GASTROENTEROLOGY IN INDIA

Helicobacter pylori in the Indian Environment

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Introduction
The first few years after the discovery of Helicobacter pylori saw a spurt of interest in India in the methods for diagnosis of the infection as well as in prevalence studies amongst various population groups; this was followed by a search for forms of therapy against the organism and thus for duodenal ulcer (DU). Along with these, other studies on disease association gave an insight into the problems in this country, and how they differ from the situation in the West.

This article reviews the data on this organism from India, and is based on a search of the literature through Medline. The key words used were Helicobacter pylori, Campylobacter pylori, peptic ulcer, duodenal ulcer, dyspepsia, India under the term 'title', and India and names of major Indian cities under 'address'. Indian medical journals not indexed by this agency, and publishing articles on related subjects, were also scanned. Abstracts of papers presented in national conferences were reviewed. Emphasis is given to articles that provided insights or revealed unique aspects of the problem in this country.

Epidemiology
The pattern of H. pylori epidemiology in India differs from that observed in developed countries. Exposure occurs in the early years, and almost all adults have evidence of previous exposure; more than half the population has active colonization by the age of 20 years.

Population studies
Among asymptomatic volunteers, H. pylori was found in antral biopsy specimens in 60-70%10,12 significantly, gastritis was present in about 80% of these subjects.9 Another study9 however found a much lower association of H. pylori with gastritis, and suggested that the organism may actually be a quiet resident of the gastric mucosa in most of our subjects. Gill et al12 found that 46% of subjects without acid-peptic symptoms but with other indications for endoscopy had evidence of H. pylori infection on antral biopsy; the peak prevalence (70%) was in the age group 20-40 years.

IgA and IgG anti-H pylori antibodies5 indicating present or past infection, were detected in 22% and 48% respectively of children in the first five years of life. Workers from Hyderabad4 found that over 80% of subjects in the second decade had had exposure to H pylori; the overall population prevalence was 84% irrespective of gender and the presence or absence of symptoms.

These studies indicate a high exposure rate to H pylori early in life in India. Some workers5,10 have interpreted this pattern to suggest possible feco-oral transmission. A higher rate of positive serology than of microbiological evidence of active infection may suggest clearance of the organism in some cases, either spontaneously or in response to anti-microbial agents administered for other indications.

Prevalence in acid-peptic diseases
H. pylori was found on antral biopsy10 in 65% of 526 patients with dyspepsia. In patients with dyspepsia or ulcer disease, Narivadekar et al10 found the overall incidence of H. pylori by rapid urease test (RUT) to be 90%, with no major differences across the age ranges. The prevalence of H. pylori infection was similar in subjects with dyspepsia irrespective of whether they were tobacco chewers or not.8

Dental plaque as a reservoir
H. pylori could be cultured from dental plaques in all the 40 Indian volunteers in whom it was tested,7 and in 98% of patients with dyspepsia,10 suggesting that the plaque may be an important reservoir of the organism in our population. Simultaneous antral H. pylori was found in 70% of the dyspeptic cases.10 These data contrast with reports from Western countries where the organism was found in the plaque in only a small proportion of subjects tested.11 The contribution of dental plaque to transmission or recurrence of infection remains to be established, but poor oral hygiene may add to the risk arising from unhygienic environs.

Most of the studies on epidemiology have been conducted at public hospitals, catering mainly to the lower and lower-middle social classes. It would be interesting to know whether the frequency and the age of acquisition are different in the higher socioeconomic
groups with better hygienic environs.

Diagnostic techniques

Culture
In probably the first published report from India, Nair et al from Calcutta could culture Helicobacter (then Campylobacter) pylori from only two of 31 antral biopsies from patients with dyspepsia. In their initial studies, Nanivadekar et al., considering only culture positivity as diagnostic, demonstrated a very low frequency of H. pylori positivity in patients with acid-peptic disease and they postulated that the organism may not be an important factor in the pathogenesis of DU in India. A year later, the same authors however showed a high prevalence of H. pylori by the RUT.

These early reports on H. pylori culture were discouraging because H. pylori is a fastidious organism, with isolation often marred by contaminant overgrowth. With improved techniques, in more recent studies the yield of culture has risen to 60-90% in tissues positive for the RUT.

