

SPECIAL SECTION

Canadian *Helicobacter pylori*
Consensus Conference Update

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Guest Editors:

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Canadian *Helicobacter pylori* Consensus Conference Update: Infections in adults

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RH Hunt, CA Fallone, ABR Thomson, the Canadian *Helicobacter* Study Group. Canadian *Helicobacter pylori* Consensus Conference Update: Infections in adults. Can J Gastroenterol 1999;13(3):213-217. The first Canadian *Helicobacter pylori* Consensus Conference took place in April 1997. The initial recommendations of the conference were published in early 1998. An update meeting was held in June 1998, and the present paper updates and complements the earlier recommendations. Key changes included the following: the recommendation for testing and treating *H pylori* infection in patients with known peptic ulcer disease was extended to testing and treating patients with ulcer-like dyspepsia; it was decided that the urea breath test (not serology) should be used for routine diagnosis of *H pylori* infection unless endoscopy is indicated for another reason; and recommended therapies were a twice daily, seven-day regimen of a proton pump inhibitor (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg) or ranitidine bismuth citrate 400 mg, plus clarithromycin 500 mg and amoxicillin 1000 mg, or plus clarithromycin 500 or 250 mg and metronidazole 500 mg. The need was reiterated to have funding for readily accessible, accurate testing for *H pylori* infection with the urea breath test. It was strongly recommended that regional centres be established to monitor the prevalence of

antibiotic-resistant *H pylori* infections. The initial consensus document referred to pediatric issues that were not addressed in this update but were the subject of a subsequent Canadian *Helicobacter* Study Group meeting, and will be published later in 1999.

Key Words: *Helicobacter pylori*, *Peptic ulcer disease*, *Practice guidelines*

Mise à jour de la conférence canadienne de consensus sur *Helicobacter pylori* : Infections chez les adultes

RÉSUMÉ : La première conférence canadienne de consensus sur *Helicobacter pylori* s'est tenue en avril 1997. Les recommandations initiales de la conférence ont été publiées au début de 1998. Une réunion de mise à jour de ces recommandations s'est tenue en juin 1998. Le présent article actualise et complète les premières recommandations. Parmi les changements clés, on note que les recommandations concernant le dépistage et le traitement de l'infection à *H. pylori* chez les patients connus pour être atteints d'un ulcère gastro-duodéal ont été

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étendues au dépistage et au traitement des patients atteints de dyspepsie mimant un ulcère. De même, il a été décidé que le test respiratoire à l'urée (pas la sérologie) devrait être utilisé pour le diagnostic systématique d'une infection à *H. pylori* à moins qu'une endoscopie ne soit indiquée pour une autre raison ; les traitements recommandés étaient l'administration d'un inhibiteur de la pompe à protons (20 mg d'oméprazole, 30 mg de lansoprazole, 40 mg de pantoprazole), deux fois par jour, pendant 7 jours ou 400 mg de citrate de bismuth associé à de la

ranitidine avec 500 mg de clarithromycine et 1000 mg d'amoxicilline ou bien avec 500 mg ou 250 mg de clarithromycine et 500 mg de métronidazole. On a réitéré la nécessité d'avoir des fonds pour dépister facilement et rapidement l'infection à *H. pylori* avec le test respiratoire à l'urée. De plus, il a été fortement recommandé que des centres régionaux soient établis pour surveiller la prévalence des infections à *H. pylori* antibiorésistantes. Le document initial de consensus faisait référence à des questions pédiatriques qui n'ont pas été traitées dans la

The management of *Helicobacter pylori* infection is evolving. Substantial progress to characterize the nature and implications of this major gastroduodenal pathogen has been made in Canada and elsewhere. This progress is helping to define the clinical implications of infection and indications for treatment. To keep pace with new scientific evidence, the Canadian *Helicobacter* Study Group (CHSG) (previously named Canadian *Helicobacter pylori* Study Group) held its second conference in Ottawa, Ontario, from June 5 to 7, 1998. The goals of the conference were to review and to update the first set of guidelines on the basis of recent advances. Such advances have helped to facilitate accurate diagnosis and effective treatment of *H. pylori* infection, thereby providing opportunities to improve patient care.

The evidence that eradication of *H. pylori* infection can cure peptic ulcer disease was a driving force behind the first Canadian Consensus Conference held in April 1997 (1). This evidence is unequivocal, establishing new treatment standards in Canada for one of the most common gastrointestinal diseases. However, the relationship between *H. pylori* and the human host is complex. Most individuals have lifelong *H. pylori* colonization of the stomach with few significant clinical consequences. A subset of infected individuals develop peptic ulcer disease, gastric cancer or gastric lymphomas.

