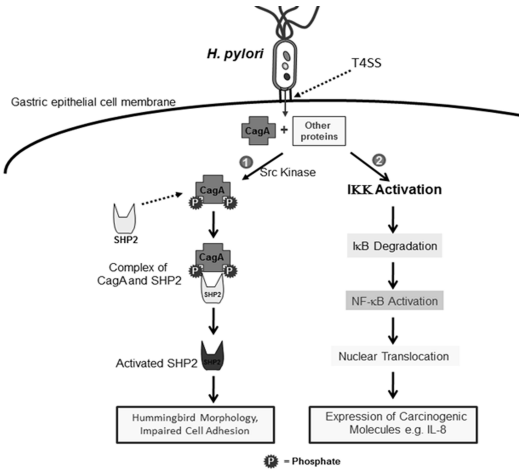

Figure 3: Host cell intracellular pathways activated by CagA. (*H. pylori: Helicobacter pylori*, T4SS: type-4 secretion system, SHP2: Src Homology Phosphatases 2)

Strains producing VacA and CagA cause more intense tissue inflammation and induce cytokine production [50]. Two other genes (picA and CagE), which are co-transcribed and genetically linked to cagA, share a homology with genes coding for toxins in other known pathogenic bacteria. The gene product of CagE induces the release of epithelial cytokines, including interleukin-8 (IL-8) [51]. This effect appears to be mediated by nuclear factor kappa B (NF-kB), which activates transcription of IL-8 mRNA. In addition, bacteria that express CagA are potent inducers of IL-8 [52]. (Figure 2)

The clinical significance of CagA positivity is demonstrated in two different disorders. Approximately 85-100% of patients with duodenal ulcers have CagA+ strains, compared to 30-60% of infected patients who do not develop ulcers. CagE positivity has also been associated with gastro-duodenal disease in adults and children [53]. CagA strains are also associated with a higher frequency of precancerous lesions and gastric cancer54. The risk of malignancy is thought to be related to specific amino acid sequences in the CagA protein [55].

Inflammatory Response

Although *H. pylorus* is a noninvasive organism, it stimulates a robust inflammatory and immune response in the host cell. Various factors may contribute to these changes, which are described below. Bacterial colonization, persistence and virulence, and resulting innate and adaptive host immune responses are all important in the pathogenesis of *H. pylori* related disease [37,56,57]. The organism produces a number of antigenic substances, including heat shock protein, urease, and lipopolysaccharide, all of which can be taken up and processed by lamina propria macrophages and activate T-cells [56]. Cellular disruption, especially adjacent to epithelial tight junctions, undoubtedly enhances antigen presentation to the lamina propria and facilitates immune stimulation. The net result is increased production of inflammatory cytokines such as IL-1, IL-6, tumor necrosis factor alpha (TNF-?), and most notably, IL-8 [57].

A B-cell response to *H. pylori* occurs locally in the gastroduodenal mucosa and systemically. The role of local antibodies in producing tissue injury or modulating inflammation in *H. pylori* infection remains controversial [56]. Prolonged stimulation of gastric B cells by activated T-cells can lead to MALT lymphoma in rare cases.

T-cells are also activated during infection and their cytokines boost bacterial binding. While T-cells are recruited to the infected gastric mucosa, they appear to be hypo responsive. B7-H1 (programmed death-1 ligand 1); a member of B7 family of proteins associated with T-cell inhibition, appears to be

involved in the suppression of T-cell proliferation and IL-2 synthesis during H. pylori infection, and thus may contribute to its chronicity [58]. Different T helper cell subsets can be distinguished by characteristic profiles of cytokine secretion. Th1 cells promote cell-mediated immune responses through elaboration of TNF- and IFN-. Th2 cells produce Il-4, IL-10 and TGF-b. It appears that during *H. pylori* infection the T-cell immunity is inappropriately skewed toward a Th1 response that promotes epithelial cell inflammatory cytokine production (IL-8 stimulated by IFN- and TNF-) and directly impacts epithelial apoptosis [59,60]. *H. pylori* infection induces a marked increase in the flux of leukocytes and in the appearance of platelet and leukocyte-platelet aggregates in gastric venules in a murine model. Circulating platelet aggregates and activated platelets were also detected in patients infected with *H. pylori*, suggesting that platelet activation and aggregation contribute to the associated micro-vascular dysfunction and inflammatory cell recruitment. Platelet aggregation mediated by an *H. pylori* interaction with von-Willebrand factor is speculated to contribute to infection related ulcer disease but also possibly non-GI manifestations of infection such as cardiovascular disease and idiopathic thrombocytopenia [61,62].