Rapid urease tests, histopathology and cytology
On comparing the different techniques for diagnosis, some authors found histopathology to be superior to the RUT; staining by the Warthin-Starkey technique gave better results (66%) than the standard hematoxylin-eosin stain (47%). Other authors found the yield with urease tests to be similar to or better than histopathology.

Nanivadekar et al. found in their early studies that the RUT became positive by 4 h in only 70% of cases. Khanna et al. compared the efficacy of urea media with nutrients (Christensen's medium) and without nutrients in the detection of H. pylori. Both these media had sensitivity and specificity rates of 90% to 100%, when read at the end of 1 hour. Using three different media for the RUT, viz liquid urea broth containing phenol red or bromothymol blue as indicator and the commercial CLO gel, Bhasin et al. found that the liquid urea broth gave quicker results as compared to CLO gel (3 min vs 101 min); the type of indicator used did not make a difference.

Crushed smear cytology has been found to be a sensitive test, giving positive results in 80-100% of cases. A 76% concordance was found between cytology and histopathology. Imprint cytology gave positivity rates similar to those with histology and higher than those with the CLO test, in a median time of 60 min, making this a convenient and reliable diagnostic method.

All the above tests require endoscopy to be performed. Non invasive tests like breath tests and detection of serum antibody are also available but have not gained much popularity in India, probably because of the cost involved and, in the former case, the non availability of facilities for radioisotope studies.

Radioisotope tests
Pulmonary 14CO2 excretion after a dose of labelled urea was found to be 100% specific and 83% sensitive in the diagnosis of H. pylori infection. Measurement of 14CO2 in 24-h urine and of 14CO2 in 15-min breath sample was also reliable for the detection of viable H. pylori colonization.

Immunologic tests
Intradermal test: Kumar et al. injected 0.1 mL of sonicated H. pylori intradermally and found a mean induration of 4.4 mm at 48 h in 27 of 36 patients with dyspepsia who were positive for H. pylori. This test, though seemingly easy, has not been used extensively for the diagnosis of H. pylori.

Serological tests for detection of anti H. pylori antibodies have been used for epidemiology studies, as stated earlier. Dixit et al. found that anti-H. pylori serology was only 75% sensitive and 93% specific as compared to culture and histology combined.

H. pylori and acid-peptic diseases
Acid and gastrin secretion
Median acid secretion in the first two hours after a meal was lower in H. pylori-negative patients; however, the difference was not significant. The authors concluded that H. pylori has no effect on acid secretion.

Post-meal gastrin levels were reported to be higher in a small number of dyspeptic subjects who had H. pylori in the gastric body and antrum, as compared to those who had the organism only in the antrum.

Chronic gastritis
Many years before H. pylori had been identified in the West, Desai et al. reported certain distinct features of gastritis and achlorhydria in Indian subjects (reviewed in Ref 27). In retrospect, these features could be attributed to H. pylori infection.

Sudden onset of achlorhydria with atrophic gastritis in patients with Zollinger-Ellison syndrome and duodenal ulcer was reported by Desai et al.; later analysis of some of the previous biopsies showed evidence of H. pylori. In 1986, Desai et al. reported development of chronic gastritis and a decrease in stimulated acid secretion in 18 of 32 subjects who underwent repeated studies over 5 years. In three of these individuals, the gastritis had developed over 1-2 months.

Some studies showed that chronic gastritis in India
was rarely accompanied by polymorphonuclear infiltration,\textsuperscript{13,32} even in patients with dyspepsia of 4 weeks' duration or less. The local mucosal response to infection by \textit{H pylori} was thought to be different in Indian patients. Other studies gave different results.\textsuperscript{21,33,34} Singh \textit{et al.}\textsuperscript{33} for example, found that about half the patients with histologic gastritis had evidence of polymorphonuclear infiltration, with significantly higher \textit{H pylori} positivity in these patients (88\% vs 43\%).

\textbf{Peptic ulcer}

Except in the earlier studies, \textit{H pylori} has been detected in the antrum in the vast majority of patients with duodenal or gastric ulcer.\textsuperscript{31,35} However, one group of workers\textsuperscript{36} found a low frequency of gastric metaplasia and of \textit{H pylori} in the duodenum, in contrast to reports from the West.

