Brief Communication

Why do we still have *Helicobacter Pylori* in our Stomachs

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Abstract

The existence of any infectious agent in a highly acidic human stomach is contentious, but the chance finding of *Helicobacter pylori* is by no means an accident. Once *H. pylori* colonises the gastric mucosa, it can persist for a lifetime, and it is intriguing why our immune system is able to tolerate its existence. Some conditions favour the persistence of *H. pylori* in the stomach, but other conditions oppose the colonisation of this bacterium. Populations with high and extremely low prevalence of *H. pylori* provide useful insights on the clinical outcomes that are associated with this type of infection. Adverse clinical outcomes including peptic ulcer disease and gastric cancer depend on a delicate balance between a harmless inflammation and a more severe kind of inflammation. Is the only good *H. pylori* really a dead *H. pylori*? The jury is still out.

Keywords: *Helicobacter pylori, survival, elimination, gastric cancer, peptic ulcer disease, stomach*

Introduction

In 1893, a spiral form of bacteria was first reported in the gastric mucosa of dogs by the well-known Italian anatomist, Bizzozero(1). However, the very existence of any infectious agents in the human stomach was contentious at that time because of the strong acidic environment of the stomach. The rest was history when Warren and Marshall found *Helicobacter pylori* (*H. pylori*) in antral biopsies of the human stomach and discovered that this bacterium is the cause of peptic ulcer disease (2). The primary colonisation of *H. pylori* usually occurs during early childhood and decreases with age, but following an episode of acute gastritis, the infection can last a lifetime (3). Although other microorganisms reside in the human stomach, only *H. pylori* can survive over long periods of time. However, the reason for this persistent colonisation is unknown.

What favours the in vitro and in vivo colonization of *H. pylori* in a hostile gastric environment?

H. pylori can penetrate deep into the gastric mucosal layer with its 2 to 6 polar flagella and also through the production of urease (4), which allows it to encounter a more friendly (pH ~ 5-6) environment. The ammonia produced from urea hydrolysis then acts as a receptor for H+ ions and generates a neutral pH in the intracellular environment. Members of the *H. pylori* outer membrane proteins (HOP) family of outer membrane proteins align with other *H. pylori* adhesion proteins and assist in the successful binding of the bacterium to the gastric epithelium (tissue tropism) (5). Bacterial phase variation by gene conversions and slipped strand mispairings enable *H. pylori* to form new subpopulations and adopt properties that allow for the neutralisation of effective human immune responses. In addition, a variety of virulence factors including b*abA2, horB, homB, iceA2, cagA,* and *dupA* ensure that *H. pylori* persists in humans (6). Although not all of the functions of these factors are completely understood, available data have shown that these genes, most of which are pro-inflammatory,

have the capacity to alter the physiology and morphology of gastric epithelial cells (7,8).

In most instances, *H. pylori* causes only minimal damage to the gastric epithelium, and the inflammation is easily offset or even ignored by the immune system. Mild inflammation in the gastric mucosa is associated with two major benefits for *H. pylori*: first, it allows for a more effective harvest of nutrients to feed the bacteria, and second, it diminishes any active invasion of immune cells. The almost invincible human immune system fails to eliminate *H. pylori* because of successful immune evasion strategies and also because of the complex intrinsic genetic variability adopted by this bacterium. The immune evasion mechanisms include the following: i) a change in the modulation of the normal function of polymorphonuclear leukocytes (PMNs) and macrophages, ii) an inhibition of lymphocyte proliferation, and iii) a down-regulation of some types of surface antigen ligands. To date, not enough evidence has accumulated to indicate an actual cellular invasion by *H. pylori*, but a most recent report has demonstrated an association between cell invasion by this bacterium and gastroduodenal diseases (9). If confirmed, the intracellular presence due to the penetration of the *H. pylori* bacterium may explain why we still have a persistent infection of *H. pylori* in our stomachs.

