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REVIEW

Is *Helicobacter pylori* good or bad?

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Abstract *Helicobacter pylori* remains a controversial organism with regards to humans, with its epidemiology still being unclear nearly two decades after its discovery. The association between *H. pylori* infection and subsequent development of chronic active gastritis, peptic ulcer disease, gastric cell carcinoma, and B cell mucosa-associated lymphoid tissue (MALT) lymphoma has been well established. Current studies, however, suggest that fewer than 20 % of all infected patients will develop any consequences from their infection. Hence, should the infection be considered a disease not at all or, on the contrary, is the microorganism harmful in only some circumstances? This article attempts to weigh the currently available evidence supporting that *H. pylori* may be good and not always bad.

Introduction

Helicobacter pylori is a Gram-negative bacterium that colonizes the gastric mucosa of more than half of the world's population. As a result of this colonization, a majority of infected individuals show histological signs of chronic gastritis; only a small fraction of infected individuals develop *H. pylori*-associated diseases, such as peptic ulcers and, more rarely, gastric adenocarcinomas [1]. So many people with *H. pylori* never developing disease has been a reason for the continuing controversy surrounding this bacteria. In the present article, the available literature is reviewed in an attempt to assign a definite role to this unique bacterium.

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Discussion

Evidences supporting the causal relationship between *H. pylori* and peptic ulcers

To the present day, it is firmly demonstrated that *H. pylori* is a definite pathogen of peptic ulcers. According to some previous studies, the most solid argument supporting the causal role of this microorganism in peptic ulcer disease is the evidence that eradicating it is associated with a dramatic decrease in the rate of ulcer relapses [2].

Despite the wide genetic diversity of *H. pylori* hampering the search for bacterial factors involved in pathogenesis, several genomic loci encoding virulence factors, such as the *cag* pathogenicity island (PAI), the toxin VacA, and the Bab2 adhesin, have been strongly associated with an increased risk of developing gastric cancer and peptic ulcer disease [3, 4]. The *cagA* gene flanks one end of the *cag* PAI in *H. pylori*. This 40-kb genomic region contains ~41 putative genes important for increased inflammation and secretion of virulence-related products, including IL-8 induction, neutrophil recruitment, tyrosine phosphorylation, and protein secretion. Heterogeneity in single genes in *H. pylori*, such as *cagA* and *vacA*, were initially linked to specific disease outcome. More recent studies suggest that this genetic heterogeneity is related to the geographical diversity of the *H. pylori* species population and reflects human social behavior and migration patterns [5]. Hence, host genetics and the environment play important roles in imparting susceptibility towards more serious outcomes of the colonization. Host factors remain ill-defined, but one possible

example is the raised gastrin-stimulated acid output seen in patients with duodenal ulcer disease.

Evidence showing that *H. pylori* may be a commensal bacterium

The relationship between humans and *H. pylori* is complex. *H. pylori* can readily colonize the human stomach and is considered to be either the most common chronic infection in man or an indigenous component of the stomach microbiome. When a specific organism exists in many people, but only a few have symptoms of disease, it is difficult to prove that the organism, and not something else entirely, is causing the condition. Proving the association between an organism and a disease is particularly difficult when the symptoms are common to a number of different conditions. Stomach pain, nausea, and burning can be attributed to a variety of conditions, such as food intolerance, acid reflux disease, or stomach viruses. The mere presence of microorganisms, even if reliably found in association with diseased tissue, does not prove that the organism causes the disease. Even by the end of the decade, it was not clear what caused peptic ulcer disease.

In 1882, the accepted standard for establishing such a causal relation was offered by Robert Koch. In the 1985 article "Attempt to fulfil Koch's postulates for pyloric *Campylobacter*," Marshall et al. reported that a normal volunteer had swallowed a pure culture of the organism. The result was "...a mild illness...which lasted 14 days. Histologically proven gastritis was present on the tenth day after the ingestion of bacteria, but this had largely resolved by the fourteenth day. The syndrome of acute pyloric *Campylobacter* gastritis is described" [6]. This constituted highly suggestive evidence that the organism caused gastritis. Perhaps more important was that the subject, who was none other than Marshall himself, failed to develop an ulcer. Note also that the disease resolved without treatment. Koch's postulates for *H. pylori* have not been fulfilled in the case of ulcer. As late as 1995, Marshall himself reviewed these studies and conceded that Koch's postulates, still the "gold standard" for demonstrating a microbial cause of a disease, had not been fulfilled for *H. pylori* and peptic ulcer disease [7].

