Epidemiology of Helicobacter Pylori Infection in Malaysia - Observations in a Multiracial Asian Population

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SUMMARY
Observations of racial differences in the prevalence of Helicobacter pylori in Malaysia have been intriguing. The Indians and Chinese consistently have a higher prevalence compared to the Malays. The racial cohort theory has been proposed to explain these differences where transmission and perpetuation of infection takes place within a racial group rather than between races, races being separate owing to the low rate of interracial marriages. Studies have demonstrated distinctive bacterial strains between races. Phylogenetic studies have shown that H.pylori isolates amongst Chinese and Indians are distinctive while Malays have Indian and other strains suggesting a more recent acquisition of the bacterium from Indians. H.pylori is recognized as the major causative factor in peptic ulcer disease and gastric cancer. Despite the high prevalence of H.pylori, Indians have a relatively low prevalence of peptic ulcer disease and a low incidence of gastric cancer. This paradox with regards to gastric cancer has been termed the “Indian enigma”. Bacterial strain differences between races may be putative but this observation may also indicate gastroprotective environmental factors or a lower genetic susceptibility to develop cancer in the Indians.

KEY WORDS:
H.pylori, Racial cohort, Indian enigma, Gastric cancer, Peptic ulcer, Malaysia

INTRODUCTION
The discovery of Helicobacter pylori in 1983 by Warren and Marshall ranks as one of the most important discoveries in medicine in recent times. The award of the Nobel Prize in Medicine to Drs Warren and Marshall in 2005 is fitting tribute to their momentous discovery. Yet it was hard to imagine that the existence of such a microorganism in the human stomach, which was first observed before the turn of the 19th century was largely ignored for so many years until the seminal observations of Warren in 1979 (Fig 1 and 2).

The great importance of H. pylori lies in its disease association with peptic ulcer disease and gastric cancer. Peptic ulcer disease had long been thought to be a chronic relapsing disease without a cure. Gastric cancer is one of the most common and deadliest cancers affecting humans, the etiology of which was largely unknown before the discovery of H. pylori. We now know that H. pylori is the cause of the overwhelming majority of peptic ulcers, its eradication leading to cure of the disease. H. pylori has also been identified as the critical permissive factor in gastric carcinogenesis. Eradication of H. pylori prevents the development of gastric cancer in patients who have not developed cancer precursor lesions.

H. pylori is a ubiquitous microorganism infecting up to half of the world’s population. However, the distribution of
infection across the world is not uniform with marked geographical differences. Numerous reports have come from different parts of the world showing widely differing prevalence rates with the less developed and poorer countries in Asia, Africa and South America carrying a heavier infection burden compared to the more developed countries in Europe and North America.

Many issues however have yet to be clarified. The exact mode of transmission of infection is still unclear and many questions arise as to why the majority of infected patients do not develop any disease. Clearly a host-bacterial-environmental interaction must be operative and it is important to understand how this interaction takes place and to identify possible risk factors for disease causation.

This article describes the burden of disease and reviews some of these issues with particular reference to Malaysian data. The first report of these issues with particular reference to Malaysian data. This article describes the burden of disease and reviews some of these issues with particular reference to Malaysian data.

**Early observations of H. pylori prevalence in Malaysia**

The first report of H. pylori in Malaysia was made in the Malaysian Pathology Society meeting in 1986 and subsequently the first publication by Goh et al in the Journal of Gastroenterology and Hepatology in 1990. The existence of differences between Malay, Chinese and Indian patients was highlighted in this report- a low prevalence amongst Malays and a significantly higher prevalence in Chinese and Indians. At the same time, Kang and colleagues in Singapore also came out with observations of similar racial differences.

Goh and Parasakthi also had the opportunity to study the seroprevalence amongst the ethnic groups of Sabah and Sarawak which were loosely grouped together and found the prevalence rates to be high 65.3% and 55.0% respectively. In a more recent study from Sarawak amongst the reclusive Penans indigenous group, a lower prevalence of 37.5% was reported. These studies reflect on the wide variability in different racial groups in the country.

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**Ethnic differences in prevalence of H. pylori**

The ethnic differences in H. pylori prevalence continue to intrigue researchers in our country. In an extensive report, Goh and Parasakthi reported on several seropidemiological studies in Malaysia and consistently found a lower prevalence amongst Malays 10-25% compared to the Chinese 35-55% and Indian- 50-60%. Similar racial differences were already observed from an early age in Malaysia. Boey et al in a seroprevalence study of more than five hundred children reported a high prevalence of H. pylori amongst Indians and Chinese compared to Malays.

