EDITORIAL

HELICOBACTER PYLORI AND BARRETT’S ESOPHAGUS: A PROTECTIVE FACTOR OR A REAL CAUSE?

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Notwithstanding the definite aetiopathogenetic path of certain diseases, the relationship between Helicobacter pylori (H. pylori) and Barrett’s esophagus (BE), a condition that increases the risk for dysplasia and consequently adenocarcinoma of the distal esophagus and esophagogastric junction, remains uncertain. This paper reviews the current scientific literature with emphasis on the protective correlation between H. pylori infection and BE and demonstrates that a causal relationship has not been disproved with certainty. Furthermore, H. pylori infection could pose a risk for the onset of gastroesophageal reflux disease (GERD), which could in turn trigger BE, a precancerous lesion, and subsequently cause cancer. By analyzing the current available data, this article tries to verify that H. pylori infection is the underlying cause of esophageal cancer.

Approximately 10^{14} microorganisms colonize the human gastrointestinal tract. Though the part with the highest microbial concentration is the colon, the oral cavity, esophagus and stomach are also colonized. This large variety of microorganisms constitutes the microbiota, a complex ecosystem of over 800-1000 different microbial species (bacteria, viruses, fungi) with more than 3 million genes. Evolutionary processes have established a symbiotic relationship between the microbiota and the host, however, sudden changes could result in dysbiosis with strong imbalances in the autonomic nervous and immune systems. Each individual possesses his/her own characteristic microbiota, a “bacterial fingerprint” composed of at least sixty common microbial species. Microbial changes are the result of infant delivery method (vaginal birth or cesarean) and/or infant feeding option (breast milk or formula

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feeds). Early exposure to maternal IgA determines a bowel cell gene pattern expression unlike that expressed by formula-fed infants who exhibit genes associated with chronic inflammatory diseases. Microbiota composition changes are also related to age, diet, stress and antibiotic use, among others (1).

Many studies have examined the function of microbiota and the relationship between healthy intestinal flora maintenance and the host’s overall health status. The microbiota is predominantly composed of two major phyla, Bacteroidetes and Firmicutes. Important functions of these phyla include the production of enzymes that foster digestion, pH adjustment, intestinal motility, the production of important vitamins, such as K and B12, and the synthesis of conjugated linoleic acid (CLA), an essential short-chain fatty acid (SCFA) known for its anti-diabetic and anti-atherogenic properties, all of which seem to implicate the prevention of colon cancer. Among the more important functions of butyric acid, are its trophic, beneficial, and protective roles of the colonic mucosa. Butyric acid may be viewed as a valuable complementary therapeutic agent if used together with traditional drugs (corticosteroids and mesalazine) for the treatment of colon cancer. Moreover, the flora modulates the intestinal immune system (gut associated lymphoid tissues, GALT) in terms of development and operation, resistance to the invasion of and colonization by territory competing drug metabolizing pathogenic bacteria (immunomodulation) and xenobiotics (2).

It is therefore easy to understand how changes in microbiota conditions (dysbiosis) could be associated with different clinical conditions, for example: metabolic diseases; autoimmune diseases; allergies; inflammatory bowel disease (IBD); irritable bowel syndrome (IBS); ulcerative colitis; and colorectal cancer. Furthermore, the data suggest how these diseases are associated with altered expression of Heat Shock Protein (HSP) to the extent that they were called chaperonopathies (3).

Numerous studies have focused on the detection of high concentrations of HSP 10 and HSP 90 in adenocarcinoma samples. The physiological function of HSPs is to help other proteins folding to guide the degradation of defective proteins. However, during evolution, HSPs have acquired additional roles and are involved in immunomodulation and tumor progression (4).

Based on this evidence, it was inferred that microbiota modulation with probiotics, which the World Health Organization (WHO) defined as beneficial live microorganisms to human health, and prebiotics, or food ingredients that contain non-digestible oligosaccharides, such as galactooligosaccharides and inulin, could be useful for the treatment or prevention of numerous disorders.

