Canadian *Helicobacter pylori* Consensus Conference

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R Hunt, ABR Thomson, Consensus Conference participants. Canadian *Helicobacter pylori* Consensus Conference. Can J Gastroenterol 1998;12(1):31-41. These guidelines were created to dispel confusion and provide guidance about how the isolation of *Helicobacter pylori* infection has led to new opportunities and initiatives to improve patient care. The guidelines are designed for practical application in management decisions, but must remain flexible and amenable to change with new information. Updated versions of the recommendations are anticipated. Although it is now clear that *H pylori* is a major gastrointestinal pathogen, the extent of the clinical consequences posed by this microorganism has yet to be fully defined.

Key Words: *Consensus conference, Dyspepsia, Gastric cancer, Guidelines,* Helicobacter pylori, *Peptic disorders*

Conférence consensuelle canadienne sur *Helicobacter pylori*

RÉSUMÉ : Ces directives ont été formulées afin d'éliminer la confusion et d'expliquer comment l'identification d'*Helicobacter pylori* a pavé la voie à de nouvelles possibilités et de nouveaux projets pour l'amélioration des soins. Les directives sont conçues pour être appliquées de façon pratique aux décisions thérapeutiques, mais doivent être souples et s'adapter aux renseignements nouveaux à mesure qu'ils se font jour. Des versions mises à jour de ces recommandations sont prévues. Même s'il est désormais clair que *H. pylori* est un important organisme pathogène gastro-intestinal, l'étendue des répercussions cliniques de ce microorganisme reste à définir dans son intégralité.

The unexpected discoveries that peptic ulcers can be caused by gastroduodenal infection with *Helicobacter pylori* and, more importantly, can be cured by its eradication, have produced a profound change in ulcer management. Even while the implications of these discoveries continue to be pursued, they have generated new opportunities to improve patient care. The Canadian *Helicobacter pylori* Consensus Conference convened in Ottawa, Ontario from April 4 to 6, 1997 to identify and maximize these opportunities (all participants are listed in the Appendix). Wherever possible, recommendations were based on scientific evidence. The aim was to determine where advances have practical application and where current knowledge is incomplete. Although it is now clear that *H pylori* is a major gastrointestinal pathogen, the extent of the clinical consequences posed by this microorganism has yet to be fully defined.

The efficacy, availability and cost benefits of diagnostic tools and therapeutic options may differ substantially across national borders. In addition, expected benefits from *H pylori* eradication may be influenced by country-specific prevalence of the gastrointestinal diseases with which this infection is associated, as well as by country-specific rates of antibiotic resistance. It is also appropriate to consider the relative role of the specialist and the primary care physician within the Canadian health care system in managing the *H pylori* infection and its complications. Thus, guidelines specific to Canada are required because other countries are developing guidelines relevant to their environments (1).

Every effort was made to ensure a broad representation of all interest groups in the Canadian *Helicobacter pylori* Consensus Conference. Participants included adult and pediatric gastroenterologists, infectious disease specialists, a family

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physician, a clinical pharmacologist, pathologists and basic science researchers. Observers from Europe, the United States, the pharmaceutical industry and the Canadian government were present. The Conference was sponsored by the Canadian Association of Gastroenterology, the Canadian Digestive Disease Foundation, the Canadian Society for Clinical Investigation, the government of New Brunswick and the Medical Research Council of Canada. Major financial support for the Consensus Conference was provided through equal unrestricted educational grants from Abbott, Astra, Axcan Pharma, Glaxo Wellcome and Solvay/Byk pharmaceutical companies. Broad representation was sought, including the invited participation of the federal government of Canada and the 10 provincial governments. Financial support was received from the federal government via the Medical Research Council. Members of the Health Protection Branch were present and were active participants, as were two representatives from the Canadian Infectious Disease Society. A 'jury' of five senior clinical investigators lead the discussion and ensured impartiality. The representatives of the five sponsoring pharmaceutical companies were encouraged to participate, but could not enter into any discussion of a competitor's product.

BACKGROUND

It has been approximately 15 years since *H pylori* was first isolated from the human stomach (2,3). Initially *H pylori* was shown to produce a chronic active gastritis of uncertain clinical significance. Subsequent studies, however, have confirmed that it is a major pathogen in duodenal and gastric ulcers (4). More recent studies have reported an association between *H pylori* infection and mucosa-associated lymphoid tissue (MALT) lymphoma (5,6), as well as between *H pylori* infection and an increased risk of gastric cancer (7,8). An increased prevalence of infection among patients with dyspepsia as well as several other conditions affecting the gastrointestinal tract is of potential clinical significance and is being evaluated (9).

