Helicobacter pylori: Inflammation and gastric cancers

Chetana Vaishnavi

Abstract

*Helicobacter pylori* is a small Gram negative bacterium, causing long-term colonization of the gastric mucosa. *H. pylori* infects approximately 50% of the world’s population and is the leading cause of peptic ulcer disease (PUD). It is estimated that life-time risk of gastritis, PUD, gastric lymphoma and gastric cancers in *H. pylori* infected population is above 100%, 10%, <1% and 1-2% respectively. The production of urease by the organism and the motility ability using flagella are essential factors for its colonization. The highest incidence of *H. pylori* is recorded in industrially underdeveloped areas, including Asia, Africa and South America. Since June 1994 *H. pylori* has been declared as a definite human carcinogen by The International Agency for Research on Cancer in 1994. Medical eradication of bacteria may halt inflammatory changes, metaplasia and proliferation of gastric mucosa thereby preventing the cascade of carcinogenesis. Gastric colonization with *H. pylori* induces histologic gastritis with neutrophilic and mononuclear cell infiltration in both the antrum and the corpus of the human stomach. It results from chronic inflammatory process. The rate of development of atrophic gastritis in patients with *H. pylori* infection is 1-3% per year of infection. Risk of gastric cancer depends on the type of gastritis and amount of acid produced. Patients with gastric ulcers are at higher risk for gastric cancers than are those with duodenal ulcers. Among the environment factors, diet and cigarette smoking enhances the carcinogenesis of *H. pylori*. *H. pylori* positive subjects have a significantly increased risk for the development of gastric MALT (mucosa associated lymphoid tissue) lymphoma. Tests available to diagnose *H. pylori* infection include histological examination of gastric tissue, bacterial culture, rapid urease testing, use of DNA probes, polymerase chain reaction and urea breath test.

Keywords: *H. pylori*, gastritis, gastric cancers, inflammation, MALT lymphoma

Full text

*Helicobacter pylori* is a small Gram negative, spiral shaped, fastidious bacterium, which causes long-term colonization of the gastric mucosa where it remains protected from low gastric pH. *H. pylori* infection is the most common human infection worldwide as approximately 50% of the population are infected by the organism. Interestingly human beings are the main reservoir. *H. pylori* is the leading cause of peptic ulcer disease (PUD). Life-time risk of gastritis, PUD, gastric lymphoma and gastric cancers in *H. pylori* infected population is above 100%, 10%, <1% and 1-2% respectively. *H. pylori* isolates possess substantial genotypic diversity, which engenders differential host inflammatory responses that influence pathologic outcome. The highest incidence is recorded in industrially underdeveloped areas, including Asia, Africa and South America. Since June 1994 *H. pylori* has been declared as a definite human carcinogen by The International Agency for Research on Cancer. Medical eradication of bacteria may halt inflammatory changes, metaplasia and proliferation of gastric mucosa thereby preventing the cascade of carcinogenesis.

Inflammation and gastric cancers

*H. pylori* infection is recognized as the main cause of chronic gastritis, PUD and gastric cancers. Most infected subjects develop no clinical symptoms and continue their life with superficial chronic gastritis which results from chronic inflammatory process. Atrophic gastritis and intestinal metaplasia can increase the risk for gastric cancer by 5-90 folds depending on the extent and severity of atrophy.

(i) Gastric cancers: Risk of gastric cancer depends on the type of gastritis and amount of acid produced. Patients with gastric ulcers are at higher risk for gastric cancers than are those with duodenal ulcers. Patients who are genetically predisposed to form atrophic gastritis in response to *H. pylori* infection are predisposed to gastric cancer. Carcinogenesis appears to be due to the induction of chronic inflammation by *H. pylori* infection. Increased oxidative stress and the formation of oxygen free radicals leads to DNA damage, increased CD4+ T cells and myeloid cells and elevated pro-inflammatory cytokine production. These all lead to accelerated cell turnover, reduced apoptosis, and the potential for faulty or
incomplete DNA repair. Among the environment factors, diet and cigarette smoking enhances the carcinogenesis of *H. pylori*.

(ii) **Gastric MALT lymphoma**: The gastric mucosa normally does not contain lymphoid tissue. At the same time *H. pylori* positive subjects have a significantly increased risk for the development of gastric MALT (mucosa associated lymphoid tissue) lymphoma due to chronic inflammation. The gastric lymphoma comprises of 8% of all non-Hodgkin's lymphoma and arises from malignant transformation of B cells from the marginal zone of MALT. Homeostatic chemokines are involved in the formation of tertiary lymphoid tissue. MALT represents a premalignant condition that can eventually lead to genesis of gastric MALT lymphoma, or extranodal marginal zone lymphoma of MALT in a small subset of chronically infected individuals. Antibiotics aimed at eradicating *H. pylori* have become the mainstay of therapy for low-grade gastric MALT lymphoma. Even patients with advanced stages of disease can regress with eradication of *H. pylori*.