A study by Gupta \textit{et al.}\textsuperscript{37} suggested that \textit{H pylori} did not affect gastric mucus production but increased cellular proliferation and cell shedding.

\textbf{Non-ulcer dyspepsia}

There has been speculation about the role of \textit{H pylori} in the causation of dyspepsia. Khanna \textit{et al.}\textsuperscript{38} found \textit{H pylori} in 74\% of patients with non ulcer dyspepsia (NUD); gastritis and duodenitis were present in most patients but was not related to \textit{H pylori} status. In a study from north India,\textsuperscript{39} \textit{H pylori} could be detected in 62\% of antral biopsies and 42\% of fundal biopsies. Presence and severity of antral gastritis have been found to correlate with the presence and density of \textit{H pylori}.\textsuperscript{17,20}

The distribution of nonsecretor status in \textit{H pylori} positive and negative dyspepsics was similar to that of the general population.\textsuperscript{38} Blood group A had a negative association, and O a positive association, with presence of \textit{H pylori}.\textsuperscript{38}

\textbf{\textit{H pylori} and other disease associations}

\textbf{Carcinoma of the stomach}

The prevalence of carcinoma stomach is low in India though the population prevalence of \textit{H pylori} is high; chronic atrophic gastritis, considered a marker of malignancy in the West, is also not uncommon here. Though \textit{H pylori}-carcinoma stomach coexistence is high in India,\textsuperscript{39,40} which is not surprising considering the high \textit{H pylori} prevalence in the general population, the infection has a low association with intestinal metaplasia in Indian subjects.\textsuperscript{39,40} This may explain the low prevalence of carcinoma stomach.

\textbf{Portal hypertension}

In the presence of vascular ectasia in portal hypertension, Navinadevan \textit{et al.}\textsuperscript{41} found a higher prevalence of \textit{H pylori} (50\% vs 20\%). They felt that vascular ectasia altering mucosal microcirculation and reducing PGE\textsubscript{2} secretion was the cause for increase in \textit{H pylori} in these patients. In another study, the severity of portal hypertensive gastropathy was independent of the presence of \textit{H pylori} infection.\textsuperscript{42} \textit{H pylori} was associated with severe gastritis.

\textbf{Other diseases}

Gastric metaplastic tissue in ileo-cecal tuberculosis was rarely colonized by \textit{H pylori},\textsuperscript{43} and Meckel's diverticulum was not.\textsuperscript{44} In chronic renal failure, Siddeshi \textit{et al.}\textsuperscript{45} found gastric \textit{H pylori} in 40\% of cases; colonization was unrelated to the presence of gastritis.

\textbf{RUT} was found to be positive in 15 of 27 children (3-14 years) with recurrent abdominal pain, only one of whom had a DU.\textsuperscript{46}

\textbf{Treatment}

\textbf{In vitro studies}

Bhatia \textit{et al.}\textsuperscript{47} observed that the growth of \textit{H pylori} was suppressed by the presence of \textit{Lactobacillus acidophilus} or the supernatant of its culture broth, and also by lactic acid, a major catabolic product of \textit{L acidophilus}. However, a subsequent study by our group\textsuperscript{48} showed no effect of \textit{L acidophilus} supplementation \textit{in vivo} on \textit{H pylori} status in patients with DU.

In an attempt to determine if the colonization by \textit{H pylori} was influenced by the type of associated gastric flora, Nair \textit{et al.}\textsuperscript{49} studied the flora in dyspeptic subjects with and without \textit{H pylori}. They found no difference except for a higher prevalence of \textit{Staphylococcus aureus} in subjects with \textit{H pylori}.

Bhasin \textit{et al.}\textsuperscript{50} showed that the addition of anti-ulcer medications to urea broth influenced the reaction of the RUT, suggesting a possibility that therapy with these drugs may lead to erroneous results with RUT.

Data from our department\textsuperscript{51} and elsewhere\textsuperscript{52} indicate a high prevalence of resistance of \textit{H pylori} to the antimicrobial agents commonly used in anti-\textit{H pylori} treatment regimens, viz metronidazole, ampicillin, amoxycillin and erythromycin. An early report of antibiotic sensitivity in two culture specimens\textsuperscript{12} had shown that the organism was sensitive to most of the common agents then; though the number studied was small, the results may also reflect greater antibiotic sensitivity at that time.

