KEYNOTE ARTICLES

Epidemiology of Helicobacter pylori in India

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Several centers from India have made significant contributions to our understanding of its epidemiology in this part of the world.

Prevalence

The prevalence of this infection in the general population varies widely, from 50%-50% in developed countries to as high as 90% in some parts of the developing world. The reported frequency in India has ranged from 31%-84%.[1,2,3] Most centers report a figure of around 60%.

Age of acquisition

The infection is acquired early in life in India. The prevalence of antibodies to H. pylori was found to rise from 22% in preschool children to 87% by age 20, in one study.[4] In another study from Bangalore, 82% of the children tested positive with the 13C urea breath test.[5]

Risk factors

A high prevalence is noted in populations with low socioeconomic status and low educational levels.[6] Increased seropositivity has been reported in endoscopists and nurses, indicating an occupational risk.[7] This increased prevalence was surprisingly not present in dental workers.[8]

Families and institutions

A high prevalence of infection is seen in family members of index cases, suggesting intrafamilial spread.[9] Spouses of infected subjects show a significantly higher prevalence of infection.[10] Institutionalized subjects also have a high prevalence of infection (87% seropositivity compared with 43% in controls), the spread occurring probably through fomites.[11] The annual seroconversion rate was also found to be as high as 7.4% compared with 1% in the normal population.[12] Using DNA fingerprinting, the same strain of the organism was found to be present in the inmates, indicating intra-institutional person-to-person spread.[13]

Reservoir

Humans are the major reservoir of H. pylori. The organism colonizes the stomach, lodging most frequently in the antrum. Its presence has been demonstrated in saliva (87%) and dental plaque (100% in one study) in reports from China and India.[14,15] The isolation rates from these sources have been very low in the West.[16]

Cats have been shown to harbor H. pylori.[17] It is presently not clear whether this has any importance to the epidemiology of the infection in humans. Using PCR and cultures, the organism has been demonstrated in water sources, suggesting that the infection is water-borne.[18,19]

Transmission

Three routes of infection have been postulated. Evidence suggesting the feco-oral route includes detection of H. pylori in feces[20] and sewage water[18] and in municipal water outlets, using PCR and culture techniques.[19] The prevalence of infection has also been reported to be higher in subjects consuming uncooked vegetables.[21] The seroprevalence of this infection closely resembles that of hepatitis A, which is known to spread by this route.[22]

Evidence to the contrary comes from a study involving 133 initially seronegative Swedes who developed at least one episode of gastroenteritis during travel to the developing world, but failed to show any serological evidence of H. pylori infection on follow up.[23]

The rates of detection of H. pylori in saliva and dental plaque make the oro-oral route of transmission highly likely.[24] In communities where infants and children are fed on food pre-masticated by the mother, the infection is more prevalent and occurs early.[25] Spouses of infected subjects also have a much higher (68%) prevalence of infection than those of uninfected ones (9%).[26] In such cases, the infecting strain has been found to be identical by DNA fingerprinting. One of the problems of attributing transmission to this route is the observation that dentists do not have the increased prevalence one would have expected.[27]

H. pylori has been found in aspirated gastric juice.[27] The gastro-oral route of transmission may account for the high prevalence of infection in endoscopists, nurses and endoscopy theater staff. Spread through fomites contaminated by vomitus might be responsible for the high infection rates seen in institutionalized children and the mentally retarded.

Nosocomial spread

Infected endoscopes can transmit the organism. This seems to occur in 1%-3% of endoscopies with manual endoscope washing.[24] The transmission frequency has been calculated as 4 per 1000 endoscopies.[29] A study from India involving patients with variceal bleeding undergoing repeated endoscopic intervention did not find any increase in infection.[30]

Prevalence in disease states

The strongest association has been noted in patients with peptic ulcer. H. pylori infection is present in 90%-100% of Western patients with duodenal ulcer.[23] The reported frequency from Indian centers is 64%-90%.[23,33] The prevalence of this infection in other gastroduodenal diseases is shown below:
The infection seems to be associated with complicated duodenal ulcer disease as well, occurring in approximately 90% with gastric outlet obstruction. Rates as low as 0% have been reported with perforated ulcers; that an etiology other than H. pylori was responsible for the perforated ulcers may not be an adequate explanation.

A strong association has been reported between chronic H. pylori infection and gastric malignancies in the West, both adenocarcinoma and MALT lymphoma. In fact, early gastric MALT lymphomas have been shown to regress after successful eradication of H. pylori infection. Chronic infection with this organism has been included in the list of known carcinogens.

