

# *Helicobacter pylori*: new developments and treatments

Sander J.O. Veldhuyzen van Zanten, MD, PhD;  
Philip M. Sherman, MD; Richard H. Hunt, MD

## Abstract

THE AUTHORS HIGHLIGHT NEW DEVELOPMENTS IN RESEARCH ON *Helicobacter pylori*. There is now consensus that all patients with newly diagnosed or recurrent duodenal or gastric ulcers who have a positive test result for *H. pylori* should be treated for the infection. Patients presenting with complications of ulcers, such as bleeding, should also be treated. *H. pylori* has recently been classified as a definite human carcinogen by the International Agency for Research on Cancer. In treatment, new combination regimens, consisting of 3 or 4 different drugs, cure the infection in more than 80% of patients. Currently, the best combinations are: (1) omeprazole (or another proton-pump inhibitor), clarithromycin and metronidazole, (2) omeprazole (or another proton-pump inhibitor), clarithromycin and amoxicillin, (3) bismuth subsalicylate, tetracycline and metronidazole, and (4) omeprazole, bismuth subsalicylate, tetracycline and metronidazole.

## Résumé

LES AUTEURS DÉCRIVENT DE NOUVEAUX PROGRÈS dans la recherche sur l'*Helicobacter pylori*. On reconnaît maintenant que tous les patients chez lesquels on a diagnostiqué un ulcère du duodénum ou de l'estomac nouveau ou récidivant et dont le test de dépistage de *H. pylori* donne un résultat positif devraient être traités contre l'infection. Les patients qui ont des complications d'ulcères, comme le saignement, devraient aussi être traités. Le Centre international de recherche sur le cancer a classé récemment le *H. pylori* comme agent cancérigène certain chez les êtres humains. Comme traitement, de nouveaux régimes combinés, constitués de 3 ou 4 médicaments différents, guérissent l'infection dans plus de 80 % des cas. Les meilleures combinaisons sont actuellement les suivantes : (1) oméprazole (ou un autre inhibiteur de la pompe à protons), clarithromycine et métronidazole, (2) oméprazole (ou un autre inhibiteur de la pompe à protons), clarithromycine et amoxicilline, (3) subsalicylate de bismuth, tétracycline et métronidazole, et (4) oméprazole, subsalicylate de bismuth, tétracycline et métronidazole.

**T**he discovery of *Helicobacter pylori* in 1982 has led to a revolution in medicine. As 2 of us (S.J.O.V.v.Z. and P.M.S.) discussed in *CMAJ* in 1994, it is now accepted that the bacterium is the most important cause of duodenal and gastric ulcers.<sup>1</sup> It is also associated with gastric cancer and may play a role in nonulcer dyspepsia.

Because research on *H. pylori* is moving rapidly, we believe it is important to review 3 areas of research that are relevant for practising physicians: (1) further evidence about the importance of *H. pylori* infection in duodenal and gastric ulcers, (2) the decision by the International Agency for Research on Cancer (IARC) to classify *H. pylori* as a group 1 (definite) carcinogen in humans<sup>2</sup> and (3) improved, short treatment regimens with greater and more predictable efficacy in eradicating the infection than previous regimens.

## Duodenal and gastric ulcers: consensus on management

The US National Institutes of Health (NIH) Consensus Conference on the



## Education

## Éducation

**Dr. Veldhuyzen van Zanten is with the Division of Gastroenterology, Dalhousie University, and Queen Elizabeth II Health Sciences Centre, Halifax, NS; Dr. Sherman is with the Division of Gastroenterology, University of Toronto, and the Hospital for Sick Children, Toronto, Ont.; and Dr. Hunt is with the Division of Gastroenterology and the Centre for Evaluation of Medicines, McMaster University, and the McMaster University Medical Centre, Hamilton, Ont.**

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role of *H. pylori* in peptic ulcers,<sup>3</sup> held in 1994, received considerable media attention and increased public awareness of the importance of this infection. There is now general agreement that *H. pylori* is the most important causal factor in duodenal ulcers, both in first presentation and in recurrence.<sup>1</sup> Confirmed eradication of the infection reduces the recurrence rate from between 60% and 80% to less than 5% during the year after treatment.<sup>3</sup> Long-term follow-up studies in developed countries have shown that the rate of re-infection is very low (approximately 1% per year)<sup>4,5</sup> and is similar to the natural rate of acquisition of the infection.<sup>6</sup> Recently, data on the role of *H. pylori* in gastric ulcers have also become available. These show that the rate of recurrence of gastric ulcers in patients with *H. pylori* infection is similarly reduced if the infection is eradicated.<sup>7</sup> Since the prevalence of *H. pylori* in patients with gastric ulcers is approximately 80%,<sup>8</sup> the NIH conference recommended treatment of *H. pylori* infection for all patients with acute or recurrent duodenal or gastric ulcers in whom *H. pylori* infection is present. The prevalence of *H. pylori* infection is somewhat lower in patients with gastric ulcers than in those with duodenal ulcers because patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) have gastric ulcers more frequently than duodenal ulcers.