In 2000, Goh and Parasakthi proposed the "racial cohort" theory to explain the racial differences in Malaysia. Owing to the relative distinctiveness of all three major racial groups in Malaysia because of low level of intermarriages between races, H. pylori has remained confined to a particular racial group. The Malays who have a low reservoir of infection to begin with, continues to have a low prevalence of infection. The authors suggested that the high prevalence amongst Chinese and Indians in Malaysia, reflected the high prevalence in Southern China and Southern India from where these races had originally come from. Even though migration had taken place more than three generations ago, the high H. pylori prevalence amongst the Chinese and Indians remains, with intra racial/inter-community spread taking place and with low cross-infection occurring between races. Evidence that supports this theory is the distinctive strains of H. pylori that have been isolated from different racial groups in Malaysia.

The "racial cohort" theory emphasizes the insular nature of the infection. Even within racial groups differences do exist. For example amongst the Malays there is a significant difference between the H. pylori prevalence between the East and West coast of peninsular Malaysia. In the west coast of Peninsular Malaysia, studies have consistently shown a higher prevalence of H. pylori than in North east Malaysia.

**Phylogeny of Malaysian H. pylori strains**

H. pylori follow the human route of migration and reflect human ancestry. The phylogeny of H. pylori strains has been used to track the migration of human population out of its origin in Africa. Recent elegant work carried out by the biomolecular laboratory of the University of New South Wales (UNSW) on multilocus sequence typing (MLST) of seven housekeeping H.pylori genes- atpA (566 bp), efp (350 bp), mutY (361 bp), ppa (338 bp), trpC (396 bp), ureC (525 bp), and yPhC (450 bp), have yielded exciting findings. The results of their analysis of different H. pylori strains from Malay, Chinese and Indian patients were compared with the global MLST data using a Bayesian statistics tool called STRUCTURE. Global H. pylori isolates have been divided into 6 ancestral populations designated as hpAfricA1, hpAfricA2, hpNEAfricA, hpEurope, hpEastAsia and hpAsia2. The overwhelming majority of strains derived from...
Chinese patients belonged to the hpEastAsia and constituted a distinct group while the isolates from Indians were from the hpAsia 2 group (Fig 3). Isolates from Malay patients were a mixed group. Although half the strains were similar to the Indians- subpopulation of hpIndia, historically, there is no evidence that ancestral Malays had migrated from India. Other Malay strains belonged to a motley group of hpEastAsia, hpEurope, and hpAfrica1. The diversity of Malay isolates and the low prevalence of infection suggest that Malays were originally free of H. pylori and have more recently acquired the infection from others and mainly from the Indians. These findings are consistent with our previous epidemiological observations of the distinctness of H. pylori strains within races and the low cross infection rate between races.

**Disease Association - peptic ulcer disease**

H. pylori infection results in peptic ulcer disease and cancer of the stomach and an uncommon mucosal associated lymphoma of the stomach (maltoma). The evidence that supports the association between H. pylori and these diseases is strong and the causal link irrefutable. Relapse of H. pylori associated peptic ulcers is virtually abolished with successful eradication of the bacterium. In an early report from the group from the University of Malaya showed a zero relapse rate with duodenal ulcers over a 2 year follow-up period38. A more recent follow-up of a larger group of patients and now exceeding 15 years have shown similar results39 with a very low reinfection rate and ulcer relapse rate.

Interesting observations on ethnic differences have been made not just on the prevalence of H. pylori infection but also on the disease outcomes in Malaysia. In an endoscopy based study of over a thousand patients in 1997, Goh recorded the H. pylori prevalence in duodenal, ulcer, gastric ulcer and non-ulcer dyspepsia patients40. While the H. pylori prevalence was lowest overall amongst the Malays compared to the Chinese and Indians, the H. pylori prevalence in ulcer patients of all three racial groups was high. What was interesting was that in the H. pylori positive group of patients, about 60% in the Chinese and Malay groups had peptic ulcer disease whereas only about 40% of the Indians had ulcers suggesting a possible ulcer protective factor or a less virulent H. pylori strain amongst the Indians41,42. In an interesting collaborative study with centers in Australia and Sweden, the prevalence of duodenal ulcer promoting (dupA) gene amongst Indian isolates (7.1%) was the lowest compared to Australian (37.8%) and Swedish (65.0%) as well as Chinese (28.9%) and Malay (35.7%) isolates from Malaysia and Singapore43. The dupA gene has been shown to induce a pro-inflammatory cytokine IL-8 in vitro. Although this study did not look specifically at ulcer patients among Indians, its finding suggest that less ulcerogenic strains may be present in Indian patients.