(iii) **Gastric adenocarcinoma**: The finding of incomplete (type II) intestinal metaplasia may be used as an indicator for early gastric carcinoma detection. *H. pylori* are greater in non-neoplastic tissue than in tumor tissue. The possible explanation could be that once a tumor arose in the location where the *H. pylori* lived, the tumor would change the microenvironment. *H. pylori* may also be engulfed by the neutrophilic granulocytes, which are abundant in the neoplastic tissue.

(iv) **Esophageal adenocarcinoma**: Esophageal adenocarcinoma has risen at an alarming rate during the past few decades, with no substantial improvement in treatment, making this cancer among the deadliest. *H. pylori* infection, especially with more virulent cagA-positive strains, decreases the risk of esophageal adenocarcinoma. The association between *H. pylori* infection and the risk of adenocarcinomas of the esophagus and esophagogastric junction is modified by polymorphisms in the proinflammatory genes *IL-1β* and *TNF-α* which regulate gastric acid secretion. Barrett's esophagus (arbitrarily defined as a circumferential segment of columnar lined epithelium 2-3 cm in length in the lower esophagus) is recognized as a precancerous lesion of esophageal adenocarcinoma in most cases of adenocarcinoma of the gastroesophageal junction. The presence of *H. pylori* and its associated diagnoses, chronic active gastritis and intestinal metaplasia, are inversely associated with Barrett’s esophagus.

Several tests – both invasive and non invasive -- are now available to diagnose *H. pylori* infection. They include histological examination of gastric tissue, bacterial culture, rapid urease test, use of DNA probes, and polymerase chain reaction (PCR) analysis. Currently available tests for the detection of *H. pylori* infection have relatively high sensitivities and specificities, but each has its limitations in clinical application. The development of molecular methods of diagnosis in recent years has potentially overcome the problems in culturing *H. pylori*. Amplification of DNA from *H. pylori* by PCR is rapidly becoming established as a method of locating very low quantities of the organism in the clinical samples. The development of the [13C] Urea breath test opened the path to the use of stable isotopes in medicine. Noninvasive tests on fecal, urine and saliva samples can also play an important role in the diagnosis of *H. pylori* infection.

**Conclusions**

*H. pylori*, is common throughout the world and is known to be linked to gastric cancers. *H. pylori* virulence factors have revealed many aspects of the relationships between this bacterium, the gastric mucosal surface, and the induction of disease. *H. pylori* associated gastric disease outcome is the result of the intricate, ongoing interplay between environmental, bacterial, and host factors. Strain to strain genetic variability in bacterial virulence factors such as vacA and cagA not only affects the ability of the organism to colonize and cause disease but also affects inflammation and gastric acid output. On the host side, variations in the host immune response to the chronic presence of *H. pylori* directly impact *H. pylori* associated gastric disease and affect gastric acid output and thereby the density and location of *H. pylori*. 
References

Author’s biography
Prof. Chetana Vaishnavi is a Medical Microbiologist working in the Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh, India. She has actively participated in teaching and research for the past 34 years at the Institute. She is presently working in the area of gastrointestinal infections, particularly on Clostridium difficile, foodborne pathogens, biofilms in biliary stents, C-reactive protein, fecal lactoferrin, fecal myeloperoxidase etc. Prof. Vaishnavi has made significant contribution to medical science for which she has received several awards inclusive of ISG-Zydus Alidac Oration and the Dr CGS Iyer Oration by the ICMR. She is the Founder and Chairperson of Gastrointestinal Infection Society of India. She has produced and edited two multi-author books on ‘Infections of the Gastrointestinal System’ (Jaypee Publisher, 2013) and ‘Gastrointestinal Tract Infections’ (Paragon International Publisher, 2008). She did collaborative research work with national and international organizations. She is a Member of several Scientific Societies and has delivered invited lectures and chaired sessions at national and international conferences. She has published over 145 well-cited research papers and 19 chapters both nationally and internationally. She is a reviewer for several reputed National and International Journals and an examiner for several Indian Universities.

Author’s Postal address and E mail address
Dr. Chetana Vaishnavi
Professor (GE Microbiology)
Department of Gastroenterology
PGIMER, Chandigarh, India.
E mail: cvaishnavi@rediffmail.com