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NATURAL HISTORY OF *HELICOBACTER PYLORI* INFECTION

Pelayo Correa, MD^{1,*} and M. Blanca Piazuelo, MD¹

¹Division of Gastroenterology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

Abstract

This report describes the modalities of chronic gastritis induced by *Helicobacter pylori* infection in different populations. The full gamut of lesions representing the precancerous cascade are very prevalent in populations of low socioeconomic background experiencing very high gastric cancer risk, as seen in the Latin American Andes Mountains. In populations of high socioeconomic standards and high cancer risk, such as Japan and Korea, the precancerous cascade also predominates and “early” cancers are diagnosed frequently. Some reports describe frequent corpus atrophy, not prominent in the former group. The so-called African enigma is seen in populations of low socioeconomic standards, usually living at low altitudes, with high prevalence of infection but low frequency of cancer and precancerous lesions. In populations in transition from high- to low-cancer risk, duodenal ulcer and antral nonatrophic gastritis are frequently seen. In affluent societies at low risk of cancer, such as Western Europe, Australia and North America, mild nonatrophic gastritis associated with low virulence *H. pylori* genotypes predominate. The varied phenotypes of gastritis may reflect secular changes in the ecology of our species.

Introduction

Helicobacter pylori (*H. pylori*) infection presently affects approximately one half of the world’s population and leads to chronic gastritis, the most frequent chronic inflammation worldwide. *H. pylori* is also etiologically associated with gastric and duodenal ulcer, MALT gastric lymphoma, and gastric adenocarcinoma. The prevalence and the severity of the infection vary considerably among populations. The infection is usually acquired during childhood and lasts for decades. Its outcome varies significantly in different populations and individuals. The diverse outcomes (Figure 1) may be related to the secular changes that have occurred in the genome of the bacterial agent as well as in ecological changes taking place in the environment of the human host. This review attempts to describe such outcomes and speculate about their poorly understood determinants.

The Bacterium and its Pathogenicity

H. pylori is a spiral-shaped bacterium that colonizes the human gastric mucosa (Figure 2). It is well known for its marked genetic diversity. Several genes of *H. pylori* have been identified as being virulence-associated and may have important clinical and

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*Corresponding author: 2215 Garland Ave. 1030 MRB IV Nashville, TN 37232-0252 Phone: (615) 343-3958 Fax: (615) 343-6229 pelayo.correa@vanderbilt.edu .

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epidemiological implications. Among them, the cytotoxin-associated (*cagA*) and the vacuolating cytotoxin (*vacA*) genes have been studied most extensively. The *cag* pathogenicity island is a 40-kb DNA region that contains the *cagA* gene and encodes a type IV secretion system involved in the export of the CagA protein into the epithelial cells [1]. The *cagA* gene is present in only some strains (50 to 60% of *H. pylori* isolates from Western countries and in >90% of isolates from East Asian countries) and may have resulted from acquisition of DNA from other bacteria [1]. Infection with *cagA*-positive *H. pylori* strains has been associated with increased risk for development of peptic ulcer [2,3] and gastric adenocarcinoma [4,5]. CagA is translocated into gastric epithelial cells, where it is phosphorylated on the tyrosine residues of some of the five-amino-acid (EPIYA) motifs and causes multiple cellular alterations [6]. The EPIYA-repeat region of CagA is highly divergent among different species of *H. pylori* and is composed of various combinations of four segments: EPIYA-A, -B, -C, and -D. Most CagA proteins from strains isolated in Western countries possess EPIYA-A, EPIYA-B, and one to three copies of the EPIYA-C motifs. Strains from East Asian countries possess an EPIYA-D motif (instead of the EPIYA-C) and appear to induce more severe cellular changes, more severe gastric atrophy, inflammation, and gastric cancer compared to Western strains [6-8]. Among Western strains, those having multiple EPIYA-C sites in CagA are associated with increased phosphorylation-dependent biological activity [7,9].

The *vacA* gene encodes a vacuolating cytotoxin which is secreted by *H. pylori* and damages epithelial cells [10]. The gene is present in all strains, and comprises two variable parts [11]. The s region (encoding the signal peptide) exists as a s1 (with subtypes s1a, s1b, and s1c) or s2 allele. The m region (middle) occurs as m1 or m2 (subtypes m2a or m2b) alleles [12]. The combination of s and m region alleles determines the production of the cytotoxin and is associated with the pathogenicity of the bacterium [11]. *vacA* m1 type strains have been associated with greater gastric epithelial damage [13] and with gastric ulcer or carcinoma compared to m2 strains [14]. *H. pylori vacA* s1, *vacA* m1, *cagA*-positive genotypes have been associated with higher degrees of inflammation, atrophy and intestinal metaplasia [15].