Reports from the developing world do not show a correlation with gastric carcinogenesis. The reported seropositivity in Indian patients with gastric cancer is low (38%-66%). Further, with the very high prevalence of the infection noted in the community, gastric malignancy is not as common as one would have expected. Similar observations from Africa raise other etiologic possibilities for gastric carcinogenesis that are currently not clear. Whether there is a "carcinogenic strain" that is fortunately not so prevalent in developing countries is yet another hypothesis that needs to be explored.

The active disease-to-infection ratio (point prevalence) has been found to be 4.7%-7.8% in Indian subjects while the life-time risk of developing peptic ulcer in seropositive subjects is estimated as 6%-20%. Strains

Of 7 species of Helicobacter known to colonize mammalian gastric mucosa, H. pylori is the only one known to infect human stomach. The entire genomic sequence of this organism has been reported. It is now known that there are several strains of H. pylori that can be identified by their ability to produce different toxins, or typed using molecular techniques. Some strains are virulent, the trait depending upon the organism's ability to produce certain toxins. A vacuolating cytoxin coded by a gene, Vac A, and a virulence factor associated with the gene Cag A have been widely studied.

Epidemiologic correlation has however not been easy. The virulent strain has been seen in persons who do not have any disease. Further, a study from Delhi found no difference in the anti-Cag A antibody titers between patients with duodenal ulcer and non ulcer dyspepsia.

Drug resistance

Eradication of infection using multi-drug regimens has proved to be effective and popular in the West. A special problem faced in India is the high frequency of drug resistance in the Indian isolates. Imidazole resistance has been reported in 60%-100% while amoxycillin resistance has been found in approximately 60%. Resistance to clarithromycin, which was virtually unknown 5 years ago, has increased to 20% in some places. Hence, the best therapeutic regimen in India needs to be determined. As the rates of resistance to different antimicrobials is likely to change with time and usage, it would require continuous local monitoring.

References


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Comments

K M Mohandas: Although there are hundreds of papers on prevalence of this infection, there is not a single large study from India using randomly selected general population to know the true prevalence. Most Indian studies are biased, hospital-based prevalence data are endoscopy-dependent and have small sample size. A majority of Indians use omeprazole and similar drugs available freely over the counter; this affects the results of the rapid urease test and histology. It is highly likely that the true prevalence of \( H. \) pylori is thus underestimated in various disease states in India. This is evident from the fact that two serological studies and one breath test study have shown very high prevalence rates even in children.

The consensus group should recommend the need to establish a national reference center for \( H. \) pylori studies under whose leadership large-scale population studies can be undertaken.

V Javanh: There are no prevalence figures available in the community, among school children, college students,
etc. Age-related prevalence figures are not available in correlation with demographic characteristics. Secondly, in India only 60% of ulcer patients are found to be H. pylori-positive; there is a need to study patients with peptic ulcer who are H. pylori-negative. Thirdly, serodiagnosis is necessary to identify large population groups with H. pylori infection as this would decrease the load on endoscopy units. We also need to determine the role of other factors, e.g., smoking and alcohol, in addition to H. pylori in patients with duodenal ulcers and gastric carcinoma. We need to involve the biotechnologist to identify the virulent strain in our country.

Prabha Sawant: The acquisition of H. pylori infection in India is during childhood and not during the teenage years; the process evolves over a longer period. This model of ‘slow infection’ is especially unique to bacterial diseases. The prevalence curves drawn from cross-sectional population studies in the past years in different countries reflect the level of infection of each group in its youth. This is the so-called cohort phenomenon.

T N Lahiri Majumdar: Prof Choudhuri mentions Cag positivity and the virulence of H. pylori. Perhaps, the study from Delhi that he refers to needs to be critically analyzed and similar studies carried out at other centers as Cag positivity-associated mitosis is being recorded frequently (Yamauchi Y, et al. Variants of Cag region of Cag A gene. J Clin Microbiol 1998;36:B2258-63).

D N Guha Mazumder: No prevalence data are available based on studies in the general population in India. Hence, the reported prevalence figures of 31%-84% from various centers suffer from bias. There is also a controversy regarding the H. pylori isolation rates in dental plaque.

Though one study from Delhi reported no difference in anti-Cag A antibody in patients with duodenal ulcer and non ulcer dyspepsia, the sample size in that study was small. Hence, we need more studies employing larger numbers of cases.