Although we have observed that the H. pylori prevalence in Malay peptic ulcer patients to be lower compared to the Chinese and Indians, Raj et al 34 in their studies from Kelantan, have noted an inordinately low H. pylori prevalence amongst their peptic ulcer patients. After excluding NSAID as a cause of peptic ulcers, there remained large group of “idiopathic ulcers”. It can be speculated that these ulcers may be related to consumption of herbal remedies and other medications peculiar to that part of Malaysia but more meticulous studies needs to be carried out to verify this.

**Disease Association - gastric cancer**

Studies on gastric cancer and H. pylori have proved even more interesting. Cancer registries from Peninsula Malaysia45 and the more established registry from Singapore46 consistently show a high gastric cancer (GCA) age standardized incidence rate (ASR) in Chinese compared to the Indians and Malays (Table I). Ecological comparison with known H. pylori prevalence rates in the different races shows that the low cancer incidence amongst Indians despite a high H. pylori prevalence is a paradox. In 2007, Goh et al 37, reported on a case control study where they found that following multivariate analysis, H. pylori and Chinese race were independent risk factors for GCA : Chinese race (OR 10.29 [2.87, 36.47]), H. pylori (OR 2.54 [1.16, 5.68]). A low level of education (OR9.81 [2.03, 47.46]), smoking (OR 2.52 [1.23, 5.15]), and high intake of salted fish and vegetables (OR 5.18 [1.35, 20.00]) were also identified as significant independent risk factors for GCA, while high intake of fresh fruits and vegetables was protective for GCA (OR 0.15 [0.04, 0.64]) 37 (Table II). The relatively low prevalence of GCA despite high rate of H. pylori infection amongst the Indian race was dubbed the “Indian enigma”. This observations have also been made Ang et al from neighbouring, Singapore48. Again as with peptic ulcer disease, H. pylori strain differences could be putative but at the same time host genetic and environmental factors could also play a role. The role of environmental factors especially different dietary items is intriguing but difficult to prove. Much has been discussed about the gastroprotective and anticancer qualities of curries and chillies with their active ingredient of cucumin 39.

H. pylori strains carrying the cagA gene are thought to be more virulent than cagA-negative strains and are associated with the development of gastric adenocarcinoma. The cagA gene product, CagA, is translocated into gastric epithelial cells and localizes to the inner surface of the plasma membrane, in
which it undergoes tyrosine phosphorylation at the Glu-Pro-Ile-Tyr-Ala (EPIYA) motif. The EPIYA motif is a crucial therapeutic target of cagA-positive *H. pylori* infection and is believed to contribute to the gastric cancer causing potential of the infection. In a collaborative study with Mitchell and colleagues at the University of New South Wales, interesting racial differences between Indian, Malay and Chinese isolates from Malaysia and Singapore with regards to different EPIYA motifs were observed. The majority of Chinese isolates showed the EPIYA ABD (87.8%) motif whereas Indian strains showed mainly EPIYA ABC (60.5%) and ABCC (27.9%) motifs. Malays strains were distributed equally between EPIYA ABC (46.2%) and ABD (38.5%) motifs. Amongst Chinese GCA patients, 85.7% showed the EPIYA ABD motif.

### ASR per 100,000 population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Malay</th>
<th>Chinese</th>
<th>Indian</th>
<th>Chinese (Shanghai)</th>
<th>Indian (Mumbai)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>6.5</td>
<td>3.4</td>
<td>21.5</td>
<td>13.5</td>
<td>8.2</td>
</tr>
<tr>
<td>Female</td>
<td>3.8</td>
<td>2.1</td>
<td>10.8</td>
<td>9.1</td>
<td>5.9</td>
</tr>
</tbody>
</table>

*Malaysia, Sing= Singapore.*

### Table II: Risk factors for gastric cancer multivariate analysis (adapted with permission from Goh et al [37])

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sig. (p value)</th>
<th>Odds Ratio</th>
<th>95.0% C.I.</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>RACE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>&lt;0.001</td>
<td>10.23</td>
<td>2.87</td>
<td>36.47</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>0.149</td>
<td>2.51</td>
<td>0.72</td>
<td>8.78</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>0.573</td>
<td>1.63</td>
<td>0.30</td>
<td>8.85</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.005</td>
<td>9.814</td>
<td>2.03</td>
<td>47.46</td>
<td></td>
</tr>
<tr>
<td>Low intake Fresh fruits and vegetables</td>
<td>0.010</td>
<td>6.66</td>
<td>1.57</td>
<td>28.25</td>
<td></td>
</tr>
<tr>
<td>High intake of salted foods</td>
<td>0.017</td>
<td>5.18</td>
<td>1.35</td>
<td>19.97</td>
<td></td>
</tr>
<tr>
<td>H.pylori +ve</td>
<td>0.020</td>
<td>2.538</td>
<td>1.16</td>
<td>5.58</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>0.011</td>
<td>2.521</td>
<td>1.23</td>
<td>5.15</td>
<td></td>
</tr>
<tr>
<td>Heavy Chili intake</td>
<td>0.192</td>
<td>1.812</td>
<td>0.74</td>
<td>4.43</td>
<td></td>
</tr>
</tbody>
</table>

