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# *Helicobacter pylori* and upper gastrointestinal diseases: A review

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## ABSTRACT

**Since its first isolation by Marshall and Warren, *Helicobacter pylori* (*H. pylori*) has been recognized to have a causal role in the upper gastrointestinal diseases development, especially in chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT lymphoma) and gastric adenocarcinoma. *H. pylori* is a spiral-shaped gram-negative flagellate bacterium that has a high genetic diversity, which is an important factor in its adaptation to the host stomach and also for the clinical outcome of the infection, an aspect that remains unclear. However, it is thought to involve a interplay among the virulence of the infecting strain, host genetics and environmental factors. This review chapter brings the principal characteristics of the diseases associated with *H. pylori* infection and summarizes some important characteristics concerning the virulence of bacterium strain, host genetics and external environment.**

## KEYWORDS

***Helicobacter pylori*; Gastritis; Peptic Ulcer Disease; MALT Lymphoma; Gastric Cancer**

## 1. INTRODUCTION

*Helicobacter pylori* (*H. pylori*) remains one of the most common worldwide human infections and, although colonization with *H. pylori* is not a disease in itself, it is a condition that affects the relative risk of developing various clinical disorders of the upper gastrointestinal tract, and possibly the hepatobiliary tract [1]. Consequently, since the successful isolation of *H. pylori* by Marshall and Warren [2], *H. pylori infection* has been recognized to have a causal role in gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT lymphoma) and gastric adenocarcinoma [3]. In 1994, the bacterium was classified as a group I carcinogen by the International Agency for Research on Cancer and is regarded as a primary factor for gastric cancer development [4]. For their revolutionary discovery, Marshall and Warren received the Nobel Prize in Physiology or Medicine in 2005.

Gastric colonization with *H. pylori* affects at least half the world's population, and, while the infection is on a fast decline in most of the western countries, mainly due to the success of therapeutic regimens and improved personal and community hygiene that prevents re-infection, the situation is exactly opposite in many of the developing countries due to failure of treatment and emergence of drug resistance [5,6].

The routes of transmission of *H. pylori* still remain unclear. Person-to-person transmission and intrafamilial spread seem to be the main route, based on the intrafamilial clustering observed in some studies [7,8]. Children are often infected by a strain which a genetic fingerprint identical to that of their parents, and they maintain this genotype even after moving to a different environment [9]. Besides, the waterborne infection remains possible [10,11].

*H. pylori* populations are highly diverse and constantly change their genome, which can be an important factor in its adaptation to the host stomach and also for the clinical outcome of the infection. The changes in its genome occur mainly due to point mutations, substitutions, insertions, and/or deletions of their genome. Moreover, mixed infections are frequent and lead to exchange of DNA fragments between different *H. pylori* strains in a single host [12,13].

 

Although *H. pylori* is primarily responsible for the upper gastrointestinal diseases, only less than 10% of people colonized with this bacterium portray disease symptoms. It suggests that host and bacterial factors also contribute to differences in *H. pylori* pathogenicity [3,14]. Besides, the environment can be important in this relationship, especially with regards to the dietary habit, smoking and alcohol consumption. For instance, the risk of developing gastric cancer is also related to genetic characteristics of the host and environmental factors, which, associated with specific bacterial strain characteristics, influence the severity of the chronic inflammatory response [15,16].

Besides, in the last decades, in studies that are expressly aimed at demonstrating how *H. pylori* may cause gastric mucosal damage and, at the same time, elude the immunological response evoked by the host [17], *H. pylori* infection has been associated with extradigestive diseases [18], such as iron-deficiency anemia [19], idiopathic thrombocytopenic purpura [20,21], cardiovascular diseases [22,23], and hepatobiliary diseases [24,25], among others.

Consequently, the aim of this review manuscript is to summarize the principal characteristics of the upper gastrointestinal diseases associated with *H. pylori* infection, including some important studies concerning this subject.

