

# Update on the role of *H pylori* infection in gastrointestinal disorders

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**H Chaun.** Update on the role of *H pylori* infection in gastrointestinal disorders. *Can J Gastroenterol* 2001;15(4):251-255. Infection with *Helicobacter pylori* is accepted as the primary cause of peptic ulcer disease, and there is evidence to suggest its role in other gastrointestinal disorders. An estimated 20% to 40% of the Canadian population is infected with *H pylori*; however, clinically relevant disease is present in only approximately 10% to 20% of these individuals. Therefore, it is crucial to identify the diseases for which eradication of *H pylori* is beneficial to ensure that patients do not receive unnecessary treatment. In patients with ulcers induced by long term treatment with nonsteroidal anti-inflammatory drugs, preliminary results suggest that eradication of *H pylori* may reduce the risk of peptic ulcer bleeding. Furthermore, a benefit has been observed for the eradication of *H pylori* before patients commence therapy with a nonsteroidal anti-inflammatory drug. An association between the presence of *H pylori* and specific dyspeptic symptoms has yet to be established; however, there may be a subset of patients with functional dyspepsia who benefit from the eradication of *H pylori*. The relationship between gastroesophageal reflux disorder and *H pylori* infection remains unclear. In Canada, the recommended therapy for the eradication of *H pylori* is seven days of twice-daily treatment with a proton pump inhibitor, clarithromycin, and amoxicillin or metronidazole. Although the proton pump inhibitors are treated as a class for use in these regimens, there is suggestion that a faster onset of action may lead to a higher rate of eradication.

**Key Words:** Functional dyspepsia; Gastroesophageal reflux disease; *Helicobacter pylori*; Peptic ulcer disease

## Rôle de l'infection à *H. pylori* dans les troubles gastro-intestinaux : mise à jour

**RÉSUMÉ :** L'infection à *Helicobacter pylori* est reconnue comme la principale cause de l'ulcère gastro-duodéal mais, selon certaines preuves, elle jouerait également un rôle dans d'autres troubles gastro-intestinaux. De 20 à 40 % des Canadiens et Canadiennes seraient infectés à *H. pylori*, mais seulement de 10 à 20 % d'entre eux souffriraient d'une maladie clinique liée à sa présence. Aussi importe-t-il de cerner les maladies pour lesquelles la suppression d'*H. pylori* s'avérerait bénéfique afin d'éviter de faire subir des traitements inutiles aux patients. Des résultats préliminaires donnent à penser que la suppression d'*H. pylori* réduit les risques d'hémorragie chez les patients porteurs d'ulcères gastro-intestinaux dus à la prise prolongée d'anti-inflammatoires non stéroïdiens (AINS). Elle s'est même avérée bénéfique avant l'amorce d'un traitement aux AINS. D'autres liens entre la présence d'*H. pylori* et certains symptômes de dyspepsie restent à établir, mais il n'est pas impossible que des patients souffrant de dyspepsie fonctionnelle tirent profit de la suppression d'*H. pylori*. Le lien entre l'infection à *H. pylori* et le reflux gastro-oesophagien n'est pas encore clairement élucidé. Le traitement recommandé, au Canada, pour la suppression d'*H. pylori* consiste en l'administration, deux fois par jour, d'un inhibiteur de la pompe à protons, de clarithromycine et d'amoxicilline ou de métronidazole, et ce, durant une semaine. Même si les inhibiteurs de la pompe à protons sont traités comme une classe de médicaments dans ce type de traitement, il semblerait que l'application encore plus rapide de mesures se traduirait par un taux plus élevé de suppression.

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The discovery in the early 1980s that *Helicobacter pylori* was associated with peptic ulcer disease (1) prompted investigations of its possible implication in other gastrointestinal disorders, such as nonsteroidal anti-inflammatory drug (NSAID)-induced ulcers, functional dyspepsia, gastroesophageal reflux disease (GERD), gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer.

In Canada, the prevalence of *H pylori* in the general population is estimated to be 20% to 40% (2). However, clinically relevant disease is present in only 10% to 20% of these individuals, which complicates the identification of patients in whom *H pylori* should be eradicated (2). This review explores the current status of the role of *H pylori* in peptic ulcers, NSAID-induced ulcers, functional dyspepsia, GERD, gastric MALT lymphoma and gastric cancer.

### PEPTIC ULCERS

*H pylori* is accepted as the primary cause of non-NSAID-induced peptic ulcer disease, with an estimated prevalence of 95% in patients with duodenal ulcers and 84% in patients with gastric ulcers (3). Indeed, eradication of *H pylori* in patients with both duodenal and gastric ulcers facilitates ulcer healing, reduces the rate of ulcer recurrence and reduces the risk of peptic ulcer bleeding (4,5). However, evidence is limited regarding the role of *H pylori* eradication in improving the symptoms associated with peptic ulcers.

