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Helicobacter pylori pathogenicity genes, cytokine polymorphisms and environmental factors affect the development of gastric diseases: an overview

Genes de patogenicidade de Helicobacter pylori, polimorfismos de citocinas e fatores ambientais afetam o desenvolvimento de doenças gástricas: uma visão geral

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RESUMO

Justificativa e Objetivos: *Helicobacter pylori* é uma bactéria Gram negativa que coloniza o estômago de aproximadamente 50% da população humana mundial. Este microrganismo é o principal agente causal de gastrite e um importante fator de risco para o desenvolvimento deúlcera péptica e carcinoma gástrico. Os fatores que determinam essa diversidade de manifestações clínicas permanecem incertos, mas podem estar relacionados com a interação dos fatores bacterianos, sistema immune do hospedeiro e variáveis ambientais. O objetivo desta revisão é fornecer uma visão geral destes fatores que influenciam na susceptibilidade a desordens severas de infecção por *H. pylori*. **Metodo:** Para isso, foram selecionados artigos originais e de revisão através da pesquisa nas bases de dados bibliográficos PubMed, Portal de Periódicos CAPES e SCIELO. **Resultados:** *H. pylori* possui um conjunto de fatores de patogenicidade, tais como *cagA*, *vacA*, *iceA*, *babA*, para colonizar a mucosa gástrica e estabelecer infecção crônica. Estes fatores bacterianos são agentes essenciais em modular a resposta imune envolvida na iniciação da carcinogênesegástrica. Os fatores genéticos do hospedeiro contribuem para regular a resposta inflamatória e para o agravamento da lesão da mucosa gástrica uma vez que a infecção gástrica por *H. pylori* induz a produção de várias citocinas pró e anti-inflamatórias no hospedeiro. O papel prejudicial dos fatores ambientais está relacionado com as precárias condições socioeconômicas, com o consumo de sal, com o tabagismo e com o consumo de álcool. **Conclusão:** Ao decifrar as regras deterministas - se houver - dessa interação entre fatores da bactéria, do hospedeiro e variáveis ambientais, será possível prever, tratar e, finalmente, prevenir graves doenças gastroduodenais.

ABSTRACT

Background and Objectives: *Helicobacter pylori* is a Gram-negative bacterium that colonizes the stomach of approximately 50% of the world´s human population. This microorganismis the major causal agent of gastritis and is an important risk factor for the development of peptic ulcer disease and gastric carcinoma. The factors that determine these diverse clinical outcomes are subject to continuous investigations and is thought to be determined by interaction of bacterial factors, host immune system and environmental variables. The aim of this review is to provide an overview of these factors that influence susceptibility to severe outcomes of *H. pylori* infection. **Methods:** For this, original and review articles were selected by searching the PubMed, CAPES Portal Journals and SCIELO bibliographic databases. **Results:** *H. pylori* possesses a set of pathogenicity factors, such as *cagA*, *vacA*, *iceA*, *babA* for colonizing the gastric mucosa and establishing a chronic infection. These bacterial factors are essential players in modulating the immune responseinvolved in the initiation of the carcinogenesis in the stomach. Host genetic factors contribute to the regulation of the inflammatory response and in the

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aggravation of mucosal damage once the gastric infection with *H. pylori* induces the mucosal production of various pro- and anti-inflammatory cytokines in the host. The harmful role of environmental factors is related to poor socioeconomic conditions, salt intake, smoking and alcohol consumption. **Conclusion:** By deciphering the deterministic rules – if any – of this interplay between factors of the bacterium, host and environmental variables, we will eventually be able to predict, treat, and ultimately prevent serious gastroduodenal diseases.