H pylori is a common infection. In Canada, the prevalence of *H pylori* in the general population is variable (approximately 20% to 40%) (10) and increases with age. In developing countries, prevalence rates reach 80% (11). Recent studies suggest that the infection is most commonly acquired in childhood, probably by fecal-oral or gastric-oral transmission. There is an inverse relationship between socioeconomic status and infection prevalence (12). The risk of infection is increased substantially by crowded living conditions and by poor sanitation. *H pylori* is a pathogen in all hosts, and it initially always causes a chronic active gastritis, although only about 10% to 20% of individuals with *H pylori* develop a clinically relevant disease. The histological abnormalities associated with *H pylori* in the upper gastrointestinal tract, such as gastritis metaplasia, result from this local response and initiate the potential for peptic ulcer development.

A local inflammatory response to *H pylori* infection may precipitate the risk of a complication. This response is probably dependent on the virulence of the organism and on host or environmental factors (13,14). An interplay among these variables leads to the release of inflammatory mediators that impair host defences and alter acid secretion (15). Persistent histological abnormalities, including intestinal metaplasia and dysplasia, may induce gastric malignant transformation, which may explain the association between *H pylori* and gastric cancer risk. The adverse effects of inflammatory mediators on smooth muscle function or on neural receptors provide theoretical explanations for a possible association of dyspepsia with *H pylori* (16).

Enormous progress towards characterizing *H pylori* and its activities in the human host has been achieved in a relatively short time, but it is important to acknowledge that this work is incomplete. On-going research will generate new insights, with the potential to alter dominant current theories regarding pathogenesis, risks of infection and clinical benefits from eradication.

EVIDENCE FOR HEALTH RISKS OTHER THAN PEPTIC ULCER DISEASE

Approximately 80% to 90% of patients who develop duodenal ulcers not associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and 70% of those who develop non-NSAID-associated gastric ulcers are infected with *H pylori* (17). In infected individuals who are not taking NSAIDs, eradication of *H pylori* almost uniformly leads to ulcer healing (18). After eradication, almost all patients remain protected against further ulcer recurrences as long as there is no reinfection (19,20). The risk of reinfection in the developed world is estimated to range between 1% and 3% over a five-year period (21-23).

The lifetime risk of peptic ulcer in infected adults is approximately twice as great as in individuals without *H pylori*. Peptic ulcers in the absence of *H pylori* or exposure to NSAIDs is uncommon in most areas of the world, although the risk may be relatively greater in North America.

More than 90% of individuals with gastric MALT lymphomas are infected with *H pylori* (24). Most patients with this low grade lymphoma achieve partial or complete regression after the *H pylori* infection is eradicated (6).

The relative risk of developing gastric adenocarcinoma is 1.6- to fourfold greater in patients with *H pylori* infection versus controls (25). It is difficult to prove that the association between *H pylori* and gastric cancer is a causal one. In Canada, about 60% of individuals with gastric cancer have positive serology for *H pylori*. The premalignant histological changes in the gastric mucosa may lead to spontaneous eradication of the organism, which may explain why active infection is seen in only 60% of these patients. In addition, direct implication that *H pylori* is a cause of gastric cancer is compromised by the long development period of this malignancy. Data from cohort studies are lacking. The strength of the existing observational epidemiological data was sufficient for the World Health Organization to categorize *H pylori* as a class I or definite carcinogen in 1994 (24). The strength of the supportive evidence is not

as strong as many would consider essential for such a significant decision.

Slightly more than half of all patients who have dyspeptic symptoms are infected with *H pylori*. Given the high frequency with which physicians see patients with dyspepsia, this association is thus of intense research interest (16,26-28). The established pathogenic role of *H pylori* in the upper gastrointestinal tract is a compelling reason to suspect that this infection is capable of causing dyspepsia in patients with ulcers. To date, however, the available evidence from controlled trials seeking an association between the relief of dyspeptic symptoms in persons without an ulcer and *H pylori* eradication has been equivocal.

One problem is that most studies have been conducted in patients with nonulcer dyspepsia (NUD), ie, patients with dyspepsia who have a normal endoscopy. NUD may represent a disease process that differs in dyspepsia patients who have a normal endoscopy versus dyspepsia patients who do not have an endoscopy performed or versus patients with dyspepsia due to peptic ulcer disease. Another criticism of past trials in patients with dyspepsia is that the trials have been of relatively short duration. Symptom resolution after eradication of *H pylori* may be slow, necessitating follow-up of at least 12 months to verify benefit (29). Definitive data are currently being sought through additional dyspepsia trials.

Other gastrointestinal conditions that have a potential association with *H pylori* include lymphocytic gastritis (30), granulomatous gastritis (31), inflammatory gastric polyps (32), Ménétrièr's disease (33) and strictures associated with Barrett's esophagus (34). The strengths of these possible associations vary, and there is little information about the effect of *H pylori* eradication as therapy or prophylaxis in these conditions.

H PYLORI AND CANADIAN HEALTH: SIGNIFICANCE OF NEW GUIDELINES

Eradication of *H pylori* in patients with peptic ulcer disease has profound implications for reducing adverse health outcomes in Canada. It is also cost effective relative to symptomatic treatment with antisecretory therapies (35-37). Although there is much to be learned about *H pylori* as a pathogen in the upper gastrointestinal tract, it is critical that clinicians recognize that diagnosis and treatment of *H pylori* infection in appropriate patients are already an essential step towards optimal management.

