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Review

Helicobacter pylori: "A benign fellow traveler or an unwanted inhabitant"

Santosh K. Tiwari[1, 2], Aleem A. Khan[1], Pratibha Nallari[3]

[1]Centre for Liver Research and Diagnostics, Deccan College of Medical Sciences, Kanchanbagh, Hyderabad 500 058, Andhra Pradesh, India.
[2]Department of Urology, College of Medicine, University of Florida, 1600SW Archer Rd, PO Box 100247, Gainesville, Florida 32610-0247, USA.
[3]Department of Genetics, Osmania University, Hyderabad 500 007, Andhra Pradesh, India.

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Corresponding author

Aleem Ahmed Khan
Scientist,
Centre for Liver Research and Diagnostics,
Deccan College of Medical Sciences,
Kanchanbagh, Hyderabad 500 058,
Andhra Pradesh, India.
E-mail: aleem_a_khan@rediffmail.com
Phone: +91 40 24342954
Fax: +91 40 24342954

Abstract

The recent decades have witnessed an alarming increase in the *Helicobacter pylori* associated diseases worldwide. In spite of this, deficiencies in our knowledge still exist about its exact epidemiology, the optimum method of its diagnosis and indeed about the precise role it plays in gastric carcinogenesis. In the present article, we review the available literature in an attempt to assign a definite role to this unique gastric pathogen. The acquisition of the *cag*-PAI has undoubtedly altered the understanding of host-microbe interactions, and growing appreciation of other potential determinants *viz: vac*A, *ice*A, *bab*A, *hrg*A etc., may enable us understand the role of this organism and its gradual transition from a commensal to a pathogen.

Keywords: *Helicobacter pylori*, commensal, pathogen.

Helicobacter pylori is a human pathogen that causes chronic gastritis, plays a causative role in gastric and duodenal ulcer and is involved in gastric carcinogenesis. Indeed, the bacterium has been classified as a definite (Class I) carcinogen of humans[1,2]. This gram negative gastric pathogen is also regarded as being a possible important factor in at least a subset of patients with functional dyspepsia[3-5].

Although there appears to be a consensus of opinion that the majority of individuals become infected with *H. pylori* during early childhood (around 4 years), there are epidemiological differences between children and adults[6,7]. In addition to the acquisition of *H. pylori* during childhood, young children also appear to be at increased risk of re-infection or recrudescence following antimicrobial eradication of the organism[8].

Many aspects of this unique pathogen still remain elusive. For example, it is still not clear as to why only a subset of infected individuals present with clinically significant disease and related complications. The spectrum of *H. pylori* disease is so variable that it is sometimes difficult to predict clinical outcome (Fig 1). The extensive research on its molecular characterization and genomics was