INTRODUCTION

Helicobacter pylori is a micro-aerophilic spiral-shaped flagellar Gram-negative bacterium that colonizes the gastric mucosa of approximately 50% of the world´s human population.[1] The prevalence in developing countries is estimated between 60–90%, and in the developed world is between 25–35%.[2]

H. pylori induces a chronic gastric inflammation, which is asymptomatic in the majority of the patients. However, it is estimated that 15 to 20% of *H. pylori* infected individuals will develop peptic ulcer, and approximately 1% will develop gastric cancer.[3] The interaction of bacterial pathogenicity factors, host factors and environmental and lifestyle factors, determine the severityof gastric damage and the clinical outcome of *H. pylori* infection (Figure 1).[4]

The *H. pylori* genome has a high plasticity, therefore, genomic variations of the strains maybe responsible for the coding of different pathogenic factors capable of determining various types of gastric lesions in the host.[5] It has been described as biomarkers of pathogenicity of *H. pylori, cagA (cytotoxin-associated gene A)*, *vacA* (*vacuolatingcytotoxin*), *iceA* (*induced by contact with epithelium*), *babA* (*blood-group antigen-binding adhesin A*), among others genes.[6-9]

The host's immune system plays an important role in the pathogenesis of gastroduodenal disorders by regulating the nature and the intensity of the inflammatory response to infection by *H. pylori*. Factors such as cytokines are involved in the initiation and regulation of this response.[10] The inflammatory cells that are recruited to the gastric mucosa during infection produce several pro- and anti-inflammatory cytokines.[11] In this sense, it is noteworthy that the polymorphism in the genes encoding interleukins (*IL*) *1β, 1RN, 6, 8* and *10* are associated with increased susceptibility to gastric diseases.[12-17]

The combined presence of environmental factors, such as, household crowding, inadequate eating habits, low socioeconomic conditions, poor hygienic, excessive alcohol consumption and smoking are related with *H. pylori* infection, especially when one takes into account