Guidelines unique to Canada are essential. The expected benefits from *H. pylori* eradication may be influ-

enced by a variety of country-specific factors, including the prevalence of infection, and the costs of diagnosis and treatment. Differences among the published guidelines for Canada, Europe, the United States and the Asia Pacific region (Table 1) reflect the influence of these factors and demonstrate how some of the more controversial issues have been variably interpreted in the absence of definitive evidence.

The Canadian update conference convened a broad representation of interest groups. Participants included adult and pediatric gastroenterologists, infectious disease specialists, primary care clinicians, pathologists, basic science researchers, pharmacists, and representatives from government and the pharmaceutical industry. The conference was organized by CHSG and was sponsored by the Canadian Association of Gastroenterology, the Canadian Digestive Disease Foundation, the Canadian Society for Clinical Investigation, the Canadian Infectious Diseases Society and the Canadian Paediatric Society. Major financial support for the Consensus Conference was provided through equal, unrestricted educational grants from Abbott Laboratories Ltd, Astra Pharma Inc, Axcan Pharma Inc, Byk Canada/Solvay Pharma Inc and Glaxo Wellcome Inc.

CONSENSUS RECOMMENDATIONS:
AN UPDATE

In the short time since publication of the Canadian *Heli-*

TABLE 1
Comparison of guidelines for treatment of *Helicobacter pylori* infection in different countries

Indications	Country guidelines			
	Europe (2)	United States (3)	Asia Pacific (4)	Canada (1)
Past or present duodenal or gastric ulcer disease* without prior treatment in patient not taking NSAIDs	Test and treat	Test and treat	Test and treat	Test and treat
Uninvestigated dyspepsia	Test and treat if patient is less than 45 years of age or has no alarm symptoms	Test and treat if patient is less than 45 years of age	Test and treat if patient has no alarm symptoms	Test and treat if patient shows symptoms for three or more months, is less than 45 years of age and has no alarm signals or features
Patients on NSAID therapy	Test and treat	Not addressed	Test and treat if patient has a history of dyspepsia	Testing not indicated

Other possible indications for *Helicobacter pylori* testing include mucosa-associated lymphoid tissue lymphoma, family history of gastric cancer and patient request for testing. *No indication of malignancy. NSAID Nonsteroidal anti-inflammatory drug

Helicobacter pylori Consensus Conference recommendations in *The Canadian Journal of Gastroenterology* in January 1998 (1), several important advances have clarified the practical management of *H pylori* infection. These include better understanding of the relative utility of available diagnostic tests or investigations, and therapeutic options. The key recommendations of the Consensus Conference have been extended from testing and treating *H pylori* infection in patients with known peptic ulcer disease to testing and treating patients with ulcer-like dyspepsia.

DIAGNOSTIC RECOMMENDATIONS

1) Testing for *H pylori* infection should be performed only in patients suspected of having an *H pylori*-related condition such as peptic ulcer disease, and only when treatment is planned if the result is positive.

Comment: Routine testing of asymptomatic individuals for *H pylori* is not endorsed because many patients harbour this infection with no significant clinical consequences. However, when infection with *H pylori* has been confirmed, failure to act on a positive result is inappropriate. Patients should either be investigated further or offered eradication treatment.

2) Nonendoscopic testing for the presence of *H pylori* infection is recommended in any patient with a current or past peptic ulcer. Testing can be considered in carefully selected dyspepsia patients with chronic symptoms consistent with peptic ulcer disease ('ulcer-like' dyspepsia) if the adult patient is younger than 50 years and has no alarm features.

Comment: If a dyspepsia patient is tested, the patient must understand that *H pylori* treatment may not improve his or her symptoms, and should understand that *H pylori* is associated with gastric cancer and can cause mucosa-associated lymphoid tissue lymphoma (MALToma). However, there is no evidence that eradicating *H pylori* in dyspepsia patients will reduce the potential risks of future disease and outweigh the current risks of antimicrobial therapy (eg, allergic reaction, antibody resistance or *Clostridium difficile*-associated complications), or the possible adverse outcome of eradicating *H pylori* (some controversial data suggest that *H pylori* may even protect against gastrointestinal esophageal reflux disease and esophageal cancer).

3) The noninvasive urea breath test should be used for routine diagnosis of *H pylori* infection unless endoscopy is indicated for another reason.

Comment: The ^{13}C or ^{14}C urea breath test is the preferred first-line diagnostic investigation because of its excellent sensitivity, specificity and ease of use. Relative to breath tests, the accuracy of serology is associated with more variability among laboratories, and serology has a higher rate of false positive results in young patients, in whom the prevalence of infection is lower. This is an especially important consideration when the prevalence of *H pylori* infection is relatively low, such as in dyspeptic patients from developed countries seen in Canada. In this setting, the rate of false positive serology tests is markedly higher. This reduces the

positive predictive value of serology testing for *H pylori* in Canadian communities with a low prevalence of *H pylori*, such as in adults younger than 45 years of age, in whom the prevalence is about 20% to 30%.