Epidemiology and Natural History

A steady decrease in the prevalence of *H. pylori* infection and the incidence of gastric cancer has been observed in most populations in recent decades, more accentuated in wealthy Western societies. The predominant bacterial genotypes also differ greatly. Populations at high gastric cancer risk generally harbor more virulent strains, compared to low risk populations. In some individuals, more than one strain of *H. pylori* colonizes the gastric mucosa, and they may vary in their virulence. Concomitantly with decreasing cancer rates and prevalence of infection, several major changes have occurred in these societies, mostly related to economic development [16]. Prominent among them are improved home sanitation, decreasing family size, less household crowding, changes in dietary habits such as less salt consumption and more intake of fruits and fresh vegetables, improvements in refrigeration at home and in transportation equipment, and control of infectious diseases. The increasing use of antibiotics to treat other diseases may have unwanted effects (inducing resistance) in *H. pylori* colonization.

Although many subjects with *H. pylori* gastric colonization are asymptomatic, those who seek medical attention may present heartburn, dyspepsia, nausea, vomiting, or halitosis. Some subjects with erosive gastritis or ulcers may present hematemesis or melena. The infection involves initially the antrum and eventually may disseminate proximally to the corpus. In patients receiving antacid medication, the colonization is predominantly in the corpus. Prolonged and severe infection may result in ulcer formation and/or loss of glandular tissue (atrophy). Subjects who develop duodenal ulcers are not at increased risk of

gastric cancer [17]. In contrast, subjects with gastric ulcers typically have multifocal atrophic gastritis and high risk of gastric cancer [17,18]. Some patients with atrophic gastritis develop intestinal metaplasia, and a very small percentage of them eventually will progress further to dysplasia and invasive adenocarcinoma. Less than 1% of the infected subjects will ever develop gastric cancer. The so-called intestinal-type adenocarcinoma [19] is more frequent in populations displaying high incidence rates of gastric cancer and is the final stage of a multistep and multifactorial process in which environmental factors (*H. pylori* infection, diet and smoking) seem to have the most important etiopathogenetic role. Diffuse-type adenocarcinoma is relatively more frequent in populations at low risk than those at high risk for gastric cancer. Although environmental agents have been thought to play a less important role than genetic factors, *H. pylori* infection has been also associated with the development of diffuse-type adenocarcinoma [5,20]. Anatomically, stomach adenocarcinomas are classified as noncardia (the majority of cases worldwide) and cardia cancers. While *H. pylori* infection is a recognized risk factor for noncardia cancer, the association between the infection and cardia cancer is unclear [21-23].

In some populations, *H. pylori* has been reported to trigger an autoimmune gastritis of the corpus mucosa characterized by presence of autoantibodies against the subunits of the gastric H^+ , K^+ -ATPase in the parietal cells. The presence of these autoantibodies is associated with a higher degree of body gastritis, increased apoptosis in the glandular epithelium and atrophy of the corpus mucosa [24].

The interactions of the different factors described above are reflected in the mucosal lesions which characterize the modalities of chronic gastritis predominant in some populations. They are described in the following paragraphs.

1- Populations of low socioeconomic status (SES) and high gastric cancer risk

These populations display the most severe and advanced lesions resulting from *H. pylori* infection. A prototype of them is represented by the Andean regions of South America. The full expression of the precancerous cascade is seen in them: from chronic active gastritis to multifocal atrophy, to intestinal metaplasia (complete and then incomplete), to dysplasia, and finally to invasive carcinoma [25-27]. The infection is acquired very early in childhood [28,29]. Higher proportions of virulent strains are observed in these populations when compared to low risk populations [30,31]. The process starts as a non-atrophic antral gastritis, characterized by severe mononuclear and polymorphonuclear neutrophil infiltration, mucus depletion, and cytotoxic intraepithelial T cell infiltrate [32]. In adults, multifocal atrophy and intestinal metaplasia are frequently seen and become more accentuated with age [26,30] (Figures 3 and 4). Gastric peptic ulcer has been frequently reported in young adult patients and tends to disappear as the atrophic lesions and their consequent hypochlorhydria advance with age. In these societies, several environmental influences may contribute to the severity of the infection and the high cancer risk. The diet tends to be high in salt [33] and low in animal proteins (Camargo et al, unpublished data) as well as in fruits and fresh vegetables [34]. Interventional measures such as *H. pylori* eradication and antioxidant supplementation have shown to slow down the progression of the gastric precancerous lesions [35,36].