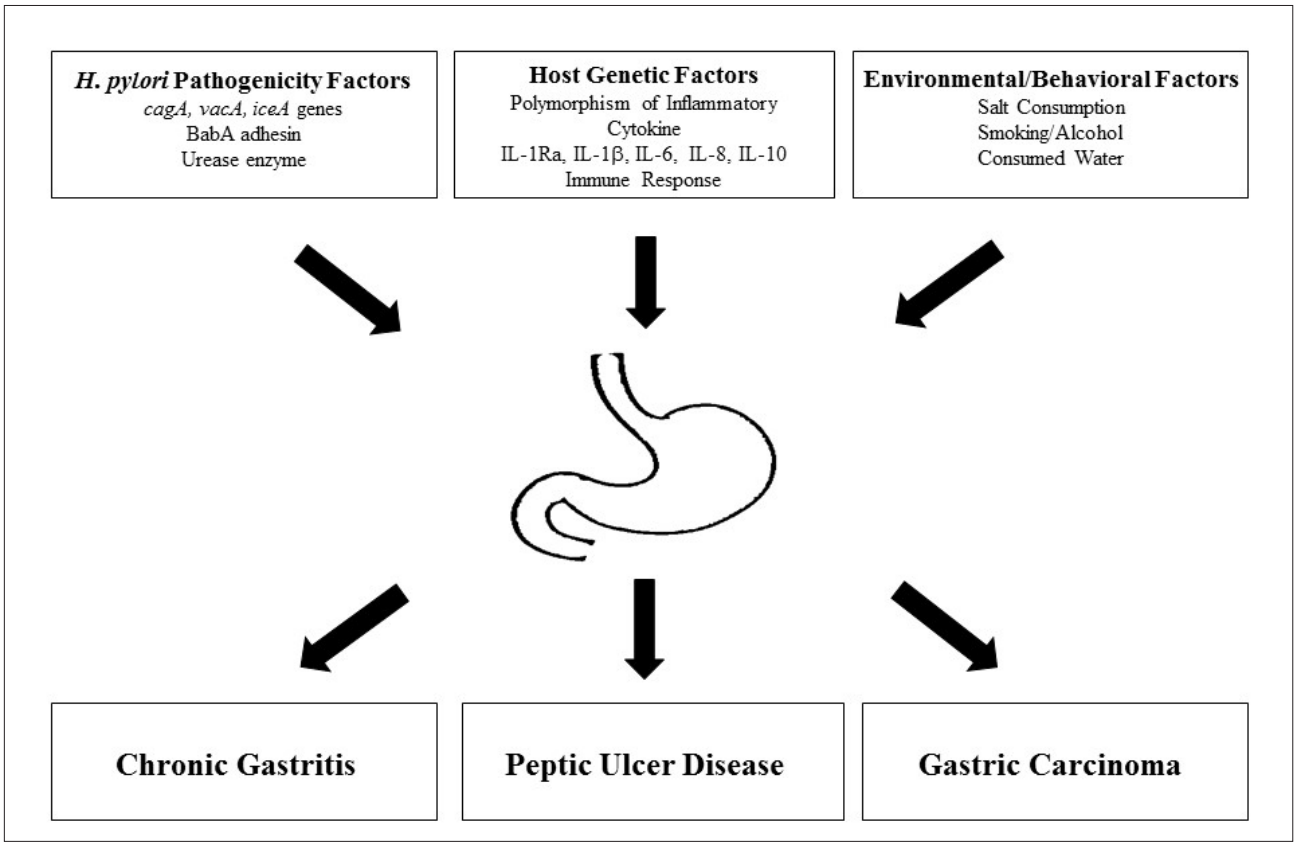

Figure 1. A schematic to explain why only certain individuals infected by *H. pylori* develop more severe gastic diseases. The interplay between bacterial, host and evironmental/behavioral factors determine the different clinical outcomes of *H. pylori* - infected patients.

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their main routes oftransmission, oral–oral and fecal–oral. Besides, factors as smoking, eating habits and alcohol consumption have been associated with a higher risk of the development of peptic ulcer and gastric cancer in people infected by *H. pylori*.[18-20]

The aim of this review is to provide an overview of bacterial, environmental, and host factors that influence susceptibility to severe outcomes of *H. pylori* infection.

METHODS

Original and review articles were selected by searching the PubMed (Literature of International Health Sciences), CAPES Portal Journals and SCIELO bibliographic databases. The selection of the articles was based on two criteria: 1) published between the years 1993 and 2015; 2) articles whose authors contributed with important insights into the issues, regardless of the year of publication. The following descriptors were used: *Helicobacter pylori,* pathogenicity genes, host genetic polymorphism, cytokine polymorphism, environmental variables, gastroduodenal diseases and epidemiology.

RESULTS AND DISCUSSION

Helicobacter pylori infection: From gastric inflammation to gastric carcinogenesis

The clinical manifestations of *H. pylori* infection can be chronic gastritis; peptic ulcer; adenocarcinoma; and gastric lymphoma mucosa- associated lymphoid tissue (MALT).[21,22] Firstly, the infection of the stomach by *H. pylori* induces inflammation of the gastric mucosa (gastritis) and is estimated that occur in the most patients infected by *H. pylori*.[23] *H. pylori* infection may be associated with decreased or increased gastric acid secretion, depending on the distribuition and severity of gastritis.[4]

The interplay of gastritis and acid secretion are key determinants in disease outcomes such as peptic ulcer and/or gastric cancer.[23] Ulceration corresponds to the loss of mucosal integrity as the result of disequilibrium between defensive mucosa-protective factors (mucus bicarbonate layer and phospholipid surfactant layer) and aggressive injurious factors (strong acid and high proteolytic activity in gastric secretions). When ulcers develop in the acid-peptic environment of the gastroduodenum, they are called peptic ulcer disease.[24] The development of duodenal ulcers is associated with gastritis and with increased gastric acid production, where as the development of gastric ulcers is related with gastritis and with gastric reduced acid production, conditions that predispose also the developing of gastric atrophy (loss of gastric glands), intestinal metaplasia (the replacement of glandular and/or foveolar epithelium by intestinal epithelium), and finally gastric cancer.[25,26]

In relation to gastric cancer, although its etiology is multifactorial, *H. pylori* is the main cause of gastric carcinogenesis and was categorized in 1994 as a carcinogen I by the International Cancer Research Agency (IARC).[27] *H. pylori* infection promotes gastric carcinogenesis by at least five different mechanisms: (1) increased endogenous DNA damage and decrease repair activities, (2) induction of mutations in the mitochondrial DNA, (3) generation of a phenotype that induces mutations in the nuclear genome (4) disruption of the balance between cell proliferation and apoptosis and (5) induction of an intense gastric inflammatory response that lasts over decades that produces chronic oxidative stress and adaptive changes in gastric epithelial and immune cell pathobiology.[28]