Primary care physicians must become involved in the effort to identify and treat *H pylori* in appropriate persons. Dyspepsia is the fourth most common diagnostic dilemma presented to primary care physicians (after headache, backache and fatigue) (38). It is important to recognize when diagnosis and treatment of *H pylori* can play a role in symptom relief in those with peptic ulcer disease.

Guidelines for the management of *H pylori* infection are now available in at least 10 other countries (39). Each one of these guidelines emphasizes the need to eradicate *H pylori* to cure peptic ulcer disease. Some guidelines encourage more aggressive *H pylori* eradication, thereby potentially controlling symptoms of dyspepsia or reducing the risk of gastric cancer (39). Other guidelines have identified different treatment options as first-line therapies based on issues of cost or availability.

In Canada, objective evidence of clinical benefit is important to guide use of our limited health care resources. Treatment and, to a lesser extent, diagnosis of *H pylori* pose risks to which infected individuals should not be exposed without the expectation of an improved outcome. It is essential that our federal and provincial Ministries of Health recognize the public health implications posed by *H pylori* infection and that they fund the appropriate use of suitable tests and treatments. Timely endorsement and funding of such tests and treatments are crucial for the effective management of this common infection and its potentially serious sequelae.

DIAGNOSIS

H pylori infection is so prevalent in the general population that diagnostic testing should be employed judiciously. Indiscriminate testing for *H pylori* threatens limited health care resources and, in asymptomatic patients, also poses ethical dilemmas. Although there are established health risks associated with *H pylori* infection, there is no objective evidence that cure of the infection is beneficial in subjects who have no symptoms attributable to *H pylori*. Thus, from a societal perspective, neither the risks nor the costs of treatment are justified for asymptomatic individuals, even if *H pylori* infection is documented unequivocally. However, physicians must also consider the patient's worries and fears regarding the presence of this chronic and potentially serious infection. Under these circumstances, refusal to treat the infection may be detrimental to the patient's general health. Although medicolegal issues have been raised, currently the risk and cost of treatment in asymptomatic individuals is not justified.

The criteria for testing and for test selection are defined below. These guidelines are intended to identify tests that can be used to improve patient care and the circumstances under which their use is appropriate. The guidelines are based on the premise that not all patients infected with *H pylori* will necessarily benefit from treatment.

Diagnostic tests for *H pylori* can be categorized conveniently as invasive and noninvasive. Invasive tests, performed in the context of an upper gastrointestinal endoscopy and mucosal biopsy, are histology (40), microbiological culture (41) or rapid urease test (42). Histology is probably the most widely used test for *H pylori* and is generally considered to be the gold standard; microbiological culture is highly specific but less sensitive and is more difficult and expensive. A positive rapid urease test may allow the physician to forego the inconvenience, delay and expense of sending biopsies for formal histological examination, although concern has been expressed that disposal of unexamined histological material is unacceptable under some hospitals' by-laws.

Noninvasive tests do not require endoscopy and include immunological tests using whole blood, serum or saliva

(43,44) and urea breath tests (45,46) using carbon isotope-labelled urea. In the latter, the carbon isotope may be stable (^{13}C) or radioactive (^{14}C). Physicians need to be aware that the accuracy of the immunological tests is quite variable. Salivary immunoglobulin A tests are not considered to be sufficiently accurate for routine use, and the results of whole blood and serum tests may be highly operator dependent. Because the sensitivities and specificities of the different tests may vary under different circumstances, it is suggested that immunological tests be validated in the local community. It should also be emphasised that immunological tests cannot be used to verify successful cure of *H pylori* infection because they are likely to give a false positive result. Immunological tests, therefore, are inappropriate after a formal course of anti-*H pylori* therapy, and they should be interpreted with caution in patients who have received antibiotics for other reasons. Immunological tests are likely to become less useful, even for epidemiological studies, as more individuals receive therapy.

Urea breath tests, on the other hand, have excellent sensitivity and specificity to diagnose *H pylori* infection, both before and after treatment. The operating characteristics of the urea breath test are not affected by the choice of carbon isotope. Currently the radioactive ^{14}C urea test is more widely available, but the ^{13}C urea test is generally more convenient and its use is likely to increase. In particular, the $^{13}CO_2$ breath samples are nonradioactive and stable, and they can, therefore, be collected locally and mailed, non-urgently, to a central analysis facility. A positive urea breath test indicates active gastric infection with *H pylori*, and it is appropriate, therefore, for family physicians and specialist gastroenterologists to order a urea breath test and to act upon the results. As is the case for other infectious diseases, false negative results may be obtained if the patient has recently received antibiotics; concurrent or very recent acid suppression may also suppress *H pylori*, leading to a falsely negative urea breath test.

