CME

# *Helicobacter pylori* and peptic ulcer disease

## *Current evidence for management strategies*

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ABSTRACT

**OBJECTIVE** To review current evidence for primary care physicians who manage *Helicobacter pylori* in peptic ulcer disease.

**QUALITY OF EVIDENCE** MEDLINE was searched to August 1997 for randomized controlled trials, systematic overviews, and consensus reports. High-quality recent reviews were often found. Randomized controlled trials presented as abstracts at recent meetings were reviewed.

**MAIN FINDINGS** *Helicobacter pylori* is found in most cases of duodenal and gastric ulcer, and eradication of *H pylori* leads to "cure" of ulcer disease and prevention of ulcer complications. Eradication of *H pylori* is not indicated for gastroesophageal reflux disease. No evidence indicates that screening asymptomatic individuals for *H pylori* infection reduces the risk of subsequent development of gastric cancer. Controversial areas are the role of *H pylori* in functional dyspepsia and screening for *H pylori* before initiating nonsteroidal anti-inflammatory drugs. In primary care, *H pylori* can be detected using serologic tests or urea breath tests (UBT), but only UBTs can be used to confirm eradication. Whether patients suspected of having ulcers can be managed with an *H pylori* test-and-treat strategy without initial investigation is controversial. The first-line recommended treatment is 1 week of twice daily triple therapy with a proton pump inhibitor, clarithromycin (Biaxin), and amoxicillin (eg, Amoxil), or metronidazole (Flagyl).

**CONCLUSIONS** *Helicobacter pylori* eradication should be first-line therapy in primary care for infected patients with peptic ulcers. Effective *H pylori* testing methods and treatments are now available.

RÉSUMÉ

**OBJECTIF** Examiner les données probantes actuelles à l'intention des médecins de soins de première ligne qui traitent contre *l'Helicobacter pylori* dans les cas d'ulcère gastro-duodénal.

**QUALITÉ DES DONNÉES** Une recherche a été réalisée dans MEDLINE, jusqu'en août 1997, pour recueillir des rapports d'essais aléatoires contrôlés, des synopsis systématiques et des rapports de concertation. Des études récentes de grande qualité sont souvent ressorties. Les essais aléatoires contrôlés qui ont fait l'objet de résumés présentés à de récentes réunions ont également été analysés.

**PRINCIPALES CONCLUSIONS** L'*Helicobacter pylori* est présent dans la plupart des cas d'ulcère du duodenum ou de l'estomac. Son éradication entraîne la "guérison" de la maladie ulcéreuse et en prévient les complications. Il n'est pas recommandé d'éliminer l'*H pylori* dans les cas de reflux gastro-œsophagien. Il n'existe pas de données probantes à l'effet que le dépistage de l'infection au *H pylori* chez les personnes asymptomatiques réduirait le risque de développer subséquemment un cancer de l'estomac. Le rôle de *l'H pylori* dans la dyspepsie fonctionnelle et le dépistage de l'*H pylori* avant de commencer le traitement aux médicaments anti-inflammatoires non stéroïdiens restent des aspects controversés. Dans les soins de première ligne, on peut détecter la présence de l'*H pylori* au moyen d'épreuves sérologiques ou de tests respiratoires de déconjugaison de l'urée, mais seules ces dernières épreuves peuvent servir à confirmer son éradication. La question de savoir si on peut avoir recours à une stratégie de dépistage de l'*H pylori* et de son traitement pour soigner les patients chez qui on suspecte la présence d'un ulcère, sans faire au préalable une investigation, demeure discutable. Le traitement de première ligne recommandé comporte une triple médication à raison de deux fois par jour pendant une semaine avec un inhibiteur de la pompe à protons, de la clarithromicyne (Biaxin) et de l'amoxicilline (comme Amoxil), ou de métronidazole (Flagyl).

