Risks and benefits of *Helicobacter pylori* eradication: Current status

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In patients with diseases known to be associated with *Helicobacter pylori* infection, such as peptic ulcer, treatment of the underlying infection is the standard of care. However, in most major consensus management guidelines, including those published in Canada, widespread testing for *H pylori* infection is not recommended. This practice is not encouraged because of insufficient evidence of cost-benefit in gastric cancer prevention, the potential for increases in antibiotic resistance and the controversial hypothesis of potential negative effects of eradication in certain clinical entities. For example, there is insufficient evidence to recommend against eradicating *H pylori* discovered in a patient with symptoms of gastroesophageal reflux disease. The management guidelines designed specifically in Canada should, therefore, continue to be applied, with *H pylori* diagnosed and treated in appropriately selected patients.

Key Words: Helicobacter pylori; *Peptic ulcer*

Le point sur les risques et les avantages de l'éradication d'*Helicobacter pylori*

RÉSUMÉ : Chez les patients dont la maladie est associée à *Helicobacter pylori*, par exemple, dans l'ulcère gastro-duoénal, on commencera d'abord par traiter l'infection sous-jacente. Or, en consultant la plupart des principales directives thérapeutiques consensuelles, y compris les directives canadiennes, on constate que le dépistage d'emblée de l'infection à *H. pylori* n'est par recommandé car il n'a pas été prouvé qu'il est rentable de prévenir le cancer de l'estomac, il existe un risque de faire augmenter la résistance aux antibiotiques et selon une hypothèse controversée, dans certaines entités cliniques, l'éradication aurait des effets potentiellement négatifs. Ainsi, on ne dispose pas preuves suffisantes pour recommander l'éradication de *H. pylori* chez un patient qui présente des symptômes de reflux gastro-œsophagien. Les directives thérapeutiques conçues spécifiquement au Canada doivent, par conséquent, continuer d'être appliquées et le cas échéant, on traitera l'infection à *H. pylori* chez certains patients sélectionnés.

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The discovery that the eradication of *Helicobacter pylori* infection leads to the cure of peptic ulcer disease was a milestone in patient care, prompting consensus groups around the world to develop treatment guidelines. The Canadian *Helicobacter* Study Group (CHSG) was organized in 1997 to bring together family physicians, gastroenterologists, pharmacists, pediatricians, infectious disease experts and basic scientists with an interest in *H pylori* and its diseases. Guidelines for Canada were first published by the CHSG in 1998 and were updated in 1999 (1,2); these were followed by pediatric guidelines in 1999 (3). An important recommendation in the Canadian guidelines, as in those published elsewhere in the world, is to screen and treat *H pylori* infection in all patients with duodenal or gastric ulcers, whether they are symptomatic or asymptomatic (4,5). There is controversy as to whether patients with dyspepsia benefit from *H pylori* eradication, but it seems that a small proportion (up to 15%) of such patients benefit from treatment (6). To date, however, screening is not recommended in asymptomatic individuals. Although *H pylori* infection inevitably leads to gastritis and is associated with gastric cancer, a favourable change in clinical outcome from eradication has not yet been demonstrated in these persons without an established *H pylori*-related disease (7,8).

Newly published information may help resolve uncertainty about the clinical significance of *H pylori* infection in asymptomatic individuals, and it is reasonable to review advances in this field periodically. At the most recent meeting of the CHSG – convened in Ottawa, June 2 to 4, 2000 – the goal was to determine whether any new factors in the relationship between *H pylori* infection and the human host warrant a change in the clinical recommendations in Canada, which now include adult care (1,2), pediatric care (3) and the approach to antibiotic-resistant *H pylori* infections (9). The meeting was not intended to provide any new recommendations from those previously published (1) in this journal (Table 1).

As at prior meetings, there was broad representation of relevant interest groups. Participants included adult and pediatric gastroenterologists, infectious disease specialists, family physicians, clinical pharmacologists, pathologists and basic science researchers (Appendix 1). Specialists with expertise in *H pylori* research were invited from Europe and the United States. Observers representing the pharmaceutical industry and government were also present. The consensus conference, which was organized by CHSG, was also endorsed by representation from the Canadian Association of Gastroenterology, the Canadian Digestive Disease Foundation, the Canadian Pediatric Society, the Canadian Infectious Diseases Society and the Canadian Society for Clinical Investigation.