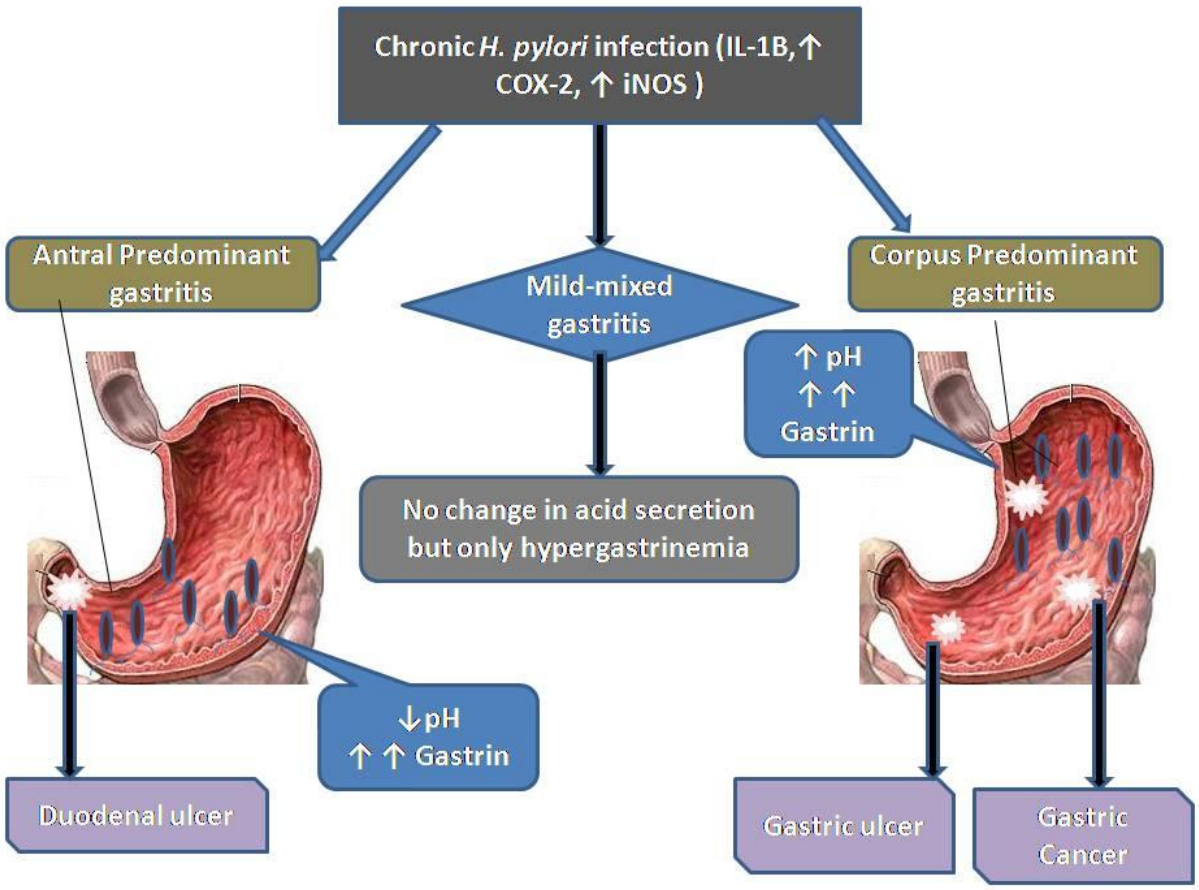

Fig 1. Shows colonization of *H. pylori* in different regions of the stomach leading to various gastro-duodenal diseases

initiated in different parts of the world in order to identify strain specific markers specific for overt manifestations of gastro-duodenal disease, but the equivalent distribution of the genotypes among normal and diseased subjects has not resolved this issue. So, is *H. pylori* a benign fellow traveler that has been associated with humans since ages or is it an unwanted inhabitant of the gut biota? This article attempts to weigh the currently available evidence.

Historical background of *H. pylori*'s association with humans

Though *H. pylori* was discovered in 1983, this microbe has been associated with humans since the pre-historic era[9]. Recent evolutionary studies have shown that *Helicobacter pylori* has likely been a part of the primitive human biota of the gut[10,11]. The gut of primordial beasts lacked acid secreting cells (parietal cells) in the stomach[12]. With the evolution of the first acid secreting stomach around 350 million years ago, *Helicobacter pylori* adapted to survive in the acidic milieu via subtle modifications, which allowed them to dwell in the mucus layer close to the mucosal cells, mostly through adaptations including urease production, spiral shape, flagella and microaerophily[13]. Gradually to utilize the nutrients from the gastric mucosa *H. pylori* acquired genes that induced inflammation, but in spite of this these organisms could not at this time pose any menace, as the life span of the host in which they resided was not long enough[9,12]. In order to survive the inflammatory process in the gut *Helicobacter pylori* gradually upgraded its mechanisms of survival principally through the elaboration of the enzymes catalase and superoxide dismutase (SOD) which protected the bacterium from the toxic effects of the compounds generated by the phagocytes.

The transformation of *H. pylori* from a silent bug to a gut pathogen

About 150-200 years ago *H. pylori* seems to have turned into a pathogen. The reasons for this have been a matter of intense debate. Some experts argue that disease of the upper gastrointestinal

tract is not because of *Helicobacter pylori*, but it is a result of change in the host physiology that has occurred with civilization probably due to increased intake of processed food, excess meat, etc.[14,15] and this selection pressure forced its adaptation to its particular ecological niche. It is also possible that it was acquisition of 'alien' DNA that altered this relationship[8]. Other experts argue that gastro-duodenal disease cannot be attributed solely either to *Helicobacter pylori* or host factors alone, but it is a complex and well coordinated interplay between *H. pylori*, host genetics, and environmental factors[16,17].