The gastric cancer classification by system Laurenclassifies gastric adenocarcinoma in intestinal or diffuse.[29] The intestinal-type is more frequently observed in older patients and it is linked closely to environmental and dietary risk factors. The pathogenesis of the intestinal type includes a sequence of events that begins with *H. pylori*-induced superficial gastritis, progressing towards chronic atrophic gastritis, intestinal metaplasia, dysplasia and finally gastric cancer. In diffuse type the patients typically are younger associated with host genetic factors and is generally less commom, with a worse prognosis than those with the intestinal type. The pathogenesis of diffuse type is poorly understood, although *H. pylori* infection is also a predisposing factor.[30] Anatomically, gastric adenocarcinomas are classified as proximal (cardia) and distal (noncardia). The longstanding inflammatory response against *H. pylori* in the gastric mucosa may cause sustained tissue injury leading to the development of distal gastric adenocarcinoma.[31]

Lastly, there are a pathogenic link between *H. pylori* infection and MALT lymphoma, so much that, according to the Maastricht III Consensus Report, *H. pylori* eradication is the treatment of first choice for *H. pylori* infected individuals with stage I low grade gastric MALT lymphoma.[32]

Role of bacterial pathogenicity genes in the gastric disorders

Determination of pathogenicity genes may provide information regarding to the prognosis of infection by *H. pylori*.[33] The first gene of pathogenicity identified in *H. pylori* was *cagA*. This gene is highly prevalent in strains from different geographic areas.[6,34] The *cagA* gene is located at one end of a 40-kb DNA insertion called *cag* pathogenicity island (*cag*PAI). This gene is secreted through the type IV secretion system (T4SS) and thentransported to host cells.[35] Once inside gastric epithelial cells, the CagA undergoes tyrosine phosphorylation in its repeat region of five amino acids Glu-Pro-Ile-Tyr-Ala (EPIYA). This phosphorylation is mediated by Src kinase, a cytoplasmic protein tyrosine kinase. CagA tyrosine phosphorylated subsequently binds to Src homology 2 (SH2) domain, that contain host cell proteins, such as, the tyrosine phosphatase SHP-2, the C-terminal Src kinase (CSK) and the adapter protein Crk. This results in cytoskeletal reorganization and cell elongation-a phenotype that leads to the dispersion of cells and morphological changes for "hummingbird phenotype".[36] The *cagA*-SHP-2 interaction constitutes the biological basis of *cagA* as

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a pathogenicity factor, due to induction of abnormal proliferation and movement of gastric epithelial cells, changes that may eventually lead to gastric atrophy and gastric cancer.[37]

The CagA protein of *H. pylori* acts as a highly immunogenic antigen. The structure of the *cagA* gene reveals a 5' highly conserved region and a 3' region containing a variable number of repeat sequences, which leads to variation in the length of the protein and can result in diverse host responses, including different degrees of inflammatory response.[5] These variations in the repeat region of *cagA*EPIYA have also been associated with pathogenicity of *H. pylori*. Four distinct types of EPIYA have been identified and classified as, EPIYA-A, -B, -C and -D. CSK specifically binds to the tyrosine-phosphorylated EPIYA-A or -B, whereas SHP-2 specifically binds to the tyrosine-phosphorylated EPIYA-C or –D.[36]*cagA* strains of *H. pylori* found in the western world typically contain EPIYA-A, -B and -C in the EPIYA repetition region in the C-terminal. In contrast, the *cagA* strains of the East Asian have EPIYA-A, -B and a specific sequence Asian CagAEPIYA-D.[38] The number of segments EPIYA-C in *H. pylori* strains from western countries have shown to influence the degree of pathogenicity as well as the oncogenic potential, and may serve as a marker for identifying high-risk populations.[39] This occurs because the presence of EPIYA-C segments of the CagA protein appears to significantly contribute to the transcriptional activation of IL-8, through activation of NF-kB (factor nuclear kappa B).[40] IL-8 plays a crucial role by chemo attracting and activating neutrophils to the site of infected gastric mucosa.[41] Batista et al. showed that increasing of the number of segments EPIYA-C was associated with precancerous gastric lesions and with decreased serum levels of pepsinogen I, which reflects the functional and morphological status of the gastric mucosa.[42]Also, it was observed that infection by *cagA*-positive *H. pylori* strains harboring multiple EPIYA-C repeats is associated with the presence of peptic ulcer.[43]