However, the microbiota affects also other body functions. A connection between dysbiosis and obesity, based on the microbiota compositions of lean and overweight subjects, indicates a prevalence of Bacteroidetes in the former and Firmicutes in the latter (5). In addition, this connection shows that alterations in the intestinal microbial composition are associated with large variations in enterochromaffin cells, via the effect of the brain-gut axis. Such results could also be linked to psychiatric and behavioral disorders, thus indicating the crucial importance of the two-way communication path between the microbiota and the brain, in health and disease (6).

**Helicobacter pylori infection**

Earlier studies focused on the microbiota of the lower segments of the digestive tract, neglecting the upper tract such as the stomach long considered sterile due to its acidic pH. However, Barry Marshall and Robin Warren, recipients of the Nobel Prize in Physiology and Medicine in 2005 for their isolation of *Helicobacter pylori* (H. pylori) in the acidic environment of the stomach, found the Gram negative bacterium (named for its spiral shape and peculiar pyloric location) scourging the stomach. Furthermore, they found an acidophilus natural habitat in the stomach. Consequently, *H. pylori* has become accustomed to living in the gastric mucus of about 50% of the population. It is actually localized in the superficial mucin and the lower epithelium as a result of adhesions. Occasionally, *H. pylori* associates with the accessing epithelial cells, however, in general, it remains immersed in the mucus gel coating...
that reduce the lower esophageal sphincter quality or that increase abdominal pressure, such as alcohol abuse, smoking, obesity, delayed gastric emptying and hypotonia of the LES musculature, contribute to GERD and consequently to the emergence of esophagitis reflux. Esophageal lesions are endoscopically visible; their extent and severity are described in the Los Angeles Classification of Gastroesophageal Reflux Diseases (9). This classification system is based on endoscopic data and provides a breakdown of the four possible clinical grades:

i) GRADE A: one or more erosions of the mucosal length, 5 mm or less in extent, with no overlap at the edges of two mucosal folds;

ii) GRADE B: one or more erosions of the mucosal length, greater than 5 mm in extent, with no overlap at the edges and continuity of two mucosal folds;

iii) GRADE C: mucous discharge with overlap between the ends of one or more folds, but involving less than 75% of the esophageal circumference;

iv) GRADE D: mucous discharge affecting at least 75% of esophageal circumference.

An interesting correlation between *H. pylori* infection and BE, a complication that affects about 10% of patients with chronic GERD, is that 1% of patients with Barrett’s will develop adenocarcinoma. Barrett’s esophagus (BE) was first described in 1950 by Norman Barrett who characterized this relatively rare condition as epithelial metaplasia of the columnar type which develops through the replacement of stratified squamous esophageal

Esophagitis and Barrett’s esophagus

The stratified squamous epithelium of the esophagus is known to be abrasion resistant, but sensitive to acid. It is now well documented that the contents of gastric reflux into the esophagus is the most common cause of esophagitis. All conditions

![Fig. 1. Sequence of cellular changes related to infection by Helicobacter pylori.](image-url)
epithelium with columnar epithelium (2). The lesion, with digits of variable lengths, originates from the gastroesophageal junction and extends in a proximal direction appearing as a ring of velvety erythematous mucosa. It is considered as an important pre-cancerous lesion for esophageal adenocarcinoma. It is also associated with microbiota variations and genetic alterations, most commonly observed in the pathological Barrett-carcinogenesis path. This path includes disorders in important cell cycle regulators, such as: the inactivation of P53; the deregulation of the TGF-β/Smad and receptor tyrosine kinases; the presence of a mitogen activated protein kinase (MAPK); and increased expression of COX-2. Each of these factors is related to increased cell proliferation. In addition, chronic exposure to the components of gastro-esophageal reflux triggers the release of inflammatory cytokines, chemokines, reactive oxygen species (ROS), and reactive nitrogen species (RNS). Such factors promote active migration of inflammatory cells, and damage in DNA, and play a crucial role in the initiation of the carcinogenic path (10). There are three variants of Barrett’s epithelium: columnar epithelium, cardia columnar epithelium gastric-fundic, and intestinal columnar epithelium.

Knowledge of the three variants is essential when evaluating the Barrett mosaic. However, the evaluation can be achieved by endoscopic examination as long as there is a histological confirmation. With BE, there is a risk of developing dysplasia and adenocarcinoma as a result of specialized intestinal metaplasia. As such, some researchers advocate for a limited definition of BE and to follow-up endoscopically only in patients with intestinal metaplasia (7, 9, 11).

