Commentary

The state of *Helicobacter pylori* infection in south east asian countries: an enigma

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ABSTRACT

**Aim:** The aim of the study is to review the state of Helicobacter pylori (H. pylori) infection and its consequences in Asian population with focus on related Asian enigma.

**Methods:** Review of literature on the subject and critical analysis of the matter.

**Results:** It is revealed in the review that the prevalence of H. pylori in most Asian countries including South East Asia (Bangladesh, India, Thailand and Pakistan) is relatively high. As the countries concerned are marching towards a developed status, the prevalence is slowly decreasing. However in these countries the corresponding rate of gastric cancer is low.

**Conclusion:** With a better understanding the molecular epidemiology of H. pylori infection, it is now possible to explain partially the basis of so called “Asian Enigma” with seroprevalence and gastric cancer prevalence rates. Vaccines against H. pylori may change the future epidemiological scenario of particular type of gastric malignancy.

INTRODUCTION

*Helicobacter pylori*, formerly known as Campylobacter pylori, was first isolated in human in 1982. This highly motile, curved gram negative rod lives within the mucus layer overlying the gastric and occasionally the duodenal and esophageal mucosal epithelium. Its incidence is high in the developing countries and lower in the developed world. The first isolation of *H pylori* in pure culture and its association with gastritis and peptic ulcer disease led to the awarding of the Nobel Prize in Medicine in 2005 to Australian physicians Barry Marshall and Robin Warren. The presence of *H pylori* increases the risk of peptic ulcer disease and gastric cancer, but decreases the risk of esophageal reflux and its consequences and may protect against childhood asthma and related disorders. Physicians are faced with the challenge of determining which patient would benefit from therapy and which may be harmful, as effective therapy to eradicate are at hand.

MICROBIOLOGY

The outstanding biochemical characteristic of Helicobacter is their high production of urease. Regulation of urease is complex, and multiple other genes are necessary for full activity. *H pylori* study suggests that they may use mutation to control phenotype, with the host selecting for the ‘most fit’ organism within a particular niche. Human may be simultaneously colonized with more than one strain of *H pylori* and recombination is an important characteristic. *H pylori* are among the most varied of all species in human biosphere. The strain specific restriction modification system diminish recombination and may permit different strain to colonize a particular host. The name of the molecule that signals the host by *H pylori* is cagA. The cag status of an *H pylori* strain is relevant to the risk of a number of clinical outcomes. Another heterogeneous locus that affects infection outcome is vacA, a conserved gene that encodes a secreted protein, a vacuolating cytotoxin that interacts with epithelial cells. It is now clear that vacA is an immunosuppressive molecule, analogous to FK-506.
(Fujimycin activator kinase, also known as tacrolimus), that down regulates T-cell activity.\textsuperscript{16}

**EPIDEMIOLOGY**

\textit{H. pylori} is indigenous to human for at least 50,000 years and its relatives in other mammals, but they are disappearing as a result of modernization. On occasion person to person transmission occurs via improperly cleaned endoscopes. Suboptimal sanitary conditions in institutions for the mentally retarded and orphanages, and in developing countries that do not reflect modern standards, suggest the occurrence of feco-oral transmission. \textit{H. pylori} has been isolated from feces especially from children, dental plaque and DNA products may be detected in saliva by polymerase chain reaction which raises the possibility of oral-oral transmission as well. Sexual transmission does not occur very frequently, if at all.\textsuperscript{17} \textit{H. pylori} cluster in families and child colonization is associated with large family size and older siblings. The prevalence of \textit{H. pylori} colonization is related to age and geographic location, in developing countries by age 10 years, more than 70% carry \textit{H. pylori} and by age 20, carriage is nearly universal. The cause of decreasing infection in developed countries is probably the result of smaller family sizes, decreased crowding, improved sanitation, and more than 60 years of widespread antibiotic use.\textsuperscript{18} As is evident from the foregoing, the overall prevalence is high in developing countries and lower in the developed and also vary within country and different areas of the countries. Transmission of \textit{H. pylori} is largely by the oral-oral or fecal-oral routes. \textit{H. pylori} infection may be acute with clinical presentation of Upper GI illness with nausea and pain abdomen, vomiting, burping and fever; most illness persist for less than 1 week. Features are marked in adults but silent acquisition occurs in childhood.