Another important disease-associated pathogenicity genes of *H. pylori* are *vacA*, *iceA* and *babA*.[7-9 The] *vacA* gene encodes a vacuolating cytotoxin (VacA), which can damage the gastric epithelial cells due to induce the formation of cytoplasmic vacuoles.[44] The gene consists of three variable regions: the signal region (*s*- encoding the signal peptide), with two alleles, *s1* (subtypes *s1a, s1b, s1c*) and *s2;* the medium region (*m*), with the alleles *m1* and *m2*; and the intermediate region (*i*), containing the alleles *i1* and *i2*.[44,45] The combination of alleles of the *s, m* and *I* regions determines the vacuolating cytotoxin production and is associated with the pathogenicity of the bacterium. In general, the strains containing *s1/m1/i1* alleles produce large amounts of vacuolating cytotoxin, reason where by this genotype seems to be associated with more severe pathologies, as peptic ulcer and gastric cancer. In contrast, strains of type *s1/m2* and *s2/m2/i2* have moderate and none cytotoxic activity, respectively.[7,46] A recent study showed that the best markers of gastric cancer and duodenal ulcer were the *vacA s1* and *i1* genotypes, and that the *s* and *i* regions were the key determinants of vacuolating cytotoxin activity.[47] Another study found that strains which carried the *vacA* s_1/m_1 gene showed significant associations with severe chronic gastritis.[48] The *iceA*gene has two alleles: *iceA1* and *iceA2*. The expression of *iceA1* is regulated by the contact of *H. pylori* with gastric epithelial cells and is associated with peptic ulcer and gastric cancer, whereas expression of *iceA2* is related to asymptomatic gastritis.[8] A study in southern Brazil showed that the *iceA1* allele was related to erosive gastritis, whereas the *iceA2* allele was associated with enanthematous gastritis.[49] The *babA* gene encodes a membrane protein, named BabA adhesin, which binds to the Lewis b blood group antigens in gastric cells. The *babA* gene is a factor of adhesion, one of the characteristics of *H. pylori* that assists in establishing persistent colonization of the gastric epithelium and contributes to its pathogenicity, by to allow intimate contact between bacterium and epithelium, and facilitate the release of factors pathogenicity. Although three alleles of the *bab*gene have been identified (*babA1*, *babA2* and *babB)*, only the *babA2* gene product is able to bind to Lewis b antigen.[50]A recent study showed that the *babA2* gene correlated positively with bacterial density score, activity of inflammation and chronic inflammation of gastric mucosa.[51]

Influence of cytokines genes polymorphisms in the gastric diseases

H. pylori induces gastric lesions that start by chronic inflammation in the gastric mucosa that is mediated by an array of pro- and anti-inflammatory cytokines.[52] Genetic polymorphisms in genes that codify proinflamatory cytokines such as *IL-1β, IL-6* and *IL-8*; and anti-inflammatory cytokines like *IL-1RN*and *IL-10*, directly influence inter-individual variation in the magnitude of the cytokine response, and this clearly contributes to an individual's ultimate clinical outcome.[53] In general, in the *H. pylori* infection, the gastric inflammation is increased and the acid inhibition is potente in patients with high producer alleles of pro-inflammatory cytokines and low producer alleles of anti-inflammatory cytokines, which results in a higher risk for the development of atrophic gastritis, gastric ulcer or gastric cancer. On the other hand, low producer allele carriers of pro-inflammatory cytokines and high producer allele carriers of anti-inflammatory cytokines have decreased inflammation and weak acid inhibition, resulting in a mild gastric inflammation.[54]

The family of the *IL-1* gene contains the genes *IL-1A, IL-1B* and *IL-1RN*.[55] *IL-1B* encodes IL-1β, a pro-inflammatory cytokine and a powerful inhibitor of gastric acid secretion, which plays an important role for initiating and amplifying the inflammatory response to *H. pylori* infection.[56] There are three single nucleotide polymorphisms (SNPs) in the *IL-1β* gene: a T-C base transition at position -31 and C-T base transitions at positions -511 and +3954 from the transcriptional start site.[57] The presence of the T allele at positions -511 and +3954; and of C allele at position -31 is associated with high levels