TABLE 1
Summary of the recent previous recommendations of the Canadian *Helicobacter* Study Group

Treatment recommendations

- All *Helicobacter pylori*-positive patients with duodenal or gastric ulcer, whether symptomatic or asymptomatic, should receive eradication treatment. Eradication is recommended whenever there is known *H pylori* infection.
- All *H pylori*-positive patients with gastric MALToma should receive eradication treatment.

Recommended therapies

- Twice daily, seven-day regimen of a PPI (omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg) or RBC 400 mg, clarithromycin 500 mg and amoxicillin 1000 mg; or
- A twice daily, even-day regimen of a PPI or RBC, clarithromycin 500 or 250 mg, and metronidazole 500 mg.

Endorsed therapies

- A twice daily, seven-day regimen of a PPI, metronidazole 500 mg and amoxicillin 1000 mg; or
- A twice daily, 14-day regimen of bismuth subsalicylate two tablets qid, metronidazole 250 mg qid and tetracycline 500 mg qid (BMT)

Treatment failure in patients who received metronidazole in the first course

- A twice daily, seven- to 14-day regimen of a PPI or RBC, amoxicillin 1000 mg and clarithromycin 500 mg; or
- A 14-day course of a PPI plus BMT.

Treatment failure in patients who received amoxicillin in the first course

- A PPI or RBC, metronidazole 500 mg and clarithromycin 500 mg; or
- A 14-day course of a PPI plus BMT

BMT Bismuth plus metronidazole plus tetracycline; MALToma Mucosal-associated lymphoid tissue lymphoma; PPI Proton pump inhibitor; RBC Ranitidine bismuth citrate

BACKGROUND

Evidence that peptic ulcer disease associated with *H pylori* infection can be cured with the eradication of the infection is unequivocal (1,2). There is also good evidence that eradication of *H pylori* results in the resolution of mucosa-associated lymphoid tissue lymphoma (MALToma) in about three-quarters of these patients (10,11). Each of these conditions justifies testing for *H pylori*, and if the test results are positive, treatment with a recommended eradication regimen. In addition, testing for and treating *H pylori* has been recommended as an approach to uninvestigated dyspepsia in young adults with no alarm features. Due to the risk of peptic ulcer disease from *H pylori* infection, and the association of *H pylori* infection with gastric MALToma and gastric cancer, eradication has been considered appropriate whenever, and for whatever reason, infection has been diagnosed.

However, screening and treatment have not been recommended for asymptomatic individuals. The costs and risks of large scale eradication strategies must be balanced against the estimate that only approximately 15% of infected individuals develop clinically significant *H pylori*-related disease in their lifetime. The estimated prevalence

of *H pylori* infection in Canada is about 20% but exceeds 40% in older persons and in some subgroups, including immigrants from developing countries and indigenous ethnic groups (12).

Despite considerable advances in knowledge about the relationship between *H pylori* infection and the human host, many aspects of the host response remain unknown. It is not known why so many infected individuals do not develop clinically significant disease. Indeed, there is speculation that, in some individuals, there may be a symbiosis between the presence of *H pylori* and gastrointestinal function (13).

The discovery that the eradication of *H pylori* infection can reduce risk in patients with *H pylori*-related disease has led to important improvements in patient care. However, an incomplete understanding of the consequences of eradication suggests that caution must be exercised where clinical studies have been inadequate to provide guidance. For example, there may be a benefit in treating *H pylori* infection to prevent the development of cancer in some individuals. However, large scale clinical trials have not yet been completed to prove that this is the case.

H PYLORI: ROLE AS A THERAPEUTIC TARGET

H pylori infection has been considered by most authorities to be a legitimate therapeutic target in anyone with a known infection. Proponents of the diagnosis and treatment of *H pylori* infection, regardless of the presence of an *H pylori*-related disease, cite the opportunity to reduce several health risks, including peptic ulcer disease, MALToma and gastric cancer. The initial concerns expressed by opponents to population-based eradication strategies are related to the costs and the risks of treatment. In particular, there is concern that indiscriminate use of antibiotics in a large number of infected asymptomatic individuals could dramatically increase the rates of antibiotic resistance, including the development of antibiotic resistance among other bacterial pathogens. Concern has also been raised about the possibility that the cure of *H pylori* may lead to the development of gastroesophageal reflux disease (GERD) or worsen existing GERD. Indeed, there is controversial evidence that some *H pylori* infections could provide benefit to the host, particularly in affording protection against GERD (14,15).