### Do we need to test patients with ulcers for *H. pylori* infection?

In the management of peptic ulcers and the treatment of *H. pylori* infection it is important to separate acute ulcers from healed ulcers or ulcers that were confirmed in the past. In clinical practice, many patients in whom a peptic ulcer is suspected are never given a diagnostic test to confirm the presence of an ulcer. The management of such cases and investigation for *H. pylori* infection are currently unclear. It is difficult to make a firm diagnosis of duodenal or gastric ulcer based on symptoms alone, since there is considerable similarity in upper gastrointestinal symptoms experienced by patients with peptic ulcers, gastroesophageal reflux and nonulcer dyspepsia.<sup>9</sup> An acute duodenal or gastric ulcer is usually diagnosed by endoscopic or barium radiographic examination of the upper gastrointestinal tract. If acute ulcer is diagnosed during an endoscopic examination, specimens should be taken for biopsy of *H. pylori* infection. If biopsy results are positive, the patient obviously needs to be treated for *H. pylori* infection. However, whether *H. pylori* infection needs to be confirmed in patients who have an ulcer documented on radiographs or who have had a documented duodenal or benign gastric ulcer in the past is less straightforward.

Does a physician have to document *H. pylori* infection

before starting treatment if infection was not assessed when the ulcer was diagnosed? If the patient was not taking NSAIDs when the ulcer was diagnosed, the probability of *H. pylori* infection is greater than 90% in cases of duodenal ulcer and greater than 80% in cases of gastric ulcer. An *H. pylori* infection can be diagnosed by histology,<sup>10</sup> culture<sup>11</sup> or a rapid urease test,<sup>12</sup> all of which require endoscopic examination of the upper gastrointestinal tract. Noninvasive alternatives are the carbon 13 or carbon 14 urea breath test<sup>13,14</sup> or serologic tests.<sup>15,16</sup> The urea breath tests take 30 minutes to 2 hours, depending on how they are performed. They are usually conducted while the patient is fasting and require an office visit. Urea breath tests are expensive (\$75 to \$100). We believe that it is a waste of resources to send a patient with a previously proven duodenal ulcer for endoscopy solely to document *H. pylori* infection. Instead, we recommend that a patient with a duodenal ulcer be treated for *H. pylori* infection after the advantages and disadvantages of the treatment, including the risk of adverse effects, are discussed with the patient. For a gastric ulcer the management is different. Because of the risk of gastric cancer, endoscopy, during which gastric specimens can be taken for biopsy, is indicated when an acute gastric ulcer is suspected. When a patient has had recurrent gastric ulcers in the past, we recommend that a diagnostic test be performed, since the prevalence of *H. pylori* infection is lower in gastric ulcers than in duodenal ulcers.

If a physician wants to have documentation of an *H. pylori* infection before starting treatment, the choice of diagnostic test may depend on the local circumstances. There are 3 options: (1) endoscopy with gastric specimens taken for biopsy, (2) urea breath test and (3) serologic tests. If a physician has access to a laboratory that can analyse serologic tests for *H. pylori* this is the test of choice, since it is the cheapest. The accuracy of serologic testing, which measures IgG antibodies against *H. pylori*, varies considerably, depending on the particular test used.<sup>17,18</sup> One recent Canadian study compared several serologic tests for the diagnosis of *H. pylori* and found marked variation in their sensitivity and specificity. Sensitivity ranged from 54% to 100% and specificity from 29% to 100%.<sup>19</sup> It is therefore of paramount importance that the accuracy of the particular serologic test for detecting *H. pylori* infection is established in the population in which it is being used before one relies on the results. The better serologic tests available currently have an accuracy rate of at least 90%.<sup>16,17</sup> Serologic testing for *H. pylori* is now available in several provinces (British Columbia, Ontario, Quebec, Nova Scotia and Saskatchewan), and we expect it to become more widely available in other provinces soon.

Algorithms for the treatment of patients with acute or previous duodenal ulcers are given in Figs. 1 and 2.