Persistent colonization, duodenal ulceration, gastric ulceration, gastric carcinoma, gastric lymphoma likely results from chronic infection. Incidence of gastro-esophageal reflux disease, Barrett’s esophagus and adenocarcinoma of the esophagus are increasing following decrease in colonization of \textit{H. pylori} in developed countries.

Gastric MALT lymphoma are linked to a chronic stomach infection by \textit{H. pylori}. Mucosa associated lymphoid tissue (MALT) lymphoma of the stomach can be treated with antibiotics. This is successful in shrinking the lymphoma. It is not known whether it produces permanent cure. Endoscopic examination 3-6 months after the antibiotic treatment is recommended.

Association of \textit{H. pylori} with idiopathic thrombocytopenic purpura (ITP) is emphasized as the association is specially marked in this region of the world i.e., East Asian countries. In past 10 years there has been an increasing number of reports, showing an epidemiologic association between the presence of \textit{H. pylori} and the diagnosis of ITP.\textsuperscript{19} \textit{H. pylori} eradication has been attempted as a therapy for ITP and the results are promising and at present for ITP patients, physicians should assess \textit{H. pylori} status and if positive should consider eradication as alternative therapeutic approach.\textsuperscript{20-21}

**Asian Enigma**, refers to the observations that there are regions where \textit{H. pylori} infection is high yet the gastric cancer incidence is relatively low. The data that led to this term were mainly epidemiological. The regions where these observations are made are India, Bangladesh, Pakistan and Thailand. To explain these ‘enigmas’, host genetics, bacterial factors and environmental factors such as diet have been invoked. However, interesting observations from other Asian countries make the causal association seem somewhat enigmatic. High prevalence of \textit{H. pylori} infection does not translate into high gastric cancer incidence in some other Asian countries.\textsuperscript{22} There is a large inter-country variation in incidence of gastric cancer and \textit{H. pylori} sero-prevalence among Asian countries. Particularly in Japan a strong link between \textit{H. pylori} infection and gastric cancer has been demonstrated. By contrast, the prevalence of \textit{H. pylori} infection is high in some countries, including India and Bangladesh, but low gastric cancer rates have been reported. These disparate observations represent the Asian enigma. Table-1 shows the incidence of \textit{H. Pylori}, Ca stomach and Cholangiocarcinoma in some countries (Source:Globalcen 2008). Table-2 shows the prevalence of \textit{H. pylori} in Asian Countries, Middle East and Pacific Rim countries, Australia (Source-Journal of Gastroenterology and Hepatology 25, 2010, 479-486). Factors that may influence the etiology of gastric cancer include the genetic diversity of the infecting \textit{H. pylori} strains and differences in the host genetic background in various ethnic groups, including gastric acid secretion and genetic polymorphisms in pro-inflammatory cytokines. These factors, in addition to environmental factors, such as personal hygiene and dietary habits, reflect the multifactorial etiology of gastric cancer. Table-3 shows childhood incidence of \textit{H. pylori} infection in selected countries (Source-Journal of Gastroenterology and Hepatology, 25, 2010, 479-486).

The status of cagA, vacA, jhp0562, and β-(1,3)galT(jhp0563) was examined in 371 \textit{H. pylori}-infected patients from Bhutan, Vietnam, and Myanmar. Each virulence factor could not explain the difference of the incidence of gastric cancer. However, the prevalence of quadruple-positive for cagA, vacA s1, vacA m1, and jhp0562-positive/β-(1,3)galT-negative was significantly higher in Bhutan than in Vietnam and Myanmar and correlated with gastric cancer incidence. Moreover, gastritis-staging scores measured by histology of gastric mucosa were significantly higher in quadruple-positive strains. It was suggested that the cagA, vacA s1, vacA m1, and jhp0562-positive/β-(1,3)galT-negative genotype may play a role in the development of gastric cancer.\textsuperscript{23}