During its years as a normal gastric colonizer, *H. pylori* appeared to offer protection against lethal diarrhoeal diseases of the children[18] by mechanisms such as the heightening of the gastric acid barrier[19], priming of the immune response in the stomach[20], etc. *H. pylori* is also believed to reduce the risk of gastro-esophageal reflux disease (GERD) and ultimately esophageal cancer in the infected subjects.

H. pylori virulence determinants involved in bacterial-epithelial interactions

The most accepted hypothesis underlying the gradual transition advocates the 'acquisition of the *cag* pathogenicity island' (*cag*-PAI) as the major evolutionary event that enabled the bacterium to become more virulent. Whole genome sequences of four different strains of *H. pylori* (J99 and ATCC 26695, G27 and HPAG1) isolated from different patients with different disease conditions have provided adequate evidences that *cag*-PAI has different G+C content (35%) in contrast to the rest of the genome (39%) thus justifying its foreign origin[21]. This ~40kb DNA fragment (of unknown origin) is mainly comprised of 30 open reading frames (ORFs). Seven genes of this 'pathogenicity island' (namely *hp0524, hp0525, hp0527, hp0528, hp0530, hp0532 and hp0544*) are known to share homology to the *vir* family of genes forming a multiprotein complex apparatus of Type IV secretory machinery (T4SS), that in other prokaryotic species, functions as a conduit for export of multimeric