## Which patients need to be treated for *H. pylori* infection?

Therapy to eradicate *H. pylori* should be considered for all patients with acute duodenal or gastric ulcers who have a positive test result for *H. pylori* infection. Currently, the largest group of patients targeted for treatment comprises those with previous ulcers proven by endoscopy or radiography who are receiving long-term maintenance therapy

with acid-suppressive drugs. Eradication of *H. pylori* infection in these patients is overwhelmingly cost-effective, since maintenance therapy is no longer required.<sup>20,21</sup>

## Is documentation of success of therapy required?

Is it necessary to document successful eradication before maintenance therapy is discontinued in patients with

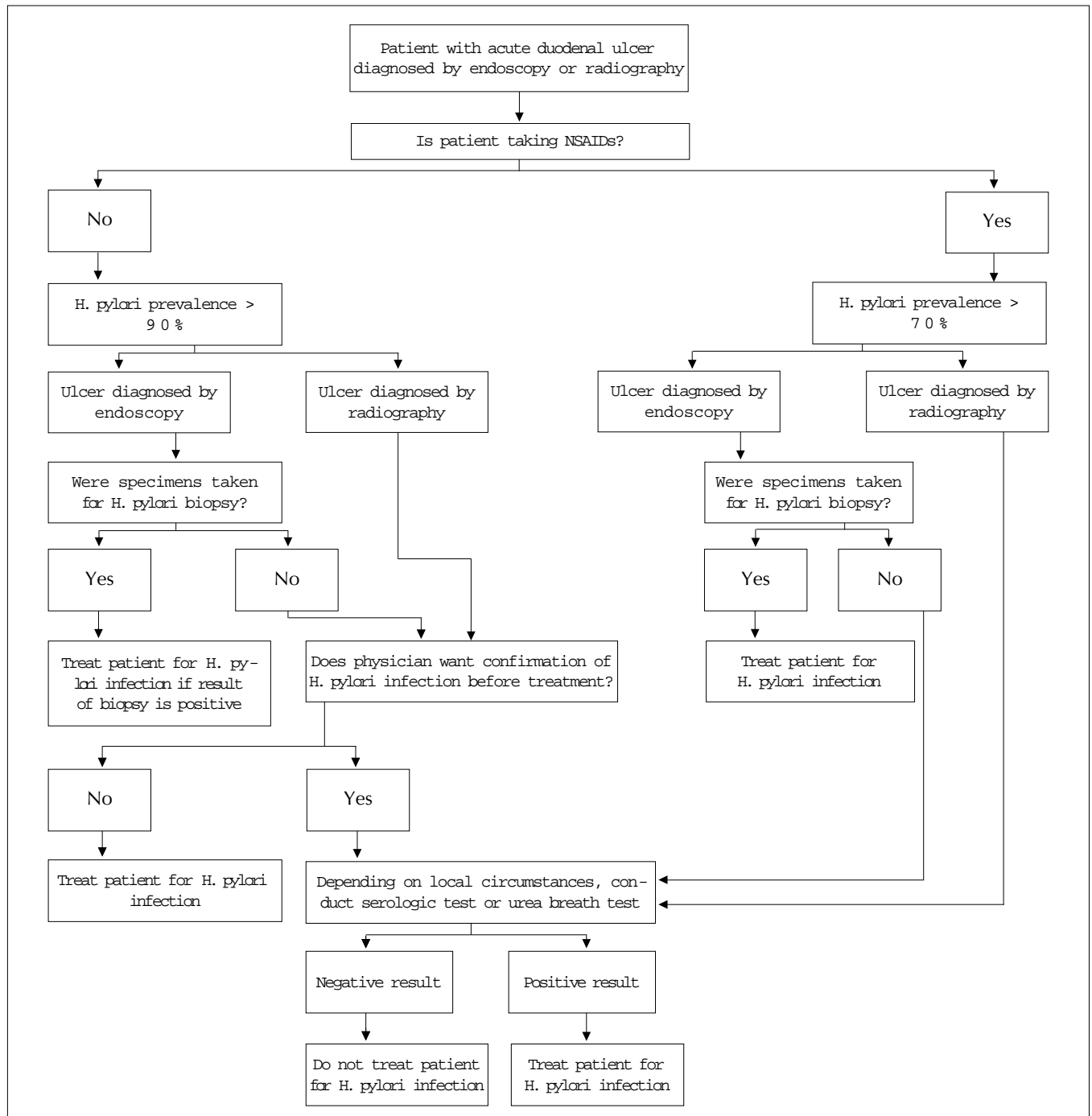


Fig. 1: Algorithm for management of patients with a diagnosis of acute duodenal ulcer.



