Controversy

The case for Helicobacter pylori eradication in India: sensationalism, skepticism and scientific salesmanship

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With tenacity and a prepared mind” the duo challenged prevailing dogmas”, said a press release from the Nobel Assembly at Karolinska Institute in Stockholm, Sweden announcing that the 2005 Nobel prize in Physiology or Medicine had been awarded to Robin Warren and Barry Marshall for their discovery that a bacterium named Helicobacter pylori causes most peptic ulcers. It is somewhat discomforting that this Journal has commissioned a debate on the need for treating H. pylori infection at a time when triumph of the ulcer-bug theory formed ‘news of the week’ for many journals and even the lay press. It thus appears unjust to wield, or at least an inopportune time for wielding, a coroner’s scalpel to exhume the odyssey. Why are we still reluctant to embrace this concept? Was it an unbridled sensationalism for over a decade that has spurred a rebound vociferous skepticism?

In the year 2006, a debate on the proficiency of H. pylori eradication would be classified as an “unfair duel”. Not the David vs. Goliath kind where the underdog wins but a duel where the result is not merely a writing on the wall but is deeply etched and engraved. Nevertheless, it provides a good opportunity to place on record the evidence that has led to the acceptance of H. pylori eradication as treatment for peptic ulcer disease. In pursuit of this objective, this article will focus on four central concepts: i) Is there irrefutable evidence that H. pylori causes peptic ulcer and gastric cancer? ii) Does eradication of H. pylori infection alter the natural history of these diseases? iii) Has the beneficial effect been exaggerated? and, iv) What are the diseases in which benefit of H. pylori eradication remains unproven?

Evidence that H. pylori causes peptic ulcer and gastric cancer

Peptic ulcer

H. pylori infection has a strong association with chronic active gastritis and duodenal ulcer (DU). Ingestion of H. pylori has been shown to produce acute antral gastritis. H. pylori infection can be detected in 90% of patients with DU and 70% of those with gastric ulcers. A critique published in 1991 determined that there was strong association between H. pylori and DU, but that evidence for biological gradient and temporality and supportive experimental evidence was insufficient. Since then, plenty of new evidence has become available.

Sipponen et al showed that 11% of individuals with H. pylori infection developed DU over a 10-year follow up, in contrast to fewer than 1% of non-infected individuals. Cullen et al studied 407 subjects and showed that DU developed in 15% of H. pylori-seropositive individuals as compared to 3% of seronegative individuals. In a Scandinavian follow-up study over 10 years, 13% of patients with H. pylori gastritis developed peptic ulcer.

Koch’s first postulate states that the organism must always be found in the diseased animals and not in healthy ones. Only 15%-20% of H. pylori infected persons develop peptic ulcer disease. However, the role of indigenous biota in human diseases is often complex. For instance, Candida albicans and Bacteroides spp. are normally present in humans and yet can at times cause life-threatening disease.

Koch’s second postulate states that ‘the organism must be isolated from diseased animals and grown in pure culture away from the animal’. This postulate was fulfilled by Marshall who succeeded in culturing H. pylori, after 34 failures.

Koch’s third postulate requires that ‘the organism isolated in pure culture must initiate and reproduce the disease when re-inoculated into susceptible animals,’ and the fourth states that ‘the organism should be re-isolated from the experimentally infected animals’. Ohkusa et al experimentally inoculated Mongolian gerbils with three strains of H. pylori; all three strains induced gastric ulceration and two strains, in addition, induced gastric metaplasia in the duodenum and duodenitis. Two gerbils developed superficial duodenal ulceration; this occurred on a background of gastric metaplasia, as in humans.

The next step is a biologically and conceptually satisfying pathogenetic mechanism for production of DU by H. pylori infection; this, however, is yet to be attained. It has been proposed that the outcome of H. pylori infection may depend on the gastric...
acid secretory ability of the infected individual; thus, persons with naturally high acid secretion are prone to develop antrum-predominant gastritis and are at increased risk of DU, whereas those with low acid secretion develop colonization of gastric body with *H. pylori*, leading to multifocal atrophic gastritis and possibly gastric cancer.\textsuperscript{14}

**Gastric cancer**

Gastric carcinogenesis is a multi-step process, the key steps being chronic superficial gastritis, chronic atrophic gastritis leading to achlorhydria, intestinal metaplasia and dysplasia. An epidemiological association between *H. pylori* and gastric cancer was initially established in three prospective case-control studies and a cohort study, followed by a meta-analysis.\textsuperscript{15-18}

Watanabe *et al* studied gastric histology in Mongolian gerbils that had been experimentally infected with *H. pylori*.\textsuperscript{20} At 26 weeks post-inoculation, all infected animals showed severe active chronic gastritis, ulcers and intestinal metaplasia. By 62 weeks, adenocarcinoma had developed in the pyloric region of 37% of the infected gerbils, fulfilling Koch’s postulates for the relationship of *H. pylori* and gastric cancer. Further, in a follow up of 1526 Japanese patients, gastric cancer developed in 3\% of *H. pylori*-infected patients but in none of the uninfected patients.\textsuperscript{21}