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of *IL-1* secretion.[25] It has been shown that *IL-1β*-31, *IL-1β*-511 and *IL-1β*+3954 polymorphisms are related with hypochlorhydria, chronic atrophic gastritis, gastric ulcer and gastric cancer in response to *H. pylori* infection.[52,58] The *IL-1RN* encodes the IL-1 receptor antagonist (IL-1ra), an anti-inflammatory cytokine that competitively binds to IL-1 receptors and thereby modulates the potentially damaging effects of IL-1.[12] IL-1RN play a decisive role in modulating the risk of developing hypochlorhydria, gastric atrophy and gastric cancer in the presence of *H. pylori* infection.[59] *IL-1RN* gene contains an 86-bp variable number of tandem repeats polymorphism (VNTR) in intron 2, which leads to the presence of 5 different alleles: allele 1 (4 repeats), allele 2 (2 repeats), allele 3 (5 repeats), allele 4 (3 repeats), and allele 5 (6 repeats).[60] The 4-repeats (*IL-1RN**1) and 2-repeats (*IL-1RN**2) alleles are the most common, whereas the others account for less than 5%.[61] The allele 2 (*IL-1RN**2) is associated with enhanced *IL-1β* production.[62] Studies in different populations revealed association between individual's carriers of the allele 2 and increased risk of developing chronic gastritis, gastric ulcer and gastric cancer.[63,64]

IL-6 is a pro-inflammatory cytokine that acts as an inflammatory mediator and endocrine regulator, playing an important role in host defense mechanisms as a messenger between innate and adaptive systems.[65]Moreover, it is involved in the regulation of various cellular functions, such as, proliferation, apoptosis and angiogenesis.[66]A nucleotide change from G to C at position -174 in the promoter region of the *IL-6* genewas described. This SNP may result in inter-individual variation in transcription and expression of the IL-6; and therefore influence an individual's susceptibility to a diverse range of diseases. MucosalIL-6 levels are elevated in *H. pylori*-associated gastritis and diminished after eradication of the infection.[55] In 2012, Liu et al. showed an increased cancer risk for individuals with the CC genotype compared to those carrying the GG genotype in African populations.[67]

The pro-inflammatory factor IL-8is recognized as a neutrophil and lymphocyte chemotactic factor and inductor of cell proliferation, migration and angiogenesis.[54,68] Gastric mucosal levels of IL-8 increase significantly after *H. pylori* infection and parallel to the severity of gastritis.[69] The *IL-8* genecontains a SNP (T-A base transition) at position -251, in the proximal promoter region. The *IL-8*-251A allele affects *IL-8* gene transcription and tended to be associated with increased IL-8 production by gastric cells and with more severe inflammation.[53] In recent years, a number of studies examining the *IL-8* -251T/A SNP showed varying results.Recent meta-analyses suggest that *IL-8* -251T/A SNP is associated with increased peptic ulcer and gastric cancer risks among Asians.[70] However, a study examining European patients did not find the correlation between the *IL-8*-251T/A SNP and gastric cancer.[71] Moreover, a Brazilian study found that individuals with A/A genotype may have protective effect for gastric cancer.[72] These contrasting results suggest that *IL-8*-251T/A SNP may be associated differently with gastric diseases depending on the ethnicity.

IL-10 is a pleiotropic anti-inflammatory cytokine produced by activated immune cells.[73] It is capable of inhibiting the production of pro-inflammatory cytokines like IFN-γ, IL-1, IL-2, IL-3, IL-6, IL-8, TNF-α, and GM-CSF and inducing B-cell proliferation and differentiation.[74,75] A C-T base transition located at positions -819, and C-A base transition at position -592 have been identified in the 5´ flanking region of the *IL-10* gene. These SNPs are related to different serum level of IL-10 in vivo.[75,76] The C allele at positions -819 and -592 has been associated with high *IL-10* production and the T allele at position -819 and the A allele at position -592 has been related with low production.[77] The low IL-10 production in patients infected with *H. pylori* results in increased gastric inflammation intensity, hypochlorhydria and increased risk of gastric atrophia and gastric cancer.[74]