duodenal or gastric ulcers? We believe that such documentation is not routinely required, since it is not cost-effective. Patients can simply be followed. Should symptoms suggestive of an ulcer recur, *H. pylori* status can then be assessed. Should a patient develop upper gastrointestinal symptoms after receiving therapy to eradicate *H. pylori* we recommend investigating, preferably by endoscopy, since it is a more sensitive method than radiography for the diagnosis of ulcers and especially esophageal mucosal damage. Moreover, specimens can be taken for a biopsy for *H. pylori* during endoscopy. Some patients may have both a peptic ulcer and gastroesophageal reflux. In a large case series, 10% of patients had reflux esophagitis after

cure of *H. pylori* infection.<sup>22</sup> It is impossible to distinguish between these 2 conditions on the basis of symptoms alone. In our practice we have seen several patients who had symptoms due to reflux esophagitis after successful eradication of *H. pylori*. Similar reports have recently appeared in the literature.<sup>23</sup>

After treatment of gastric ulcers, repeat endoscopy is usually performed to document that the ulcer has completely healed, since gastric ulcers can be malignant and gastric cancer can be missed at the initial endoscopic examination. During the second endoscopic examination, specimens can be taken for biopsy, to document whether the *H. pylori* infection has been cured.

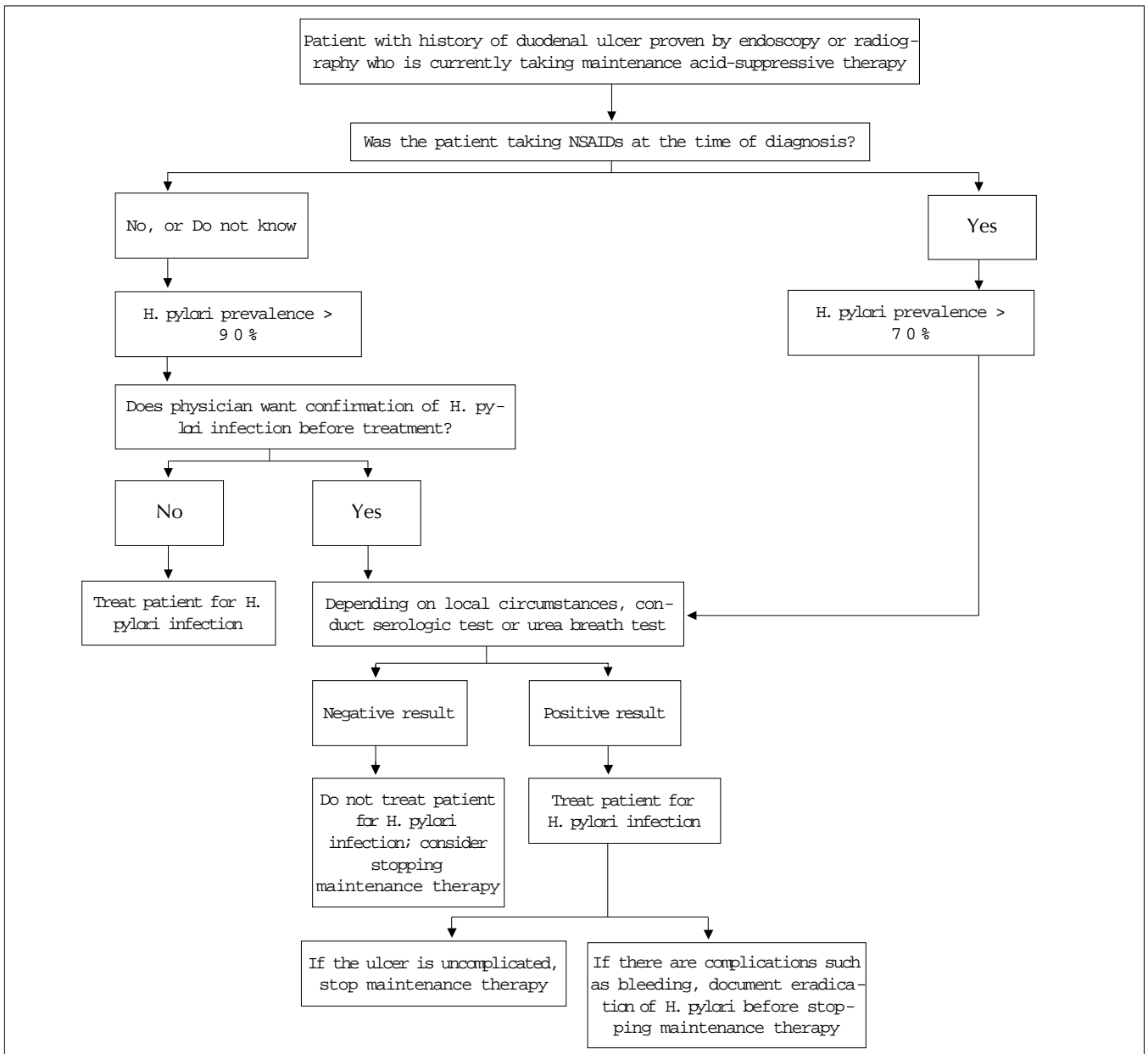


Fig. 2: Algorithm for management of patients with a previous diagnosis of duodenal ulcer who are currently taking maintenance therapy.