DIAGNOSIS RECOMMENDATIONS

1) Testing for *H pylori* is appropriate only when treatment is planned.
Comment: Testing should have an impact on clinical management. A positive result must be an impetus for further investigation or therapy. A negative result should prompt further investigation or provide reassurance that further diagnostic procedures are not required. If the presence of *H pylori* is sought, this implies that eradication treatment will follow if the test is positive.

2) *H pylori* testing is not appropriate in asymptomatic individuals without previous peptic ulcer disease.
Comment: Currently there is no evidence of benefit from *H pylori* eradication in individuals without symptoms of dyspepsia and in those not known to have a past history of peptic ulcer disease. Asymptomatic patients who are referred for *H pylori* testing because of a strong family history of gastric cancer in close relatives should be tested. Screening asymptomatic persons should be employed only in the context of formal clinical research protocols. If an asymptomatic individual requests *H pylori* testing, testing should be discouraged. If the patient insists, then testing should be performed only after a full discussion of the implications of a positive result, such as the consequences associated with the development of antibiotic resistance in the community and the antibiotic-associated adverse effects in the individual.

3) Nonendoscopic tests for *H pylori* can be used by primary care physicians for patients with documented peptic ulcer disease (current or past) or with chronic symptoms consistent with peptic ulcer disease, providing that the patient is younger than 50 years and has no alarm symptoms or signs.
Comment: While endoscopic confirmation of a suspected peptic ulcer is preferred, resolution of typical ulcer-like symptoms after *H pylori* eradication is reassuring. Gastroscopy is advised after age 50 years because of the risk of malignancy and in any patient of any age with alarm symptoms (eg, weight loss or anemia) because of the risk of an ulcer complication or malignancy. Testing for *H pylori* is not appropriate if the person's predominant symptoms are characteristic of gastroesophageal reflux disease (GERD) (heartburn) or irritable bowel syndrome (lower abdominal discomfort and/or bloating).

4) Confirmation of *H pylori* eradication by endoscopy or urea breath testing is not required in patients treated for an uncomplicated duodenal ulcer, unless symptoms persist.
Comment: Current treatment regimens eradicate *H pylori* and heal duodenal ulcers sufficiently well that follow-up endoscopy is not routinely justified. Ulcer healing and success in infection eradication should be confirmed by endoscopy in patients with bleeding or perforated ulcers in whom failure of eradication therapy could require maintenance therapy with antisecretory agents to prevent recurrent complications (47-50). Patients previously treated for *H pylori* infection without documentation of infection and who have persisting symptoms need further investigation. Prior treatment with a proton pump inhibitor (PPI) without a diagnosis can make accurate evaluation of the patient more difficult, eg, PPIs may suppress *H pylori*.

5) Testing for *H pylori* before eradication therapy is recommended in patients taking NSAIDs who present with a peptic ulcer.
Comment: More data are needed about the interaction between *H pylori* and NSAIDs relative to the risk of peptic ulcers. It remains controversial whether testing and *H pylori* eradication should be considered before prescribing planned long term NSAID therapy in patients with a history of peptic ulcer. For patients with a high risk of developing NSAID gastropathy, mucosal protective prophylaxis is necessary, even if an associated *H pylori* infection has been eradicated.

6) Selection of *H pylori* tests should be based on knowledge of the operating characteristics, availability, costs and appropriateness of the relevant tests for an individual patient.
Comment: Sensitivities and specificities of available tests vary. Therefore tests selected should be validated.

7) Microbiological studies to test *H pylori* antibiotic sensitivity are not necessary in routine clinical practice.
Comment: Although in vitro resistance to antibiotics recommended for *H pylori* eradication is increasing (51), the most effective therapies show high rates of eradication even in the presence of resistant organisms. Furthermore, routine culture of mucosal biopsy specimens is not generally indicated because of the sensitivity and speed of the urease test, and the high rate of response to presumptive therapy. Standards are needed for *H pylori* culture and antibiotic sensitivity testing procedures. The problem of resistance should not be dismissed, however, and the high eradication rates observed in some studies may be due to a low overall prevalence of antimicrobial resistance in the populations in which the studies were performed.

8) If documentation of *H pylori* eradication is required, endoscopy and biopsy or a urea breath test is appropriate, but should be performed at least four weeks after completing the eradication therapy and at least seven days after stopping PPI or H_2 receptor antagonist therapy (52).
Comment: In the majority of cases there is no need for follow-up testing after eradication. The histological presence of persistent *H pylori* infection may be concealed by recent therapy with antibiotics, PPIs or H_2 receptor antagonists (53). PPIs, H_2 receptor antagonists and antibiotics affect the location and density of *H pylori* colonization (54), with fewer organisms seen in the gastric antrum and more in the body. Conversely, raised antibody titres to *H pylori* may persist for six or more months despite successful eradication, rendering serological tests inappropriate for confirmation of eradication because of variable sensitivity and specificity (55). When performing a histological diagnosis, whether for primary diagnosis of *H pylori* or confirmation of eradication, four biopsies should be obtained: two from the antrum and two from the body of the stomach (56,57). Serological tests are inappropriate to confirm eradication of *H pylori* (29,55).