**CONCLUSIONS** L'éradication de l'*Helicobacter pylori* devrait constituer la thérapie de première ligne pour les patients souffrant d'un ulcère gastro-duodénal qui en sont infectés. Il existe maintenant des méthodes efficaces pour dépister et traiter l'*H pylori*.

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Isolation of *Helicobacter pylori* in 1983[1] revolutionized management of peptic ulcer disease. The Canadian *Helicobacter pylori* Education Group, consisting of five academic gastroenterologists with *H pylori* research experience and one consultant family practitioner, was established to create a continuing medical education program about *H pylori* and peptic ulcer disease.

The initial program was peer reviewed by more than 60 gastroenterologists and endorsed by the Canadian Association of Gastroenterology's education committee. The third update of this program was completed in September 1997. This paper discusses which patients should be tested for *H pylori*, describes how they should be tested and treated, and addresses controversial issues.

## Quality of evidence

MEDLINE searches provided recent, high-quality reviews, systematic overviews,[2-9] and consensus conference reports.[10-14] Although some of the most recent data are still in abstract form, as much as possible, evidence was sought from published studies of optimum design for the question at hand, usually randomized controlled trials or systematic overviews. The strength of the evidence is reviewed for each topic.

## Duodenal and gastric ulcer disease

*Helicobacter pylori* is present in more than 90% of duodenal ulcers (DU) and 80% of gastric ulcers.[15] Ulcers negative for *H pylori* are commonly caused by nonsteroidal anti-inflammatory drugs (NSAIDs). A systematic overview[5] has shown that the median 12-month DU recurrence is 67% if *H pylori* persists but is reduced to only 6% if *H pylori* is eradicated, with similar results for gastric ulcers (59% vs 4%).

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## Preventing recurrence of ulcer bleeding

Some randomized placebo-controlled studies show that eradication of *H pylori* prevents recurrent DU bleeding. In patients with bleeding DUs and persistent *H pylori* infection, the rate of ulcer rebleeding is 27% to 37% yearly, but if *H pylori* is eradicated, rebleeding risk is virtually 0.[16-18]

## Indications for *H pylori* eradication

Eradication of *H pylori* is indicated as primary treatment for infected patients with active DUs and gastric ulcers whether or not NSAIDs are used concomitantly. Eradication therapy is also indicated for infected patients with previous proven ulcers, whether currently symptomatic or not; for patients receiving maintenance therapy; and for patients with ulcer-related complications, such as bleeding.[10,11] There is international[10-13] and Canadian[14] consensus for these recommendations. *Helicobacter pylori* eradication is the most cost-effective approach to curing ulcer disease.[19,20]

There is good evidence[21,22] that uncomplicated, active DUs heal without continuing ulcer-healing drugs beyond the duration of eradication therapy. This reduces the cost of treatment. With the high efficacy of present therapy, it is unnecessary to confirm *H pylori* eradication routinely in these patients. However, in patients with an ulcer complication, such as bleeding, ulcer-healing therapy should be continued until *H pylori* eradication has been confirmed to prevent risk of rebleeding. Once *H pylori* eradication has been documented, maintenance acid-suppressive therapy likely can be withdrawn safely.[16-18] It is necessary to wait at least 1 month after the end of treatment to test whether eradication was successful. Patients should not be using proton pump inhibitors (PPI), high-dose $H_2$ receptor antagonists,[23] or bismuth compounds, as these can suppress *H pylori* and lead to false-negative results.

Patients with gastric ulcers should have endoscopic biopsies to exclude malignant disease and document ulcer healing. Ulcer-healing drugs probably should be given for another 4 to 8 weeks, as gastric ulcers heal more slowly than DUs.

*Helicobacter pylori* infection can cause a rare low-grade gastric mucosa–associated lymphoid tissue (MALT) lymphoma. Eradication of this infection could result in endoscopic and histologic regression of these MALT lymphomas[24] in some patients. Practitioners should be aware of this association, although treatment and follow up of this disease requires specialist care (ie, gastroenterologist and hematologist or oncologist).

