

Editorial

The endangered gastric pathogen *Helicobacter pylori*: To eradicate or not?

Helicobacter pylori is a bacterium that colonizes the harshly acidic niches of the human stomach. More than half of the world's population is colonized with this bug. Infection rates vary among the developed and developing countries of the world. *H. pylori* infection is on a steep decline in most of the western countries mainly due to the success of combination therapies and improved personal and community hygiene to prevent re-infection. The eradication in some of the countries has been so effective that the pathogen has recently been declared as an endangered bacterial species¹. However, the situation is not improving in many of the developing countries due to failure of treatment regimens and emergence of drug resistance. The infection results in chronic superficial gastritis, chronic active gastritis, peptic ulcer disease and gastric adenocarcinoma²⁻⁴.

One of the most distinctive features of *H. pylori* is the genetic diversity between clinical isolates obtained from different patient populations. Recasting of the genome is the norm with this bacterium, which changes its genome approximately every 40 yr! There have been a lot of allelic and phase variations, posing difficulties in development of diagnostics and therapeutics.

Post-genomic analyses have revealed interesting attributes of *H. pylori* pathogenicity and novel mechanisms of causation of ulcer disease and cancer have been dissected out. Efforts to know the cause and potential benefits of the genetic diversity of this bacterium have led to some interesting discoveries relating to its co-evolution with the human host, micro-evolution during infection, quasi-species development, virulence determinants and eradication strategies. Recent studies aim at testing the speculation about whether *H. pylori* may be beneficial to human health in certain circumstances⁵⁻⁷ and whether eradication

of this organism is always necessary? Concerted efforts in clinics and epidemiological studies are needed in the context of such intriguing hypotheses. Results obtained from such studies might enable the development of a high-throughput screening system for high risk groups within the huge population of *H. pylori*-infected individuals. Recent studies⁷ have shown that *H. pylori* infection protects against gastro-oesophageal reflux and oesophageal carcinoma. So it will be important to selectively eradicate *H. pylori* in people that are at the highest risk of developing gastric carcinoma. Eradication of highly pathogenic *H. pylori* specifically from high risk groups would markedly reduce the worldwide incidence of ulcer and gastric cancer.

How long humans have carried *H. pylori* is still controversial. However, it is accepted that this organism has colonized humans possibly for many thousands of years, and the successful persistence of *H. pylori* in human stomach for such a long period may be because this organism offers some advantages to the host. Unfortunately, however, the *H. pylori* infection is in sharp decline in the western world. This may sound good news to many gastroenterologists around the world, but many argue that having a *H. pylori* colonization may be advantageous for the gut. It has been shown that *H. pylori* produces cecropin-like peptide (antibacterial peptide) with high antimicrobial properties⁵. Another study⁶ revealed that children infected with *H. pylori* were less likely to have diarrhoea than children without an infection, implying that *H. pylori* may be beneficial to human hosts. Interestingly, there has been a marked decline in the instances of peptic ulcer disease and gastric cancer in the 20th century. Concurrent with this is a dramatic increase in the incidences of gastro-oesophageal reflux disease (GERD), Barrett's oesophagus and adenocarcinoma of the oesophagus

in western countries⁷. This observation led to the speculation that *H. pylori* may in some way be associated with these diseases and perhaps capable of preventing their onset. Studies have also shown that *cagA*⁺ *H. pylori* strains have a more protective effect than *cagA*⁻ strains⁸. 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 oesophagus and adenocarcinoma of the oesophagus. Conversely, arguments have been made that, although *H. pylori* may prevent these reflux-associated diseases, the risks of acquiring gastric cancer via *H. pylori* infection far outweigh any possible benefits it may provide⁹. However, it has been stated that if *H. pylori* does provide protection from GERD, the notion of restriction of anti-*H. pylori* treatment to only a few cases (peptic ulcer disease and MALT lymphoma) could be justified¹⁰. In spite of this controversy, recent reports have demonstrated a protective role for *H. pylori* in erosive reflux oesophagitis^{11,12}. However, as safe and potent antisecretory drugs to prevent gastro-oesophageal reflux are available¹³, it seems unjustified to use a dangerous organism that has been associated with extremely dangerous outcomes such as a carcinoma. Some experts opine that not eradicating the bug and moving with it is just like carrying a hand grenade in your pocket with the pin pulled out!