9) It is important to be aware of the comparative aspects of *H pylori* tests.
Comment: Please see Table 1 for a comparison of the *H pylori* tests.

TABLE 1
Comparative aspects of *Helicobacter pylori* tests

Test	Sensitivity	Specificity	Cost
Endoscopic tests			
Histology*	95-99	95-99	$$$$$
Urease*	90-95	95	$$$$$
Culture*	80	90-100	$$$$$
Nonendoscopic tests			
^{13}C urea breath	90-95	90-95	$$$
^{14}C urea breath	90-95	90-95	$$$
Blood serology (laboratory)	85-95	85-90	$$
Blood serology (office)	85-90	85-90	$

**These values are estimates only. The cost of histology, the urease test and culture relate largely to the expense of the endoscopy, including the physician's fee and hospital costs including purchase of equipment and nursing costs; $ Less than $100; $$ $100- 200; $$$ $200-300; $$$$ $300-400; $$$$$ $400-500*

TREATMENT

Although *H pylori* is associated with significant health risks, testing and treatment are not uniformly indicated because the majority of infected individuals do not appear to experience adverse health consequences. Serious complications from eradication therapies are rare. However, minor side effects are reported in 15% to 70% of patients (58).

The following recommendations are designed to identify areas where clear benefit of eradicating *H pylori* has been demonstrated and areas where more clinical trials are needed. There is a strong potential for future information updates and modifications to these recommendations.

TREATMENT RECOMMENDATIONS

1) All *H pylori*-positive patients with an unequivocal duodenal or gastric ulcer, whether active or inactive, should receive eradication treatment. Even if NSAIDs are the suspected etiological agent, eradication of documented *H pylori* infection is appropriate.
Comment: Endoscopic or radiological verification of peptic ulcer may not be necessary in all patients (see Diagnosis Recommendations, Section 3). In patients with a complicated ulcer (eg, bleeding or perforated), cure of *H pylori* infection should be confirmed before permanently stopping antisecretory drugs (29). In patients with a gastric ulcer who are not taking NSAIDs, endoscopic follow-up with biopsy should verify healing and confirm the absence of malignancy (29).

2) Patients with chronic dyspepsia (pain or discomfort experienced in the upper abdomen) which is persistent (lasting more than three months) and/or frequent (on average occurring in one out of every four weeks) who are younger than 50 years old and without alarm features (such as anemia or weight loss) can be considered on a case-by-case basis for noninvasive *H pylori* diagnostic testing (serology or urea breath test) and treated if positive.
Comment: Current data are equivocal that eradication of *H pylori* will lead to a sustained improvement in dyspeptic symptoms (59). Most studies, however, were undertaken in persons with NUD (absence of ulcers on endoscopy). By definition, such patients are not representative of uninvestigated dyspeptic patients (no endoscopy performed) at risk of having or developing peptic ulcers. Patients whose predominant symptoms are characteristic of gastroesophageal reflux

