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H pylori 1997: Testing and treatment options

KEY POINTS:

Testing for *H pylori* infection is important in patients with peptic ulcer disease, as a negative test focuses the subsequent diagnostic evaluation on other causes of ulcers (eg, NSAID use, gastrinoma).

Serologic testing is the noninvasive method of choice for detecting *H pylori*. However, serologic tests are not useful for documenting eradication, as test results may remain positive for up to 3 years after infection.

Breath tests are the ideal noninvasive method for confirming that *H pylori* has been eradicated after treatment. However, not all patients need to be tested to confirm eradication.

If an initial course of antibiotic therapy fails, subsequent attempts may be less successful. Therefore, patient education to ensure compliance is vitally important.

The approach to patients with dyspepsia is controversial.

***H pylori* is implicated in the pathogenesis gastric cancer.**

ABSTRACT: Although the discovery of *Helicobacter pylori* infection in peptic ulcer disease is revolutionizing ulcer diagnosis and treatment, the role of universal empiric therapy for infected patients with dyspepsia or peptic ulcers is not fully elucidated. This article reviews current thinking on the diagnosis of *H pylori* infection in 1997.

If *Helicobacter pylori* infects 95% to 100% of patients with duodenal ulcers and 70% to 80% of patients with gastric ulcers,[1] and if eradicating the infection greatly reduces the rate of ulcer recurrence,[2] why not just empirically treat all patients with suspected ulcers with antibiotics and antisecretory drugs? Such a strategy would have several advantages:

- It could greatly decrease the risk associated with ulcers—including the 10% mortality rate in patients with bleeding ulcers.
- It might also decrease the risk of gastric cancer and lymphomas from *H pylori*-associated gastritis.
- It would eliminate the costs of endoscopy and other tests.
- It would simplify clinical decision-making.

This approach also has several disadvantages:

- There is no proof it would be effective in curing more people of ulcers or decreasing the incidence of gastric cancer infection.
- The drugs used are expensive.
- It would contribute to antibiotic resistance.
- It would expose many more patients to possible adverse effects of antibiotics.

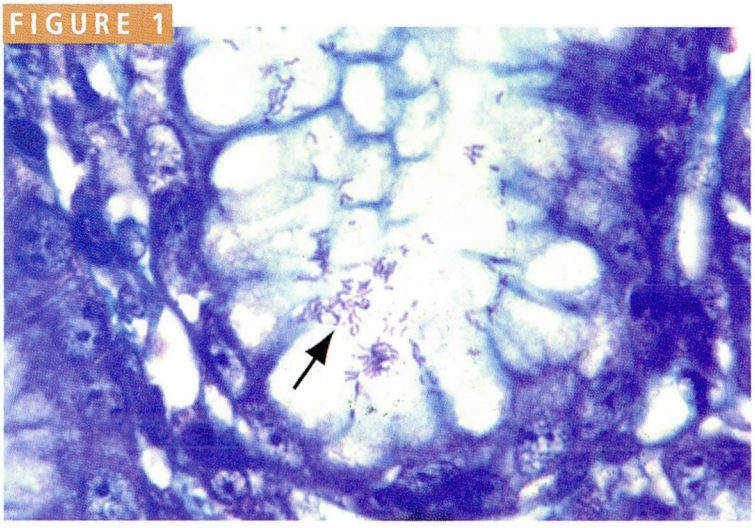
WHY DO MOST INFECTED PATIENTS REMAIN WELL?

H pylori infection is common and increases in prevalence with age—more than 50% of persons older than 60 years have it. Prevalence is also greater in persons in lower socioeconomic classes.[3]

Chronic active gastritis is universal in persons infected with *H pylori*, but only a minority of patients go on to develop duodenal or gastric ulcers and even fewer develop gastric adenocarcinoma or lymphoma of the stomach.

Why this wide range of outcomes? The clinical consequences of *H*

FIGURE 1



Photomicrograph of *H pylori* (arrow) on gastric mucosa (Giemsa stain X 40)

Strains expressing the *vacA* and *cagA* genes are associated with peptic ulcers

pylori infection depend on a complex interplay between host response to infection, environmental factors (eg, smoking, nonsteroidal anti-inflammatory drug [NSAID] use), age at the time of infection, and differing virulence of strains of *H pylori*. Strains expressing the protein products of the vacuolating cytotoxin A (*vacA*) gene and the cytotoxin-associated gene A (*cagA*) are associated with peptic ulcer disease.[4] However, commercially available tests do not yet distinguish strains of *H pylori*, and no combination of clinical factors predicts which infected persons will develop ulcers.

