Eradication of *Helicobacter pylori* in nonulcer dyspepsia

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**Nonulcer dyspepsia (NUD)** is defined as pain or discomfort in the upper abdomen in the absence of structural cause on clinical and endoscopic evaluation. NUD is found in nearly 20% to 40% of the normal population in Western countries. In a population-based study of over 2400 subjects in Mumbai, we found that approximately 10% complained of significant dyspepsia, with abdominal pain and fullness as the most common symptoms.1

**Does *Helicobacter pylori* have a role in NUD?**

The evidence that *H. pylori* plays a role in the pathogenesis of NUD is not convincing. In India, the prevalence of *H. pylori* infection varies between 30% and 80% among patients with NUD. This rate, though high, is comparable to that among healthy subjects. The prevalence in the general population is higher in subjects from developing countries as compared to those from industrialized countries; yet, the incidence of NUD is similar.2

Secondly, *H. pylori* is the most frequent cause of chronic gastritis, which is a common histologic finding among patients with NUD. However, the severity of *H. pylori*-associated gastritis does not correlate with that of symptoms. Further, whereas *H. pylori* infection and consequent gastritis are persistent, symptoms of NUD are often intermittent, and there is no temporal relationship between *H. pylori* infection, gastritis, and the onset of symptoms.3

Thirdly, *H. pylori* infection has been shown to be associated with gastric acid hypersecretion, dysmotility and hypersensitivity in a subset of patients; these abnormalities have previously been shown to be associated with and are considered as possible responsible for NUD symptoms.4,5 Small intestinal sensory thresholds are also lower in NUD, but these have no relation with *H. pylori* status.6 The effects of *H. pylori* infection on gastroduodenal motility or sensation are inconsistent and eradication of infection has not resulted in consistent improvement in these parameters. Also, asymptomatic infected subjects can have similar abnormalities.

Several other factors have been implicated in the pathogenesis of NUD. These include visceral hypersensitivity, psychiatric disorders, infection with parasites like *Giardia lamblia*, dietary and other environmental factors. Treatment directed at these factors has been shown to ameliorate NUD symptoms. For instance, anxiolytic drugs were shown to be superior to *H. pylori* eradication.7 Symptom response also occurs after eradication of giardia.8 A large proportion of NUD patients have relief of symptoms with administration of placebo.9 Also, many of these patients respond to cytoprotective agents like sucralfate10,11 and prokinetic agents,12 irrespective of *H. pylori* status. Some patients with NUD also have associated symptoms of irritable bowel syndrome1 and evidence of gall bladder dysmotility,4 which are irrespective of the *H. pylori* status.

Thus, NUD is not a single disease but a syndrome which has been classified into subtypes based on symptomatology. *H. pylori* infection has not been shown to be associated with any one subtype. In fact, there is no difference in the nature of symptoms among patients with *H. pylori* infection and those without.1,13

**Results of *H. pylori* eradication in NUD**

Very few studies have systematically evaluated the effect of *H. pylori* eradication on symptom relief. Most initial studies were uncontrolled or used only colloidal bismuth subcitrate (CBS) for *H. pylori* clearance.10,11 In addition, most of the studies concentrated on the efficacy of eradication of *H. pylori* rather than on clinical improvement.

Initial short-term studies using *H. pylori* eradication therapy showed benefit in terms of symptoms as well as healing of gastritis in a subgroup of patients with NUD. However, most of these studies had major limitations. In 1994, Talley15 identified 16 published trials of *H. pylori* eradication in NUD; 8 reported that anti-*H. pylori* therapy was efficacious whereas 8 did not detect significant benefit in symptoms. Limitations of these trials included failure to randomize patients, absence of placebo control, lack of adequate follow up and inadequate study power in the negative studies.

Laheij et al16 reviewed 10 studies of NUD treatment; symptom improvement was found in 73% of patients who became *H. pylori*-negative and 45% of those who remained *H. pylori*-positive. McCarthy et al17 found that improvement in symptoms following *H. pylori* eradication persisted at one year after therapy. Jaakkimainen et al18 reviewed 5 trials published between January 1983 and March 1999; they found that the odds ratio for improvement in dyspeptic symptoms in patients in whom *H. pylori* was eradicated was 1.9 (95% CI 1.3 to 2.6). However, they had not included recently published long-term follow-up studies in their meta-analysis.

