Helicobacter pylori infection in India: the case against eradication

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Helicobacter pylori infection is common in the Indian subcontinent. Exposure occurs in childhood and approximately 80% of adults have been infected at some time. Sero-surveys indicate a seroprevalence of 22%-57% in children under the age of five, increasing to 80%-90% by the age of 20, and remaining constant thereafter.1-4

More than 10 years following the initial report of H. pylori gastritis, the National Institutes of Health, USA, recommended H. pylori eradication as the standard of care in treatment of duodenal ulcer (DU) and gastric ulcer (GU) associated with H. pylori infection,5 and evidence suggests that eradication of the organism reverses some low-grade MALT lymphomas of the stomach. Innovative investigators have attempted to implicate H. pylori infection in the causation of a variety of diseases ranging from vascular disease to bile duct cancers. Against this background, it is not surprising if some practising physicians take the view that the organism must be eradicated whenever detected.

Duodenal ulcer

The strongest indication for eradication of H. pylori is in patients with duodenal ulcer; 90%-95% of Indian subjects with duodenal ulcer are positive for H. pylori compared to 80% of asymptomatic healthy individuals in the community.6 Elegant studies from the West showed that eradication of H. pylori resulted in healing of ulcer, and that H. pylori-related DU did not recur unless there was recurrence (either recrudescence or re-infection) of the infection. Thus, Marshall et al showed that H. pylori eradication resulted in greater DU healing rate (92% vs. 61%) and lower 12-month relapse rate (21% vs. 84%) than non-eradication.7 In a meta-analysis of 34 trials with 3910 patients, eradication therapy was superior to drugs causing acid inhibition in healing DU (RR 0.66) and superior to placebo (RR 0.20) in prevention of ulcer recurrence.8 Studies from India suggest that between 75%-90% of DU in India heal with antibiotic therapy aimed at H. pylori eradication.9,10

Ulcer relapse rates after antibiotic therapy may be slightly higher in India than those reported in the Western literature. For instance, after an 11-month follow up, 5 of 31 (16%) patients who became H. pylori negative had DU relapse compared to 8 of 12 patients (67%) who remained H. pylori positive.9 Nanivadekar et al reported that among 66 cases with healed DU under follow up and undergoing 152 endoscopic examinations, ulcer relapse was seen in 6 of 61 (10%) examinations without recurrence of H. pylori infection and in 58 of 91 (63%) examinations with recurrence of H. pylori infection.11

Gastric disease – ulcer, cancer and MALT lymphoma

Studies in Western populations indicate definite roles for H. pylori eradication in the management of gastric ulcer disease and low-grade MALT lymphoma of the stomach. A meta-analysis revealed that eradication therapy was similar in efficacy to ulcer-healing drugs (RR 1.32) in healing GU and superior to no treatment (RR 0.28). There is no evidence to suggest that eradication of the organism is useful in patients with gastric cancer or high-grade gastric lymphoma. No studies on this aspect are available from India, presumably because of the lower incidence of gastric ulcer and MALT lymphoma relative to duodenal ulcer disease. Prevention of gastric cancer in high-incidence communities by identifying and treating infected subjects in the community has been advocated as a possibility,12,13 but there is no objective evidence to support this suggestion.

Reflux esophagitis

A negative association has been shown between H. pylori infection and gastro-esophageal reflux disease.14 This protection has been attributed to the tendency for H. pylori infection to lower gastric acid secretion with advancing age of the individual. On the other hand, concern has been expressed that prolonged proton-pump inhibitor therapy in H. pylori-infected subjects might increase the risk of gastric cancer.15,16 At present, it is unclear whether H. pylori infection should be eradicated in patients with gastro-esophageal reflux disease.17 There are no data on this subject from India.