A K Jain: Dental plaque may have 100% positivity using the rapid urease test, but H. pylori isolation is very low; following eradication therapy, dental plaque still remains positive but ulcer recurrence rate is quite low. Hence, whether dental plaque has some other urease-producing organism is unclear. Moreover, dentists do not have higher prevalence of infection.

There are several studies, including from India, showing H. pylori prevalence in perforated ulcer comparable to that in uncomplicated ulcer. Moreover, after closure of the perforation, relapse of ulcer has been shown to be related to whether H. pylori has been eradicated.

K Vineetkumar Nair: Low socioeconomic status appears to be single most important factor favouring H. pylori infection, although the exact mode of spread is still speculative. Until more carefully planned epidemiological studies are available this will remain enigmatic.

Since iatrogenic spread through contaminated endoscopes may spread the infection, meticulous care in disinfection procedures must be followed.

The low prevalence of H. pylori in association with gastroduodenal diseases reported from this country is likely to be due to inadequate or faulty diagnostic techniques.

More studies are required to evaluate drug resistance from various regions to assess the magnitude of the problem and to formulate drug regimens.

Bajrang Pratap: Prevalence rates differ in different parts of the country and depend on age, socioeconomic status, sanitation, and the method used for diagnosis. At our center, H. pylori prevalence was 54% using the rapid urease test in persons with non-upper GI symptoms. In another study from Hyderabad using serology, 80% of the population up to the second decade were positive for H. pylori irrespective of the gender; this reflects present or past exposure to H. pylori. The prevalence we found in disease states is as follows: duodenal ulcer 85%, gastric carcinoma 6%, gastric ulcer 6%, gastric lymphoma 0%, non ulcer dyspepsia 56%, dental plaque 5%.

S P Thyagarajan:

Table 1: Cumulative data on H. pylori culture positivity rates in different disease groups

<table>
<thead>
<tr>
<th>Center</th>
<th>Total</th>
<th>DU</th>
<th>CU</th>
<th>NUD</th>
<th>Gastric Ca</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucknow</td>
<td>1744</td>
<td>12/18</td>
<td>02/03</td>
<td>07/14</td>
<td>03/05</td>
<td>03/04</td>
</tr>
<tr>
<td>Chennai</td>
<td>560/10</td>
<td>34/47</td>
<td>09/14</td>
<td>12/22</td>
<td>01/02</td>
<td>02/25</td>
</tr>
<tr>
<td>Chandigarh</td>
<td>325/8</td>
<td>04/11</td>
<td>01/06</td>
<td>27/41</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hyderabad</td>
<td>171/34</td>
<td>70/100</td>
<td>01/05</td>
<td>94/19</td>
<td>05/00</td>
<td>01/04</td>
</tr>
<tr>
<td>Varanasi</td>
<td>20/20</td>
<td>16/33</td>
<td>02/04</td>
<td>06/17</td>
<td>04/09</td>
<td>03/02</td>
</tr>
<tr>
<td>Total</td>
<td>3146/616</td>
<td>136/309</td>
<td>15/29</td>
<td>146/313</td>
<td>13/25</td>
<td>04/40</td>
</tr>
<tr>
<td>% positivity</td>
<td>50</td>
<td>44</td>
<td>52</td>
<td>47</td>
<td>52</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 2: Bacteriological data on H. pylori isolates

<table>
<thead>
<tr>
<th>Cultures</th>
<th>Chennai</th>
<th>Hyderabad</th>
<th>AIIMS Delhi</th>
<th>PGI Chandigarh</th>
<th>SGPGI Lucknow</th>
<th>BHU Varanasi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>6/33</td>
<td>103/334</td>
<td>24/72</td>
<td>24/72</td>
<td>24/120</td>
<td>11/54</td>
</tr>
<tr>
<td>Dental plaques</td>
<td>2/33</td>
<td>0/194</td>
<td>0/68</td>
<td>0/69</td>
<td>1/23</td>
<td>0/22</td>
</tr>
<tr>
<td>Metronidazole resistant</td>
<td>85%</td>
<td>100%</td>
<td>100%</td>
<td>12%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Molecular study of representative isolates is in progress in three centers in India (PGIBMS, Chennai; AIIMS, New Delhi and PGI Chandigarh). The preliminary results reveal that isolates from patients with proven acid-peptic disease or gastric carcinoma behave differently in terms of their virulence factors — vacuolating/cell adherent factor studies. An in-house ELISA for IgG antibodies has been standardized and awaits evaluation by the participating centers.