On the other hand, eradication also is not an ultimate choice. Some ulcers recur even after successful eradication of *H. pylori* in non-users of non-steroidal anti-inflammatory drug (NSAID). In addition, the incidence of *H. pylori*-negative, non-NSAID peptic ulcer disease (PUD) (idiopathic PUD) is reported to increase with time. Moreover, it appears that *H. pylori*-positive ulcers are not always *H. pylori*-induced ulcers because there are two paradoxes of the *H. pylori* myth, first the existence of *H. pylori*-positive non-recurring ulcer and secondly, recurring ulcer after cure of *H. pylori* infection. To intone, *H. pylori* is not the only cause of peptic ulcer disease. Therefore, it is still necessary to seriously consider the need for eradication in all cases of PUD, which may exist even after the elimination of *H. pylori*.

In our opinion, the intricacies of the role of *H. pylori* in health and disease may be fully ascertained only if we analyze genetic diversity of the pathogen as juxtaposed to the host diversity and the environment (food and dietary habits). A possible working hypothesis may be that among the ocean of molecular host-pathogen interactions that occur with micro-evolution of this bacterium during colonization, some could prove advantageous where the bacterium and the host negotiate nearly a 'symbiotic' and balanced relationship. Such a 'friendship' might have taken thousands of years to develop. If so, why has this bacterium survived for such a long time? Microbes that have long been persisted in humans may be less harmful than recently emerged microbes, such as the human immunodeficiency viruses (HIV). This suggests that the colonization may either be beneficial or of low biological cost to the host¹⁴. In addition to characterization of bacterial virulence genes that are for sure linked to disease outcome, host responses to such factors must also be examined hand in hand to completely ascertain mechanisms that lead to gastroduodenal disease. For instance, polymorphisms linked to the host immune apparatus, such as interleukin (IL)-1 β , tumour necrosis factor-alpha (TNF- α), and IL-10, which are responsible for vigorous proinflammatory potential of the strains. These polymorphisms, increase the risk for atrophic gastritis and distal gastric adenocarcinoma among *H. pylori*-infected persons. Cancer of stomach is a highly lethal disease and establishment of *H. pylori* as a risk factor for this malignancy deserves an approach to identify persons at increased risk; however, infection with this organism is extremely common and most colonized persons never develop cancer. This is particularly true in case of Indians where the gastric cancer incidence is extremely low to negligible. This brings into focus a third dimension that is environment (diet?). It may be speculated therefore that Indians enjoy some unknown nutritional benefits on account of their fiber rich diet with a lot of natural herbs, spices and vegetables. Nevertheless, screens to identify high risk sub-populations must use high-resolution biological markers.

Fortunately, this task appears to be highly simplified due to the availability of biological tools that were never thought in the past. Genome sequences

(*H. pylori*, *H. hepaticus*, *E. coli*, Salmonellae, Human, *Caenorhabditis elegans*), quantitative phenotypes (*cagA* phosphorylation, *oipA* frame status, *vac A* allele status), and practical animal models (Mongolian gerbils) can be harnessed to decipher the molecular basis of *H. pylori*-associated malignancies, which should have direct clinical applications.

To sum up, it is important to gain more in-depth passage into the pathogenesis of *H. pylori*-induced gastric ulcers and adenocarcinoma. This will not only help develop more effective diagnostics and treatment for this common cancer, but also will help validate the role of chronic, persistent inflammation in the genesis of other tumors of the gut.

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