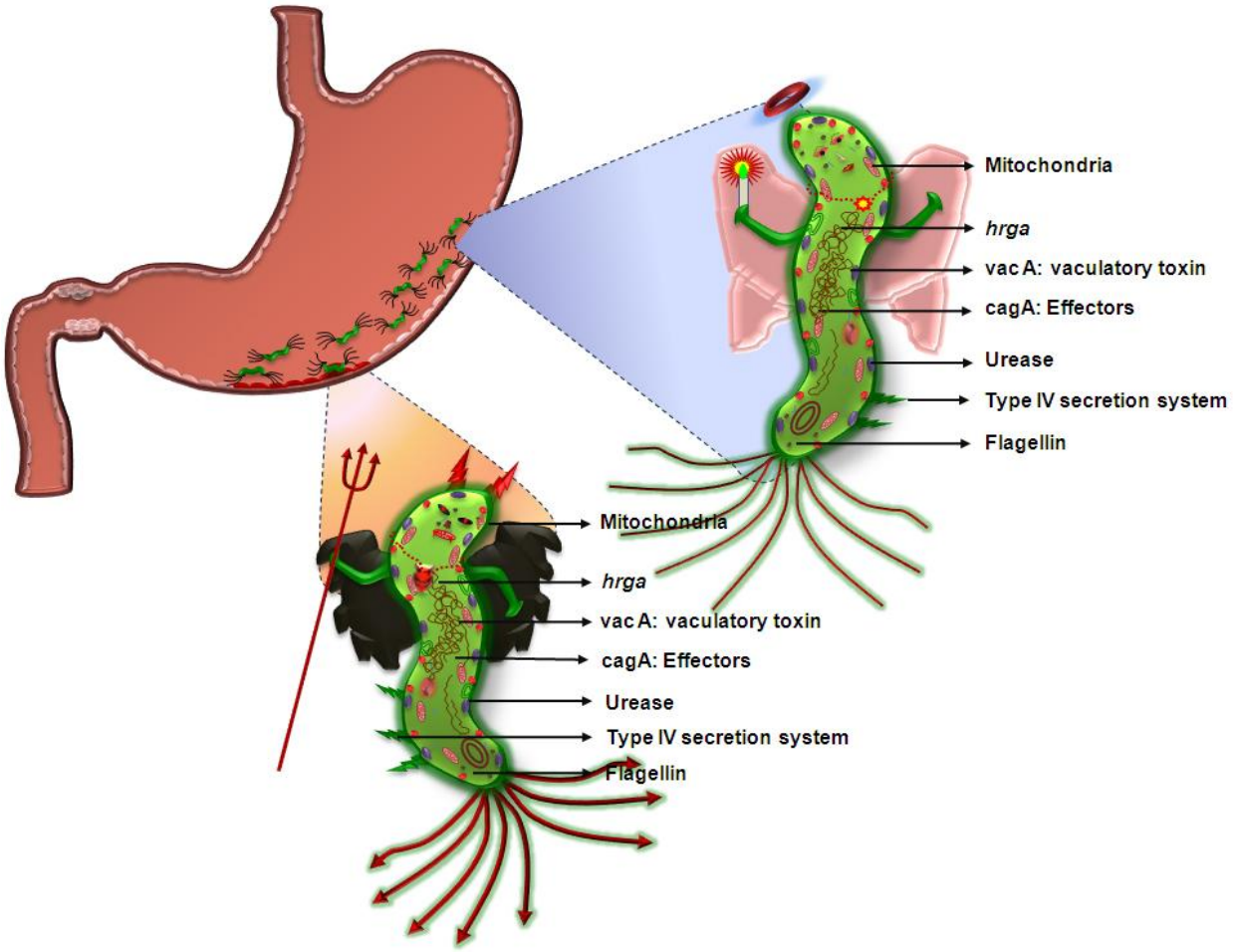

Fig 2. An animated view of 'good' and 'bad' *Helicobacters* with arsenal of virulence factors

proteins and nucleoproteins across both the inner and outer bacterial membrane. The *cag*-PAI in *H. pylori* is required for both translocation of bacterial proteins into host cells and induction of proinflammatory cytokine release thus validating the recent findings that the *cag*A island of genes has biological significance. This may provide an explanation for the observation that *Helicobacter pylori* with complete *cag*-PAI are more interactive with the host than those with partial and complete deletions[21,22]. There are also reports that corroborate various genes of the *cag*-PAI in *H. pylori* with disease outcome thus contending that *H. pylori* with functional *cag*-PAI could be potentially more harmful to humans than those lacking them[16,23]. If this indeed is the case, can we assume that prehistoric *Helicobacters* that existed before the acquisition of the *cag*-PAI rendered positive health benefits? Besides the *cag*-pathogenicity island there are other virulence determinants of *H. pylori* such as vacuolating associated cytotoxin gene A (*vac*A), flagellins (*fla*A &*fla*B), induced by contact with epithelium gene A (*ice*A), *Helicobacter pylori* restriction endonuclease replacing gene A (*hrg*A), and blood group antigen binding adhesin gene (*bab*A) etc., that have been discovered, that influence disease outcome in infected individuals (Fig 2).

Unsolved conundrums

What was the role of these pathogenic markers? Were they potentially functional before the acquisition of *cag*-PAI or were they non-contributory to the causation of disease? Did the acquisition of this foreign DNA change the behavior of the other genes? In what way did the *cag*-PAI alter the expression of the toxins released by the above genes? Further research is required to validate or disprove the long-standing stance in favor of the 'good' *Helicobacter pylori* that might have existed in the past era. Though the genes of the *cag*-pathogenicity island are largely responsible for imparting a virulence trait to *Helicobacter pylori* they clearly do not tell the complete story. Epidemiological studies have already confirmed *vac*A, *ice*A, *hrg*A, flagellin genes and other virulence determinants as probable risk factors for various gastric diseases independent of the *cag*-pathogenicity island[24,25]. Further screening of virulence genes such as *vac*A, *ice*A, *bab*A, *hrg*A, and eludidation of their respective roles pre- and post- acquisition of *cag*-PAI in pre-historic human gut would enable us to understand the gradual transition of from a commensal to a hostile pathogen.

Conclusion

In conclusion, *H. pylori*, is a threat that extinguishes more than a million lives each year, and causes substantial distress to almost all infected individuals. In spite of its origins as a benevolent fellow traveler this fascinating spiral organism has now evolved as an undesirable commensal dweller of gastric mucosa. Though there exist studies that favor its positive health benefits are there is substantial evidence that implicates its role as a pathogen in gastro-duodenal disorders.