A number of genetic polymorphisms seem to correlate with an increased risk of gastroduodenal disorders in the infected host (10). For instance, a relatively high expression of certain IL-1β polymorphisms in infected humans has been shown to increase the risk of gastric atrophy and gastric adenocarcinoma. In vitro studies have also revealed a significant link between the expression of TNF-α and aberrant β-catenin signalling and gastric adenocarcinoma. In addition, polymorphisms in IL-10 are associated with severe gastric diseases including gastric cancer in *H. pylori*-positive individuals. Even among populations with an extremely low prevalence of *H. pylori*, genetic variations in the *UFM1, THBS4, CYP2C19* and *MGST1* genes are associated with atrophic gastritis, complete intestinal metaplasia, incomplete metaplasia and dysplasia, respectively (11). These genetic polymorphisms are also the reasons why *H. pylori* persists in susceptible hosts, but the exact functions of these genetic variations are not yet entirely clear. Epigenetic mechanisms may play a role as well. For instance, the epigenetic silencing of *FOXD3* by *H. pylori* has been shown to be an early event in gastric carcinogenesis (12).

What Opposes the Persistence of *H. pylori* Infection?

Antibiotics are major obstacles to the survival *H. pylori* in the human stomach (13). Available eradication regimes are highly effective against *H. pylori* although sporadic reports of resistance to metronidazole and clarithromycin have been published. More recently, it has been shown that *H. pylori* can potentially evade the lethal effects of antibiotics through point mutations in certain genes (14) (e.g., *rdxA, 16s rRNA, 23s rRNA* and *gyrA*).

Probiotics, especially Lactobacilli, may play a role in the inhibition of *H. pylori* colonization (15) because some studies have reported an inverse correlation between the colonisation of *H. pylori* and the density of Lactobacilli in the human stomach. Furthermore, certain foods with antimicrobial properties may be the reason for the observed low prevalence of *H. pylori* infection in certain populations such as the Malays (16).

It is known that the distribution of *H. pylori* is not homogeneous within the stomach and that this may be a result of constant and strong peristaltic movement (17). It is also possible that peristalsis within the stomach acts as a deterrent to the survival of *H. pylori*.

The expression of protective genes in the host may explain the low prevalence of *H. pylori* infection in certain populations. For example, in the Malays vs the Chinese or the Indians, genetic polymorphisms in the *C7orf10, TSTD2, SMG7,* and *XPA* genes were found to be significantly associated with an absence of *H. pylori* infection (18). Although the exact functional roles of these polymorphisms remain to be determined, these genes may code for enzymes that are involved in the metabolism of compounds that inhibit the survival of *H. pylori*, and they may also code for proteins that allow for the repair of aberrant genomes.

Lessons from Populations with a High and Low Prevalence of *H. pylori* Infection

Populations with a high prevalence of *H. pylori* infection (above 60%) such as China, Japan, and Korea also have a high incidence of *H. pylori*-associated diseases including gastritis and gastric adenocarcinoma. However, these diseases do not occur solely as a result of *H. pylori*, but frequently, other associated environmental factors including poor sanitation and hygiene promote the transmission of the bacterium. Moreover, the

concomitant use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and or traditional preparations that contain steroids can injure the epithelium of the stomach (19). As described in the above sections, bacterial factors would also be important in the perpetuation of infection and of *H. pylori*-associated diseases(20). It is unclear, however, why the rate of gastric cancer is low among Indians and Africans despite the high prevalence of *H. pylori* in these populations (Asian enigma). Again, environmental, genetic and bacterial factors may be important (21). For example, in the Indian province of Kashmir, the reported rate of gastric cancer is 3-6 times higher than that in other districts including Bangalore, Madras and Bombay. The high consumption of salt and preserved foods in the Kashmir population compared with the consumption of fresh fruits and vegetables by Indians in the southern districts may explain the inverse relationship between the presence of *H. pylori* and gastric cancer. Populations with a low prevalence of *H. pylori* infection including Malays in South-East Asia also have a low incidence of *H. pylori*-associated diseases (22). Environmental factors including consumption of foods with inhibitory activities against *H. pylori* as well as protective genetic factors may be the reasons for the low prevalence of infection and diseases (22). Moreover, the diverse virulence factors in *H. pylori* are important bacterial factors that can influence clinical outcomes. Mixed virulence genotypes, especially the less virulent types in Malays, may have provided them with protection against *H. pylori*-associated diseases (23).