## 2. UPPER GASTROINTESTINAL DISEASES

### 2.1. *Helicobacter pylori*-Induced Gastritis

Gastritis is an inflammatory condition of the gastric mucosa that can affect different regions of the stomach and show different degrees of mucosal injury. Many kinds of agents may lead the stomach into an inflamed state. For instance, it could be due to non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, naproxen and ibuprofen, usually used in some specific illness such as rheumatoid arthritis; due to abrasive compounds or unbalanced diets where the stomach is damaged by its own gastric acid; due to a long-term physical and/or mental stress that result in the production of excessive amounts of gastric acid; and, finally, due to *Helicobacter pylori* (*H. pylori*) infection. Besides, infections such as cytomegalovirus, chronic idiopathic inflammatory and autoimmune disorders such as Crohn's disease and pernicious anemia and chemical damage due to alcohol abuse are other causes of gastritis.

In fact, the history of chronic gastritis can be divided into two phases: before and after the isolation of *H. pylori* [2]. Until then, lack of knowledge of its biological nature has resulted in non interest of most clinicians and gastroenterologists, who considered the chronic gastritis not as an etiopathogenic factor, but a result of an event or a consequence of gastric diseases. Many researchers considered that gastric mucosa was always swollen (infiltrated with mononuclear inflammatory cells), similar to the lining of the distal intestine and, consequently, this condition was not used having a great importance in the clinical practice and diagnostic. Consequently, nowadays, there is no doubt that *H. pylori* infection is responsible for the majority of cases of gastritis [1,26].

Colonization with *H. pylori* virtually leads to infiltration of the gastric mucosa in both antrum and corpus with neutrophilic and mononuclear cells. Gastritis can be classified as an acute or chronic gastritis and it can involve all parts of the stomach or just the fundus, corpus or antrum. The chronic active gastritis is the primary condition related to *H. pylori* colonization, and other *H. pylori*-associated disorders, in particular, resulting from this chronic inflammatory process [1], as atrophic gastritis, causing an elevated risk of gastric cancer [27].

#### 2.1.1. Acute Gastritis

The acute phase of colonization with *H. pylori* may be associated with transient non-specific dyspeptic symptoms, such as fullness, nausea, and vomiting, and with some considerable inflammation of both the proximal and distal stomach mucosa, or pangastritis. This phase is often associated with hypochlorhydria, which can last for months [1]. It is unclear whether this initial colonization can be followed by spontaneous clearance and resolution of gastritis and, if so, how often it occurs. Follow-up studies of young children suggested that infection may spontaneously disappear in some patients in this age group [28-30]. This condition has not been observed in adults other than under specific circumstances, such as the development of atrophic gastritis. Consequently, some individuals are prone to *H. pylori* colonization while others may be able to prevent colonization or clear an established infection [1].

#### 2.1.2. Chronic Gastritis

When colonization does become persistent – chronic gastritis, a close correlation exists between the level of acid secretion and distribution of gastritis. This correlation results from the counteractive effects of acid on bacterial growth *versus* those of bacterial growth and associated mucosal inflammation on acid secretion and regulation. This interaction is crucial in the determination of outcomes of *H. pylori* infection.

Chronic gastritis due to *H. pylori* infection may be separated into distinct, clinically relevant phenotypes [31]. Nonatrophic pangastritis occurs in the majority of *H. pylori*-infected individuals with no predisposition to peptic ulcer disease or gastric atrophy. Prominent mucosal inflammation in chronic active gastritis often is evident in the antrum (antral-predominant gastritis), predisposing

 

to hyperacidity and duodenal ulcer disease. In contrast, multifocal atrophic pangastritis and atrophic corpus-predominant gastritis result from long-standing infections and are characterized by glandular atrophy, intestinal metaplasia, and sparse inflammatory cells [32]. Both forms of atrophic gastritits and the presence of intestinal metaplasia are associated with an increased risk of gastric adenocarcinomas development [33].

Virulence factors of bacterium strains are important factors here because depending on them, in conjunction with host characteristics and environment, some individuals may develop severe diseases as peptic ulcer and gastric cancer.