Non-ulcer dyspepsia

Most studies have not shown any role for eradication
of *H. pylori* infection in non-ulcer dyspepsia. A recent meta-analysis of 17 randomized controlled trials that included 3186 patients concluded that there was an 8% relative risk reduction in dyspeptic symptoms after *H. pylori* eradication.\(^{18}\) This implied that by treating 18 patients with dyspepsia using antibiotics it would be possible to cure one patient permanently. In the only study from India that examined the role of eradication in non-ulcer dyspepsia, *H. pylori* eradication therapy was superior to sucralfate in providing symptom relief (81% vs. 33%); relief lasted for about 12 weeks.\(^{19}\)

**Uninvestigated dyspepsia in primary care**

Guidelines of several associations and societies for primary-care physicians now include a “test-and-treat” approach towards *H. pylori* infection in primary care without documentation of ulcer disease.\(^{20,21,22}\) This approach is restricted to patients under the age of 50 or 55 years with ulcer-like dyspepsia and without ‘alarm’ symptom such as weight loss or hematemesis. It has been suggested that this “test-and-treat” strategy is preferable in populations with infection rates higher than 10% in the general population.\(^{22}\) However, a recent Cochrane Database Systematic Review did not find significant evidence to favor this approach, concluding instead that it would increase costs in primary care and would not improve symptoms.\(^{23}\)

### Is *H. pylori* eradication effective in the Indian setting?

The environment in India is contaminated and gastrointestinal infections – symptomatic and asymptomatic – are very common. Secondly, antibiotic use or misuse is widely prevalent; the resultant high frequency of antibiotic resistance implies that treatment regimens for *H. pylori* eradication may not be effective. Due to cost considerations, one of several fixed-dose combinations of proton-pump inhibitor with amoxicillin and tinidazole is the most widely prescribed *H. pylori* eradication therapy in clinical practice in India. In these fixed-dose combinations the dose of amoxicillin is suboptimal, being 750 mg BID rather than 1 g BID as recommended.

In a multi-center study from India, 259 isolates of *H. pylori* were tested for *in vitro* susceptibility to antibiotics; of these, 77.9% had resistance to metronidazole, 44.7% to clarithromycin, and 32.8% to amoxicillin.\(^{24}\) In another study of 67 clinical isolates of *H. pylori* from Kolkata, 85% were resistant to metronidazole and 7.5% to tetracycline, but most were sensitive to clarithromycin, furazolidone and amoxicillin.\(^{25}\) These high rates of antibiotic resistance imply that eradication rates of *H. pylori* infection in most Indian patients treated with fixed-drug combinations are likely to be less than those reported in the Western literature.

Data on *H. pylori* eradication rate in Indian patients are available from several clinical trials (Table). Many of these trials used a single test (rapid urease test) to determine clearance of *H. pylori* infection. When rigorous criteria (i.e., a combination of negative urease test, negative histology and negative urea breath test) were applied, as in a prospective trial from northern India, the eradication rate was considerably lower.\(^{30}\) In this trial, 146 patients were randomized to receive either lansoprazole, amoxicillin and tinidazole or lansoprazole, amoxicillin and clarithromycin. Using an intention-to-treat analysis, only 31% and 46% of patients receiving the two combinations respectively had eradication of *H. pylori* infection.

Second, rates of recurrence of *H. pylori* infection may be expected to be high in India. *H. pylori* re-infection rates are very low in Western populations,\(^{31}\) being less than 0.5 per patient-year. In one Indian study of 45 patients followed up following eradication of *H. pylori*, recurrence of infection was detected in only one patient (2.4%) after one year.\(^{28}\) However a rigorous search was not performed to detect recurrent infection. The only other full publication on re-infection in the Indian literature suggests that recurrence of infection occurs in around 60% of patients.\(^{11}\)

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**Table: Helicobacter pylori eradication rates after antibiotic treatment**