Will *H. pylori* Continue to Infect our Stomachs? A Verdict

Figure 1 summarises the forces that favour and oppose the survival of *H. pylori*. The balance seems to favour the persistence of *H. pylori*, but lessons from populations with a low prevalence of infection suggest that humans are probably better without *H. pylori* than for the bacterium to persist in the stomach. Is the only good *H. pylori* a dead *H. pylori*? No one really knows the answer. More than half of the world's population harbours *H. pylori*, but only a minority of individuals subsequently develop severe forms of gastric diseases, especially gastric adenocarcinoma and peptic ulcer disease.

Without the symbiotic or commensal relationship with human hosts that has developed over thousands of years, it may have been difficult for *H. pylori* to persist. The maintenance of a

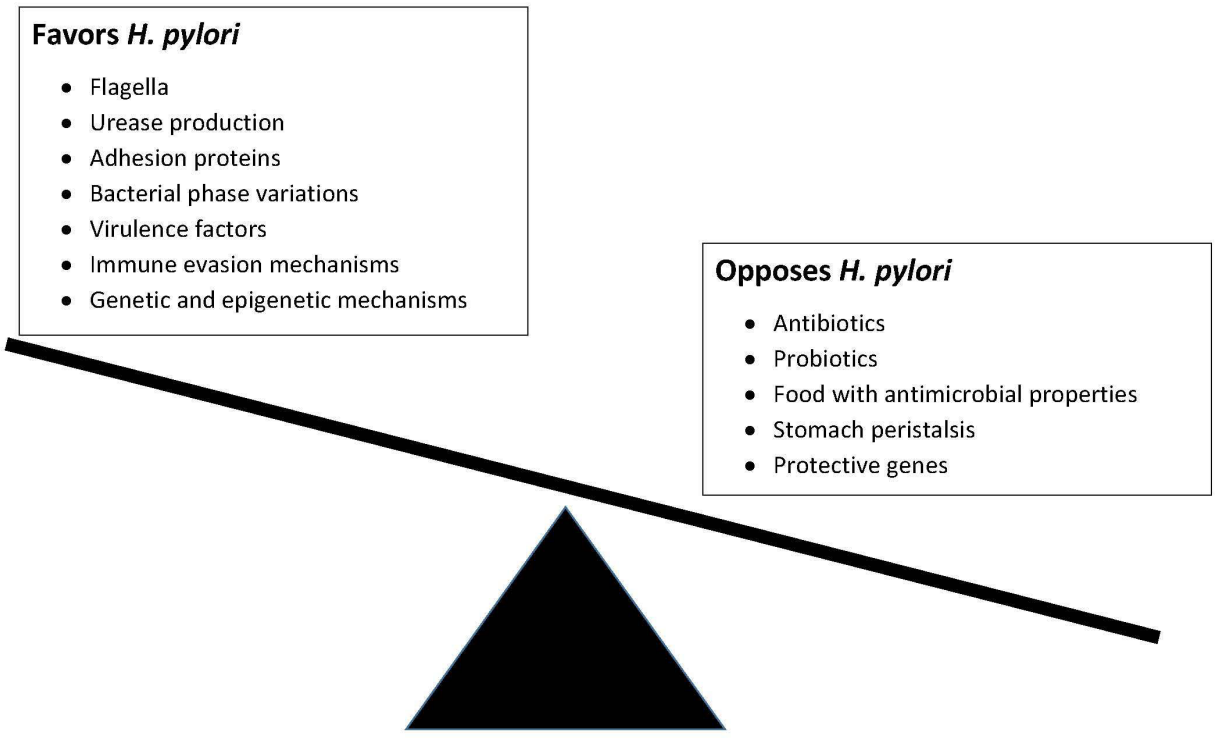

Figure 1: Conditions or forces that favor survival or elimination of H. pylori in the human stomach.