WHICH TESTS ARE MOST USEFUL AND COST-EFFECTIVE?

Testing for *H pylori* infection is important in patients with peptic ulcer disease. A negative test focuses the subsequent diagnostic evaluation on other causes of ulcers (eg, NSAID use, gastrinoma) and obviates antimicrobial therapy. False-negative results can occur, however, in patients who have received treatment with proton pump inhibitors, bismuth, or antibiotics, which may temporarily suppress *H pylori*.

Noninvasive *H pylori* tests

Serologic testing is the noninvasive method of choice for detecting *H pylori*. An enzyme-linked immunoadsorbent assay (ELISA) can detect IgG antibodies to *H pylori*. Inexpensive ($50–$75) and simple to perform, this test has a sensitivity of up to 99% and a specificity of up to 100%.[5] Tests that can be performed in a physician's office have slightly lower sensitivity and specificity. Unlike the breath tests, however, serologic tests are not useful for documenting that *H pylori* has been eradicated, since test results may remain positive for as long as 3 years after infection.[5]

Breath tests are the ideal noninvasive method for confirming that *H pylori* has been eradicated after treatment. However, not all patients need to be tested to confirm eradication. Patients needing testing are those with peptic ulcer disease complicated by bleeding, perforation, or obstruction, or patients with recurrent symptoms of dyspepsia after treatment.

In breath tests, patients ingest a pudding that contains urea labeled with either carbon 14 (which is radioactive) or carbon 13 (which is stable). The carbon 13 test is commercially available. *H pylori*, if present, breaks down the urea into ammonia and labeled carbon dioxide, which can be detected in the breath 30 minutes later (patients provide a breath sample by blowing up a balloon).

The carbon 13 breath test has an excellent sensitivity and specificity (90% and 96%, respectively).[1] In addition, it exposes patients to no radiation and, unlike serologic tests, reflects current infection only. Breath tests cost approximately $200 to $300.

Invasive (endoscopic) *H pylori* tests

The Campylobacter-like organism (CLO) test detects bacterial urease. It is the endoscopic test of choice for detecting *H pylori*, as it is fast, simple, and inexpensive, and has approximately 90% sensitivity and 100% specificity.[6] The CLO test costs approximately $10 (excluding the cost of endoscopy, which is considerable).

Histologic study, the gold standard, is mainly used if the CLO test is negative but *H pylori* infection is still suspected. Culture is tedious and no more sensitive than histologic

review of a biopsy specimen. The organism is best seen with special stains, such as Warthin-Starry or Giemsa (FIGURE 1). To increase the biopsy yield, it is advisable to sample both the fundus and the antrum. These tests are expensive because they involve endoscopy. Another drawback is that they require several days' wait to obtain results. Histologic analysis costs approximately $150.

WHICH TREATMENT REGIMENS ARE MOST EFFECTIVE?

H pylori eradication is difficult. No drug regimen is 100% effective, and in vitro sensitivity to antibiotics does not predict clinical efficacy. Treatment regimens are often complex and hence difficult to comply with. Furthermore, antibiotic resistance, especially to metronidazole and possibly to clarithromycin is a problem. There are a number of different regimens available (TABLE).

The major treatment regimens

Bismuth, metronidazole, and tetracycline ("triple therapy") is inexpensive and yields consistently high eradication rates, approaching 90%.[7] Side effects are common with this regimen, however, and dosing is complex and inconvenient.