Conflict of interest: None

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References

1. Farthing MJ. *Helicobacter pylori* infection: an overview. Br Med Bull 1998; 54:1-6.
2. Schistomes, Liver flukes and *Helicobacter pylori*. IARC working group on the evaluation of carcinogenic risks to humans. Lyon, 7-14 June 1994. *IARC* Monogr Eval Carcinog Risks Hum, 61:1-241, 1994.
3. Maeda S, Kanai F, Ogura K, et al. High seropositivity of anti-CagA antibody in *Helicobacter pylori*-infected patients irrelevant to peptic ulcers and normal mucosa in Japan. Dig Dis Sci 1997; 42:1841-1847.
4. Khulusi S, Mendall MA, Patel P, et al. *Helicobacter pylori* infection density and gastric inflammation in duodenal ulcer and non-ulcer subjects. Gut 1995; 37:319-324.
5. Lieber CS, Puspok A, Oberhuber G, et al. *Helicobacter pylori* and Non-Ulcer Dyspepsia. N Engl J Med 1999; 340: 1508-1511.
6. Smith K and Parsonnet J. In: Bacterial infections of Humans: Epidemiology and control. A. S. Evans and P. S. Branchman (Eds), Plenum, New York, pp.337-353, 1998.
7. Ahmed KS, Khan AA, Ahmed I, et al. Prevalence study to elucidate the transmission pathways of *Helicobacter pylori* at oral and gastro-duodenal sites of a South Indian population. Singapore Med J 2006; 47(4):291-296.
8. Leal-Herrera Y, Torres J, Monath JP, et al. High rates of recurrence and of transient reinfections of *Helicobacter pylori* in a population with high prevalence of infection. Am J Gastroenterol 2003; 98:2395-2402.
9. Linz B, Balloux F, Moodley Y, et al. An African origin for the intimate association between humans and *Helicobacter pylori*. Nature 2007; 445(7130):915-918.
10. Blaser MJ. *Helicobacters* are indigenous to the human stomach-duodenal ulceration is due to changes in gastric microecology in the modern era. Gut 1998; 43:721-727.
11. Blaser MJ. Science Medicine, and the future-*Helicobacter pylori* and gastric diseases. Br Med J 1998; 316:1507-1510.
12. Lee A. *Helicobacter pylori* is pathogenic flora. In: *Helicobacter pylori*: Basic mechanisms to clinical cure. Academic Medical Centre, Amsterdam, The Netherlands, pp.31, 2000.

13. Levin BR. The evolution and maintenance of virulence in microparasites. Emerg Infect Dis 1996; 2:93-102.
14. Susser M and Stein Z. Civilization and peptic ulcer. Lancet 1962; i: 115-119.
15. Kato I, Nomura A, Stemmerman GN, et al. A prospective study of diet gastric and duodenal ulcer and its relation to smoking, alcohol, and diet. Am J Epidemiol 1992; 135:521-530.
16. Kauser F, Khan AA, Hussain MA, et al. The *cag* pathogenicity island (*cag*-PAI) of *Helicobacter pylori* is disrupted in majority of patient isolates from different human populations. J Clin Microbiol 2004, 42: 5302-5308.
17. Ahmed N, Khan AA, Alvi A, et al. Genomic analysis of *Helicobacter pylori* from Andhra Pradesh, South India: Molecular evidence for three major genetic clusters. Curr Sci 2003; 85:101-108.
18. Lu H, Hsu PI, Graham DY, Yamaoka Y. Duodenal ulcer promoting gene of *Helicobacter pylori*. Gastroenterol 2005; 128:833-848.
19. El-Omar E, Peaman I, Dorrian CA, Ardrill JE, McColl KE. Eradicating *Helicobacter pylori* infection lowers gastrin mediated acid secretion by two thirds in patients with duodenal ulcers. Gut 1993; 34: 1060-1065.
20. Maltsson A, Lonroth H, Quiding-Jarbrink M, Svennerholm AM. Induction of B-cell responses in the stomach of *Helicobacter pylori*-infected after oral cholera vaccination. J Clin Invest 1998; 102:51-56.
21. Censini S, Lange C, Xiang Z, et al. *cag*, A pathogenicity island of *Helicobacter pylori*, encodes type-I specific and disease- associated virulence factors. Proc Natl Assoc Sci 1996; 93:14648-14653.
22. Odenbreit S, Puls J, Sedlmaier B, et al. Translocation of *Helicobacter pylori* CagA into gastric epithelial cells by type IV secretion. Science 2000; 287:1497-1500.
23. Tiwari SK, Manoj G, Kumar GV, et al. Prognostic significance of genotyping *Helicobacter pylori* infection in patients in younger age groups with gastric cancer. Postgrad Med J 2008; 84(990):193-197.
24. Lu H, Graham DY, Yamaoka Y. The *Helicobacter pylori* restriction endonuclease replacing Gene, *hrg*A and clinical outcome: Comparison of East Asia and western countries. Dig Dis Sci 2004; 49(9):1551-1555.
25. Bulent K, Murat A, Esin A, et al. Association of *cag*A with *vac*A presence with ulcer and non-ulcer dyspepsia in a Turkish population. World J Gastroenterol 2003; 9(7):1580-1583.