## Diseases for which treatment is generally not recommended

A current, excellent review[6] presents evidence that *H pylori* plays no role in causing gastroesophageal reflux and esophagitis. Thus, *H pylori* eradication is not recommended for these patients.

The World Health Organization has classified *H pylori* as a class I (definite) human carcinogen.[25] The overall prevalence of *H pylori* infection is estimated to be 30% to 40% in Canada[26]; however, gastric carcinoma is rarely seen and its incidence is declining. No prospective data show that *H pylori* eradication prevents gastric cancer. Thus at present, screening asymptomatic individuals for *H pylori* to prevent gastric cancer is not recommended.

Most patients presenting with upper gastrointestinal dyspeptic symptoms will, after investigation, have no structural cause identified for their symptoms and thus have functional dyspepsia. While pooled data show the prevalence of *H pylori* in functional dyspepsia is greater among symptomatic patients than among asymptomatic controls,[7] there is no convincing evidence that *H pylori* causes symptoms. Furthermore, eradication of *H pylori* does not consistently improve symptoms.[8,9] A subgroup of patients with ulcerlike dyspepsia experienced some symptomatic improvement from *H pylori* eradication,[27] but this finding needs confirmation in larger, well-designed studies. It is unclear whether patients with functional dyspepsia will improve; therefore, at present, it does not seem logical to treat all functional dyspepsia patients who test positive for *H pylori*.

So far only one randomized placebo-controlled trial[28] in highly selected patients suggests a benefit to eradicating *H pylori* before starting NSAIDs to prevent ulcers from forming. Two other large, double-blind, randomized controlled trials reported contrasting results. These compared omeprazole (20 mg or 40 mg once daily) with ranitidine[29] and misoprostol[30] for healing acute NSAID-induced ulcers while patients continued to receive NSAIDs. After the ulcers healed, patients were re-randomized to maintenance therapy with omeprazole, or ranitidine, or misoprostol, or placebo. Risk factor analysis identified that omeprazole-treated patients had better healing and ulcer remission if they were infected with *H pylori*. Thus *H pylori* appeared to have a beneficial effect on NSAID-induced ulcers. Current evidence does not suggest recommending testing and treating for *H pylori* before initiating NSAID therapy.[29,30]

## Diagnosing *H pylori*

For family practitioners, nonendoscopic, noninvasive methods of serology or urea breath tests (UBTs) are available for detecting *H pylori* (**Table 1**). Serologic tests are the cheapest. Immunoglobulin G antibodies can be determined in serum with sensitivities and specificities around 90%.[31-34] Office antibody kits using whole blood obtained by fingerprick are now available. These are qualitative tests and report only whether antibody to *H pylori* is present or not, whereas serum serologic tests are quantitative because a titre is given. Current data suggest that whole blood tests might be sufficiently sensitive for clinical practice,[35] although serum remains better.

A positive serology test for *H pylori* does not necessarily prove present active infection and reflects previous exposure to *H pylori*. After eradication of the bacteria, antibody titres decrease slowly over many months and usually remain positive despite successful eradication. Thus, serologic tests should not be used to prove eradication.

**Table 1. Diagnosis of *H pylori* infection**

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|---|
| **INVASIVE TESTS (REQUIRE ENDOSCOPY)** |
| Histology |
| Rapid urease test |
| Culture |
| **NONINVASIVE TESTS** |
| Serology: serum, whole blood |
| $^{13}C$- or $^{14}C$-urea breath test |

The $^{13}C$- or $^{14}C$-UBTs depend on the high urease enzyme activity of *H pylori* to break down ingested urea to form $CO_2$. The labeled $CO_2$ can then be detected in the breath to indicate presence of active *H pylori* infection. Because the natural isotope measured in the $^{13}C$-UBT is not radioactive, the test can be done in the office. The radioactivity of the $^{14}C$ is negligible, but regulations require it to be administered in a nuclear medicine facility.[36-37] An advantage of the UBT is that it can be used to confirm *H pylori* eradication in patients who do not require repeat endoscopy.[36-38] Unfortunately, UBTs are not yet readily available across Canada although the Canadian *H pylori* Consensus Conference[14] recommended that they become widely available.