McCull and colleagues (6) evaluated the effect of *H pylori* eradication on dyspeptic symptoms in 97 patients with active peptic ulcers. After a follow-up of one to three years, dyspeptic symptoms resolved in 55% of the 86 patients in whom *H pylori* had been successfully eradicated. No change in dyspeptic symptoms was observed in the 11 patients in whom eradication therapy was unsuccessful. Stratification of the 86 successfully eradicated patients for the presence of GERD before treatment demonstrated that dyspeptic symptoms resolved in significantly fewer patients who had GERD than patients who had no evidence of GERD (27% versus 68%, respectively;  $P < 0.01$ ). Therefore, it appears that eradication of *H pylori* assists in symptom resolution in patients with peptic ulcers but that symptom improvement is limited in patients with coexisting GERD.

The abundance of evidence for the relationship between the presence of *H pylori* and peptic ulcer disease is reflected in the current Canadian Consensus Guidelines, which recommend the eradication of *H pylori* in all patients with confirmed *H pylori* infection and past or current peptic ulcer (2). In Canada, seven days of twice-daily treatment with a proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole is currently recommended for the eradication of *H pylori*. Management strategies may change in the future because of the increase in the proportion of patients in the United States with non-NSAID-related ulcers who are not infected with *H pylori*, but Canadian data are necessary before a change is warranted (7).

### NSAID-INDUCED ULCERS

NSAID use is implicated in approximately 10% to 30% of peptic ulcers, with an increased risk of ulcer in older NSAID users, patients with previous peptic ulcer, and patients who use steroids, high doses of multiple NSAIDs or anticoagulants (8). The role of *H pylori* in NSAID-induced ulcers is less clear, but some evidence exists to imply that eradication may be indicated in these patients.

The prophylactic eradication of *H pylori* in patients before treatment with the NSAID naproxen was evaluated by Chan and colleagues (9). The investigators randomly assigned 100 *H pylori*-positive patients to eight weeks of treatment with naproxen ( $n=50$ ) alone or to a one-week course of eradication therapy (bismuth subcitrate, tetracycline, metronidazole [ $n=50$ ]) before treatment with naproxen. All patients had no prior exposure to NSAID therapy and did not have pre-existing ulcers. Of the 92 patients who completed the trial, 12 (13%) treated with naproxen alone and three (3.3%) treated with eradication therapy developed ulcers ( $P=0.01$ ). It was concluded that eradication of *H pylori* before treatment with NSAIDs reduced the incidence of NSAID-induced peptic ulcers.

The results of a study conducted by Hawkey and colleagues (10) appear to contradict the findings of Chan et al (9). In this study, the eradication of *H pylori* in long term users of NSAIDs with prior or current peptic ulcer disease or dyspepsia did not affect the incidence of peptic ulcers or dyspepsia. However, unlike the trial by Chan et al (9), the eradication therapy in the trial by Hawkey et al (10) did not contain bismuth, a substance that may have cytoprotective properties.

One of the more dangerous complications of NSAID-induced peptic ulcers is the risk of bleeding or perforation of the ulcer. A case controlled study evaluating the association of *H pylori* infection and bleeding peptic ulcers in current users of NSAIDs (including analgesic or antithrombotic doses of acetylsalicylic acid [ASA]) determined that NSAID users who were infected with *H pylori* had almost two times the risk of bleeding compared with those who were not infected with *H pylori* (11). The results of this study suggest that infection with *H pylori* is an independent risk factor for peptic ulcer bleeding in NSAID users. Furthermore, prospective evaluation of whether eradication of *H pylori* reduces the risk of recurrent peptic ulcer bleeding in high risk NSAID users demonstrated that eradication of *H pylori* protects against recurrent bleeding of peptic ulcers in ASA users but not in other NSAID users (Table 1) (12).