Metaplasia is a major factor in the development of GERD, which can be caused by *H. pylori* infection. The build-up of material in the esophagus along with bile acid induces such transformation, however, a mucosal resistance to insult the refluxate takes place. Moreover, cancer risk increases in direct proportion to the length and severity of the reflux and increases even more if the GERD is associated with hiatal hernia, esophagitis, or ulcer (11).

Our investigation is based on reading and evaluating most studies that examine the relationship between *H. pylori* and BE. Our analysis depicts discrepancies among the studies. For example, some studies emphasize that both the protection from Barrett in subjects Cag A positive (11-14) and the possible mechanisms through which *H. pylori* may decrease the risk of BE are due to their association with atrophic gastritis and the resultant damaging effects of acid produced by parietal cells. Because of the loss of parietal cells, esophageal exposure to the harmful stomach acid effects would be less likely, thus reducing the likelihood of acid reflux, erosive esophagitis, and BE (15). However, other studies support the cause and effect relationship between *H. pylori* and BE, or indicate that the primary cause of *H. pylori* infection is chronic GERD (16-20).

**DISCUSSION**

Though the mechanisms underlying the pathogenic action of *H. pylori* are largely unknown, one could still distinguish bacterial virulence factors from those related to the inflammatory reaction of the host. Key virulence factors contributing to the onset of symptoms include first, the microbe’s gastric motility, which allows bacterial penetration of the mucus layer covering the mucous membrane. Second, the production of high amounts of urease, an enzyme necessary for the colonization of the area, hydrolyzes the urea present in the gastric lumen, and ultimately produces ammonia and bicarbonates that thoroughly neutralize the immediate vicinity. And third, the secretion of hydrochloric acid by gastric parietal cells creates an acidic pH around the bacterium, which promotes bacterial penetration of the mucus layer covering the mucous membrane. Metaplasia is a major factor in the development of GERD, which can be caused by *H. pylori* infection. The build-up of material in the esophagus along with bile acid induces such transformation, however, a mucosal resistance to insult the refluxate takes place. Moreover, cancer risk increases in direct proportion to the length and severity of the reflux and increases even more if the GERD is associated with hiatal hernia, esophagitis, or ulcer (11).

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Table I. Comparison between studies on *Helicobacter pylori* and gastrointestinal diseases.

<table>
<thead>
<tr>
<th>STUDIES</th>
<th>POSITIVE RELATIONSHIP</th>
<th>NEGATIVE RELATIONSHIP</th>
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| *Vicari J et al*\(^1\)\(^8\)  
*Helicobacter pylori* and acid peptic disorders of the esophagus: is it conceivable? |  | X |
| *Ghoshal UC et al*\(^1\)\(^9\)  
Gastroesophageal Reflux disease and *Helicobacter pylori*: What may be the relationship? |  | X |
| *Lai CH et al*\(^2\)\(^0\)  
Lower prevalence of *Helicobacter pylori* infection with vacAs1a, cagA-positive, and babA2-positive genotype in erosive reflux esophagitis disease. |  | X |
| *Kountouras J et al*\(^1\)\(^6\)  
*Helicobacter pylori* infection might contribute to esophageal adenocarcinoma progress in subpopulations with gastroesophageal reflux disease and Barrett's esophagus. | X |  |
| *Rossi G, Gambi R. et al*\(^1\)\(^7\)  
Severe gastritis with double *Helicobacter* spp. infection associated with Barrett's esophagus in a cheetah. |  | X |
| *Rubenstein JH et al*\(^1\)\(^1\)  
Association between *Helicobacter pylori* and Barrett's esophagus, erosive esophagitis, and gastroesophageal reflux symptoms. |  | X |
| *Loffeld RJ et al*\(^1\)\(^2\)  
Colonization with cagA-positive *Helicobacter pylori* strains inversely associated with reflux esophagitis and Barrett's esophagus. |  | X |
| *Lord RV et al*\(^1\)\(^3\)  
Prevalence of *Helicobacter pylori* infection in 160 patients with Barrett's oesophagus or Barrett's adenocarcinoma. |  | X |
| *Fischbach LA et al*\(^1\)\(^4\)  
The association between Barrett's esophagus and *Helicobacter pylori* infection: a meta-analysis. |  | X |
| *Corley DA et al*\(^1\)\(^5\)  
*Helicobacter pylori* infection and the risk of Barrett's oesophagus: a community-based study. |  | X |
to be subject to variations between the numerous bacterial strains. Some forms are associated with the presence of duodenal ulcer, while others with the absence of significant inflammatory lesions or symptoms. All strains of \textit{H. pylori} are capable of hosting the VacA gene. However, for unknown reasons, the gene is active only in a percentage of the strains of \textit{H. pylori}. VacA interacts with numerous receptor molecules of the host surface and can trigger a number of responses including insertion in the cell membrane, endosomal function changes, and apoptosis. A second factor is the pathogenetic CagA (\textit{cytotoxin associated gene}) pathogenicity island which consists of approximately thirty genes that appear to be injected into the skin cell to induce the production of IL-8. Together, IL-8 and other cytokines produced during the inflammatory reaction induce the massive destruction of cell junctions and the loss of cell polarity. Hence, the neutrophils experience a chemotactic action emanating from the lamina propria capillaries which eventually infiltrate the epithelium. The release of protease and the derivative, ROS, coupled with vacuolation, may be the mechanism that \textit{H. pylori} uses to cause peptic ulcers (20).