## Bleeding duodenal ulcers

We strongly recommend that *H. pylori* eradication be documented before discontinuing acid-suppressive maintenance therapy in patients with ulcers complicated by bleeding or perforation. There is increasing evidence that recurrent bleeding and ulcers are reduced markedly after therapy to eradicate *H. pylori*.<sup>24-27</sup> Since maintenance therapy with acid-suppressive drugs alone prevents most recurrences of bleeding ulcers,<sup>28</sup> we believe that, in patients with complicated ulcers, ulcer healing and eradication of *H. pylori* should be confirmed by endoscopy before discontinuing maintenance therapy.

## *H. pylori* and NSAIDs

NSAIDs are the most common cause of duodenal and gastric ulcers in patients who do not have an *H. pylori* infection.<sup>29,30</sup> However, since the prevalence of *H. pylori* is so high and the use of NSAIDs is so common in the general population, many patients have *H. pylori* infection and are taking NSAIDs when an ulcer is diagnosed. It is unclear whether there is synergy between NSAIDs and *H. pylori* infection in the formation of ulcers; the data available suggest that there may not be.<sup>31</sup> Nevertheless, the most cost-effective strategy for these patients is to cure the *H. pylori* infection; we recommend this and so did the NIH consensus conference.<sup>3</sup> Should patients with a history of ulcers still require NSAIDs after cure of *H. pylori* infection, prophylaxis to prevent the formation of ulcers is still required.

## Gastric cancer

There are more and more data showing that *H. pylori* infection also plays a causal role in gastric cancer, both adenocarcinoma and the much rarer gastric mucosa-associated lymphoid tissue (MALT) lymphoma.<sup>32-36</sup> The recent data on gastric MALT lymphoma are important, since these monoclonal tumours often regress completely after eradication of *H. pylori*,<sup>37,38</sup> making it unnecessary for patients to undergo a gastrectomy. Whether such remission provides a long-lasting cure remains to be confirmed. Close follow-up of patients with MALT lymphoma, preferably by a gastroenterologist in conjunction with a hematologist or oncologist, is essential.

The IARC recently categorized *H. pylori* as a group 1 carcinogen, meaning that it is a definite human carcinogen and putting it in the same category as, for example, hepatitis B virus, which causes hepatoma. Most of the evidence of a link between *H. pylori* infection and gastric cancer comes from 3 cohort studies that showed a pooled relative risk of gastric cancer of 3.8 (range 2.8 to 6.0) with *H.*

*pylori* infection as well as 9 retrospective case-control studies that had estimated relative risks ranging from 1.2 to 4.2.<sup>39</sup> Potential confounding factors, including dietary and other factors such as smoking that have previously been associated with gastric cancer, were not assessed in these studies. The relative risk of 2.8 to 6.0 is considerably lower than, for example, the relative risk of hepatoma resulting from hepatitis B virus infection, which is more than 28.<sup>40,41</sup> However, in some of the studies in which serum samples were obtained before gastric cancer was diagnosed, the relative risk of gastric cancer increased significantly with increasing periods between the collection of the serum sample and the diagnosis of gastric cancer.<sup>42</sup> This temporal relation provides a strong argument in favour of a causal relation between *H. pylori* infection and gastric cancer. To date, no randomized studies have demonstrated that long-term eradication of *H. pylori* infection (or prevention of *H. pylori* infection by vaccination) is followed by a reduction in the risk of gastric cancer. It seems doubtful that such studies will ever be conducted. Nevertheless, although *H. pylori* itself is probably not oncogenic, the infection certainly appears to be at least a cofactor in the development of gastric cancer. There is evidence that, in some patients, chronic *H. pylori* infection progresses from a chronic gastritis to an atrophic gastritis with intestinal metaplasia, both conditions known to be associated with an increased risk of gastric cancer.<sup>43</sup> For example, in a stomach free from infection, the annual increase in the prevalence of multifocal atrophic gastritis in the gastric body is 0.3% per year, whereas it is 0.9% per year in a stomach colonized by *H. pylori*.<sup>44</sup> In Canada, as in most developing countries, the incidence of gastric cancer has declined steadily over the last 50 years.<sup>45</sup> This has been explained by improvements in sanitation, water supply and food handling, which have likely resulted in a lower rate of acquisition of *H. pylori* during childhood.<sup>46</sup> The lack of data on the efficacy of eradication in decreasing the risk of gastric cancer suggests that, at least for the foreseeable future, cancer prevention is not an indication for treatment of *H. pylori* infection.