### 2.2. *Helicobacter pylori*-Associated Peptic Ulcer Disease

*H. pylori* infection is one of the most common chronic bacterial infections worldwide with up to a half of the world's population infected [13]. It is believed that bacterium has been colonizing the gastric mucosa of modern humans since their migration out of Africa 60,000 years ago [34]. Although the majority of subjects infected with bacterium remain asymptomatic, essentially all develop chronic inflammation [35]. However, peptic ulcer disease (PUD) and gastric carcinoma occur only in a subset of individuals chronically infected with *H. pylori* and both bacterial and host factors contribute to this differential response [36].

Interestingly, during *H. pylori* infection, a subset of the colonized subjects can develop antral-predominant gastritis, which is associated with gastric hyperchlorydria and an increased risk of duodenal ulcer (DU); another subset of the colonized subjects can develop corpus gastritis, that is associated with gastric hypochlorydria, gastric atrophy, gastric ulcer (GU) and an increased risk of non-cardia gastric cancer [37-39].

The relationship between *H. pylori* and PUD and also peptic ulcer bleeding (PUB) has been extensively studied. In fact, *H. pylori* infection is the major cause of PUD and its eradication is vital for ulcer healing in the absence of proton pump inhibitors (PPI) [40]. Furthermore, effective *H. pylori* eradication reduces the rate of ulcer recurrence and it is believed that bacterial eradication also prevents recurrence of PUB [41]. As a consequence of *H. pylori* eradication therapy, the prevalence of PUD has been declined.

In 2001, a meta-analysis of 24 studies including 2102 subjects demonstrated that ulcer healing rates in *H. pylori*-eradicated patients were significantly higher compared with patients with persistent infection (98% vs. 57.5% for DU and 97.1% vs. 60.9% for GU) [42]. In relation to PUB, a meta-analysis conducted in 2002 confirmed that the association between *H. pylori* infection increased the risk of bleeding (OR 1.79) [43].

Considering the use of NSAID and *H. pylori* infection, both of them are considered independent risk factors for the development of PUD and ulcer bleeding. However, there is a synergistic effect for the development of bleeding when these factors are both present [44]. There are sufficient data to suggest that *H. pylori* significantly damages the gastric and duodenal mucosa through direct pathogenic mechanisms, whereas NSAIDs indirectly promote injury through disruption of mucosal defensive mechanisms [45,46]. Therefore, current guidelines recommend *H. pylori* screening and treatment prior to initiating long-term NSAID therapy in patients with a history of PUD [44].

In addition, the role of environmental factors other than *H. pylori* and NSAID, as well as social factors, in the natural history of ulcer has not been adequately explored. Diet may be the most important of these factors, the others being alcohol, tobacco, stress and shift work [47]. A review study about diet and duodenal ulcer performed in 2000 demonstrated that fibre, mainly soluble fibres from fruit and vegetables, and perhaps poly-unsaturated fatty acids, vitamin A and C, appear to be inversely associated with the occurrence of duodenal ulcer, while refined sugars seem to be directly associated with the disease [48].

In relation to *H. pylori* virulence factors in the development of PUD, the role of *cagA* gene and *vacA* gene was verified in a systematic review of 44 studies. CagA positivity was associated with an increased risk for PUD [(OR 1.69 (95% CI 1.12 - 2.55)] and individuals infected with s1m1 strains were also associated with PUD [OR 2.04 (1.01 - 4.13)] [49]. More recently, a novel virulence factor, duodenal ulcer promoting gene A (*dupA*) has been identified and found to be associated with duodenal ulcer in some populations. A current meta-analysis investigated the relationship of *dup*A genotypes and *H. pylori*-related clinical outcomes in 2358 patients from around the world with *dupA*-positive genotypes. It was observed that *dupA* was associated with duodenal ulcer in 48% of subjects [p = 0.001, OR = 1.4, (CI = 1.1 - 1.7); however, the *dupA* positivity and its association with disease differed among the various regions around the world [50]. In a Brazilian study, *dupA* was found both in early and advanced gastric adenocarcinoma, suggesting that, together with cagA gene, it could be an important virulence factor in the development of this disease [51].