Studies from New Delhi19,20 showed significant symp-
tomastic improvement in most patients with NUD after _H. pylori_ eradication at short-term follow up. Other studies do not show any benefit of _H. pylori_ eradication on symptoms in patients with NUD, even though gastritis improved in these patients. On the other hand, significant improvement after _H. pylori_ eradication has been observed in patients with ulcer-like NUD even in the long term. _Lazzaroni et al._, in a placebo-controlled study, found that the symptom response to CBS and metronidazole was similar to placebo at six months, after which patients who eradicated _H. pylori_ fared better than those who did not.

Recent studies with better methodologies too failed to resolve this issue. A large, controlled study from the UK showed improvement in symptoms in 21% of NUD patients receiving _H. pylori_ eradication therapy as compared to 7% of patients who received omeprazole; the major benefit was seen in patients with short duration of symptoms. However, the authors did not divide their patients into the subgroups of NUD. Inclusion of a high number of patients at high risk of peptic ulcer may have led to an increased probability of favorable result in this study.

On the contrary, a double-blind, randomized, controlled study failed to find significant effect of _H. pylori_ eradication on symptoms; eradication therapy did not fare better than short-term omeprazole (27% vs 21% response rate) at one year. Greenberg and Cello found the change in dyspeptic symptoms at 1 year was -24.0 (95% CI, -69.0 to 21.0) in a group receiving _H. pylori_ eradication therapy and -24.2 in the placebo group (-70.0 to 21.6). Surprisingly, patients with persistent _H. pylori_ infection had a greater, but not significant, improvement in symptoms.

Talley et al. found no difference between groups in the rate of successful treatment at 12 months (relative likelihood of success with active treatment, 0.93; 95% CI, 0.73 to 1.18). The rates were also similar when patients were analyzed according to the type of dyspepsia. In another multicenter study, there was no difference between the proportion of patients treated successfully by intention to treat in the eradication arm (24%, 95% CI 17 to 32) and in the placebo group (22%, 95% CI 15 to 30). In the largest, randomized study to date, Moayyedi et al. studied more than 1000 patients in each arm; treatment for _H. pylori_ produced only a 5% reduction in dyspepsia. This small benefit had no impact on quality of life.

A study from Ireland revealed that improvement after _H. pylori_ eradication was evident in the "ulcer-like" dyspepsia group at all times, but in the "reflux-like" and "motility-like" groups at 6 months only. Schütte _et al._ found symptom improvement even in patients in whom _H. pylori_ persisted after eradication therapy; symptoms reappeared at one year irrespective of _H. pylori_ status.

There is thus inconsistent evidence that cure of _H. pylori_ infection will improve symptoms. While it is possible that _H. pylori_ may be responsible for symptoms in a small proportion of patients with NUD and in some of these cases anti-_H. pylori_ therapy may be beneficial, this remains to be established.

### Cost Considerations and Potential Risks of _H. pylori_ Eradication Therapy

The First Asian Pacific Working Party on Functional Dyspepsia recommended that "in patients without alarm features, treatment be provided for 2-4 weeks with an empirical antisecretory or prokinetic agent, followed by investigation using noninvasive _H. pylori_ testing and treatment for patients who do not respond or relapse." These recommendations may not be applicable to all populations even in this region.

In India, a few problems need to be kept in mind when deciding on the appropriateness of _H. pylori_ eradication therapy for patients with NUD. First, most subjects with NUD are likely to test positive for _H. pylori_, as indeed most healthy adults would. Thus, the use of this strategy will imply that most, if not all, patients with dyspepsia in India will have to be treated with eradication therapy, greatly increasing the cost and risk of side-effects. Second, _H. pylori_ reinfection rates after initial eradication in our population may be high (approximately 18% per year) and are likely to offset any benefit of such a strategy. Third, effective anti-_H. pylori_ combination therapy is frequently associated with adverse effects. Four, widespread use of _H. pylori_ eradication therapy, is likely to lead to appearance of antibiotic-resistant _H. pylori_ strains. That this is already happening is clear from the observation that a majority of _H. pylori_ isolates in India are resistant to nitrimidazoles, which are used indiscriminately here.

Further, we have a question of numbers. Supposing that treatment of NUD patients with evidence of _H. pylori_ infection with antimicrobial therapy is effective, given the high population prevalence of NUD (approximately 10%), and high prevalence of _H. pylori_ among these patients (approximately 80%), nearly 8% of our population will qualify for such therapy. The cost of such an undertaking will be exorbitant. Also, the effect of such a massive antimicrobial use on microorganisms cannot be estimated.