Not all *H. pylori* infected individuals develop clinical disease. Host genetics are important in determining the physiologic and clinical response to infection. Host polymorphism of IL-1 appears to determine the degree of inflammatory response to infection, resulting alteration in acid secretion (hyper or hypo secretion), and risk for subsequent gastric cancer [63,64]. One series of meta-analyses investigated genes coding for the interleukin proteins (IL-1B, IL-1RN, IL-8, and IL-10) and for TNF-. Gastric cancers were stratified by histologic subtype and anatomic location, by *H. pylori* infection status, by geographic location (Asian or non-Asian study population), and by a quantitative index of study quality. Results consistently supported increased cancer risk for IL-1RN2 carriers; the increased risk was specific to non-Asian populations and was seen for intestinal and diffuse cancers, distal cancers, and, to a lesser extent, cardia region cancers. In Asian populations, reduced risk was observed in association with IL-1B-31C carrier status. These results indicate the importance of stratification by anatomic site, histologic type, *H. pylori* infection, and country of origin. Study quality considerations, both laboratory and epidemiologic, can also affect results and may explain, in part, the variability in results published to date [65].

Interleukin-8

Research has centered on epithelial IL-8 production induced by different strains of *H. pylori* 48. IL-8 is a potent chemotactic factor, activates neutrophils, and recruits acute inflammatory cells into the mucosa. *H. pylori* appear to activate transcription factor NF-B via IKB kinase (IKK) pathway, which in turn increases IL-8 production 52. NF-B also regulates the expression of additional inflammatory response genes, and may play a role in the mucosal epithelial response to other bacterial infections in addition to *H. pylori*. (Figure 2)

Bacteria that express CagA and VacA are more potent inducers of IL-8; however, the gene primarily responsible for IL-8 induction is CagE, which is located upstream of the CagA gene48 CagA/VacA-positive strains are also more often found in patients with clinical manifestations of H. pylori infection, indirectly suggesting that IL-8 may play an important pathophysiologic role in gastro-duodenal disease. TNF- can also augment IL-8 production by the inflamed mucosa. Following successful eradication of H. pylori, mucosal levels of mRNA for both TNF- and IL-8 are reduced in parallel with the decline in local inflammation 37.

Survival of H. pylori

H. pylori itself is in part able to survive this inflammatory onslaught by producing the enzyme, catalase. This enzyme neutralizes the damaging reactive oxygen metabolites liberated by neutrophils[41]. With time, the host appears to down regulate the acute inflammatory response, making it easier for

the organism to persist and proliferate39.

Antibody Response

Most infected individuals systemically produce specific antibodies to a variety of *H. pylori* antigens. The antibody response changes as infection progresses from an acute to a chronic stage. Detection of IgM antibodies is an insensitive indicator of acute infection and generally is clinically not useful, even in children [35,36,37]. IgA and IgG antibodies are produced in response to infection, remain present as long as infection is active, and quantitatively decrease after infection is cured. Antibodies to CagA protein are detectable in gastric tissue and serum and permit the identification of infection with presumably more virulent organisms 37.

The role of local antibodies in the immunopathogenesis of gastro-duodenal mucosal injury is unclear [56]. Virtually all infected persons have a specific gastric mucosal IgA and IgG response. IgA antibodies may modulate mucosal injury by inhibiting antigen uptake, disrupting bacterial adherence and motility, and neutralizing various toxins. IgG presumably augments inflammatory injury by activating complement and facilitating neutrophil activation.

An antibody response may also be seen against autoantigens, including IL-8, antral epithelium and homologous host and bacterial epitopes (eg, LewisX, lipopolysaccharide, and heat shock protein). The immunoglobulin specificity of MALT lymphoma may be for such autoantigens [37, 57].

CONCLUSION

In spite of the large number of studies published on the epidemiology of H. pylori little has been added to our current understanding of the subject. The risk factors for developing the infection are similar in most of the studies and are in concordance with previous data. Much that was known before has just been confirmed. The pathophysiology of *H. pylori* infection and its eventual clinical outcome should be viewed as a complex interaction between the host and the bacterium. This interaction is influenced by the environment and modulated by a number of largely as yet unidentified factors. Tissue injury induced by *H. pylori* depends upon bacterial attachment and the subsequent release of enzymes and other microbial products that can cause cellular damage.

Further studies are therefore required to gain more insight into the epidemiology and pathogenesis of *H. pylori*-induced peptic ulcer disease and gastric cancer, not only to develop more effective treatments for these diseases, but also because it might serve as a paradigm for the role of chronic inflammation in the genesis of other clinical squeal within the gastrointestinal tract.

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