Several alternative diagnostic methods are under evaluation; these include assays for stool antigen and serum labelled bicarbonate, which may provide alternative nonendoscopic tests and be less costly than urea breath tests, while retaining validity for confirming eradication of infection after eradication treatment.

One emerging and important finding that will alter future management recommendations is the evidence that the proportion of patients with duodenal ulcer due to causes other than *H pylori* or nonsteroidal anti-inflammatory drugs (NSAIDs) is increasing. This observation has been made primarily in the United States, and Canadian data are urgently needed.

A related, unresolved issue concerning diagnosis is the need for antibiotic sensitivity testing. Current antibiotic combination therapies used to eradicate *H pylori* infection appear to overcome some degree of resistance to metronidazole or clarithromycin, but resistance is associated with lower rates of response. Therefore, it is important to have more than one regimen (as listed in the 'Recommended therapies' section) to address local resistance patterns. Prospective information about resistance in Canada is considered important, and necessary to verify that treatments are effective and, thus, appropriate. Monitoring of antibiotic resistance patterns is strongly recommended. A Canadian resistance network is now being established and is funded by CHSG through contributions from sponsors.

TREATMENT RECOMMENDATIONS

- All *H 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.

COMMENTARY ON TREATMENT RECOMMENDATIONS

Although the World Health Organization has designated *H pylori* as a group 1 carcinogen, there is no unequivocal evidence that eradication can reduce the risk of a subsequent gastric cancer, even in high risk populations. Potential benefits remain theoretical. A number of long term intervention studies are underway, and the first results are anticipated in three to five years. The relationships between *H pylori* infection and gastroesophageal reflux disease, NSAID-associated ulcer and nonulcer dyspepsia remain unresolved.

TREATMENT REGIMENS

Treatments have been classified as 'recommended' when

controlled trials have demonstrated at least an 80% eradication rate by an intention to treat analysis. Alternative treatments of potential benefit are considered 'endorsed', even when associated with lower cure rates; such treatments may, for example, be useful in special circumstances, such as when a patient is allergic to a certain antibiotic or does not have an appropriate reimbursement plan to cover first-line therapies. Although the most common reasons for treatment failure include poor compliance and antibiotic resistance, it should be noted that the regimens listed for consideration in treatment failures have not been shown, in controlled trials, to have specific efficacy for this indication.

RECOMMENDED THERAPIES

- Twice daily, seven-day regimen of a proton pump inhibitor (PPI) (omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg) or ranitidine bismuth citrate (RBC) 400 mg, clarithromycin 500 mg and amoxicillin 1000 mg; or
- A twice daily, seven-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 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 (bismuth plus metronidazole plus tetracycline [BMT])

Treatment failure in patients who received metronidazole in the first course:

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

Treatment failure in patients who received amoxicillin in the first course:

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

OTHER CONSIDERATIONS IN THE MANAGEMENT OF *H PYLORI* INFECTION

Much work remains to define the relationship between *H pylori*

infection and diseases other than peptic ulcer. A periodic review of the guidelines is appropriate. Reassessments to accommodate new information are essential. The risk posed by *H pylori* infection for life-threatening conditions, such as cancer, may prove to be great enough to justify more aggressive strategies of testing and treatment recommendations. Conversely, *H pylori* colonization of the human stomach may modify pH level or other factors to ameliorate (offer some protection from) some diseases in certain specific disease states (ie, gastrointestinal esophageal reflux disease and NSAID-induced ulcers).

A key focus is pediatric *H pylori* infection. In part due to lack of information, there has been relatively little clinical guidance provided for clinicians confronted with *H pylori* infection in children. The Canadian Consensus Conference on *H pylori* infection in childhood took place in November 1998 to address specifically guidelines for the management of *H pylori* in the pediatric population. The conclusions and guidelines will be reported later in 1999.

SUMMARY

Eradication of *H pylori* infection in patients with peptic ulcer disease has profound implications for reducing adverse health outcomes in Canada. Moreover, eradication treatments are cost effective relative to symptomatic treatment with antisecretory therapies. Despite the increasing availability of effective and readily tolerated treatment regimens, much still needs to be done to ensure widespread availability, acceptance and use of urea breath testing, and appropriate reimbursement by provincial and third-party payers. Primary care physicians must join with specialists in the effort to identify and treat *H pylori* infection in appropriate patients. Recognizing when diagnosis and treatment of *H pylori* infection can improve patient care is important. The present guidelines are designed for simplicity and ease of implementation as an update to the recommendations from the previous Canadian Consensus Conference (1997) (1).

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1.

APPENDIX: PARTICIPANTS IN THE UPDATE CONFERENCE OF THE CANADIAN *HELICOBACTER PYLORI* CONSENSUS CONFERENCE

The following people were participants in the update conference of the Canadian *Helicobacter pylori* Consensus Conference and are co-authors of the present paper:

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