Blaser, one of the pioneer workers on *H. pylori*, states that *H. pylori* may exhibit symbiotic or pathogenic properties, depending on the context. He further proposed that gastric colonization in humans represents "eutopia," i.e., normal biota colonizing their usual niche, and duodenal ulceration represents "dystopia," i.e., normal biota in unusual places [8].

Song et al. [9] have suggested that *H. pylori* may belong to the normal oral micro flora. Monstein et al. [10] too have suggested that, in the absence of gastric inflammation, *Helicobacter* spp. appeared to be a part of a complex, presumably indigenous microbial flora found in the biopsy specimens from the stomach.

Boulos et al. [11] have suggested that *H. pylori* was (at least) less commonly present before 6 months. It is possible that *H. pylori*, although nearly always present after 6 months, is not present at the onset of the disease. Confirmation of this finding would imply that infection with the organism is not the cause of duodenal ulceration, but a factor producing recurrence and chronicity. Hence, in the early stages of the disease, a patient with duodenal ulcer is likely to show no evidence of intragastric infection with *H. pylori*. This investigation supports the result reported by Dres Pest et al. [12] from Argentina, who found a 78 % incidence of *H. pylori* infection in patients with a history of chronic ulceration and only a 41 % incidence in patients with a short history. They suggest that many patients with a short history may be free from *H. pylori* infection. In another study, Hobsley and Tovey suggested that duodenal ulceration does occur independently of *H. pylori* infection and that *H. pylori* infection, which may be coincidental or be acquired subsequently, contributes to the chronicity of the ulceration [13].

The observations such as occurrence of acid peptic disease in only 20 % of infected individuals, significant sex-wise difference in the occurrence of peptic disease, and non-association of the bacterium with gastric adenocarcinoma [14], especially in Indian subjects, supports its role as a commensal. Despite the high prevalence of *H. pylori*, Indians have a relatively low prevalence of peptic ulcer disease and a low incidence of gastric cancer. This paradox with regards to gastric cancer has been termed the "Indian enigma." The "Indian enigma"—a low gastric cancer burden despite a high *H. pylori* prevalence—suggests a relative protection against the development of gastric cancer in a particular race. Another possible hypothesis posited for this anti-correlation is that enteric helminth infection in developing countries can attenuate *H. pylori*-induced atrophy and premalignant lesion by modulating the Th1-driven immune response to bacterial infection [15, 16]. The low rates in India compared with Western countries may be due to lifestyle and environmental factors. In India, there exists wide variability in dietary patterns, physical activity levels, and environmental exposures. There are unique aspects of diet, including high intakes of the spice turmeric, containing curcumin with anti-carcinogenic properties [17].

Several studies have reported an increased prevalence of CagA-positive *H. pylori* in gastric cancer. The *cagA* gene product, CagA, is translocated into gastric epithelial cells and localizes to the inner surface of the plasma membrane, in which it undergoes tyrosine phosphorylation at the Glu-Pro-Ile-Tyr-Ala (EPIYA) motif. The EPIYA motif is a crucial therapeutic target of *cagA*-positive *H. pylori* infection and is believed to contribute to the gastric cancer-causing potential of the infection. In a collaborative study

of Schmidt et al. at the University of New South Wales, interesting racial differences between Indian, Malay, and Chinese isolates from Malaysia and Singapore with regards to different EPIYA motifs were observed [18]. The majority of Chinese isolates showed the EPIYA ABD (87.8 %) motif, whereas Indian strains showed mainly the EPIYA ABC (60.5 %) and ABCC (27.9 %) motifs. Malay strains were distributed equally between the EPIYA ABC (46.2 %) and ABD (38.5 %) motifs. Amongst Chinese gastric cancer patients, 85.7 % showed the EPIYA ABD motif.

