# *H. pylori:* The view from 2002

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In this article:

1. What is *H. Pylori*?
2. How is it transmitted?
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Two decades ago, Marshall and colleagues discovered *Helicobacter pylori (H. pylori)*, elucidated its role in peptic ulcer disease and threw the world of peptic ulcer disease into a tizzy. Since then, knowledge of this species of bacteria has been accrued at a spectacular rate. In this article, the author will briefly review where the medical community stands in the second year of the new millennium with regard to the pathophysiology of *H. pylori* infection and the role of *H. pylori* in various human diseases.

## What is *H. pylori*?

Recently, Passaro et al., and Suerbaum and Michetti reviewed this area and their respective articles should be consulted.[1,2] To put it briefly, the stomach is a hostile place for bacteria to grow and, until the discovery of *H. pylori*, it was widely, intuitively and incorrectly assumed that the stomach was sterile. *H. pylori*, however, is a clever and resourceful bacterium and due to its motility, its adhesion to gastric epithelium and its urease system, it can wriggle through the gastric mucus layer, cling to epithelial cells, produce ammonia to create an acid-free milieu and thrive.

*H. pylori* causes continuous inflammation and chronic gastritis. Most strains of *H. pylori* have a 29-gene, 37-kb fragment called the cagA Pathogenicity Island (cagA).[3] *H. pylori* does not invade the gastric epithelium, rather, only the cagA island translocates into the epithelial cells, where phosphorylation occurs and it becomes bound to a tyrosine phosphatase. This leads to a cellular response (*i.e.,* neutrophiles, T and B lymphocytes, plasma cells and macrophages) and to the production of cytokines, including several interleukins and tumour necrosis factor. Among these, IL-8, which activates neutrophiles, seems to be the key player.[4] *H. pylori* does bind to major histocompatibility antigens, thereby inducing apoptosis of surface epithelial cells.

As a kind of unifying hypothesis, it is posited that if the infection is acquired in childhood, as is the case in the Third World, then it is likely that the entire stomach will be affected, acid secretion will be diminished, gastritis will be profound and a possible clinical outcome will be a gastric ulcer or gastric cancer. If the infection is acquired in adulthood, a more likely scenario in developed countries, then the infection is antral, gastric acidity is not particularly diminished and the clinical outcome is more likely to be a duodenal ulcer. This scheme does not adequately explain the remarkable observation that

# Helicobacter pylori

## Practice Pointer

**Who should be tested for *H. Pylori*?**

Only test if you intend to treat. Test and treat all ulcer patients and all patients with gastric lymphoma. You do not have to test or treat gastroesophageal reflux disease patients or young people with dyspepsia. It is uncertain, but probably a reasonable idea to test and treat patients about to go on conventional nonsteroidal anti-inflammatory drugs.

non-Hodgkin's lymphoma of the stomach — particularly the mucosa-associated lymphoid tissue (MALT) type lymphoma — is closely related to *H. pylori* and eradication may lead to either regression or cure of the lymphoma.

The lifetime risk of infection is 90% in Third World countries and much less in the developed world.[5] Within the U.S., fewer Caucasians have *H. pylori* infections than African- or Mexican-Americans. It is important to remember that, while the vast majority of the world's population is infected with *H. pylori*, only a small percentage will develop ulcers or cancers. In fact, peptic ulcer diseases (and gastric cancer) are declining in incidence and prevalence. In North America and Europe, at least, there is a slow but steady decline in *H. pylori* infections. Unfortunately, esophageal cancers, particularly

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## Practice Pointer

**How do I verify eradication?**

It is only worth doing for patients who have had serious or complicated ulcers or lymphoma. Use a breath test four weeks after all therapy has been stopped.

those associated with Barrett's esophagus and totally unrelated to *H. pylori*, are increasing in prevalence.[6,7]

## How is it transmitted?

Most authorities feel that the person-to-person route transmits *H. pylori*, but other routes of transmission, such as food- or water-borne routes, are possible. There is probably a genetic susceptibility to infection as shown in Scandinavian twin studies.[8] Reinfection after eradication is an uncommon event, even if other household members remain infected and untreated.

## What are the tests?

While there are many ways to test for the presence of *H. pylori*, perhaps the most relevant question in this regard is: Why is one performing any test for this bacteria? Clearly, the simple and correct answer is that one should test only if one intends to treat or verify eradication of *H. pylori*. If one does not intend to treat, then one should not look for *H. pylori*.