<table>
<thead>
<tr>
<th>Authors*</th>
<th>Treatment regimes</th>
<th>Number</th>
<th>Time of testing</th>
<th>HPE rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dayal(^ {19}) 1997</td>
<td>BC/T4/M</td>
<td>57</td>
<td>1 month</td>
<td>54</td>
</tr>
<tr>
<td>Ahuja(^ {10}) 1998</td>
<td>LAS</td>
<td>21</td>
<td>6 and 12 weeks</td>
<td>86</td>
</tr>
<tr>
<td>LCS</td>
<td>18</td>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPS</td>
<td>21</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhasin(^ {24}) 1999</td>
<td>OC</td>
<td>22</td>
<td>1 month</td>
<td>68</td>
</tr>
<tr>
<td>OAC</td>
<td>20</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC/A/M</td>
<td>22</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhasin(^ {27}) 2000</td>
<td>LAC 2 weeks</td>
<td>24</td>
<td>1 month</td>
<td>96</td>
</tr>
<tr>
<td>LAC 1 week</td>
<td>22</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bapat(^ {26}) 2000</td>
<td>O/BC/T4/F</td>
<td>50</td>
<td>3 months</td>
<td>82</td>
</tr>
<tr>
<td>Pai(^ {29}) 2003</td>
<td>LAC</td>
<td>35</td>
<td>1 month</td>
<td>82</td>
</tr>
<tr>
<td>L/BC/T4/M</td>
<td>33</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhatia(^ {10}) 2004</td>
<td>LAT</td>
<td>70</td>
<td>1 month</td>
<td>31</td>
</tr>
<tr>
<td>LAC</td>
<td>76</td>
<td>41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Eradiation has not been uniformly defined in these studies. HPE = *H. pylori* eradication. A = amoxicillin. BC = tripotassium dichlorate bismuthate. C = clarithromycin. L = lansoprazole. M = metronidazole. O = omeprazole. S = seemidazole. T = tinidazole. T4 = tetracycline. Wherever possible, intention-to-treat figures have been calculated for eradication rate.

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\(^{18}\) Gupta S, Rege D, Prabhu S, et al. Meta-analysis of randomized controlled trials of *Helicobacter pylori* eradication therapy in clinical practice. 20, 21, 22


**Should H. pylori infection be eradicated?**

Despite the paucity of Indian data on recurrence rate of *H. pylori* infection, it is possible for the treatment protagonists to argue that patients with DU and GU who harbor *H. pylori* should receive therapy to eradicate this infection. This argument must be tempered with the realization that the drug combinations used most commonly to treat this infection in Indian practice are relatively inefficient. Widespread use of antibiotics is likely to further increase the prevalence of antibiotic resistance in the community, and this undesirable outcome needs to be balanced against the low possibility of therapeutic benefit to the individual.

There is an increasing thrust for universal eradication of *H. pylori*. A long-established study in the UK was recently reviewed and interpreted to suggest that there is economic benefit in taking the battle for *H. pylori* eradication to the community. There are clear arguments against adopting such a practice in India. Helicobacter infections are highly prevalent in the gastrointestinal tracts of mammals. In man, there is evidence to suggest that *H. pylori* infection is probably present since time immemorial. The organism is well adapted to humans, with persistent infection and low-level disease, suggesting that for the most part it has a commensal rather than a pathogenic relationship with man.

*H. pylori* strains are genetically highly diverse, and certain markers of virulence in *H. pylori* have been identified. It is likely that most individuals in the community have infection with avirulent strains of *H. pylori*, which may in fact be beneficial to the host. For example, heightened gastric acidity produced by many *H. pylori* may act as a barrier to ingested pathogens. They may produce as yet unknown factors that may stimulate innate immune pathways in the host and protect against other pathogens. They may also exert biochemical effects on the host that are yet to be elucidated. Infection with the organism is most common in populations with poor sanitary and hygiene conditions; in developed societies with better sanitation and hygiene, the levels of infection are lower. Associated with this increasing level of hygiene, there is a higher incidence of allergic and autoimmune diseases including asthma and Crohn’s disease. It is possible therefore that *H. pylori* infection may protect populations in countries such as India from the allergic and autoimmune diseases that are increasingly prevalent in the developed world.

Until we better understand the nature of the *H. pylori* organism and its relation to the human host in (the majority of) asymptomatic individuals, indiscriminate eradication of this infection is likely to do more harm than good at the community level.

**References**

16. Jensen RT. Consequences of long-term proton pump blockade: insights from studies of patients with gastrinomas.