The implication of *H pylori* in NSAID-related peptic ulcers requires further elucidation before eradication in such patients is universally indicated. Therefore, treatment with acid suppression is still required to promote ulcer healing and may also be used as prophylaxis once ulcers have healed. The current Canadian Consensus Guidelines recommend testing for *H pylori* and eradication therapy in all patients who present with peptic ulcers but do not recommend prophylactic eradication in ulcer-free patients who

**TABLE 1**  
**Comparison of maintenance acid suppression therapy with eradication of *Helicobacter pylori* for the prevention of recurrent bleeding of peptic ulcers in high risk users of nonsteroidal anti-inflammatory drugs (NSAIDs) or specifically acetylsalicylic acid (ASA)**

	NSAID users		ASA users	
	PPI	Eradication therapy	PPI	Eradication therapy
Number of patients	53	47	34	29
Gastric ulcer	29	19	23	15
Duodenal ulcer	24	28	11	14
Rebleeding	1/46 (2%)*	8/41 (20%)	1/31 (3%)	1/27 (3%)
Death	1 (2%)	0 (0%)	2 (6%)	1 (3%)

\*P<0.01. PPI Proton pump inhibitor. Data from reference 12

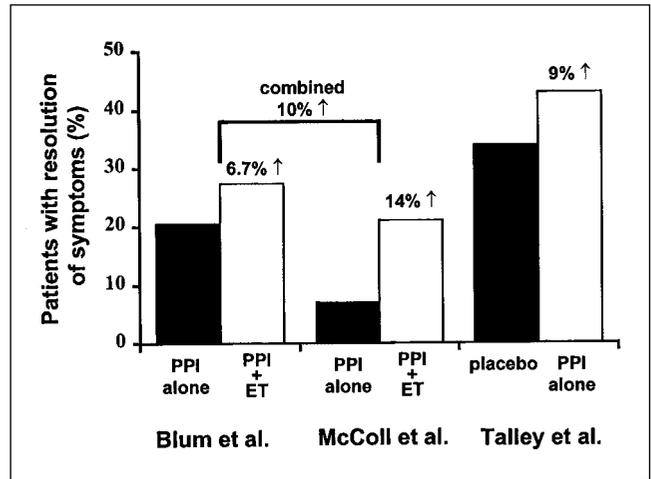
will be starting or are currently using NSAIDs (2). However, the Canadian guidelines do recommend prophylactic mucosal protection in patients with a high risk of developing NSAID-induced ulcers (2).

**FUNCTIONAL DYSPEPSIA**

Dyspepsia, characterized by pain and discomfort centred in the upper abdomen, is a common gastrointestinal complaint, with an annual prevalence of up to 40% in Western countries (13). However, a probable cause of dyspeptic symptoms is only evident in approximately 50% of cases (14). Thus, a high percentage of patients suffer from functional dyspepsia, defined as three or more months of dyspepsia with no structural or biochemical explanation for the symptoms. The possible pathophysiological and etiological factors implicated in functional dyspepsia include increased acid secretion, disordered motor function, dysfunction of the central nervous system, altered visceral sensitivity and infection with *H pylori* (13).

Gastritis induced by *H pylori* is present in 30% to 60% of patients with documented functional dyspepsia; however, this incidence rate is similar to that of the general population, and attempts at linking the presence of *H pylori* with a specific symptom profile have proved to be inconclusive (13,14). Although studies have demonstrated that patients with functional dyspepsia experience prolonged gastric emptying and higher gastric sensitivity than healthy control subjects, no difference in these findings was observed between patients with functional dyspepsia who were infected with *H pylori* and those who were not (15,16). Similarly, in an evaluation of patients with dyspeptic symptoms and chronic superficial antral gastritis, Testoni and colleagues (17) found no correlation between the presence of *H pylori* and specific symptom complaints or worsening dyspeptic symptoms.

Investigation into whether eradication of *H pylori* improves the symptoms associated with functional dyspep-



**Figure 1** The effect of eradication of *Helicobacter pylori* on symptoms of functional dyspepsia. ET Eradication therapy; PPI Proton pump inhibitor. Data from references 18-20

sia has provided interesting results. In a large, multicentre study conducted by Blum and colleagues (18), 328 patients with functional dyspepsia and confirmed infection with *H pylori* were randomly assigned to receive one week of eradication therapy with a PPI plus amoxicillin and clarithromycin, or one week of treatment with a PPI alone. Although the proportion of patients without gastritis was significantly higher in the patients treated with eradication therapy than in those treated with a PPI alone (75.0% versus 3.0%, respectively; P<0.001), treatment success, defined by the overall relief of dyspeptic symptoms, was similar between the groups (27.4% versus 20.7%, respectively; P=0.17). Thus, at one year, dyspeptic symptoms had resolved in 6.7% more patients treated with eradication therapy than in those treated with a PPI alone. In contrast, in a single-centre study conducted by McColl and colleagues (19), 21% of patients with functional dyspepsia and infection with *H pylori* who were treated with two weeks of eradication therapy (PPI plus amoxicillin and metronidazole) experienced resolution of dyspeptic symptoms compared with 7% of those who were treated with a PPI alone (P<0.001). Overall, 14% more patients treated with eradication therapy had resolution of dyspeptic symptoms than those treated with a PPI alone. A combination of the results from these two trials suggests that a 10% increase in improvement of dyspeptic symptoms occurs with eradication therapy compared with treatment with a PPI alone. This is similar to the improvement that was observed in *H pylori*-positive patients with functional dyspepsia who were treated with PPIs in a large study that compared the efficacy of PPIs with that of placebo (Figure 1) (20).