*H. pylori* is also an important factor for gastric MALT lymphomas, although it is difficult to prove an association because of a low incidence of this disease.\textsuperscript{22}

A few befuddling questions remain. Why do only 1\% and 15\% of infected people develop gastric cancer and peptic ulcer, respectively? Why is *H. pylori* infection most prevalent among the elderly whereas peptic ulcer is a disease of the young? Why has the incidence of DU gone up in the last century, while the prevalence of *H. pylori* was on the downslide?

Attempts have been made to answer these questions. *H. pylori* has been a part of the gastric biota since antiquity. The ultra-low biological activity of its lipopolysaccharide and expression of Lewis antigens facilitate its persistence in human hosts. Changes in modern life are however gradually eliminating it from being only a commensal. Peptic ulcer disease was uncommon when *H. pylori* colonization was nearly universal. The incidence of peptic ulcer started rising, as in the last century, as the colonization rate of *H. pylori* began to decline. This increase in incidence of peptic ulcer could be related to changes in gastric microecology related to improved nutrition, changes in nature of *H. pylori* colonization, and immune response to the organism related to older age at the time of acquisition of infection. Also, differences in response of individual hosts, in strains of *H. pylori*, in environmental factors, and in age of the patient at the time of acquisition of the infection may determine the variable response to infection.

**Eradication of *H. pylori* infection and natural history of peptic ulcer disease**

The most persuasive argument in support of a pathogenic role for *H. pylori* in peptic ulcer disease relates to a dramatic decrease of spontaneous relapse rate of DU after successful eradication of infection with this organism.\textsuperscript{23} Hopkins *et al* reviewed 14 studies on DU and eight on gastric ulcer and found that ulcer recurrence was significantly less common among patients with cured *H. pylori* infection (6\% vs. 67\% for DU, 4\% vs. 59\% for gastric ulcers).\textsuperscript{24} This reduction is sustained for at least seven years following *H. pylori* eradication. Eradication of *H. pylori* also reduces the rate of recurrence of ulcer hemorrhage more effectively than does long-term maintenance treatment with either ranitidine or omeprazole.\textsuperscript{25}

The overwhelming reduction in ulcer recurrence rates after *H. pylori* eradication has made this a standard treatment for patients with peptic ulcer disease. However, epidemiological differences may restrict a simple extrapolation of these data from developed countries to developing countries. Due to a high frequency of infection, overcrowding and lower standards of hygiene, the *H. pylori* re-infection rate after treatment may be higher in the latter countries. This, combined with lower eradication rates, may partially nullify the long-term benefits of *H. pylori* eradication on the natural history of peptic ulcer disease in developing countries.\textsuperscript{26}

However, does this mean that we stop attempts at eradicating *H. pylori* infection, or should we devise more effective strategies to treat this infection and prevent re-infection? For instance, if drug resistance were frequent among patients with tuberculosis and treatment delivered poor results, would we look for alternative etiologies for such patients or rather develop more effective treatment strategies?

**Has the beneficial effect been exaggerated?**

The arguments that *H. pylori* may not be the primary cause of DU are as follows: prevalence of *H. pylori*-negative DU is increasing; early cases of DU are
more often *H. pylori* negative than chronic cases of DU; colonization of gastric metaplasia in duodenum with *H. pylori* is infrequent; and rate of recurrence of *H. pylori* infection is higher in developing countries.

One needs to recognize that *H. pylori*, though an important cause of peptic ulcer, is not the only cause. Laine’s meta-analysis showed that the 20% recurrence rate of peptic ulcers after successful eradication of *H. pylori* infection may be because non-*H. pylori*, non-NSAID induced ulcers are more common than previously believed. Therefore, ulcers in patients with *H. pylori* infection are not always *H. pylori* induced, since we are currently unable to differentiate virulent and commensal *H. pylori*.

Presence of *H. pylori* anywhere does not imply that it should be treated instantaneously. Blaser has strongly argued that *H. pylori* forms normal biota of the human stomach and infection with it should be treated selectively. He believes that *H. pylori* infection is beneficial and protects humans against gastroesophageal reflux disease and cardia cancer. Hence, elimination of *H. pylori* infection is needed only in defined settings, as discussed above. The issue would become clearer when we have accurate and convenient tests to discriminate between virulent and non-virulent *H. pylori*, somewhat akin to the situation with *Entamoeba dispar* and *E. histolytica*.