Then, researchers continue to explore the complexities of *H. pylori* infection, trying to explain why some individuals have asymptomatic infection, whereas others experience clinical disease. The importance of treating *H. pylori* infection in patients with gastrointestinal problems has been confirmed in recent years especially in the prevention of the development of PUD and gastric cancer.

### 2.3. *H. pylori*-Associated Gastric MALT-Lymphoma

Primary gastric lymphoma (PGL) is a rare tumour, accounting for <5% of primary gastric neoplasms [52]. Most PGL is non-Hodgking type B lymphoma, derived from mucosa associated lymphoid tissue (MALT) that represents about 4% to 20% of non-Hodgkin lymphoma and more than 50% of the PGL [53-55].

The MALT lymphomas were first described in 1983 for Isaacson and Wright [56] and represent an extranodal lymphoma consisting mainly of morphologically heterogeneous small B cells [57]. Histologically, MALT lymphomas are characterized by lymphocytic infiltrate with invasion and partial destruction of the gastric glands and the crypts by aggregates of tumor cells infiltrating the lamina propria diffusely and growing around reactive follicles [58].

The lymphoid tissue is not commonly found in the stomach and its appearance is related, in general, to *H. pylori* infection [59]. In fact, *H. pylori* infection is associated with approximately 80% of gastric MALT lymphomas [60]. The first study correlating the bacteria with MALT lymphoma was carried out by Wotherspoon *et al.* (1991) [61] that not only observed the presence of bacteria in almost all cases of gastric MALT lymphoma that they studied, but also showed that infection resulted in accumulation of MALT in gastric mucosa. These results were further confirmed by other researchers [62-64]. Additionally, experimental studies using rats and mice infected with *H felis* also supported these findings [65-67].

In 2002, a review of 24 studies including 780 patients found that complete lymphoma regression after *H. pylori* eradication was achieved in 35% - 100% of patients, depending on the disease stage [68]. After that, a systematic review involving a total of 1844 patients from 38 studies demonstrated that the prevalence of *H. pylori* infection in MALT lymphoma was 79%, with higher rate in low-grade (79%) than in high-grade (60%) cases [58]. In other studies, the eradication of *H. pylori* caused a complete remission in 60% - 80% of patients with MALT lymphoma [1,69] and a 10-year sustained remission in up to 64% of patients [70]. Then, there is a consensus that *H. pylori* eradication should be performed in all cases of gastric MALT lymphoma, regardless of stage of disease and prognostic factor status, considering that it is a fast and simple strategy to avoid a bacterial trigger of the immune response [71].

The pathogenic mechanism of *H. pylori* infection in MALT lymphoma remains unclear, although the causal relationship between infection and disease has been proven. It is well established that *H. pylori* infection induces an immune response of Th1 type mediated by several proinflammatory cytokines, leading to chronic gastritis with formation of lymphoid follicles in the stomach [72,73]. As well as triggering immunological responses that stimulates the growth of malignant B cells, *H. pylori* infection also triggers inflammatory responses by attracting and activating neutrophils, which release reactive oxygen species (ROS). These ROS can evoke a wide range of gastric damage and might therefore have a role in the acquisition of genetic abnormalities in gastric MALT lymphoma [74]. The severity of DNA damage occurring in an infected individual will depend on a number of factors, including the bacterial virulence, the severity of the inflammatory response and the individual's ability to detoxify ROS [75].

Recently, progress has been made in understanding the molecular basis of MALT lymphoma and three specific major chromosomal translocations have been reported. The t(11; 18) (q21; q21)/(API2-MALT1) is found in 25% - 30% of gastric MALT lymphomas and is associated with advanced and unresponsive lymphomas [76,77]. By contrast, MALT lymphomas that are negative for this translocation commonly show a wide range of chromosomal aberrations, including trisomy of chromossomes 3, 12 and 18 [78,79]. Another translocation is the t(1; 14) (p22; q32) and it might confer to the tumor an increased capacity of autonomous growth by means of inactivating mutations and overexpression of the *BCL*10 gene and the t(14; 18) (q32; q21) translocation is most often seen in folicular lymphoma [80]. It is interesting to note that these genetic abnormalities share a common pathogenic mechanism mediated by the activation of the NF-κB signaling pathway and might confer additional oncogenic activities as indicated by the aberrant pattern of BCL10 expression in some cases of MALT lymphoma [74].

