Helicobacter pylori eradication
Cost-benefit: the case against

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Helicobacter pylori is an important human pathogen, implicated in the pathogenesis of peptic ulcer disease, gastric cancer, and perhaps also in other non-gastrointestinal disease. There is little doubt that in peptic ulcer disease at least, there is a strong argument for its eradication on both clinical and economic terms. The majority of subjects infected with Helicobacter pylori never develop clinically overt disease, and it is this group that the clinical and financial benefit of eradication needs to be closely examined.

Over the last 15 years, it has become clear that Helicobacter pylori is an important human pathogen, playing a fundamental role in the pathogenesis of peptic ulceration in those patients not taking non-steroidal anti-inflammatory drugs, in the development of gastric adenocarcinoma, and in the aetiology of gastric lymphoproliferative diseases. Some authorities have also suggested that infection with this organism also contributes to the development of non-ulcer dyspepsia, ischaemic heart disease, and to growth retardation in children. Cure of infection, with modern drugs regimens, is successful in approximately 90% of cases, well tolerated, and relatively inexpensive. It is thus not surprising that recommendations for eradication of the infection have progressed from treating those with recurrent proven peptic ulcers to treating all H. pylori infected persons regardless of symptoms or underlying disease. There is, therefore, considerable confusion among gastroenterologists and primary care physicians regarding when and who to treat with eradication therapy. Despite the unquestioned clinical benefit of eradication of H. pylori in peptic ulceration, available data suggest that less than 20% of infected individuals will ever develop clinical consequences of their infection. Treatment strategies which support widespread and non-selective use of eradication therapy would necessarily involve treating large numbers of subjects who would not experience clinical benefit from such treatment while imparting a considerable financial burden on an already stretched health service. Therefore, before we can recommend widespread eradication of H.
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*pylori*, careful consideration of clinical risk/benefit and of economic implications associated with non focused eradication strategies is required.

There are several clinical situations in which eradication of *H. pylori* may be considered appropriate and it is perhaps valuable to consider these groups individually.

**Peptic ulcer disease**

The most widely reported benefit of *H. pylori* eradication has been in uncomplicated peptic ulcer disease. Many studies have now confirmed that eradication of infection substantially reduces recurrence of both duodenal and gastric ulceration\(^2,11,12\). These data have resulted in a statement from the National Institute of Health that endorses the use of antimicrobial agents in combination with antisecretory agents to treat ulcer patients whether on first presentation or on recurrence of the illness\(^13\). Assessment of the economic implications of *H. pylori* eradication in peptic ulcer patients has been hampered by the lack of head-to-head trials of eradication treatment versus traditional treatment. As a result, most studies examining the financial implications of *H. pylori* eradication therapy have adopted decision analysis models which, through the integration of available information from the literature and assumptions based on clinical practice, provide a plausible conclusion where such information is otherwise unavailable.

Using such pharmaco-economic modelling techniques, several studies have now examined the potential benefits of *H. pylori* eradication in proven ulcer disease compared to a strategy of maintenance or intermittent antisecretory therapy. Economic benefits of eradication therapy in the short-term and over the period of 5–10 years have been confirmed in both American and European populations\(^14,16\). Regardless of the cost of such an approach, however, the clinical benefits of *H. pylori* eradication therapy in duodenal ulceration are probably sufficient to overshadow any unfavourable economic argument. Thus, in this group at least, we can confidently support a policy of widespread *H. pylori* eradication.

**H. pylori without peptic disease**

The vast majority of individuals infected with *H. pylori* does not have, or will never have, evidence of peptic ulceration. It is in this much larger group that the economic benefit of *H. pylori* eradication must be closely examined. Although the prevalence of *H. pylori* in patients with dyspepsia is of the order of 40–60%, some studies have shown a similar
or even higher incidence of infection in an equivalent asymptomatic population\textsuperscript{17,18}. Indeed, despite considerable effort to demonstrate benefit of eradication in this group, there is little evidence in the literature, to date, that eradication of the organism leads to improvement in symptoms and, by inference, lower health care costs.

Support for empirical eradication of \textit{H. pylori} in dyspeptic patients comes from several other decision analysis based studies\textsuperscript{16-19}. A strategy of empirical eradication appears to be economically advantageous when the alternative involves endoscopic intervention followed by appropriate treatment. However, when non-interventional strategies are compared, \textit{e.g.} empirical eradication versus empirical antisecretory therapy, there is little to separate these approaches in financial terms\textsuperscript{20}. Thus, in patients with \textit{H. pylori} infection but without evidence of peptic disease, there is at present little evidence to suggest that widespread treatment confers either a clinical benefit, or is financially advantageous.