**Disease associations where benefit of *H. pylori* eradication is still unproven**

**Gastroesophageal reflux disease (GERD)**

The issues that require examination are: (i) Is there an epidemiological association between GERD and *H. pylori*? (ii) How does eradication of *H. pylori* infection affect GERD in patients with DU or reflux esophagitis, and in the healthy population? and, (iii) Does one need to eradicate *H. pylori* infection if long-term proton pump inhibitor (PPI) therapy is planned for GERD treatment?

It is not merely the presence of *H. pylori* but its density and distribution in the stomach that determine gastric acid secretion, and hence the impact of this infection on GERD. Thus, antral colonization with *H. pylori* is associated with increased gastric acid secretion and increased propensity to develop GERD. On the other hand, colonization of the gastric corpus is associated with reduced gastric secretion and may protect against GERD. Thus, both a direct and an inverse association between *H. pylori* and GERD are theoretically plausible. Raghunath et al. examined 20 studies and obtained a pooled odds ratio of 0.60 (95% CI 0.47-0.78) for the presence of *H. pylori* in patients with GERD, suggesting that *H. pylori* infection protected against GERD.

Evidence for this protective role is three-fold: theoretical plausibility, negative epidemiological association, and cagA strains having an even greater negative association. To prove the protective role of *H. pylori* for GERD, we need to (i) determine the effect of *H. pylori* eradication on GERD outcomes (reflux esophagitis and heartburn) in patients with DU, and (ii) determine the effect of *H. pylori* infection on reflux esophagitis. Data are available from 13 trials in patients with DU, which estimated proportion of patients newly developing reflux esophagitis following *H. pylori* eradication therapy. These show that *H. pylori* eradication status had no effect on rates of persistence of pre-existing GERD or fresh development of GERD. This is not surprising because patients with DU have high acid secretion, which decreases following *H. pylori* eradication. It follows that the likelihood of their developing GERD should decrease, not increase, after *H. pylori* eradication.

The next issue is the effect of *H. pylori* infection and eradication in patients with GERD. A prospective, double-blind study failed to find any difference in the severity of GERD between patients with and without *H. pylori* infection. Three randomized controlled trials have looked at the effect of *H. pylori* eradication in patients with reflux esophagitis and found no worsening of symptoms or of acid reflux. Moayyedi et al. concluded that treatment of *H. pylori* gastritis in healthy population did not lead to symptoms of GERD over a 2-year period. Hence, negative epidemiological association between *H. pylori* infection and GERD is not supported by clinical data, and *H. pylori* eradication does not induce or worsen GERD, either in patients with DU or pre-existing GERD or in the healthy population.

The last issue is whether patients receiving long-term PPI therapy for the treatment of GERD require prior *H. pylori* eradication. Administration of PPI to *H. pylori*-infected subjects induces a corpus-predominant gastritis, a recognized risk factor for gastric cancer; yet we do not know whether such corpus atrophic gastritis progresses with time. Also, eradication of *H. pylori* infection may reduce the efficacy of PPI in controlling GERD since PPI therapy has been shown to be much more potent in *H. pylori*-positive subjects. However, since eradication of *H. pylori* infection does not worsen GERD in patients with both DU and GERD, it is unlikely to harm patients with GERD alone. Thus, treatment may be used in patients who are candidates for long-term
PPI therapy, though there is no conclusive proof yet in favor of this approach.

Functional dyspepsia

Several clinical trials have studied the role of *H. pylori* infection in non-ulcer dyspepsia (NUD). However, six well-designed large studies reached contradictory conclusions, suggesting that functional dyspepsia was a heterogeneous disorder. Similarly, five meta-analyses on the subject have shown conflicting results. Interestingly, Laine et al concluded that symptom relief after *H. pylori* eradication therapy was no better than with a placebo, whereas a Cochrane systematic review showed a 9% (95% CI 4-14) relative risk reduction after *H. pylori* eradication.

This lack of consistency suggests that eradication of *H. pylori* infection may be useful in a small subset of patients with NUD. However, this argument may not be applicable globally. In particular, there are no Indian data to either support or refute a role for eradication of *H. pylori* infection in patients with NUD. Thus, it appears impractical to provide *H. pylori* eradication therapy to a huge number of *H. pylori*-infected persons with NUD till further data on the predictors of response to such treatment are available.

Conclusions

It is evident that *H. pylori* infection has a causal link with peptic ulcer and gastric cancer and that its successful eradication dramatically reduces the risk of ulcer recurrence. Therefore, an attempt at eradication of this infection should be the first-line approach for all patients with *H. pylori*-associated peptic ulcer disease.

It is quite apparent that much of the skepticism about the bug-ulcer relationship was spurred by the initial sensationalism, the exaggerated attention that *H. pylori* received soon after its discovery, and the unsubstantiated early revelry for claims of curing the disease. It is however now time to shed this skepticism and move on to embrace the scientific evidence supporting the relationship. Perhaps, George Bernard Shaw’s words sum it all well: “All great truths begin as blasphemies.”

References