In 2008, Mishra et al. observed that the overall *H. pylori* positivity in saliva was 45.7 % and in feces was 42.8 % of the asymptomatic subjects by nested polymerase chain reaction (PCR) targeting the *HSP60* gene [19]. High detection rates in saliva and stool samples of asymptomatic subjects raise several questions. Why does only a small group of *H. pylori*-infected patients develop clinical symptoms and most infected individuals remain largely asymptomatic? Whether *H. pylori* has anything to do with dyspeptic symptoms and ulcer formation or is it just normal biota of the upper gastrointestinal tract? In the author's opinion, high detection rates in saliva and stool samples suggest that it may be a commensal after all and not a pathogen. In another study, Elitsur et al. reported on many asymptomatic children who harbored antibodies to the virulent strain. These data may suggest that either the *cagA* gene locus is inactive in children or other factors are involved in the development of duodenal ulceration and in the determination of their clinical outcome [20]. In the author's opinion, there are three types of possibilities to answer the above questions:

1. Some normal bacterial flora may play a role in affecting the *H. pylori* growth by producing bacteriocin-like inhibitory proteins against *H. pylori* strains. Due to the loss of these normal bacterial flora, there is an increase in the number of *H. pylori*. Hence gastric acid production increases, resulting in ulcer formation.
2. Some strains are highly virulent and a host factor(s) is (are) responsible for disease causation.
3. Another possibility could be that *H. pylori*, being the normal flora of the stomach, merely colonize the ulcer site as a secondary infection, the ulcer being already present due to other causative factors. Other acid-tolerant bacteria might also colonize the ulcer site and, thus, enhance the problem as *H. pylori* is projected to be doing.

H. pylori may exert beneficial effects on the host

H. pylori is just one bug that is isolated from a bacteria-rich stomach environment. And, like many bacteria in our digestive system, it is not only harmless when kept in balance with the other microbes, but may even be beneficial. Possible symbiotic relationships have been debated since the discovery of this pathogen. However, the debate has been intensified in recent years, as some studies have posed the possibility that *H. pylori* infection may be beneficial in some humans [21, 22]. Infection with the organism is most common in populations with poor sanitary and hygiene conditions; in developed societies with better sanitation and hygiene practices, the levels of infection are lower. Associated with this increasing level of hygiene, there is a higher incidence of allergic and autoimmune diseases, including asthma and Crohn's disease [23]. It is possible, therefore, that *H. pylori* infection may protect populations in countries such as India from the allergic and autoimmune diseases that are increasingly prevalent in the developed world. Recent surveys suggest that infection with the microbe may actually protect against cancer of the esophagus, gastroesophageal reflux disease (GERD), and asthma—ailments that are on the rise in developed countries. Studies [24] have suggested that *H. pylori* infection protects against gastroesophageal reflux. One study [25] revealed that children infected with *H. pylori* were less likely to have diarrhea than children without an infection, implying that *H. pylori* may be beneficial to human hosts. While many researchers are now convinced that the pathological outcomes of *H. pylori* infection are far more damaging than any beneficial effects of its inhabitation, there are enough strong evidences that the absence of *H. pylori* from the stomach may lead to cancers of other gut regions. The incidence of GERD increased after *H. pylori* eradication [26], suggesting that the bacteria play a protective role. Moreover, *H. pylori*-induced corpus gastritis has been shown to reduce acid secretion and, thus, prevent patients from contracting GERD [27]. Studies have also shown that *cagA*+ *H. pylori* strains have a more protective effect than *cagA*− strains [28]. The presence of *cagA*+ *H. pylori* strains can reduce the acidity of the stomach, and it is believed that the raising of the pH by *H. pylori* prevents GERD, Barrett's esophagus, and adenocarcinoma of the esophagus. GERD is the major risk factor for Barrett's esophagus, which, in turn, is a strong risk factor for esophageal adenocarcinoma [29–31]. Therefore, there is an urgent need to thoroughly assess the risks and benefits of *H. pylori* and the role of chronic infection in the development of cancers of the gut and to provide for a basis to launch global strategies to fight this problem and settle the debate.

Conclusion

Helicobacter pylori often resides in the mucosal layer of the stomach, but its role as an obligate pathogen remains questionable. One of the challenges of *H. pylori* research is to ascertain out why so many people carry it, around half the world's population, but only about 20 % become sick.

However, it is clear that there is a paucity of well-designed studies of asymptomatic populations. These studies are clearly required so that current guidelines can be adapted to reflect this evolving information. Until we can better understand the nature of *H. pylori* and its relation to the human host in asymptomatic individuals, indiscriminate eradication of this infection is likely to do more harm than good at the community level. The controversy over whether *H. pylori* should be eradicated in all infected individuals or just in symptomatic patients reflects the risk to benefit ratio. Hence, *H. pylori* infection could be beneficial for humans; we may need to rethink the commonly used medical approaches to treat *H. pylori* infections.

Conflict of interest The author declares that they have no conflict of interest. The author does not have any financial relationship with the organization that sponsored the research.

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