2- Populations of high SES and high gastric cancer risk

This is presently the case of Japan and probably South Korea. In general, these societies have high prevalence of multifocal atrophic gastritis and intestinal metaplasia [37], as observed in other high risk populations. These two countries for many years displayed the highest cancer incidence and mortality rates in the world. The reasons for such high rates are poorly understood, but may be related to the high virulence of the prevalent *H. pylori* strains

[38,39]. Nearly all East Asian strains possess CagA protein with EPIYA-D motifs, shown to be more active in the induction of cellular changes than Western strains [6,9]. Some recent reports have suggested a relatively high frequency of gastric corpus atrophy, not seen frequently in low SES populations. It is not clear if this is a new development in such populations and if it may be related to recent ecological changes.

In these societies, the high SES is relatively recent and has been accompanied by changes in their diet, especially lower salt intake [40]. A nationwide screening and early detection program for gastric cancer has been conducted in Japan for several decades. Multiple highly developed endoscopic units are available in these communities with masterful use of the technique of endoscopic mucosal resection of dysplasias and “early” cancers, associated with excellent prognosis and high rates of survival [40,41]. As a result, decreasing mortality rates in the presence of continued high incidence rates have been observed in Japan [16,40].

3- Populations of low SES and low cancer rates. The African enigma

These societies are represented by most African countries and some coastal and low altitude regions of Latin America [42-45]. They usually have a high prevalence of *H. pylori* infection starting early in childhood [28,45]. The type of gastritis observed is predominantly non-atrophic (Figure 5) with very low proportion of metaplastic changes [46]. Studies suggest that they may have a higher proportion of low virulence strains when compared to populations at high gastric cancer risk, but it is doubtful that the differences in strains are large enough to fully explain their differences in cancer risk [30,31]. Alternative explanations for the “enigma” have been offered. One main difference is the diet: communities on the coastal regions tend to consume more frequently fish and seafood as well as tropical fruits and fresh vegetables than do high risk populations. These types of foods are rich in antioxidants. Another possible factor has to do with the type of immune reaction of the host to the *H. pylori* infection. Intestinal parasites, especially helminthes, are more frequent in the warm tropical climates. They tend to drive an anti-inflammatory Th2-type immune response against the *H. pylori* chronic infection that may lead to decrease in gastric cancer risk later in life [47,48]. Eosinophilic infiltration of the gastric mucosa, linked to Th2-type response, may be prominent (Piazzuelo et al, unpublished data). In an animal model, supporting this hypothesis, concurrent helminth infection reduced considerably *Helicobacter*-associated gastric inflammatory cytokines and chemokines associated with a Th1 response and gastric atrophy [49]. A similar phenomenon has been reported in a population indicating that a concurrent helminth infection (*Schistosoma japonicum*) modifies the immune response to *H. pylori* and reduces the probability of developing corpus atrophy [50].

4- Populations in transition from high- to low- gastric cancer risk

It has been reported that duodenal ulcer frequency began to rise in Europe and the United States in the 19th century and is becoming less frequent in recent decades [51,52] displaying the temporal pattern of an epidemic. Patients with duodenal ulcer typically have an antral diffuse non-atrophic, active chronic gastritis. The strains of *H. pylori* infecting them are virulent: usually Cag A positive [3,53]. The decline in duodenal ulcer incidence is related to the decline in the prevalence of *H. pylori* infection [53]. It would appear that the “epidemic” of duodenal ulcer displays a different timing in other populations. The reasons behind the rise in duodenal ulcer in the 19th century in Europe and the United States are obscure. It coincided with the beginning of the decline in *H. pylori* infection. It has been proposed that that the initial increase in duodenal ulcer reflects a change in the equilibrium that existed for centuries between *H. pylori* and its human host [53]. The alteration in that equilibrium could have affected the pattern of colonization of *H. pylori* in the gastric mucosa, brought by ecological changes in the host’s environment. This altered equilibrium could have resulted

in excessive acid secretion, a forerunner of duodenal ulcer. It has also been reported that the first infection with *H. pylori* occurs later in life in patients who develop duodenal ulcer, compared with those who develop gastric ulcer or gastric cancer [52,54]. The dynamics of the relationship between host and infectious agent may differ according to the age at first infection. It has been hypothesized that a very early infection may colonize the gastric mucosa at a time when the acid secretion apparatus has not been fully matured to permit duodenal ulcer development. Such subjects may present early development of atrophy with increased risk of gastric ulcer and carcinoma [54].