The most simple and least expensive method of testing is by serology, which is readily performed by provincial health laboratories. This technique is only of value in previously untreat-

ed patients. In the treated patient, the antibody may be measurable for a long time after treatment. Unless serial-specific immunoglobulin A (IgA) and immunoglobulin G (IgG) titres are available, it is best not to use *H. pylori* serology to follow responses to therapy.[5]

Since *H. pylori* is richly endowed with the enzyme urease — the enzyme that catalyzes the breakdown of urea into ammonia and carbon dioxide ($CO_2$) — many test systems are based on placing the bacteria into contact with urea and measuring, often qualitatively, the strongly alkaline ammonia generated. Alternatively, one may label the urea with $^{13}C$ or $^{14}C$ carbon and measure the labelled $CO_2$ generated.

Breath tests using either $^{13}C$ or $^{14}C$ urea may be used before and after therapy, but are expensive. The $^{14}C$ tests use radioactive carbon and, thus, are not favoured even though they are relatively cheap. It is the author's opinion that the amount of radioactivity involved in $^{14}C$ testing is minuscule and comparable to that in cosmic radiation, so the anti-$^{14}C$ prejudice is foolish. The $^{13}C$ tests are not radioactive, but involve the use of relatively expensive mass spectrometry techniques. These tests may be used in untreated patients and in post-treatment patients to verify eradication.

Since acid-suppressing medications may give false-negative results on breath tests, the patient must be off proton pump inhibitors (PPIs) or histamine(2)-receptor antagonists (H2RAs) for several weeks before submitting to these tests. Provided this condition is met, breath tests are simple and accurate.

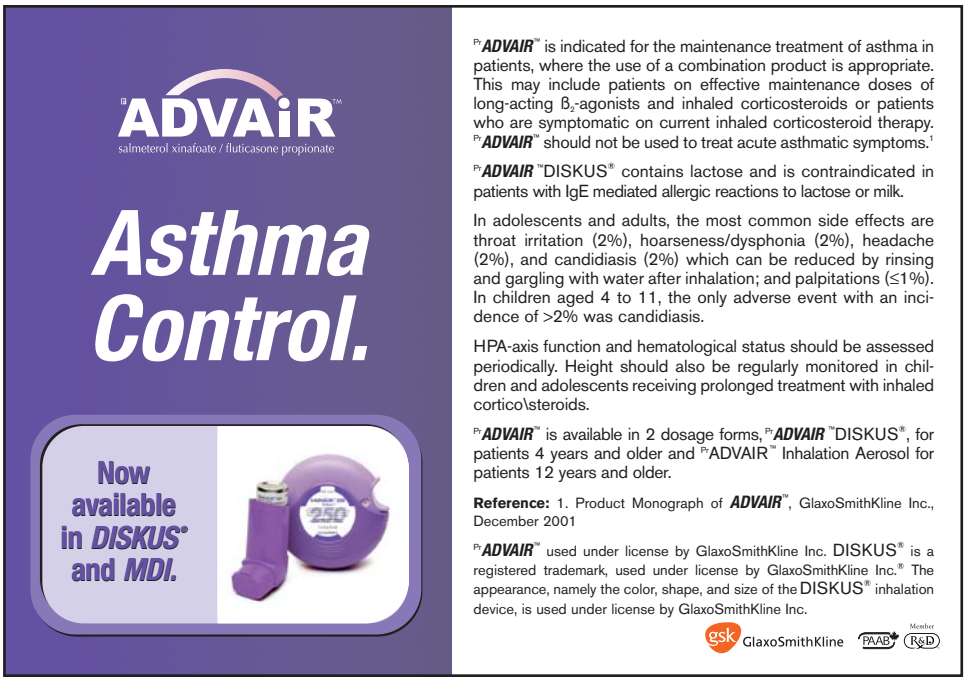
Rapid urease testing of endoscopic biopsies, by briefly incubating a minuscule biopsy of stomach with a urea-rich substrate containing a pH indicator that responds to the alkaline ammonia generated, is also an effective method of diagnosis. Obviously, this must be performed at the time of an endoscopy, which may not otherwise be indicated and, thus, would be needlessly expensive.