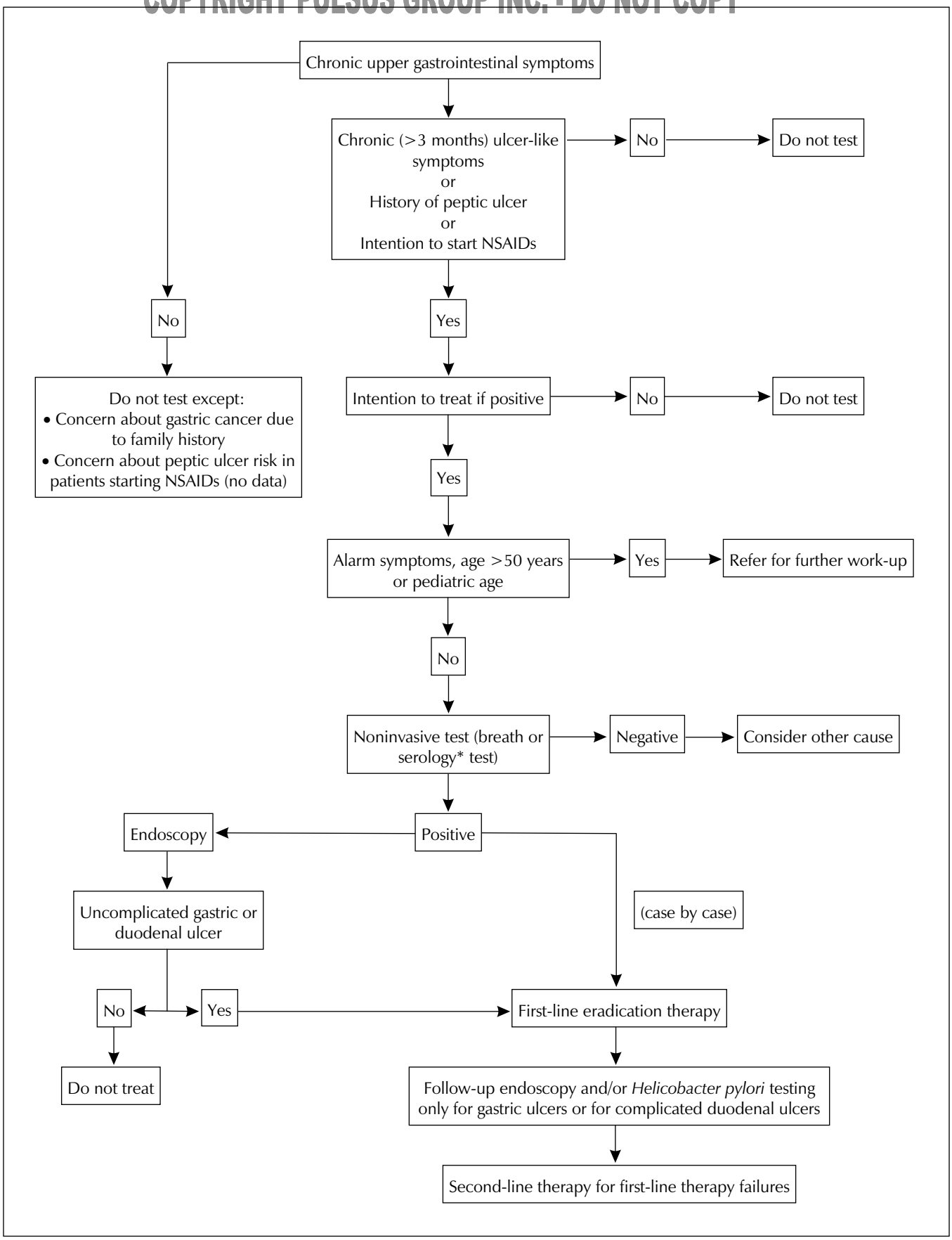

Figure 1) *Algorithm outlining a pragmatic approach to treatment selection in adults. *Secondary if no prior* H pylori *therapy. NSAIDs Nonsteroidal anti-inflammatory drugs*

(heartburn) or symptoms associated with the irritable bowel syndrome (lower abdominal discomfort and/or bloating) should not be tested for *H pylori*. Patients with atypical dyspepsia should be considered for an endoscopic investigation before treating for *H pylori* infection because clinical response may be unpredictable. If a patient is seen shortly after *H pylori* eradication therapy, endoscopic findings may be obscured temporarily by their treatment.

3) All patients with confirmed gastric MALT lymphomas should be tested for *H pylori* and treated if positive.
Comment: Eradication of *H pylori* in patients with gastric MALT lymphomas has been associated with significant disease regression (6). For patients at an early stage of this disease, complete remission has been observed. Diagnosis, treatment and long term follow-up of gastric MALT lymphomas should be performed by a gastroenterologist, preferably in collaboration with a hematological oncologist.

4) Despite the association between *H pylori* infection and an increased risk of gastric cancer, no studies have shown that *H pylori* eradication prevents this malignancy. Eradication can be considered in patients at increased risk of gastric cancer (such as Japanese-Canadians or those with a family history) but benefits remain theoretical.
Comment: Although intervention studies are underway, eradication of *H pylori* has not yet been shown unequivocally to reverse intermediate markers of gastric cancer risk, such as gastric atrophy or intestinal metaplasia, or to provide prophylaxis against malignancy (60). Despite the epidemiological association between *H pylori* and gastric cancer, the clinical implications of this relationship are unclear. However, eradication results in healing of chronic active gastritis, and earlier intervention may prevent progression to intestinal metaplasia and gastric atrophy.

5) In *H pylori*-infected patients with severe histologically demonstrated gastritis, eradication of *H pylori* will reverse inflammation and therefore treatment can be considered.
Comment: The theoretical benefits of eradication of *H pylori* may outweigh the potential risks of persistent severe gastritis, anemia or histological changes associated with progression to atrophy and increased cancer risk. There are no controlled trials, however, confirming that eradication will produce clinical benefits.

6) No relationship has been established between *H pylori* infection and GERD. Routine testing for *H pylori* in patients with GERD is not recommended.
Comment: There are insufficient data to support a published assertion that *H pylori* infection may accelerate the development of atrophic gastritis (61), a marker for gastric cancer, in patients with GERD on long term PPI therapy (62). However, if a patient with GERD on long term PPI therapy is already known to be *H pylori*-positive, treatment may be offered on a case-by-case basis.