5- Affluent Western societies at low gastric cancer risk

These societies are represented by some Western European countries, Australia, and Caucasian populations in the US and Canada. Among them, the prevalence of *H. pylori* infection is low, and the great majority of infected subjects are asymptomatic. The diagnosis of the infection may be an incidental finding during routine health screening procedures. The proportion of low virulence strains of *H. pylori* (*cagA*-negative, *vacA* s2 m2) tends to be higher than in high risk populations [55]. Colonization with such strains leads to mild non-atrophic gastritis, with well-preserved gastric architecture [3]. Some of such populations have a history of high risk for gastric cancer decades before. Probably the type and severity of chronic gastritis were different then. Since clinically tangible sequelae of the infection are absent, it could be argued that anti-*H. pylori* treatment is not justified. The decrease in prevalence of *H. pylori* infection over recent decades has been associated with an increase in the frequency of gastroesophageal reflux disease, chronic esophagitis, Barrett's esophagus, and esophageal adenocarcinoma [53,56,57]. These conditions are associated with hyperacidity, which has been reported after curing the *H. pylori* infection with antibiotics. Accordingly, a protective effect of *H. pylori* against such esophageal diseases has been suggested.

Epilogue

Chronic gastritis is the unavoidable manifestation of *H. pylori* infection. It varies considerably in type and severity among populations and individuals. Its phenotype and consequences are determined by a complex interaction of etiologic factors derived from the bacterium and its human host as they have co-evolved throughout the centuries. In populations at high cancer risk, the full spectrum of the precancerous cascade is observed: from non-atrophic to metaplastic to dysplastic lesions. Corpus atrophy has been associated with higher gastric cancer risk and usually represents an extension to the corpus of a multifocal atrophic gastritis. Corpus atrophy without antral atrophy is characteristic of autoimmune gastritis, as seen in the pernicious anemia syndrome, less frequently observed at the present time. Gastric peptic ulcer is part of the multifocal atrophic gastritis complex. By contrast, duodenal peptic ulcer is not associated with atrophy, does not increase cancer risk, and seems to follow an epidemic pattern in populations in transition from high- to low-gastric cancer risk. Populations with low gastric cancer risk and low SES may have high prevalence and early infection of *H. pylori*; in them, chronic gastritis tends not to progress to intestinal metaplasia and beyond.

Affluent Western populations present low *H. pylori* infection prevalence and gastric cancer risk. Among them, gastroesophageal reflux-related diseases are increasing in incidence, coinciding with further decrease in *H. pylori* infection prevalence. Another possible negative influence of the absence of *H. pylori* infection in the community may be related to the so-called "hygiene hypothesis". It postulates that improvements in sanitation and widespread use of antibiotics have resulted in the disappearance of infections of the respiratory and digestive systems, especially in children, required to shape and maintain the homeostasis of the human immune system [58,59]. The increasing incidence of asthma, eczema and auto-

immune diseases in developed countries seem to reflect a bias in the development of the immune system towards Th2-type responses. Studies suggest that *H. pylori* has been part of the human microbiota during tens of thousands of years [60], indicating that important adaptations may have occurred between bacterium and host to maintain an equilibrium.

The spectrum of *H. pylori* infection and its outcomes seem to be in a slow flux, mainly determined by ecological changes in human populations.

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Green Boxes

Practice points

- *H. pylori* infects approximately one half of the world's population and may cause a broad spectrum of gastric lesions, including gastric cancer, mostly preceded by chronic gastritis.
- The chronic gastritis phenotype presents marked inter-population differences depending on the socioeconomic status and the gastric cancer risk.
- *H. pylori*'s genetic diversity, as well as environmental factors (socioeconomic status, diet, and smoking) and host genetic susceptibility are related to the outcome.

Research agenda

- To increase our knowledge in *H. pylori*'s virulence factors and mechanisms of mucosal damage in gastric carcinogenesis.
- Identification of genetic markers of host susceptibility to gastric cancer.

Figure 1.
Schematic representation of the clinical outcomes following *H. pylori* infection.

Figure 2.
Histological section of gastric antral mucosa infected with *H. pylori*. Abundant microorganisms are observed in the luminal surface and attached to the epithelium. (Modified Steiner silver stain)

Figure 3. Multifocal atrophic gastritis in a Colombian subject residing in a high gastric cancer risk area, infected with a *cagA*-positive *vacA* s1m1 *H. pylori* strain. Marked inflammatory infiltrate and loss of glandular structures are observed. (H&E stain)

Figure 4.

Multifocal atrophic gastritis with intestinal metaplasia (colonic type) in a Colombian subject residing in a high gastric cancer risk area, infected with a *cagA*-positive *vacA* s1m1 *H. pylori* strain. Normal glands seen on the left side display neutral mucins (magenta). Metaplastic epithelium, on the right side, displays acidic mucins (purple) in the goblet cells and neutral mucins in the columnar cells. (AB-PAS stain)

Figure 5. Non-atrophic chronic gastritis in a subject residing in a low gastric cancer risk area, infected with a *cagA*-negative *vacA* s2m2 *H. pylori* strain. Mild to moderate mononuclear infiltrate and well preserved glandular structures are observed. (H&E stain)