**Key points**
- *Helicobacter pylori* causes most cases of duodenal or gastric ulcer.
- Eradication of *H pylori* leads to a "cure" of ulcer disease and prevents ulcer complications.

## *Helicobacter pylori* in dyspeptic patients

In dyspeptic patients with non-NSAID DUs, it is unnecessary to confirm presence of *H pylori* before giving eradication treatment, because the prevalence of *H pylori* is high (>90%) and additional testing adds little information.[15] However, it would not be inappropriate to test for *H pylori* with serology (or UBT if available) to confirm its presence. If an ulcer is associated with NSAID use, the prevalence of *H pylori* infection will be lower, at about 70%.[15,39] Thus, it is advisable to test for infection before treating in these circumstances.[15]

Only about 10% to 15% of dyspeptic patients will suffer from ulcer disease.[40-42] Remember that it is impossible to diagnose an ulcer on history alone and some investigation is necessary to confirm the presence of ulcers.[43-47] Unfortunately, it is impossible to evaluate every dyspeptic patient with endoscopy to make a firm diagnosis.

No randomized controlled study evaluated a strategy of screening uninvestigated dyspeptic patients with *H pylori* serology and treating positive results with eradication therapy. Patients who have positive results include most patients with ulcer disease who will benefit from *H pylori* eradication; some patients with non-ulcer dyspepsia could also benefit. The Canadian *H pylori* Consensus Conference[14] recommended this test-and-treat strategy without initial investigation on a case-by-case basis for patients younger than 50 who are suspected of having ulcers, without any "alarm" symptoms. Patients older than 50 should have diagnostic tests before treatment. Patients with undiagnosed dyspepsia should not be treated with *H pylori* eradication therapy without first confirming infection.

## Eradication therapy

Eradicating *H pylori* has been difficult, and numerous regimens have been used. Keeping up with the latest regimens is difficult. We relied on systematic overviews, individual papers, and abstracts from the most recent meetings.

Recommended first-line therapies are proton-pump inhibitor (PPI) triple therapies (**Table 2**). Proton-pump inhibitors are very effective in relieving symptoms rapidly and healing ulcers. Proton-pump inhibitor triple therapies achieve eradication rates of around 90%.[48-52] Omeprazole (Losec),[49] lansoprazole (Prevacid),[50] or pantoprazole (Pantoloc)[53-56] can be used. These regimens are well tolerated; few patients drop out due to drug intolerance. Taste disturbance can be a problem with PPIs, clarithromycin, and metronidazole (PCM) and PPIs, clarithromycin, and amoxicillin (PCA); loose stools or diarrhea are most frequently encountered with PCA. These regimens are all given twice daily for only 1 week and this improves compliance. Costs for PCM are on average $28 per treatment course less than PCA (**Table 2**) primarily because of the lower dose of 250 mg bid of clarithromycin (Biaxin) used with PCM.[49,50]

Thus far, in Canada, *H pylori* resistance to clarithromycin appears to be a minor problem (<2%)[57,58]; however, a recent report showed a high 11.6% resistance[59] that is worrisome. Metronidazole (eg, Flagyl) resistance ranges from 18%[57] to 38%.[58] It is unclear to what extent metronidazole resistance affects PCM efficacy; some studies show reduced success,[60,61] and others show no detrimental impact.[62,63] The recently reported MACH2 study showed that when omeprazole was added to the two antibiotics clarithromycin and metronidazole, metronidazole-resistant *H pylori* strains could be effectively eradicated.[64] Amoxicillin (eg, Amoxil) allergy is common, and this is a contraindication to PCA. Because this regimen does not contain metronidazole, however, there is some rationale for using it for patients with suspected or documented metronidazole-resistant strains.[65]