GERD

The potential that cure of *H pylori* infection could increase the risk of GERD complicates efforts to calculate a risk to benefit ratio for an asymptomatic individual. The balance is particularly problematic if an uncertain risk of developing gastric cancer and peptic ulcer is weighed against an uncertain likelihood of the patient developing GERD, which itself is a risk factor for adenocarcinoma of the esophagus (16).

The potential for an association between *H pylori* eradication and an increased risk of GERD was first reported in a retrospective analysis (14). In this study, the risk of erosive esophagitis was twofold higher in *H pylori*-positive patients with duodenal ulcer in whom *H pylori* infection was successfully eradicated than in those in whom it was not eradicated (26% versus 13%, $P<0.001$). In a retrospective analysis of a prospective trial conducted in Canada (15), both GERD symptoms and esophagitis were almost three times more prevalent in patients whose eradication therapy failed than in those in whom *H pylori* infection was cured (37% versus 13%, $P=0.04$). In contrast, a double-blind, randomized, controlled trial presented in abstract form did not show an increased risk of development of GERD after eradication of *H pylori* (17). Other trials have also not substantiated a relationship between the eradication of *H pylori* and the development of GERD (18,19). Indeed, in one study, eradication of *H pylori* was associated with a reduced risk of heartburn, although this study was not specifically designed to address GERD (20).

One possible explanation for the disparity in results between studies is a failure to control for the presence of pre-existing GERD. It has been suggested that symptoms of GERD may be unmasked in some individuals once the more pronounced symptoms of peptic ulcer are controlled by eradication of the *H pylori* infection. However, some studies, including one conducted in Canada (21), excluded patients taking antisecretory agents or those with known esophagitis. This diminishes the likely influence of this confounding variable of pre-existing GERD.

Also, it has been suggested that these discrepant findings may be explained by differences in the virulence of *H pylori* strains (22). The hypothesis that the most virulent strains of *H pylori* are present in those with peptic ulcer disease and that such patients are at a low risk of GERD evolved from evidence that greater bacterial virulence is associated with more inflammation in the gastric corpus. This, in turn, would be expected to inhibit acid secretion and, thus, decrease the subsequent risk of GERD (23). In fact, *cag*A has been associated with a reduced rate of Barrett's esophagus (23). In Canada, a prospective trial demonstrated an inverse relationship between the presence of virulent strains, with the *cag*A and *vac*A S1 genotypes, and the presence of GERD (15).

GASTRIC CANCER

Epidemiological evidence indicates that *H pylori* infection increases the risk of gastric adenocarcinoma by a multiple of 1.7 to 4.0 (24,25). Postulated mechanisms include changes in the cell cycle, molecular characteristics and alterations in immune function induced by chronic gastritis, together with environmental factors. Chronic gastritis may progress to mucosal atrophy, intestinal metaplasia and then dysplasia, from which adenocarcinoma can arise. However, the absolute risk of cancer is determined by multiple cofactors, including both genetic and environmental factors.

Eradication of *H pylori* infection has not yet been shown to prevent gastric cancer because the interventional studies aimed at assessing this have not had sufficient time to

detect a benefit. However, eradication prevented progression of gastric atrophy, which may be a cancer precursor (26,27).

GASTRIC PATHOLOGY AND LONG TERM USE OF PROTON PUMP INHIBITORS

The hypothesis that eradication of *H pylori* infection in duodenal ulcer patients increases the risk of GERD remains very controversial. The potential for *H pylori* infection of the fundus of the stomach to provide protection against GERD is one of the most frequently cited examples of a possible symbiosis between infection with this organism and the human host (13,28). The idea that the presence of *H pylori* is part of the indigenous microbial flora of the human stomach is based on the observation that more than half of the human population is infected (13). Although infection rates are relatively low in Westernized countries, this appears to be a phenomenon confined to the past century, when environmental changes, particularly improvements in hygiene, reduced the prevalence of *H pylori* infection (8,28).