\textbf{In vitro studies}

Eradication of \textit{H pylori} has been one of the treatment
modalities for dyspepsia in the past few years. Using colloidal bismuth alone, Khanna et al. found that relief of symptoms was achieved in over 80% of patients at the end of one month, with H. pylori clearance in 70%. Bismuth alone in similar dosage could eradicate H. pylori in 25% of dyspeptic patients whereas norfloxacin and a combination of amoxycilllin and tindazole failed to eradicate the organism. In the presence of active gastritis, 20 of 21 cases cleared the organism with bismuth therapy, with return of the mucosa to normal.

Tindazole (600 mg bid) alone cleared H. pylori in only two of 16 cases with peptic ulcer or gastritis, while amoxycillin alone (500 mg bid) cleared the organism in 21 of 25 cases; four of the patients who cleared the organism had also received ranitidine. Omeprazole alone was found to eradicate H. pylori and heal gastritis and DU in 64% of patients. No such effect on H. pylori was found in another study.

To overcome problems with drug resistance, dual and triple drug therapy have been tried. The higher cost and incidence of side-effects were offset by better clearance rates. In patients with NUD, triple drug therapy (bismuth, tetracycline and metronidazole) improved clinical symptoms and gastritis when compared to sucralfate. A similar triple drug regime healed ulcers in 93%, with H. pylori eradication in 67%. Combinations using omeprazole and other antimicrobials for shorter durations gave similar results with fewer side-effects.

H. pylori eradication in antral mucosa by triple drug therapy was not associated with eradication of the organism in the dental plaque.

In patients with DU resistant to H2-receptor antagonists, colloidal bismuth alone healed ulcers in 73% of cases and H. pylori clearance occurred in 75%.

Relapse of H. pylori

Over a three-month follow-up period, Nanivadekar et al. found that the relapse of H. pylori infection was lower with a bismuth-amoxycillin combination as compared to bismuth alone for eradication of the organism.

The same workers followed up 66 patients with healed DU after H. pylori eradication. A majority of these patients had evidence of H. pylori re-infection and ulcer recurrence within months of the initial eradication. Dayal et al. found 16% ulcer recurrence over 11 months in patients in whom H. pylori had been eradicated. These studies lend credence to the argument that H. pylori eradication may be a largely futile exercise in countries with poor hygiene.

There has been little basic research directed towards H. pylori in India; while this may be an appropriate assigning of priorities, it leaves lacunae in our knowledge of differences in species and pathogenicity that may exist. Research in other areas has not lagged behind that in the West. In fact, in some areas, e.g., documenting the occurrence of spontaneous achlorhydria and gastritis, identification of the dental plaque as a reservoir, and recognizing the emerging antibiotic resistance of the organism, our research workers have highlighted problems specific to the country.

Conclusions

H. pylori infection in India, as in the underdeveloped European countries, is widespread, probably as a consequence of poor hygiene. This probably suggests fecal-oral transmission especially since the organism has now been isolated in the feces from dyspeptic patients with antral H. pylori colonization. The dental plaque as an important sanctuary for the organism in India also probably reflects poor hygiene. This may not only increase the risk of cross-infection because of the impenetrability of the site to the common systemic antimicrobials, but may also be a source of self-re-infection.

Another disconcerting feature is the increasing in vitro resistance of the organism to the antimicrobials commonly used against it. This may reflect the fact that these drugs are all available over-the-counter in India and are subject to misuse.

The bottom line, of course, is a debate on whether eradication is desirable in India in the first place. With studies showing high re-infection rates, and no study able to document a permanent 'cure' for DU unlike in the West, eradication may be a futile exercise, at least till better hygiene can be ensured.

The association of H. pylori in India with other gastrointestinal problems, eg stomach carcinoma or lymphoma, does not appear significant with present evidence, again questioning the benefits from eradication.

Scope for further research

There are no data available on the intrafamilial spread of H. pylori or its prevalence in the higher socio-economic strata in India.

A search for forms of control in the community context may be a worthwhile strategy against this organism in the long term, if its association with serious disease states is more convincingly established.

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