\textbf{\textit{H. pylori} and gastric cancer prevention}

Although there are no controlled data supporting diagnosis and treatment of \textit{H. pylori} in the absence of peptic disease, the recent convincing epidemiological evidence linking long-term \textit{H. pylori} infection to gastric cancer raises questions on the clinical and/or economic benefits of eradication with regard to cancer prevention\textsuperscript{3-4}. Recently, some investigators have recommended treating patients at increased risk of cancer, such as those with precursor lesions, a family history of gastric cancer or patients undergoing long term proton pump inhibitor therapy\textsuperscript{21}. However, no data exist at present to demonstrate that screening and eradication of \textit{H. pylori} decreases gastric cancer incidence in asymptomatic individuals. Indeed, it is doubtful whether eradication facilitates reversal of established histological precursor lesions, such as atrophy or metaplasia\textsuperscript{22,23}. Indirect evidence of benefit of eradication in terms of cancer prevention stems from the finding that gastric mucosal proliferation is decreased following successful treatment\textsuperscript{24,25}, thereby presumably decreasing the frequency of mutational events thought to be associated with carcinogenesis. There is also some suggestion that, in Japanese populations, \textit{H. pylori} eradication may reduce the incidence of metachronous gastric neoplasia in patients undergoing endoscopic mucosal resection of early gastric cancer\textsuperscript{26}. Nonetheless, definitive evidence of clinical benefit of eradication in preventing gastric cancer lies in population based treatment trials. Although several such studies are underway, results must be awaited before any firm recommendations can be made.
Parsonnet and colleagues have explored the potential cost-effectiveness of *H. pylori* screening to prevent gastric cancer again using a decision analysis model\(^27\). In this model, the cost of a screening and eradication strategy in three groups with a low, average, and high probability of gastric cancer were analysed. Assumptions included a 90% efficacy of treatment and no progression to cancer would occur if treatment was successful. Their data suggest that, if using optimistic estimates of the effects of eradication on gastric cancer risk, screening individuals at the age of 50 years would cost approximately $25,000 per life saved. Cost efficacy declined considerably if the effects of treatment were less optimistic, or in younger age groups due to the lower prevalence of *H. pylori* and accruement of other costs. Thus, although their study suggests a possible benefit of screening and eradication in older adults with a high risk of gastric cancer, widespread screening and treatment of adults cannot be recommended until further studies support this approach.

Because of the association of *H. pylori* with both malignancy and peptic disease, there is increasing effort to justify global eradication of the organism. These organisms are extremely diverse, however, both at a genetic level and in the pathologies with they are associated. Recently, it has become clear that *H. pylori* strains vary in their ability to induce clinically significant disease. For example, *cagA*\(^+\) strains are more virulent than *cagA*\(^-\) strains, and more likely to be associated with peptic ulceration\(^28,29\) and gastric cancer\(^30\), leading to the possibility that some strains are in fact avirulent. This suggests that the risk-benefit of screening and eradication may not be uniform and, in some cases, the benefits may actually be low or even non-existent.

What about the possibilities that *H. pylori* eradication may be detrimental to the host? Given that the majority of persons with *H. pylori* are asymptomatic and suffer no clinical consequence from their infection, the 10% morbidity associated with treatment will, in some patients at least, outweigh any benefit from treatment. Furthermore, Labenz and colleagues have recently shown that the development of reflux oesophagitis in patients with peptic ulceration who have had the organism eradicated was almost twice that in those treated with conventional antisecretory therapy\(^31\). This would suggest that *H. pylori* may, in fact, protect against reflux disease and impact negatively against widespread eradication in financial terms. This hypothesis is also supported by epidemiological data. For example, the observed decrease in the prevalence of *H. pylori* infection in developed countries\(^32\) is paralleled by an increasing incidence of oesophageal cancer as a result of reflux disease\(^33\). Additionally, reflux oesophagitis is uncommon in black populations\(^33\) who have a high incidence of *H. pylori* infection\(^34\).

Recent studies also suggest that *H. pylori* induced gastritis may protect from cancer in the cardia\(^35\).
Does *H. pylori* infection confer any benefit to the host? Apart from perhaps offering some protection against reflux disease as outlined above, there is little evidence to date that long-term infection with this organism does us any good. However, there is a growing body of evidence that humans have been colonised with *H. pylori* for perhaps thousands of years\(^\text{36}\). Conventional evolutionary theory would suggest that microbial parasitism often tends towards symbiosis with carriage conferring some benefit to the host. Selection would certainly not favour survival of strains that cause substantial mortality before the end of reproductive life in humans. It is, therefore, not unreasonable to postulate that colonisation with the organism provides some, as yet, unrecognised benefits. For example, in African populations, it is possible that low-grade chronic infection protects against more serious, potentially fatal, enteric infections perhaps by upregulating the immune system or by increasing acid secretion. Gastric acid is known to offer some protection against enteric infection. Certainly, *Salmonella* and *Campylobacter* infections are more common when gastric acid production is reduced pharmacologically or surgically\(^\text{37,38}\).

## Conclusion

Although certain *Helicobacter pylori* strains are clearly pathogenic to humans, and a strong economic argument can be made for eradication in certain circumstances, such as proven or suspected peptic disease, we are, I believe, some way off recommending global eradication of the organism. Both in financial terms and in clinical terms, we may yet discover that not all *Helicobacter* organisms are dangerous and that some are better left well enough alone!

## References

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