## *H. pylori* infection and nonulcer dyspepsia

An important current clinical question is whether *H. pylori* infection plays a role in unexplained dyspepsia, often referred to as nonulcer dyspepsia. A detailed discussion of this important topic is beyond the scope of this article, and we refer the readers to other reviews.<sup>47-49</sup> However, routine treatment of all affected patients cannot be currently recommended because most trials of treatment of *H. pylori* infection in patients with nonulcer dyspepsia do not stand up to critical appraisal.<sup>50,51</sup> A few studies with



small samples have shown positive results.<sup>52-55</sup> However, these results need to be confirmed in large placebo-controlled studies.

## New treatments

*H. pylori* is a difficult organism to eradicate from the human stomach. Most treatment combinations now in use have been developed by trial and error.<sup>56</sup> Very little is known about the pharmacokinetics of antibiotics across the gastric mucosa and in the stomach. For example, it is unknown whether antibiotics work topically against *H. pylori* as they pass through the lumen of the stomach, or whether absorption from the small bowel into the systemic circulation, with subsequent secretion across the gastric mucosa into the gastric lumen, is required to eradicate the organism.

Until recently, the best treatment regimen that had been evaluated was the triple combination of bismuth, metronidazole and tetracycline, which achieved eradication rates of more than 80%.<sup>57</sup> This combination appears to be 5% to 10% more efficacious than bismuth, metronidazole and amoxicillin.<sup>57</sup> Although the treatment duration for the combination of bismuth, metronidazole and tetracycline has been reduced from 14 to 7 or 10 days, compliance is still a significant problem, since 16 to 18 tablets need to be taken daily. Most studies of treatment including bismuth have involved colloidal bismuth subcitrate, whereas only bismuth subsalicylate is available in Canada. Whether treatment involving bismuth subsalicylate for 7 days is as effective as treatment for 10 or 14 days has not been firmly established.<sup>57</sup> Side effects, although usually mild to moderate, affect a mean of 30% of patients taking triple therapy involving bismuth,<sup>58-60</sup> but these side effects do not usually lead to withdrawal from trials.<sup>60</sup> The most common side effects are nausea, soreness of the mouth, taste disturbance and diarrhea, which disappear soon after treatment is completed. Poor compliance adversely affects the success rate of this combination, as does resistance to metronidazole.<sup>57,61-63</sup>

There are wide geographic variations in the prevalence of metronidazole-resistant strains: from 20% to 80% in western Europe to almost 100% in Africa.<sup>64,65</sup> The reasons for this variation are unclear, although frequent over-the-counter use of metronidazole in Africa is one explanation.<sup>66</sup> The prevalence of metronidazole resistance in *H. pylori* also appears to vary in Canada: it is 18% in Quebec<sup>67</sup> and 38% in Nova Scotia.<sup>68</sup> Little is known about the mechanisms by which this resistance develops or is transmitted, although some progress in this area has been reported recently.<sup>69,70</sup> The addition of a bismuth compound to the antibiotic therapy of *H. pylori* infection offers some protection against the development of metronidazole resistance.<sup>71-73</sup>

Histamine (H<sub>2</sub>)-receptor antagonists have no known anti-*H. pylori* activity, in contrast to proton-pump inhibitors such as omeprazole and lansoprazole, which have documented inhibitory effects against the organism in vitro.<sup>74,75</sup> Omeprazole or lansoprazole, when given alone, does not eradicate *H. pylori*.<sup>76-79</sup> Initial reports suggested that the combination of omeprazole and high doses of amoxicillin resulted in eradication rates of up to 80%.<sup>80,81</sup> However, subsequent results from this combination have been variable.<sup>82-85</sup> The combination of omeprazole and clarithromycin has shown higher and more consistent eradication rates than the combination of omeprazole and amoxicillin (71% v. 61%).<sup>86,87</sup> Although dual therapies consisting of omeprazole and 1 antibiotic are clearly better than monotherapy, several studies have now shown that triple therapies consisting of omeprazole in combination with 2 antimicrobial agents eradicate *H. pylori* in more than 90% of patients.<sup>83,88,89</sup> In a recent large study involving 700 patients with proven duodenal ulcers, 2 treatment combinations achieved eradication of *H. pylori* in more than 90% of patients: omeprazole (20 mg twice daily), clarithromycin (250 mg twice daily) and metronidazole (400 mg twice daily) as well as omeprazole (20 mg twice daily), clarithromycin (500 mg twice daily) and amoxicillin (1 g twice daily).<sup>90</sup> The duration of these regimens was 7 days. The fact that clarithromycin is part of these combinations is not surprising, given that this antibiotic, when prescribed alone, achieved eradication of *H. pylori* in 54% of patients, the highest rate achieved by a single agent thus far.<sup>91</sup> Why a higher dose of clarithromycin is required in combination with amoxicillin but not in combination with metronidazole is unknown. Whether a 7-day regimen is the optimal duration for these combinations requires further study. Compliance with these regimens was very high, and side effects were mild and resolved soon after treatment was completed.