Relationship of environmental factors with the *H. pylori* infection

The knowledge of the epidemiology and mode of transmission of *H. pylori* is important to prevent its spread, since this bacterium is present in nearly half the world's population. Such knowledge may be useful in identifying high-risk populations, especially in areas with higher rates of peptic ulcer and gastric cancer.[5,78,79]

The transmission of *H. pylori* occursfrom person to person by oral–oral (through saliva, dental plaque, backflow of gastric contents) or fecal–oral (through water contaminated) routes.[78] Yu et al. (2015) showed that dental plaque is risk factor of oral *H. pylori* infection.[80] In Brazil, studies showed that mothers infected with *H. pylori* represent a greater risk factor to infected their children; and that breastfeeding does not protect against acquisition of *H. pylori,* conversely, an infected mother can transmit of the disease to the child. [81,82]

The theory that the major risk factors for infection are poor socioeconomic and hygienic conditions beginning in childhood was supports by Chen et al. (2014).[83] Childhood infections, such as, tonsillitis, diarrhea and diphtheria, are associated with decreased secretion of gastric acid, as well as with malnutrition. Regions where childhood infections and malnutrition are common provide the ideal environment for *H. pylori* colonization.[84]

There is a strong correlation between poor socioeconomic conditions and *H. pylori* infection. In general, inadequate sanitation practices, low family income, poor hygiene and household crowding may be related to a higher prevalence of this infection.[19] The transmission of *H. pylori* occurs from infected mothers to their offspring and among siblings.[85] A study, with Brazilian children, showed that the number of siblings and nursery attendance were positively associated with *H. pylori* infection and also that the house location (served by paved road or not) is a potential risk factor for infection, indicating that contaminated soil may be a source of infection, and concluding that the *H. pylori* infection in children is highly related to poor hygiene and crowded conditions.[86]A study conducted in six Latin-American countries also reported that crowding was positively associated with *H.*

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pylori infection and suggested the occurrence of repeated transmission of *H. pylori* (same or different strain) between the individuals who live in the same household, due to a greater opportunity of personal contact.[19]

In addition to the factors described above, other variables, such as smoking, alcohol consumption and diet may influence the infection by *H. pylori*. The smoking can be involved in the transmission of infection due the handling and sharing of cigarettes among smokers.[87] A population-based prospective study with Japanese men suggested that cigarette smoking and *H. pylori* infection are significant risk factors for gastric cancer.[88] The strong oxidising effect of cigarette smoke is able to dramatically induce oxidative DNA damage.[4]

Regarding alcohol consumption, Sánchez-cuen et al (2014) found that the risk of infection by *H. pylori* is 1.45 times higher in people who consume alcohol who do not consume it.[18] It is postulated that alcohol consumption facilitates *H. pylori* infection presumably by damaging the gastric mucosa and/or promoting *H. pylori* adherence to gastric mucosa.[68]

Another factor that influences the infection by *H. pylori* is the diet that may provide noxious agents that contribute to *H. pylori* pathogenicity. The high salt concentration in the stomach destroys the mucosal barrier, favors colonization by *H. pylori*, and leads to inflammation and damage-causing gastritis and diffuse erosion.[4] Inadequate dietary habits are associated with intense neutrophilia, higher degree of inflammation and with the development of gastric cancer.[20]

Lastly, a recent study demonstrated a statistically significant increase in *H. pylori* infection among betel chewers compared to those who did not chew betel. This observation supports the hypothesis that betel chewing may affect periodontal health and thus predispose individuals to colonization with *H. pylori*.[83]

CONCLUSION

There are evidences that genes of bacterial pathogenicity, such as, *cagA, vacA s1/m1/i1, iceA1, babA2;* host genetic polymorphisms, such as, *IL-1RN* *2, IL-*1β (*-31C) *(-511T) (+3954T),IL-8 (-251A), IL-10 (-592A) (-819T)*; and environmental factors as smoke, alcohol consumption and diet play a major role in inducing severe gastric disorders. Future research must focus on developing a diagnostic tool for detect *H. pylori* and also bacterial and host genes associated with a higher severity of gastric disease. The identification of patients infected with *H. pylori* that present a high risk of develop peptic ulcer or gastric cancer may to determine the most appropriate therapeutic intervention and the better treatment.

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