The gold standard in diagnosis is actually identifying the organisms in biopsies of the stomach. This is even more expensive than rapid

## Practice Pointer

***How do you treat H. pylori and for how long?***

Triple therapy: a proton pump inhibitor plus clarithromycin plus either amoxicillin or metronidazole. Treat for 10 to 14 days, with a preference towards 14.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urease testing, even in Canada with its global hospital budgets. The recently developed fecal antigen tests are not being routinely used in Canada. Bacterial cultures and sensitivities are used mainly in research centres for evaluating strains of *H. pylori* resistant to common antibiotic combinations.

Confirmation of eradication is only indicated in patients who have had serious ulcers or those who have had MALT lymphomas.

**Table 1**
**Treatment of *H. pylori***

| Regimen | Number of studies | Cure (%) |
|---|---|---|
| PAC | 87 | 86 |
| PCM | 122 | 87 |
| PAM | 82 | 82 |
| RAC | 6 | 88 |
| BTM | 64 | 79 |
| BAM | 78 | 77 |
| AMTP | 26 | 91 |

Legend: R = ranitidine; A = amoxicillin; C = clarithromycin; M = metronidazole; P = proton pump inhibitor; T = tetracycline; B = bismuth subsalicylate

Adapted from Laheij RJ, Rossum LG, Jansen JB, et al: Evaluation of treatment regimens to cure *Helicobacter pylori* infection. A meta-analysis. Aliment Pharmacol Ther 1999; 13(7):857-64.

## What are the treatment regimens?

There are many combinations of pharmaceuticals used to treat *H. pylori*, and virtually all of them are effective in about 85% of cases. While this rate of cure is commendable, the fact that a sizable minority of treated cases is now resistant to first line therapies is worrisome.

As seen in Table 1, most regimens involve the use of two antibiotics and an acid-lowering agent. The most commonly used combinations involve twice daily PPIs, clarithromycin and either amoxicillin or metronidazole. While we were quite confident a few years ago that a one-week course of therapy would be maximally effective in *H. pylori* eradication, the American Food and Drug Administration (FDA) now suggests 10 to 14 days of treatment, followed by additional treatment with PPIs. Alternative combinations may include bismuth and second line antibiotics, such as tetracycline or bismuth-tetracycline combination tablets, along with metronidazole.

While these treatments may be cheaper, the dosing schedule may be cumbersome, which could lead to diminished compliance. The popular *H. pylori*-PAC — a packaged combination of lanzoprazole, clarithromycin and amoxicillin — comes as a one-week supply, so two *H. pylori*-PACs should be prescribed and used for 10 to 14 days.

Patients with serious illnesses (*i.e.,* ulcers or MALT lymphoma) who have resistant infections should be referred to interested gastroenterolo-

### Practice Pointer

***I have an elderly frail patient who is on nonsteroidal anti-inflammatory drugs and who is allergic to penicillin and does not tolerate metronidazole. How do I treat her?***

You don't. Keep her on a proton pump inhibitor forever.

## Practice Pointer

***I treated a non-ulcer dyspepsia (NUD) patient and she felt well on treatment, but sick after finishing the medications. Should I verify eradication? Should I treat with another combination?***

Congratulations. You made her feel better, which is remarkable in NUD. She probably has gastroesophageal reflux disease. Treat her with a proton pump inhibitor alone and see how she does. It is not worthwhile doing cultures or treating her with an exotic combination of drugs.

**Table 2**
**Current Guidelines for the Treatment of *H. Pylori***

| |
|---|
| **Strongly recommended for treatment** |
| Duodenal or gastric ulcer (active or historical). |
| Mucosa-associated lymphoid tissue lymphoma. |
| Atrophic gastritis. |
| Gastric cancer. |
| Close relatives of gastric cancer patients. |
| Patients who desire treatment. |
| **Advised for treatment** |
| Functional dyspepsia. |
| Gastroesophageal reflux disease. |
| Nonsteroidal anti-inflammatory drug users. |

Adapted from Bazzoli F: Key points from the revised Maastricht consensus report: The impact on general practice. Eur J Gastroenterol Hepatol 2001; 13(Suppl. 2):S3-7.

gists at institutions prepared to do cultures and bacterial sensitivities on *H. pylori* for second-line, and usually quadruple-agent therapy.