Few studies have been conducted to verify the role of *H. pylori* virulence factors in the development of gastric MALT lymphoma. Interestingly, none of the virulence factors known for this bacterium, including the presence of the *cag* pathogenicity island (PAI) or the Vac toxin, could be associated with this pathology except for the *vacAm*2 allele [81-83]. Similar results were described when analyzed the prevalence and correlation between *H. pylori* virulence factors (*cagA*, *cagE*, *vacA*, *iceA*, *babA*, *hopQ* and *oipA*) and adhesins (*subA* and *hopZ*) by comparing a collection of 43 strains isolated from patients with low-grade MALT lymphoma to 39 strains isolated from patients with gastritis only. None of the genes tested were associated with MALT strains and authors concluded that MALT pathogenesis is not linked with more proinflammatory *H. pylori* strains. Furthermore, they demonstrated that in MALT patients infected with strains harboring the *iceA*1 allele, *subA* and *hopZ* status, the odds of developing a MALT lymphoma were 10 times higher. However, these strains were less prevalent rendering a low-sensitivity marker for MALT *H. pylori*

 

strains.

Therefore, scientists have concentrated their efforts to better understanding the molecular events in the pathogenesis of gastric MALT lymphoma. Although a large body of data has implicated the role of *H. pylori* in the development of the disease, future investigations considering the polymorphisms involved in the immune response and molecular genetics of the host, in association with virulence factors of bacteria, are needed to clarify the pathomechanism by which gastric MALT lymphoma occurs.

### 2.4. *H. pylori* and Gastric Adenocarcinoma

Gastric cancer continues to be a major global health problem [84], and, despite the decreasing incidence and mortality rates observed worldwide over the last 50 years, it still ranks as a leading cause of cancer-related deaths in many parts of the world [85]. As symptoms are often absent or nonspecific in patients with the early stages of the disease, gastric cancer is usually diagnosed in an advanced stage, when curative options are limited. With exceptions in countries that have developed screening programs for early diagnoses, most patients reach treatment with cancers already in advanced stages [86]. Consequently, gastric cancer carries a poor prognosis, with an overall five-year survival rate of less than 20% [87].

The vast majority of gastric cancers are adenocarcinomas, which can be prevalently divided into two types, the intestinal and the diffuse [88], which corresponds, respectively, to the well-differentiated type and the poorly-differentiated type, in the Japanese classification [89]. In contrast to the diffuse type, often associated with familial distribution and developed in the stomach following chronic inflammation, especially in the cardia [85], intestinal type adenocarcinomas are generally thought to be preceded by a sequence of precursor lesions [90]. It postulated that the intestinal type of gastric cancer was the end of progressive changes in the gastric mucosa, starting with chronic gastritis, followed by multifocal atrophic gastritis and intestinal metaplasia. The model was updated in 1988 and 1992 [91,92]. The following consecutive steps were recognized as: normal gastric mucosa, superficial gastritis (later renamed non-atrophic gastritis, multifocal atrophic gastritis without intestinal metaplasia, intestinal metaplasia of the complete (small intestine) type, intestinal metaplasia of the incomplete (colonic) type, low-grade dysplasia (low-grade noninvasive neoplasia), high-grade dysplasia (high-grade noninvasive neoplasia) and invasive carcinoma [93](Correia e Piazuelo, 2012).

Unlike patients with advanced gastric cancer, patients diagnosed in an early stage of the disease present an excellent prognostic, in which a five-year survival rate is more than 90%. This disorder is defined as the adenocarcinoma that is confined to the mucosa or submucosa, irrespective of lymph-node invasion. Many early gastric cancers are believed to go through a life cycle consisting of ulcerations, followed by healing, then reulceration, and some tumors remain at this early stage for years even without treatment [94] Nevertheless, some early tumors rapdly became advanced and it is one of the principal questions concerning gastric carcinogenesis.