delicate balance between a harmless inflammation and a more severe form of inflammation seems to be the determining factor for adverse clinical outcomes (Figure 2). The imbalance in this relationship probably occurs because the human host becomes weak at some point, which allows the bacterium to become stronger (more inflammation and therefore more severe disease) and vice versa. In reality, if Darwin could have his way, the stronger survivor will win.

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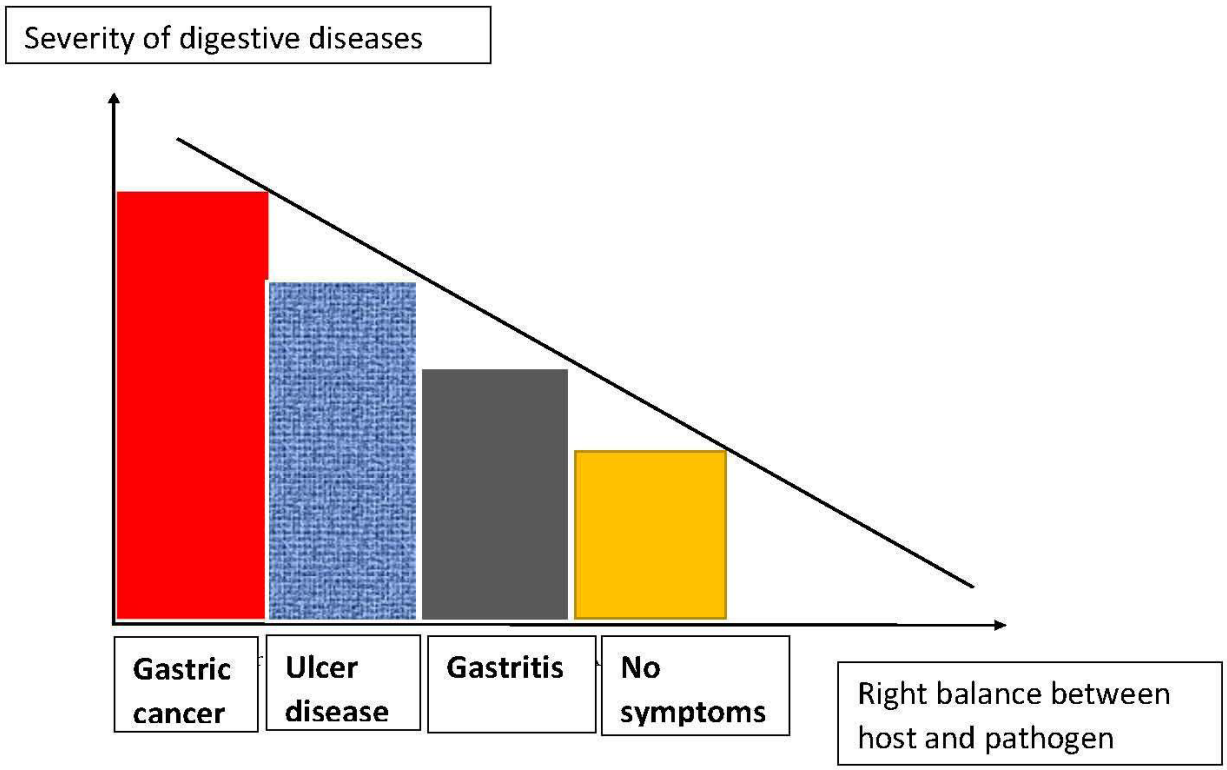

Figure 2: Increasing severity of digestive diseases in the case of imbalanced relationship between H. pylori and the human host.

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