Compliance is a key factor in predicting the success of this treatment. In one study, patients who took less than 60% of their trial medication had an eradication rate of only 69%, compared with 96% for those who took more than 60%.[8]

Omeprazole and clarithromycin was the first FDA-approved therapy for *H pylori* infection. This combination has approximately 83% efficacy and has a much simpler dosing schedule than does conventional triple therapy, but it costs more than $200.[9]

Ranitidine, bismuth, and clarithromycin is another FDA-approved regimen for *H pylori* infection. This combination has an efficacy of approximately 83% and is also simple to take and well tolerated.[10]

Omeprazole, metronidazole, and clarithromycin is another well-tolerated combination, with an eradication rate of approximately 90%.[11]

Omeprazole, bismuth, metronidazole, and tetracycline ("quadruple therapy"). Adding omeprazole to the triple-drug regimen increases its efficacy. In one study, omeprazole 20 mg twice daily plus five daily doses of bismuth 108 mg, metronidazole 200 mg, and tetracycline 250 mg eradicated *H pylori* in 122 (98%) of 125 patients (98%)—a previously unheard-of level of efficacy.[12] Adverse effects included nausea (7%) and oral discomfort (5%). The dosages we use for quadruple therapy are listed in the TABLE.

TABLE

COST AND EFFICACY OF DIFFERENT TREATMENT REGIMENS FOR *H PYLORI* INFECTION

Regimen (14 days)		Cost	Efficacy (%)
Bismuth	2 tablets four times a day	$30	90
Metronidazole	250 mg four times a day		
Tetracycline	500 mg four times a day		
Blister pack:		$75	90
Bismuth	2 tablets four times a day		
Metronidazole	250 mg four times a day		
Tetracycline	500 mg four times a day		
Omeprazole	20 mg twice a day	$132	95
Bismuth	2 tablets four times a day		
Metronidazole	250 mg four times a day		
Tetracycline	500 mg four times a day		
Omeprazole	20 mg twice a day	$177	95
Blister pack (Helidac):			
Bismuth	2 tablets four times a day		
Metronidazole	250 mg four times a day		
Tetracycline	500 mg four times a day		
Ranitidine/bismuth (Tritec)	400 mg twice a day	$186	80
Clarithromycin	500 mg three times a day		
Omeprazole	40 mg daily	$239	80
Clarithromycin	500 mg three times a day		
Omeprazole	20 mg twice a day	$201	90
Metronidazole	500 mg twice a day		
Clarithromycin	250 mg twice a day		

The author's treatment recommendations

Physicians should familiarize themselves with several regimens and prescribe one they are comfortable with. Patient compliance, patient education, adequate physician time to review medications, and cost all influence choices. The best eradication rates are obtained with quadruple therapy, which has an intermediate cost but complex dosing. Simpler regimens such as omeprazole and clarithromycin or ranitidine and clarithromycin may lead to improved compliance but decreased eradication rates. Dual therapy with amoxicillin and omeprazole is no longer appropriate, because of poor efficacy.

Patient education is vital

Patients in the "quadruple therapy" study mentioned above received both printed and oral instructions, which raises an important point. If an initial course of antibiotic therapy fails, subsequent attempts may be unsuccessful. Therefore, patient education is vitally important.

Physicians should emphasize that the regimen being prescribed is the patient's best hope of a cure, and talk about dosing, side effects, and implications of successful therapy.

Frequent side effects of anti-*H pylori* therapies include diarrhea, taste disturbance (especially with macrolides), and black stool (with bismuth).

WHOM TO TREAT?

All patients with active peptic ulcer disease who are documented to have *H pylori* infection should be treated.

Other patients who should undergo antibiotic therapy:

- Patients with ulcers in remission.
- *H pylori*-positive patients undergoing maintenance therapy with histamine$_2$ receptor antagonists (H_2 blockers) for chronic peptic ulcer disease.
- Patients with mucosa-associated lymphoid tissue (MALT) lymphoma, if staging indicates local disease.

Systemic symptoms call for immediate biopsy

Whom to possibly treat

Possible candidates for eradication treatment if infected with *H pylori* are:

- First-degree relatives of gastric cancer patients.
- Immigrants from countries with high prevalence of gastric cancer, such as Japan and third-world countries.
- Infected patients committed to long-term therapy with proton pump inhibitors.
- Patients with atrophic gastritis with intestinal metaplasia (determined by biopsy).
- Dyspeptic patients without ulcers. Counsel such patients about the ben efits and risks and costs of treatment. Inform them of the 50% chance that treatment will not relieve symptoms. Determine the patient's attitude after counseling, before proceeding with treatment.