### Table III: *H. pylori* prevalence (%) according to time period and diagnosis (reprinted with permission) [42]

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Malay</th>
<th>Chinese</th>
<th>Indian</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>172/57</td>
<td>1104/1928</td>
<td>406/746</td>
</tr>
<tr>
<td>DU</td>
<td>56/70</td>
<td>450/494</td>
<td>113/123</td>
</tr>
<tr>
<td>GU</td>
<td>46/54</td>
<td>241/276</td>
<td>49/58</td>
</tr>
</tbody>
</table>

### Table IV: *H. pylori* prevalence (%) according to diagnosis and race and time period (adapted with permission from Goh et al [42])

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Malay</th>
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<td>241/276</td>
<td>49/58</td>
</tr>
</tbody>
</table>

**Is *H. pylori* decreasing in prevalence?**

The decline in *H. pylori* prevalence has been widely observed both in clinical practice as well as in formal research studies. In a recent review, Tan and Goh have discussed the decrease in burden of *H. pylori* infection in Asia as well as the reasons behind it. Only one study from Malaysia has been published to date documenting the decline in prevalence of *H. pylori*. In a large endoscopy based study of almost 8000 subjects from the University of Malaya Medical Centre, the prevalence of upper gastrointestinal diagnoses and *H. pylori* prevalence were studied at 2 time periods over a 10 year interval. The *H. pylori* prevalence had declined from 51.7% in 1989/1990 to 30.3% in 1999/2000 (Table III). With no change in the indications of upper gastrointestinal endoscopy or referral pattern and patient base, these figures would be considered reflective of a true change that has occurred over time. While the prevalence of duodenal and gastric ulcers have both declined, it was also important to note that the proportion of non-*H. pylori* ulcers had also increased: duodenal ulcers from 9.9% to 31.2% and gastric ulcers from 13.4% to 43.2%. This was particularly marked with Malay ulcer patients but less so with Chinese and Indian patients and more pronounced with gastric ulcers compared to duodenal ulcers (Table IV). At the same time a significant rise in erosive reflux esophagitis from 2.0% to 8.4% was also noted.
DISCUSSION

Two issues have been highlighted: firstly the differences in susceptibility to H. pylori infection between the three major races in Malaysia- Malay, Chinese and Indian and secondly the differences in disease outcomes with H. pylori infection.

Amongst the major races in the country, Indians and Chinese have the highest prevalence. Even after controlling for possible confounding factors, Indian and Chinese race stand out as independent predictive factors for H. pylori infection. This difference is likely to be environmental in origin. As discussed previously, an infection which requires close contact for transmission and spread during early childhood and exposure over a long period of time such as contact for transmission and spread during early childhood for H. pylori will remain confined to predefined cohorts which in the case of Malaysia, is ethnic based. The distinctness of H. pylori strains between different races supports this premise. Genetic susceptibility is unlikely to play a significant role. Studies from East Malaysia looking at native groups who are ethnicity from the same racial stock but socioculturally distinct from the Malays have shown a relatively high prevalence.

This racial cohort phenomenon has an analogy in another common infection in South East Asia- hepatitis B infection. Transmission of hepatitis B infection occurs predominantly in the Far East during the perinatal and neonatal period (mother to child transmission) and leads to life-long carriage of the virus. In Malaysia, the Chinese have significantly higher hepatitis B carrier rates compared to the Indians and Malays 43,44. Hepatitis B is another infection (apart form parenteral infection) which requires close contact between family members particularly during the neonatal period and childhood for spread of infection.

However host genetic factors would likely play a significant role in the pathogenesis of gastric cancer. The "Indian enigma" - a low gastric cancer burden despite a high H. pylori prevalence, suggests a relative protection against the development of gastric cancer in a particular race. The lower propensity of Indians to develop cancers in general is well known and has previously been reported in other studies 45. The past 30 years from the time of the discovery of H. pylori have been heady years in gastroenterology research. But the past 30 years from the time of the discovery of H. pylori have been heady years in gastroenterology research. Helicobacter pylori eradication: results of a 2-year follow-up. Lancet. 2005; 365: 1437-42.

REFERENCES