TREATMENT REGIMENS

Eradication regimens should be administered in the context of appropriate medical care that includes advice to stop smoking and to discontinue or minimize the use of acetylsalicylic acid and NSAIDs. Primary care physicians should test for and treat *H pylori* infection in patients with a history of uncomplicated peptic ulcers or with chronic symptoms consistent with peptic ulcer. Referral to a gastroenterologist is appropriate in patients older than 50 years, for individuals with alarm features (see Diagnosis Recommendations, section 3) or in the event of treatment failures. In gastric ulcer patients, ulcer healing should be confirmed by endoscopy. A pragmatic approach to treatment selection in adults has been outlined in an algorithm (Figure 1).

On the basis of simplicity, safety and efficacy, two first-line regimens are recommended for eradication of *H pylori*. Both are 'triple' therapies with a PPI and two antibiotics given twice daily for one week. The two regimens have had comparable efficacy in controlled trials (greater than 85% on an intention-to-treat basis).

FIRST-LINE 'TRIPLE' ERADICATION REGIMENS

Twice daily for one week: PPI, 500 mg clarithromycin and 1000 mg amoxicillin

OR

Twice daily for one week: PPI, 500 mg clarithromycin and 500 mg metronidazole

Comment: The triple regimens are as easy as '1 2 3' – one week, twice a day, three medications. There is the significant problem of acquired resistance after failed treatment with nitroimidazoles and clarithromycin. If a treatment regimen fails to eradicate *H pylori*, ideally the antibiotics that were used should not be reused in subsequent courses of therapy because resistance to the original antibiotics (metronidazole or clarithromycin) may develop.

The 500 mg dose is recommended because only 250 mg tablets and 500 mg capsules are available in Canada, and because most controlled trials with metronidazole have been conducted using a 400 mg dose. A 250 mg dose of clarithromycin is adequate when combined with a PPI and metronidazole. In contrast, the 500 mg dose of clarithromycin is superior to the 250 mg dose in PPI triple therapy regimens with amoxicillin. Thus, for simplicity it was advocated in both regimens.

In patients who fail triple therapy more than once, a 'quadruple' drug regimen may be considered. Quadruple drug regimens are considered second-line therapies because they require a more complex dosing schedule and are less well tolerated and complied with. Two quadruple drug regimens are recommended (please see the next section).

Canadian and international experts participating in the Conference concluded that only therapies that achieve an intention-to-treat eradication rate of at least 80% should be

recommended. For this reason, the combination of bismuth subsalicylate, metronidazole and tetracycline was not recommended because a cumulative meta-analysis based on intention-to-treat data found it had an eradication rate of 78%, below the arbitrary cut-off rate. Most controlled studies with a PPI have used either omeprazole (20 mg) or lansoprazole (30 mg) given twice a day. These doses appear to offer comparable efficacy. Available studies using pantoprazole (40 mg bid) with clarithromycin and either metronidazole or amoxicillin indicate intention-to-treat eradication rates of over 80%. It should be noted, however, that there have been no reported studies directly comparing *H pylori* eradication with these three PPIs and similar antibiotic combinations.

SECOND-LINE 'QUADRUPLE' ERADICATION REGIMENS

Seven days: bismuth, metronidazole, tetracycline and a PPI (PPI-BMT)

OR

Fourteen days: bismuth, metronidazole, tetracycline, and an H_2 receptor antagonist

Comment: The colloidal bismuth salicylate is given as 120 mg (equivalent Bi_2O_3) qid, the metronidazole as 250 mg qid, the tetracycline as 500 mg qid and a PPI as bid. The bismuth preparation available in Canada (bismuth subsalicylate) is different from that used in most studies to date (colloidal bismuth subcitrate), and is given as two tablets qid.

The most common causes of treatment failure are inadequate patient compliance and bacterial resistance. Compliance with treatment regimens may be suboptimal because of the poor tolerance to some of the medications. It is important that the patient take all of the medications as directed to achieve the eradication rates documented in the literature. In compliant patients, eradication rates with recommended first- or second-line therapies exceed 85% in controlled trials.

FUTURE DIRECTIONS

It is important to recognize that eradication of *H pylori* is a dynamic area of current clinical research, making an expansion of therapeutic options possible. Relevant to these guidelines, considerations for future modifications are listed below.

1) Simpler regimens will be attractive if they can offer safety and efficacy commensurate with current combination regimens.

Comment: A PPI plus one antibiotic, even when administered over 14 days, offer relatively low eradication rates. Trials combining ranitidine bismuth citrate, a new chemical entity, with one antibiotic for 14 days show that eradication rates with this therapy may be comparable with current first-line strategies; ranitidine bismuth citrate 400 mg bid with clarithromycin 500 mg bid for 14 days gave greater than 80% eradication on pooled intention-to-treat analysis. This suggests that eradication rates with this therapy may be comparable with currently recommended first-line strategies. This two-drug regimen received regulatory approval by the Health Protection Branch after this Consensus Conference.