Treatment of *H. pylori* should be well-tolerated, but side effects, such as *Clostridium difficile* diarrhea after amoxicillin, and dysgeusia ("metal mouth") and nausea after metronidazole, will occur with some frequency. Sometimes, it is safer and wiser to treat the frail ulcer-bearing elderly patient with long-term PPIs than to heroically try to eradicate the *H. pylori*.

# Who should be treated?

A recent consensus conference listed the indications for *H. pylori* eradication (Table 2).[9] While one seldom thinks of consensus guidelines as contentious documents, this one does have points of controversy. In part, the document seems more like the agenda of a debating society than a consensus statement by experts.

***The uncontroversial indications for treatment.*** In our times, no one would disagree with treating duodenal or gastric ulcer patients with eradication therapy. The relapse rate for these diseases in the uneradicated is many times higher than in the treated. Similarly, the evidence in favour of treating MALT lymphoma is dramatic and striking. There is less compelling evidence for the treatment of patients with atrophic gastritis.

***The controversial indications for treatment.*** *Treating patients who "want to be treated."* Despite the classification of *H. pylori* as a carcinogen, there are no data that prove eradicating *H. pylori* in North America will further lower the already low and diminishing rate of gastric cancer. The present postulate is that gastric cancer occurs after a lifetime of childhood-acquired *H. pylori* infection with atrophic gastritis and metaplasia. For this reason, the indication in a consensus statement that patients who want treatment should be granted it is bizarre advice. In the face of a rising incidence of drug-resistant

helicobacter and other bacteria, such as vancomycin resistant enterococci (VRE) and methicillin resistant *Staphylococcus aureus* (MRSA), and at a time when the medical profession is valiantly trying to stop the misuse and overuse of antibiotics in viral or other non-serious infections, we should not cave into frivolous demands for treating *H. pylori* until it has been shown that eradication is beneficial.

*Treating "patients" who are close relatives of gastric cancer patients.* There is only emotional evidence for the treatment of relatives of gastric cancer victims.

***Even muddier indications for H. pylori eradication.*** *Treating gastroesophageal reflux disease (GERD) with H. pylori eradication.* There are many gastroenterologists who resist testing GERD patients for *H. pylori* infection for two possibly related reasons. First, the eradication of *H. pylori* will result in an increase in acid secretion and a worsening of acid reflux, at least transiently.[10] Second, there is a small amount of evidence showing that GERD sufferers infected with *H. pylori* are less likely to have Barrett's esophagus than uninfected sufferers. On the other hand, there is some fear that massive acid suppression with PPIs in untreated *H. pylori*-infected GERD patients may worsen *H. pylori* gastritis.

*H. pylori eradication in patients about to take acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs).* The role of eradication therapy in patients about to go on long-term NSAID therapy for rheumatologic disorders, or for cancer-prevention, is by no means settled. While it seems intuitively obvious that an ulcer-promoting bacteria should be eliminated before using an ulcer-promoting drug, the data are far from clear and eradication strategy is not, at present, a recommendation for policy-setting rheumatologic organizations.[11] Recent studies, however, show that low-dose ASA users who were infected and had a gastrointestinal complication were as protected by eradication as by long-term PPI medication. NSAID users who had a gastrointestinal bleed and who were treated with eradication therapy, were not protected from further bleeds and still required maintenance PPI medication.

*H. pylori eradication in non-ulcer dyspepsia patients.* By far the most contentious recommendation of the Maastricht guidelines relates to *H. pylori* eradication in functional dyspepsia. Many years ago, this condition was known as X-ray-negative dyspepsia. As technology advanced, it became known as endoscopy-negative dyspepsia

Asthma is a variable disease.

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## Take-home message

There was a brief ray of hope, doubted by experienced and, therefore, nihilistic gastroenterologists, that the discovery of *H. pylori* would answer the dilemma of non-ulcer dyspepsia (NUD). This has not been the case. The largest and best studies on the role of eradication in NUD have failed to show any benefit leading to eradication.[12,13] Quite astoundingly, the highly rated Cochrane database systematic review found enough evidence from controlled trials to suggest that eradication may be effective in NUD. Fortunately, the authors conceded that the ice on which they were skating with this suggestion was perilously thin.[14]

and is now often called non-ulcer dyspepsia (NUD). This is now the fashionable designation for unhappy young people, mostly women, with "ulcer" symptoms and no morphologic evidence of acid-peptic disease. CME

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