The role of *H pylori* in functional dyspepsia remains controversial; however, a subset of patients with functional dyspepsia appear to benefit from eradication therapy. Thus, the current Canadian Consensus Guidelines recommend that patients less than 45 years of age with uninvestigated dyspepsia who have had dyspeptic symptoms for more than

three months but do not have alarm symptoms or features should be tested and treated for infection with *H pylori* (7).

### GERD

Possibly the most controversial issue of *H pylori* infection in gastrointestinal disorders is that of its relationship to GERD. The occurrence of de novo GERD following eradication of *H pylori* in patients with peptic ulcer disease has been observed in several reports (21,22), including a trial that prospectively examined the incidence of GERD in patients who received successful or unsuccessful eradication therapy for the management of duodenal ulcers (23). However, this evidence is largely anecdotal, and results are emerging to suggest that the incidence of GERD does not increase after eradication of *H pylori* (24). In the above-mentioned trial conducted by McColl and colleagues (6), a possible benefit of eradication therapy was demonstrated in patients with GERD. Of the 86 patients in whom *H pylori* was successfully eradicated, 27 had GERD upon initial presentation. Interestingly, the proportion of patients who experienced resolution of GERD symptoms increased with time after successful eradication of *H pylori*; after more than two years of follow-up, 44% of these patients had experienced resolution of their symptoms. Of the 59 patients with no evidence of GERD before eradication therapy, only three developed de novo GERD following eradication of *H pylori* – an incidence rate similar to that of GERD in the general population. These results suggest that eradication of *H pylori* in patients with peptic ulcers does not induce de novo GERD and may, in fact, be implicated in the resolution of GERD symptoms. Until further assessments of the relationship between *H pylori* and GERD are available, the Canadian Consensus Guidelines do not advocate routine testing for the presence of *H pylori* in patients with GERD; however, eradication therapy may be offered on a case by case basis in patients with known *H pylori* infection (2).

### GASTRIC MALT LYMPHOMA AND GASTRIC CANCER

There is strong evidence to suggest that infection with *H pylori* is implicated in low grade gastric MALT lymphomas (5). Eradication of *H pylori* in patients with gastric MALT lymphoma results in complete resolution of disease in most cases; therefore, the Canadian Consensus Guidelines recommend eradication of *H pylori* in all con-

firmed cases of this type of lymphoma (2). The presence of *H pylori* also appears to increase the risk of noncardia gastric cancer, possibly because the progression of *H pylori* infection results in diffuse chronic atrophic gastritis, a predisposing factor for this type of cancer (25,26). In contrast, the presence of *H pylori* may have a protective effect against cancer of the gastroesophageal junction, although this possible relationship may result from increased protection against *H pylori* infection in high risk patients (26).

### CONCLUSIONS

Infection with *H pylori* appears to be implicated in several upper gastrointestinal disorders. However, the incidence of *H pylori* infection in the general population is high; thus, widespread testing for *H pylori* is inappropriate. Selection of patients for whom presence of *H pylori* should be tested remains controversial. It is clear that eradication of *H pylori* is the primary management strategy for patients with non-NSAID-induced peptic ulcer disease. Eradication of *H pylori* may also reduce the risk of bleeding in patients with NSAID-induced ulcers; however, the available evidence is preliminary and warrants further assessment. Although the role of *H pylori* in functional dyspepsia is unclear, some patients may benefit from eradication therapy. Patients with GERD should not be tested for the presence of *H pylori* because proper management of the infection in these patients remains to be elucidated. Further trials are required to establish the relationship between dyspeptic symptoms and infection with *H pylori*, as well as to determine whether *H pylori* is implicated in the pathogenesis of GERD.

The currently recommended eradication therapy for use in Canada is seven days of twice-daily treatment with a PPI, clarithromycin, and amoxicillin or metronidazole (2,7). Use of the PPIs that are currently approved in Canada for use in these regimens has produced eradication rates of 80% to 95% (27-30). However, it has been suggested that the rapidity of the onset of action of the PPI may have an effect on the rate of eradication. Therefore, a new generation of PPI drugs that will soon be available in Canada may offer improved rates of eradication because they have been shown to be more potent and have a faster onset of action than the currently available PPIs (31). Trials that directly compare eradication therapies are required to further elucidate this effect.

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