**DIAGNOSIS**

Confirmation of \textit{H. pylori} colonization is made invasively by endoscopy and biopsy or noninvasively by serologic analysis, breath test, or fecal antigen analysis. Each of these tests if correctly done has diagnostic accuracy exceeding 95%.
Therapy for infection include:

<table>
<thead>
<tr>
<th>Regime</th>
<th>Drugs</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton pump inhibitor (PPI) triple therapy</td>
<td>PPI + amoxicillin + clarithromycin</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Quadruple therapy</td>
<td>PPI+ metronidazole + tetracycline + bismuth</td>
<td>10 days</td>
</tr>
<tr>
<td>Sequential therapy</td>
<td>PPI + amoxicillin followed by PPI + clarithromycin + tinidazole</td>
<td>5 days</td>
</tr>
<tr>
<td>Levofoxacin triple therapy</td>
<td>PPI + amoxicillin + levofoxacin</td>
<td>10 days</td>
</tr>
<tr>
<td>Rifabutin triple therapy</td>
<td>PPI + amoxicillin + rifabutin</td>
<td>10 days</td>
</tr>
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The potential of turmeric to treat GI problems in particular, has received lot of attention from a section of scientific community. In a recent study to investigate turmeric and its active component curcumin, on the growth of *H.pylori* found a discrepant result in which the rate of cure with Omeprazole, Amoxicillin, Metronidazole (OAM)therapy was 78.9% and with curcumin only 5.9%. Extract of turmeric, borage, parsley were able to inhibit the adhesion of *H. pylori* strains in the stomach sections. It could be concluded that ingestion of the plants with anti adhesive properties could therefore provide an alternative for *H. pylori* infection therapy.24

PREVENTION

*H. pylori* has co-evolved with its human host over millennia; eliminating colonization in a population may have distinct disadvantages. There are risk factor related to gastrosophageal reflux disease (GERD) complications, including esophageal adenocarcinoma. Asthma, obesity and even type2 diabetes mellitus has a chance to emerge from the eradication. An economic evaluation of the use of a potential *H. pylori* vaccine in babies found its introduction could, at least in the Netherlands, prove cost-effective for the prevention of peptic ulcer and stomach cancer.25

**H. PYLORI IN BANGLADESH**

Prevalence of *H. pylori* infection in Bangladesh has been established by various detection technique including Rapid urease test after endoscopic biopsy, IgG against *H.pylori* gastric aspirate assays and stool antigen detection method. Culture is not employed as the organism requires special media (Skirrow’s selective media) and environment for required yield but sometimes non-selective chocolate agar media may be used. A pilot study employing serological test involving more than 2000 Bangladeshi asymptomatic subjects found 92% to be positive for *H. pylori*.22 Another study with biopsy specimens in 241 patients with dyspepsia, in the Department of Medicine at Korea Friendship Hospital, Savar, Bangladesh, showed 168 Bangladeshis (69.7%) were Campylobacter like organisms (CLO) positive.28 A study by Hossain MR, Hossain MD, Haque WS, in 50 patients in Armed Forces Institute of Pathology (AFIP) Dhaka cantonment employing rapid urease test (hematoxylin eosinopinic stain) showed 37 cases (74%) to be positive and in the same series histopathologic detection under H/E stain showed 35 patients (70%) biopsy were positive for *H.pylori*. Another study in the Immunology Department of AFIP, Bangladesh revealed 323(35%) of 917 subjects to be IgG positive. The state in India is similar to Bangladesh which show antibody to *H.pylori* prevalence of up to 79% in a study.29 In Thailand in 31-60 years age group patients with gastritis had 98.2% association with *H. pylori*. High prevalence (74%) of *H. pylori* infection in Isalmabad, Pakistan is comparable to the data in developing countries. *H. pylori* infection was significantly associated with presence of household animals and more family members in the local population.30

CONCLUSION

Like the Western World, the prevalence of *H. pylori* infection in Asia is changing over the past few decades. With a better understanding the molecular epidemiology of *H. pylori* infection, it is now possible to explain partially the basis of so called “Asian Enigma” with sero-prevalence and gastric cancer prevalence rates. Firm steps are required to be taken to adopt a strategy of primary prevention of gastric cancer by *H. pylori* eradication program in high risk population to reduce the burden of tumor.

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