### Recommendations from Consensus Meetings

Initial recommendations from various international societies stated that eradication of _H. pylori_ infection in NUD patients is not required. The extreme recommendation was "routine endoscopic gastric biopsies looking for _H. pylori_ in patients with NUD should be abandoned." This view changed in the West after the World Health Organization declared _H. pylori_ as a carcinogen. The subsequent Maastricht meeting recommended that eradication therapy was "advisable" with "equivocal" evidence in _H. pylori_ positive NUD patients. On the other hand, the Working Party report of the Gastroenterological
Society of Singapore stated in 1996 that “NUD patients with or without H. pylori infection have identical symptom patterns and pathophysiological parameters. Studies on the efficacy of H. pylori treatment in NUD give equivocal results to date. We therefore do not recommend treatment for H. pylori in NUD”. The consensus meeting at the First National Workshop on H. pylori in India in 1997 also recommended that H. pylori does not require eradication in patients with NUD. Similar views were expressed at the Digestive Disease Health Initiative International Update Conference on H. pylori in 1997.

Summary

1. NUD is a multifactorial disorder. H. pylori may be a causative factor in only a small proportion of patients with this disease.
2. H. pylori can be detected in 50%-80% of patients with NUD in India and a similar proportion of healthy adults.
3. H. pylori eradication does not appear to benefit a majority of patients with NUD and H. pylori infection.
4. H. pylori eradication therapy in NUD is associated with significant costs and risk of adverse effects and development of antimicrobial resistance.

Recommendations

Based on current knowledge, there is little evidence to suggest a pathogenic role for H. pylori in NUD. Therefore, H. pylori eradication should not be considered in patients with NUD. However, well-designed, placebo-controlled trials should be done to identify subgroups of NUD patients who might respond to H. pylori eradication.

References

22. Gilvary J, Buckley MJ, Beattie S, Hamilton H, O’Morain CA. Eradication of Helicobacter pylori affects symptoms in...


**Comments**

K M Mohandas: Anti-*H. pylori* therapy should not be given to any patient with dyspepsia without a minimal initial work-up. This will prevent indiscriminate use of irrational schedules, which is soon going to lead to multi-drug-resistant strains. Endoscopy must be recommended in high-risk patients (e.g., those on NSAIDs, high gastric cancer region, etc.) before starting anti-*H. pylori* therapy.

V Jayanthi: Long-term follow up of *H. pylori*-positive NUD patients, especially their histologic changes, when receiving only supportive therapy, should be done.

D N Guha Mazumdar: On repeated endoscopy, some patients with NUD may show duodenal ulcer. It is possible that these patients are duodenal ulcer whose ulcer had healed at the time of presentation, due to use of over-the-counter acid or H2 blockers. These patients might be misdiagnosed as a subset of NUD, with beneficial effect from anti-*H. pylori* therapy.

K Vinayachandran Nair: A large number of patients with dyspepsia undergoing endoscopy may have gastritis and *H. pylori*. Should these patients be given eradication therapy?

S P Thyagarajan: It has recently been reported that *H. pylori* has a protective role against a spectrum of gastroesophageal reflux diseases, including Barrett's esophagus. *Am J Gastroenterol* 1998;93:1800-2.

Is there any role of HLA in affording resistance to atrophic gastritis and gastric adenocarcinoma by *H. pylori* infection? Studies (Cancer 1998;82:1013-8) have shown that the DQA1*1*02 allele may contribute to resistance against *H. pylori*-associated gastric atrophy and the intestinal type of gastric adenocarcinoma.

V G Mohan Prasad: The Maastricht Consensus Report (1997) of the European *H. pylori* study Group has extended *H. pylori* therapy to *H. pylori*-positive patients with functional dyspepsia in whom no other possible causes of symptoms are identified by the specialist.

The 1997 Asia Pacific Consensus Conference concluded that patients with NUD can be considered for treatment of *H. pylori* infection on a case-by-case basis, after discussing with the patient that the therapy may not alleviate their symptoms in the short term and may even aggravate them.

The European *H. pylori* Study Group (1998) advised empirical eradication therapy without gastroscopy in young (<45 years) *H. pylori*-positive dyspepsia patients who do not exhibit alarm symptoms.

Three of four papers presented at the Digestive Disease Week, 1998 reported no difference in symptom improvement between anti-*H. pylori* therapy and placebo.