It is important to stress that in this study the metronidazole dose was 400 mg rather than 500 mg, which is the usual dose used in Canada.<sup>90</sup> The 400-mg dose is the standard dose in the other 4 countries in which the study was conducted. It seems unlikely that the difference between a dose of 400 mg and one of 500 mg twice daily would result in a clinically important difference in the rate of cure of *H. pylori* infection or in the frequency of side effects.

Most studies involving proton-pump inhibitors have used omeprazole. The high success rates of these triple therapies is likely due to an effect of this class of drugs, and similarly high eradication rates can be achieved with other proton-pump inhibitors such as lansoprazole or possibly pantoprazole.<sup>92</sup> Although fewer patients have been treated with lansoprazole than with omeprazole in studies to date, several studies suggest that lansoprazole is equally effective.<sup>93-96</sup>



Recently, another regimen of 4 drugs cured *H. pylori* infection in more than 90% of patients.<sup>97</sup> This quadruple therapy consists of the addition of omeprazole (20 mg once daily) to the triple combination of bismuth, metronidazole and tetracycline. Two other studies have confirmed the high eradication rates achieved with this combination.<sup>98,99</sup> As with combination therapy of bismuth, metronidazole and tetracycline, the studies have been performed with the use of colloidal bismuth subcitrate, not bismuth subsalicylate.

A new bismuth-ranitidine compound has recently been developed for treatment of *H. pylori* infection.<sup>100</sup> This drug is not available in Canada at the moment, but its use in combination with clarithromycin was recently approved by the US Food and Drug Administration for treatment of duodenal ulcers in patients with *H. pylori* infection.

Considerable research efforts are also being devoted to the development of a vaccine against *H. pylori*. Given the high prevalence of this infection in developed countries (where approximately 30% of the population has the infection) and developing countries (where more than 50% of the population has the infection),<sup>46,101,102</sup> a reliable vaccine would be an attractive and cost-effective option. Interest in a vaccine has greatly increased as a result of several animal studies that showed that vaccination cured established *H. pylori* infection in animals, meaning that vaccination could be therapeutic as well as prophylactic.<sup>103-105</sup> However, developing such a mucosal vaccine for humans will be difficult and will likely take 5 to 10 years.<sup>106</sup>

It is currently unknown whether patients with an acute duodenal ulcer need to continue acid-suppressive therapy after the 7 days of anti-*H. pylori* therapy. We do not con-

sider continued treatment necessary in all patients; however, it may sometimes be required to accelerate healing and relieve epigastric pain.

The Health Protection Branch of Health Canada has recently approved dual therapies consisting of omeprazole and clarithromycin or omeprazole and amoxicillin for treatment of *H. pylori* infection. Although these treatments are effective, as discussed earlier we believe that better options are available. The 4 best treatment options available are given in Table 1. The least expensive of these regimens is the combination of bismuth subsalicylate, metronidazole and tetracycline, which, in Ontario, costs \$29. By comparison, in Ontario the combination of omeprazole, clarithromycin and metronidazole costs \$74, the combination of omeprazole, clarithromycin and amoxicillin costs \$125 and quadruple therapy with bismuth subsalicylate, metronidazole, tetracycline and omeprazole costs \$45.<sup>107</sup> If acid-suppressive therapy is added to the \$29 drug combination, its price advantage is diminished. Resistance to metronidazole or clarithromycin needs to be monitored, since resistance adversely affects the success rate of these therapies.<sup>108</sup> Clarithromycin resistance is low in Canada (0% to 3%)<sup>67,109</sup> but is higher in countries such as Belgium and France where macrolide antibiotics such as clarithromycin are commonly used.<sup>110,111</sup> As long as patients comply with therapy, resistance to metronidazole is the most likely cause of failure to cure the infection when combinations that include metronidazole are used. In cases of metronidazole resistance, the combinations of omeprazole or another proton-pump inhibitor, clarithromycin and metronidazole and of bismuth subsalicylate, metronidazole, tetracycline