The relationship between the risks posed by *H pylori* infection, GERD and gastric adenocarcinoma is further complicated by studies suggesting that the long term use of proton pump inhibitors (PPIs) for the treatment of GERD can influence progression of atrophic gastritis in people infected with *H pylori* (27). Not all prospective trials support this suggested relationship (29); however, some leaders in the field are increasingly advocating the eradication of *H pylori* infection in patients with GERD who require long term treatment with PPIs to maintain symptom control.

Controversies surrounding the possible relationship among *H pylori* infection, GERD and PPI therapy were not addressed in the 1999 revised guidelines (1). However, the available data do not permit definitive statements to be made. The risk posed by eradication of *H pylori* infection for GERD has not been proven, and would not preclude treatment in the presence of peptic ulcer disease or gastric MALToma. Similarly, the clinical significance of gastric atrophy in patients on long term PPI therapy is unknown and cannot be shown, with the available evidence, to pose a great enough threat to require routine testing and eradication in patients being considered for this treatment.

Overall, the major recommendations in the revised CHSG guidelines regarding the diagnosis and treatment of *H pylori* infection remain intact (1). The study of the relationship between *H pylori* infection and the human host is an evolving field. Therefore, future discoveries could substantially alter current concepts about the significance of asymptomatic infection.

CONTROVERSIES IN *H PYLORI* ERADICATION AND CURRENT GUIDELINES

Emerging controversies about the relationship between *H pylori* infection and the human host warrant a review of our current management guidelines. In Canada, where the prevalence of *H pylori* infection is decreasing and an increasing proportion of peptic ulcers are caused by factors other than *H pylori* (30,31), it is appropriate to ensure that the risks and benefits support existing guidelines. As outlined in previous consensus recommendations (1,2), testing for *H pylori* infection should be performed in patients suspected of having an *H pylori*-related peptic ulcer. In addition, testing should not be performed to detect the presence of *H pylori* without an intention to treat if the test result is positive. In the more recent published guidelines, *H pylori* eradication was recommended in asymptomatic patients whose infection becomes known by any means (1). These recommendations remain appropriate (Table 1).

In patients with *H pylori*-associated disease, there is no evidence that the expected benefits of treatment have changed. In patients with peptic ulcer disease, eradication of *H pylori* infection is cost effective. In addition, the risks posed by untreated ulcer disease, including the complications of bleeding, perforation and death, should be markedly reduced (32-34). In patients with MALToma, eradication is associated with disease regression in the majority of patients followed over two years and, in some individuals, may be associated with cure of the disease (10,11).

The widely used test and treat strategy in patients with symptoms of dyspepsia is a subject of ongoing debate. In patients under the age of 50 years with chronic dyspepsia but no alarm signals (such as unexplained weight loss or evidence of bleeding), noninvasive testing for *H pylori* infection and then treating the infection if the results are positive is cost effective and safe (35-37). This cost-benefit ratio is achieved through a reduction in the need for referrals to specialists to perform diagnostic upper gastrointestinal endoscopies or follow-up office visits, and in the cost of medications. However, other trials have suggested that eradication of infection only adds, at most, a small benefit (5% to 25%) for patients with nonulcer dyspepsia (NUD) (38-40).

It is important to distinguish NUD (investigated) from uninvestigated dyspepsia. The most comprehensive meta-analysis to date on the question of the benefit of treating *H pylori*-positive NUD was recently published (6). The Canadian Adult Dyspepsia Empirical Treatment, *H pylori* Positive (CADET-*Hp*) program study of patients with uninvestigated dyspepsia showed that 50% of patients randomly assigned to anti-*H pylori* treatment had long term symptomatic benefit, compared with 30% in the placebo group ($P<0.02$) (35).

CONCLUSIONS

The relationship between *H pylori* infection and the human host is proving to be complex. Risks posed by infection may involve differences in host susceptibility and relative virulence of *H pylori* strains, as well as other factors yet to be identified. Although some patients tolerate life-long infection without apparent clinical consequences, it is important to recognize that *H pylori* infection can pose a significant health risk that can be diminished by eradication treatment

in appropriately selected patients. The management guidelines designed specifically for Canada should continue to be applied to both improve patient care and decrease the risk of disease complications arising from *H pylori* infection.

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