2) Although antibiotic resistance in Canada does not so far appear to be a significant clinical concern in terms of treatment failure, this may change. High rates of metronidazole resistance of *H pylori* are already reported. Clarithromycin resistance is less common. In vitro resistance may predict clinical failure of therapy.

Comment: In some areas of Canada, up to 40% of *H pylori* isolates are resistant to metronidazole when tested in vitro (63). Resistance to clarithromycin ranges between 0% and 7% (64). Resistance to amoxicillin has not been reported. More data are needed to determine whether routine microbiological sensitivity testing is appropriate in patients who fail current first-line therapies. Recommended first-line triple therapies with clarithromycin and second-line quadruple therapies with PPI-BMT have not maintained high levels of eradication in the presence of metronidazole resistance.

SUGGESTED FUTURE DIRECTIONS IN *H PYLORI* RESEARCH

There are several areas in which research has the potential for substantially altering how *H pylori* infection is characterized and managed. In addition to expanding the indications for treatment, on-going and proposed research may alter diagnostic, prophylactic and therapeutic techniques. Areas of study that should be encouraged for their promise to improve clinical management include the following.

1. Establish route of transmission. A more detailed understanding of how *H pylori* is transmitted could be useful to public health programs directed at reducing the prevalence of this infection. Little is known about the relative roles of the spiral and coccoid forms in infection transmission or in relation to clinical disease.

2. Characterize host vulnerability to complications. Little is known about host factors (such as diet, smoking, alcohol consumption, NSAID ingestion, genetic factors, stress or the immune response to infection) that may contribute to susceptibility to complications from *H pylori* infection.

3. Establish carcinogenic potential of *H pylori*. Despite the strong association between *H pylori* and gastric cancer, a pathogenic role has yet to be clearly established. In addition, the prophylactic effects of eradication are unknown.

4. Characterize the relationship between *H pylori* and dyspepsia. The pool of persons to be considered for eradication may expand dramatically if *H pylori* is found to have a causative role in at least some forms of dyspepsia (other than the dyspepsia caused by peptic ulcer disease). Benefits should be assessed individually in important patient subgroups, such as those with uninvestigated dyspepsia or NUD.

5. Identify virulence factors and host response to infection. Bacterial virulence factors may alter the relative risk of complication development from *H pylori* infection. Knowledge of these virulence factors should help to identify and treat infected individuals at risk of more severe disease manifestations. The ability of investigators to characterize the relative virulence of organisms may also reconcile the disparity between in vivo and in vitro effects of *H pylori*-suppressing drugs.

6. Establish antibiotic susceptibility criteria. While the distinction between clarithromycin-sensitive and -resistant strains is usually evident, the narrow interval between sensitivity and resistance when assessing metronidazole resistance has probably led to the equivocal results in clinical trials to date. Several laboratory factors, such as inoculum density and the composition and pH of media, may directly influence in vitro susceptibility testing, and the need for clarification and standardization should be emphasized. Better biological models for predicting the susceptibility of *H pylori* to antibiotics may be useful to identify obstacles to successful treatment, such as resistance or inadequate tissue penetration.

7. Determine the optimal drug regimens to eradicate *H pylori*. The optimal dose and duration of currently recommended therapies, as well as the use of new combinations or new chemical entities, need to be established for children as well as for adults. Optimal drug regimens may lead to a better targeted, more selective and cost-effective approach to the therapy of *H pylori*-related disease.

8. Establish guidelines for children. The approach to *H pylori* disease in children may differ from that in adults for the following reasons.

- Peptic ulcer disease is much less prevalent in children than in adults. In children, duodenal ulcers are more prevalent than gastric ulcers.
- The most common presentation of peptic ulcer disease is abdominal pain. Of all children presenting to family physicians and pediatricians with abdominal pain, fewer than 5% will have peptic ulcer disease. In addition, current evidence does not support *H pylori* infection having a causal role for recurrent abdominal pain of childhood.
- About 15% to 20% of duodenal ulcers in children are non-*H pylori* related, even excluding NSAID-related ulcers (65).
- Barium studies have both high false positive and false negative rates for the diagnosis of ulcer disease in children (as well as in adults).
- Many serological tests have not been standardized for use in children.

Therefore the following is recommended.

- In children presenting with abdominal pain, neither serological testing nor urea breath testing is indicated to determine whether *H pylori* is present.
- In children presenting with abdominal pain, neither empiric treatment of suspected *H pylori* nor treatment of a positive serological test for *H pylori* is indicated.
- The few children suspected of having peptic ulcer disease should undergo endoscopy with biopsies to determine whether peptic ulcer disease is present and if so, whether it is *H pylori*-related.
- Currently, children with *H pylori*-associated ulcer disease may respond to a 14-day course of a PPI plus two antibiotics (omeprazole, metronidazole and clarithromycin), with compliance monitored (66). Other simpler, shorter therapeutic options will probably be available soon.

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APPENDIX: Participants in the Canadian *Helicobacter pylori* Consensus Conference

JURY

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Astra
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Axcan
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