Recommended alternative therapy (**Table 2**) is 1 week of PPI with bismuth triple therapy (ie, bismuth, metronidazole, and tetracycline [PBMT]). This regimen has the highest pooled eradication rates (>90%).[66] Either omeprazole[67] or lansoprazole[68] can be used as the PPI. It can be an effective regimen for treatment failures, and even metronidazole-resistant strains can be successfully eradicated.[69] The greatest drawback of this regimen is that a total of 18 pills must be taken four times daily. Side effects are frequent, but generally mild, and most patients can complete the treatment if forewarned of side effects. This therapy is less convenient than PPI triple therapies, which require only 6 to 8 pills daily, and offers no cost advantage over PCM.

Another alternative therapy uses ranitidine bismuth citrate (RBC), a new chemical entity specifically developed for *H pylori* eradication that has recently been approved in Canada (eg, Pylorid). When combined with clarithromycin as per protocol, eradication rates

range from 82% to 93%, with intent-to-treat eradication rates of 70% to 82%.[70-72] It has the convenience of twice daily dosing; however, treatment must be given for 2 weeks and is most costly (**Table 2**).

The rare but most serious complication of antibiotic therapy, *Clostridium difficile* colitis, can occur with any regimen. Indiscriminate antibiotic use is discouraged.

## Conclusion

*Helicobacter pylori* is the most important cause of ulcers, and its eradication "cures" ulcer disease and prevents complications. In primary care, *H pylori* can be detected without endoscopy by using serology and UBTs. Effective therapy is now available and allows family practitioners to cure patients, particularly those on maintenance $H_2$-receptor antagonist therapy with proven previous peptic ulcer disease.

*Helicobacter pylori* is one of the most common infectious diseases on earth. In developing countries where the prevalence of *H pylori* is high, antibiotic treatment is impractical. Important work on vaccines to prevent infection is progressing slowly, and clinically applicable vaccines are at least 7 to 10 years away.

Experts caution against indiscriminate prescribing of antibiotics. *Helicobacter pylori* antibiotic resistance, particularly to metronidazole and clarithromycin, is an emerging problem and could, in future, limit the usefulness of our current best therapies.

There are many controversial areas for which no clear evidence supports *H pylori* eradication. Particularly important is undiagnosed dyspepsia where *H pylori* has not been convincingly shown to cause symptoms nor eradication to improve them. Ongoing *H pylori* research is expected to produce exciting results in the years ahead.

**Table 2. How to treat *H pylori***

TREATMENTS OF CHOICE

PCM: PPI + clarithromycin (250-500 mg) + metronidazole (500 mg)
- Clarithromycin can be used at a low 250-mg bid dose without loss of efficacy
- All medication is given twice daily for 7 days
- Efficacy is around 90%
- Cost per course: range $82-$87*

PCA: PPI + clarithromycin (500 mg) + amoxicillin (1 g)
- All medication is given twice daily for 7 days
- Efficacy is around 90%
- Cost per course: range $110-$115*

ALTERNATIVE THERAPIES

PBMT: PPI (either omeprazole 20 mg bid or lansoprazole 30 mg bid) + bismuth subsalicylate (2 tablets qid) + metronidazole (250 mg qid) + tetracycline (500 mg qid)
- All medication is given twice daily for 7 days
- Efficacy > 90%
- Can be effective for treatment failure
- Cost per course: approximately $80*

RBC plus clarithromycin: RBC (400 mg bid) + clarithromycin (500 mg bid) for 2 weeks
- Cost for 2 weeks: $149*

PPI—*omeprazole (20 mg bid), lansoprazole (30 mg bid) or pantoprazole (40 mg bid);* RBC—*ranitidine bismuth citrate.*
**Costs are based on $8.99 prescription fee and Ontario Drug Benefit reimbursements.*

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