THE DILEMMA OF DYSPEPSIA

Although we now understand the role of *H pylori* infection in peptic ulcers, its role in dyspepsia—persistent or recurrent abdominal pain or discomfort centered in the upper abdomen—is not as well understood. As a result, there is considerable debate about the proper approach to the diagnosis and treatment of patients with this common complaint.

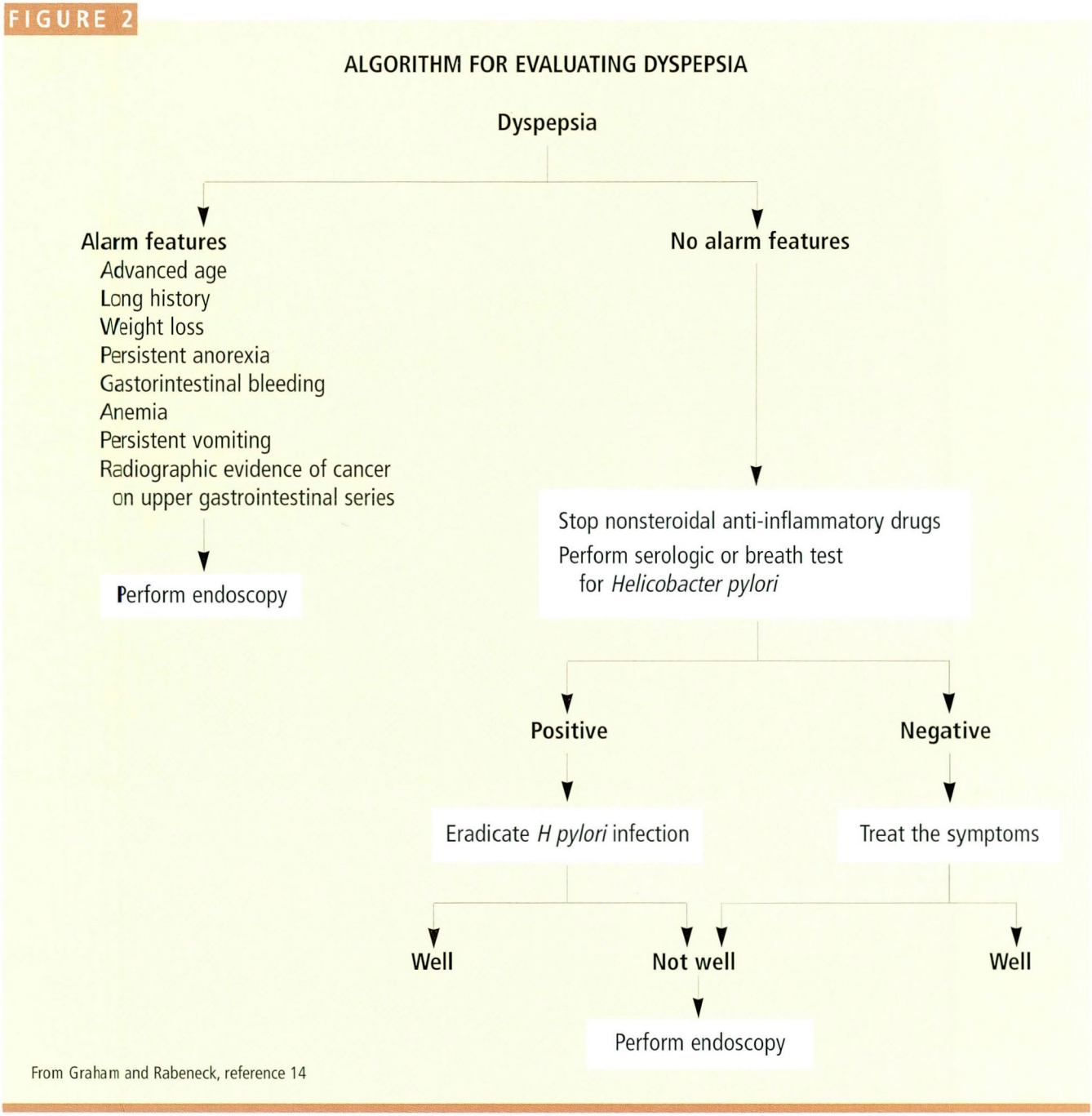
Currently, there are three possible approaches: a short trial of empiric antisecretory therapy with H_2 blockers or proton pump inhibitors, immediate endoscopy, or empiric antibiotic therapy for *H pylori*. In 1985 the American College of Physicians endorsed the approach of empiric antisecretory therapy, but this recommendation has not been updated for the *H pylori* era.