**Table 1: Drug combinations for reliable treatment of *Helicobacter pylori* infection**

Regimen	Dosage	Treatment period, d	% of patients in which infection is eradicated
Proton-pump inhibitor*	Amount varies, bid	7	> 90
Clarithromycin	250 mg bid		
Metronidazole	500 mg bid		
Proton-pump inhibitor*	Amount varies, bid	7	> 90
Clarithromycin	500 mg bid		
Amoxicillin	1 g bid		
Bismuth subsalicylate†	2 tablets qid	7-14‡	> 80
Metronidazole	250 mg qid		
Tetracycline	500 mg qid		
Bismuth subsalicylate†	2 tablets qid	7	> 90
Metronidazole	250 mg qid		
Tetracycline	500 mg qid		
Omeprazole	20 mg od		

\*To date, most patients have been treated with the proton-pump inhibitor omeprazole (20 mg bid), but recent data show that similarly high eradication rates can be achieved with other proton-pump inhibitors such as lansoprazole (30 mg bid) or pantoprazole (40 mg bid).

†Most studies performed to date have included colloidal bismuth subcitrate rather than bismuth subsalicylate.

‡It is unclear whether 7-day treatment is as effective as 10- or 14-day treatment.



and omeprazole appear to be logical second-line treatments. If the combination of omeprazole, clarithromycin and amoxicillin is used initially, without success, the other triple therapies can be tried.

Further randomized controlled trials comparing different combination therapies are needed to establish the most successful regimen with the fewest side effects.

## Canadian consensus conference

A Canadian consensus conference on *H. pylori* was held Apr. 4 to 6, 1997, in Ottawa, as this article was being prepared for press. The Canadian and international experts participating in the conference concluded that only therapies that achieve an eradication rate of 80% or more, according to intention-to-treat analysis, should be recommended. For this reason, the combination of bismuth subsalicylate, metronidazole and tetracycline was not recommended, since a cumulative meta-analysis according to intention to treat found that this regimen had an eradication rate of 78%, just below the cut-off rate.<sup>112</sup> All of the other treatments given in Table 1 achieved rates above the 80% target. Furthermore, although most patients to date have been treated with omeprazole, the most recent data confirm that all of the proton-pump inhibitors, including lansoprazole and pantoprazole, achieve similar eradication rates when given with the 2 antibiotics. The combination of an H<sub>2</sub>-receptor antagonist and bismuth subsalicylate, metronidazole and tetracycline given for 14 days was added to the list of treatments because it has an eradication rate greater than 80%. In this regimen, the dosage of the H<sub>2</sub>-receptor antagonist is 300 mg of ranitidine twice daily or equivalent, and the other drugs are prescribed 4 times daily.

## Conclusion

Since the publication of our previous article, much more evidence confirming that *H. pylori* is the most important causal factor in duodenal and gastric ulcers has been published. The link between the organism and gastric cancer has also been more clearly established, although the exact mechanisms by which gastric cancer develops need to be determined in further studies. Although treatment will likely change in the future, several treatment combinations now available can reliably cure *H. pylori* infection in more than 80% of patients.

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**Reprint requests to:** Dr. Sander J.O. Veldhuyzen van Zanten, Division of Gastroenterology, RC Dickson Centre, Queen Elizabeth II Health Sciences Centre, Rm. 4087, 1278 Tower Rd., Halifax NS B3H 2Y9; fax 902 473-4406; zanten@is.dal.ca

## Training Program in International Health 1997

### Pan American Health Organization/World Health Organization

The purpose of the program is to promote leadership in international public health by enabling participants to develop a broader vision of international and regional health trends and a more profound understanding of technical cooperation in this field. The program is oriented toward young health professionals from the Americas who possess a demonstrated capacity for leadership and an interest in deepening the international dimension of their activities in the health area. Participants in the program are known as "residents" and are incorporated into the work of PAHO for a period of 11 months starting in January.

The following are requirements for participation in the Training Program in International Health:

**Training:** Master's Degree in Public Health or equivalent graduate degree, including Social Sciences applied to health

**Experience:** Minimum of 2 years' experience in directing programs, projects or services in education or health research

**Age:** Age limit is 35 at deadline for application

**Nationality:** Be a permanent resident of one of the PAHO member countries

**Language:** English with a working knowledge of Spanish

**Compensation:** Each participant receives a subsistence stipend of US\$2193.64 per month. In addition, financial support is provided to cover setting-in expenses (travel, moving/housing arrangements), as well as to cover the purchase of books or instructional material needed for the purpose of the program.

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**Deadline for submission of applications: July 15, 1997**