Various studies suggest the importance of *H. pylori* virulence factors as important keys in gastric mucosa inflammation and, consequently, in the development of gastric cancer. The principal of them is the cag pathogenicity island (cagPAI), a genetic locus that encodes a type IV secretion system (Censini *et al*., Franco *et al*.) [95,96]. Infection with cagA positive strains has been associated with higher degrees of inflammation of the gastric mucosa; consequently, the gene seems to play an important role in the development of gastric cancer, being crucial to the formation of the pre-cancerous lesions present in cases of intestinal type gastric adenocarcinoma [97-101]. Upon delivery into host cells, CagA protein leads to dephosphorylation of host cell proteins and morphological changes in the cell [102,103]. Additionally, CagA has been shown to interfere with $\beta$-catenin signaling [104,105] and apical-junctional complexes [106], events that have been linked to increased cell motility and oncogenic transformation in a variety of models [107,108].

Obviously, gastric carcinogenesis involves the interaction of the etiologic agent (especially *H. pylori*), the host characteristics and the external environment [109]. As regards to *H. pylori*, many virulence genes have been reported to determine clinical outcomes; among those of potential significance, especially with regards to gastric cancer, are the cytotoxin-associated gene A (cagA), which was described before, the cytotoxin-associated gene T (cagT), the vacuolating cytotoxin gene (vacA), the duodenal-ulcer promoting gene (dupA) and the outer inflammatory protein gene (oipA).

Concerning to the host susceptibility, polymorphisms in a wide variety of genes that are present within a significant proportion of the normal population may modify the effect of environmental exposure. These gene-environmental interactions could explain the high variation in the incidence of gastric cancer observed around the world [110]. Among these genes, for example, there are cytokine genes (TNF-$\alpha$, IL-10, IL-8, IFN-$\gamma$) involved in the adaptive immune system [111,112] and pattern recognition factors (TLR-4, NOD-1, NOD-2) involved in initiating the innate immune system [113,114].

Host related factors for the development of disease can indicate genetic susceptibility (or resistance) or acquired influences, which may stimulate defenses of the host against environmental carcinogens like *H. pylori* [115]. The relationship between host genetic polymorphisms

 

(for instance, in the IL-1) and bacterial virulence factors appears to have a crucial role in the development of the cancer, especially in infections with cagA positive, vacA s1m1 and oipA positive strains.

Finally, concerning to environmental factors, particularly diet and smoking play an important role in the pathogenesis of gastric cancer. Diets rich in complex carbohydrates, salt, pickled or smoked foods, dried fish, and cooking oil has been linked with an increased risk, while diet rich in fresh fruits and vegetables has been associated with a low risk of gastric cancer [110,116].

Smoking also represents an important factor in gastric cancer development. A large study that included smoking men demonstrated an increased risk for the development of differentiated-type distal gastric cancer [117]. In Japan, a study offered persuasive evidence that tobacco smoking moderately increases the risk of gastric cancer among the Japanese population [118]. Another study that analyzed forty-two articles and compared current smokers and nonsmokers provided solid evidence to classify smoking as the most important behavioral risk factor for gastric cancer [119]. Finally, a recent study also concluded that smoking is an important factor associated with the risk of developing gastric cancer [120].

## 3. CONCLUSION

Since the discovery of *H. pylori*, several studies have focused on elucidating the microorganism pathogenicity mechanisms that are associated with disease outcome [121]. *H. pylori* is associated with chronic gastritis, pepticulcer disease, MALT-lymphoma and gastric cancer, including the precancerous cascade. The development of clinical outcomes depends on the interaction among *H. pylori* strain, and its virulence factors, host genetic characteristics and the external environment. To understand the clinical relevance of *H. pylori* genotyping in predicting infection outcomes, prospective studies in large populations and with appropriate controls are needed to elucidate its pathophysiology and genetics. Besides, studies considering the host characteristics and the environmental are also needed, in order to help to make *H. pylori*-related diseases preventable, especially gastric cancer, that continues to be an important mortality factor worldwide.

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