Even using the old approach of empiric antisecretory therapy, physicians must remember that immediate endoscopy is indicated for a subgroup of patients with obvious systemic symptoms such as weight loss, bleeding, nausea, and vomiting. Also, immediate diagnostic endoscopy is appropriate for patients with new onset dyspepsia who are over the age of 45 to 50 in whom gastric neoplasia is a possible diagnosis.

Because of the high prevalence of *H pylori* infection in patients with peptic ulcers, there are now advocates of empiric antibiotic therapy for patients with dyspepsia, to treat a presumed *H pylori* infection (with or without serologic confirmation of infection).[13]

It may still be premature to follow such an approach for a number of reasons. First, dyspepsia can represent a number of conditions: peptic ulcers, gastroesophageal reflux disease, gastroparesis, gallstones, functional dyspepsia, and gastric cancer. Diseases other than ulcers that can cause dyspepsia would go undetected with such a strategy, and presumably not benefit from therapy.

FIGURE 2



From Graham and Rabeneck, reference 14

Also, most patients with dyspepsia do not have ulcers and do not go on to develop ulcers, so they will not benefit from antibiotic therapy, but will increase their risks of developing antibiotic resistance and side effects. Finally, there are no prospective randomized clinical trials of empiric drug therapy for infected patients with dyspepsia.[13]

Instead of treating all dyspeptic patients with antimicrobial drugs, perhaps an approach similar to the one proposed by Graham and Rabeneck should be followed.[14] In this protocol, certain "alarm features" call for immediate endoscopy: advanced age, long history, weight loss, persistent anorexia, gastrointestinal bleeding, anemia, persistent vomiting, or radiographic evidence suggestive of cancer on an upper gastrointestinal series. Other patients undergo noninvasive tests for *H pylori* (FIGURE 2).

As for patients with functional dyspepsia, in which no clear cause can be found, the role of *H pylori* infection is confusing. Approximately 50% of patients who complain of symptoms of dyspepsia are infected with *H pylori*, but that is probably no greater than asymptomatic controls. Recent trials assessing

treatment of *H pylori*-infected patients with functional dyspepsia had serious methodological flaws.[15] Aggressive attempts to eradicate *H pylori* in patients with functional dyspepsia are still not warranted, as functional dyspepsia is most likely attributable to abnormal visceral perception of events in the stomach.

WHAT ABOUT *H PYLORI* AND CANCER?

The value of eradicating *H pylori* to prevent cancer is also unclear. Although the incidence of gastric cancer is declining in the United States, it remains the second leading cause of cancer death worldwide, and *H pylori* is associated with 40% to 60% of gastric cancers.[16]

Although the majority of patients with *H pylori* infection will not develop gastric cancer, factors such as diet, the strain of *H pylori*, and length of infection probably play a role. A recent study by Hannson et al found that the risk of developing gastric cancer was lower in persons with duodenal ulcers than in the general population, and only slightly higher than in the general population in people with gastric ulcers.[17]

Recent findings have shown that long-term therapy with proton pump inhibitors in patients with gastroesophageal reflux disease (GERD) and *H pylori* infection can result in more severe gastritis and, after 5 years of treatment, leads to gastric atrophy in 31% of patients. Gastric atrophy is a precursor of gastric cancer. Therefore, detection and eradication of *H pylori* is indicated in patients with GERD who will be committed to long-term proton pump inhibitor therapy.[18]

According to Parsonnet et al,[16] screening all persons between the ages of 50 and 54 years for gastric cancer might prevent 7500 cancer deaths per year, but would cost $996 million, or $25 000 per year of life saved.

H pylori infection is also associated with non-Hodgkin's lymphoma and MALT lymphoma, a low-grade subtype of non-Hodgkin's lymphoma of the stomach. Eradication of *H pylori* may cure up to 70% of persons with MALT lymphoma.[19] ■

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