Gastric and duodenal \textit{H. pylori} mucosal infections are consistently associated with an inflammatory reaction. This reaction is characterized by an immune response, both humoral and cellular, which is directed towards bacterial antigens and extracellular surfaces. The interaction between the bacteria and the mucosal surface gives rise to the release of pro-inflammatory factors, particularly interleukin-8, which regulates polymorphonuclear leukocyte accumulation. Epithelial cells are induced to express class II histocompatibility antigens which are self-induced to introduce bacterial antigens to the immune system, thus amplifying inflammation. The numerous inflammatory mediators present in the gastric mucosa, in particular TNF-\(\alpha\) and several cytokines (IL-6, IL-12, CCL2-5), may exert a pathological effect on the mucosa. Furthermore, the activated leukocytes release, into the interstitial spaces, oxygen free radicals which tend to produce genetic damage to the DNA of skin cells and B lymphocytes. These mutations, which accumulate with persistent infection, encourage the progression to neoplastic transformation (12-14).

In addition to gastritis and peptic ulcer, \textit{H. pylori} infection has been linked to GERD and its countless manifestations in chronic BE. Roughly 40\% of patients with GERD experience infection. This infection seems to increase with age regardless of sex. Some other studies consider \textit{H. pylori} as a risk factor and that its presence might aggravate GERD (17-19). Others saw it as a protective factor, confirming that the infection signals the onset of GERD in patients in whom \textit{H. pylori} was eradicated. Therefore, several explanations have been proposed regarding the aetiopathogenetic mechanism. In brief, \textit{H. pylori} can influence gastric acid secretion in two ways:

i) Inflammation limited to the stomach is associated with the destruction of the D cells, which secrete somatostatin, therefore, there is no negative feedback on gastric acid secretion which would result in hyperchlorhydria, leading to an increase in the severity of reflux disease gastroesophageo (20);

ii) Helicobacter-induced gastritis leads to the destruction of the parietal cells which secrete acid and cause gastric atrophy, resulting in hypo- or achlorhydria which can reduce the severity of GERD and its complications.

This dual, hypothetical, yet opposing vision is the foundation of our question: Is \textit{H. pylori} a protective or a causal factor? Hereby, some studies are presented in tabular form in support of each of the two hypotheses.

**CONCLUSIONS**

This review confirms the protective theory, with an \textit{H. pylori}-Barrett association visibly negative. However, there are many studies that say the exact opposite. The evaluated case-control studies, meta-analysis, and cohort studies were significantly more in support of this theory. Though multiple confounding factors appear to have been thoroughly evaluated, several issues remain inexplicable, thus pointing the need for a large cohort, therefore, requiring further investigation.
REFERENCES