Our Number	674224
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Service Type	Copy non returnable	Service Type	Loan
Media Type	Other	Media Type	Printed

Bibliographic Details	
Author	Lippincott Williams & Wilkins.
Title	Journal of clinical gastroenterology.
ISBN/ISSN	0192-0790
Control Number	000001415245, J16715000, 79642938, 2002214085
Publisher	Raven Press [etc.]
Call Number	JOU
Verification source	CISTI/INNOPAC
Article Details	
Volume/Issue	21 (supp 1)
Article Title	Managing acid peptic disease in the Helicobacter pylori era
Article Author	Marshall, BJ
Article Date	1995
Pagination	s155-9

Service Level	Core
Item Format	Print Journal
Request Created Date	25 Jul 2011 10:13
Expiry Date	05 Aug 2011
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J Clin Gastroenterol 1995;21(Suppl. 1):S155–S159.

Review

Managing Acid Peptic Disease in the *Helicobacter pylori* Era

Barry J. Marshall, M.D.

The advent of new diagnostic and therapeutic modalities for *Helicobacter pylori* allows any physician to offer curative antibiotic regimens to patients with peptic ulcer disease and gastritis. This article describes new management strategies and discusses the advantages of each. In the old strategy, endoscopy was performed on patients with dyspepsia, in the hope of detecting a treatable peptic ulcer. In the new strategy, patients with dyspepsia are investigated with serology to detect those with *H. pylori* and potentially curable peptic ulcers. Patients with persistent symptoms require a urea breath test and only those who are now *H. pylori*-negative undergo endoscopy. The cost-effectiveness of these strategies will depend on the expense of each diagnostic test, particularly endoscopy. Whether a noninvasive strategy can be implemented safely may depend also on the incidence of gastric carcinoma in a particular population and the effectiveness of antibacterial therapy at reducing cancer risk.

Key Words: *Helicobacter pylori*—Peptic ulcer disease—Gastritis—Management strategies.

Ten years after *Helicobacter pylori* was identified as "unidentified curved bacilli associated with gastritis and peptic ulceration" (1), most physicians and many gastroenterologists have still not embraced the new opportunities for therapy of these important diseases. With the recent consensus conference at the National Institutes of Health in Washington (2), the standard of practice for treatment of peptic ulcer has changed such that all peptic ulcer disease warrants investigation for presence of the new bacterium and treatment with antimicrobial therapy if evidence of *H. pylori* infection is found.

For the majority of doctors, principles of *H. pylori* management are unclear because they have not treated many patients and because the tools required for diagnosis and therapy have not been generally available. In view of the large number of patients with *H. pylori* and the massive increase in workload this new disease could produce in clinics where the disease is common, efficient and cost-effective plans are necessary. I propose here several algorithms that might achieve this goal. Although the necessary comparison studies have not been performed to validate these methods, I have used them successfully in my own clinic over the past 10 years.

WHOM TO TREAT?

The diseases associated with *H. pylori* are gastritis, peptic ulceration, and gastric cancer. The link between nonulcer dyspepsia and HP is less certain and is discussed briefly below. Of the above three, the main indication for therapy is peptic ulceration. In the patient who does not take nonsteroidal anti-inflammatory drugs (NSAIDs), at least 80% of gastric and duodenal ulcers are associated with *H. pylori*. Both types of ulcers heal well when antimicro-

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bial therapy is added to current regimens, and relapse rates are greatly reduced after *H. pylori* eradication (3–5). Even in patients who do take NSAIDs, *H. pylori* should be considered, because it may be the easiest risk factor to remove in those who cannot easily discontinue the NSAID. Although the most important factor (*H. pylori* or NSAID) cannot always be determined in individual cases, eradication of *H. pylori* should at least return an inflamed mucosa to normal and may ultimately decrease acid secretion (6). According to the National Institutes of Health (NIH) consensus statement, all ulcer patients should be tested for *H. pylori* and treated if they have it.

The need for *H. pylori* investigation and antimicrobial therapy in patients with gastric adenocarcinoma is uncertain, because once cancer has developed it is unlikely that eradication of the bacterium will cause remission (therapy, if any, will usually be surgical). On the other hand, a patient with adenocarcinoma who is vomiting may present a risk to his or her family from disseminated *H. pylori*. Each case should be considered on its individual merits.

Gastric lymphoma (both MALT type and other non-Hodgkin's lymphoma) has been associated with *H. pylori* in a number of studies. Remarkable remissions have been reported by a few authors when the low-grade MALT-type lymphoma is treated by eradication of associated *H. pylori* (7). Further data are required, but at present it appears prudent to eradicate *H. pylori* before committing a patient with relatively indolent disease to chemotherapy or surgery (8–10).

WHOM TO DIAGNOSE?

The patients in whom *H. pylori* is diagnosed should be those in whom therapy is deemed worthwhile. In addition to the obvious examples cited above, diagnosis and therapy might be considered in patients with chronic upper gastrointestinal complaints that are consistent with a clinical diagnosis of peptic ulcer. Whether an actual peptic ulcer must be demonstrated before the doctor embarks on therapy is uncertain and controversial at present. In my opinion, because *H. pylori* is now easy to diagnose and safe to treat, only the cost-effectiveness of such a "blunderbuss" approach needs to be debated. For example, if antimicrobial therapy of ulcer cures the disease, we could easily treat all symptomatic patients with *H. pylori*, with the result that ulcer patients (perhaps 30% of this group) will all be cured in the process. It may be cheaper to do it this way rather than to investigate all patients with barium study or endoscopy where three investigations would be necessary to detect one ulcer patient. In countries where endoscopy is relatively inexpensive (e.g., Japan), there may be cost savings in obtaining a more accurate initial diagnosis in all patients rather than using the above approach. In the United States however, it would cost about $3,000 to diagnose one ulcer, so it is less expensive to treat three patients ($450) even if two do not have an ulcer. Diagnosis might also be worthwhile in first-degree relatives of patients with stomach cancer, because these relatives might have a higher incidence of gastric cancer (11). Finally, when patients undergo reinfection or repeated treatment failures, reinfection from a close family member (spouse) needs to be considered. In this case, it makes sense to test the spouse for *H. pylori*, regardless of clinical state, and to treat him or her if *H. pylori* is present.

METHODS OF DIAGNOSIS

Noninvasive Methods

Serum Antibody Tests ("Quick Tests," Yes/No Answer)

Latex agglutination and membrane colorimetric tests are examples. These tests are usually performed on serum, but whole-blood versions are becoming available. About 10–15% of test results are incorrect (false-positives and false-negatives). Nevertheless, in patients with a high index of suspicion, therapy can be initiated on the basis of a positive test. If a positive "quick test" becomes negative 3 months after therapy, then cure can be assumed. A persistent false-positive test is common after therapy (6–12 months), so these should be confirmed with another method before further treatment of *H. pylori* is performed.

Lab-Based Tests (Quantitative Titer)

If a physician's office does not have "quick" serology (see above), laboratory-based serum tests are a more accurate and convenient alternative. They can also be used to confirm a "quick" test and to obtain a quantitative baseline antibody titer before therapy is commenced. Laboratory-based serum tests use an ELISA reader to accurately quantitate the amount of antibody present. Falling antibody titers at both 3 and 6 months after therapy, even if still in the positive range, will indicate cure of *H. pylori*.

Although serologic tests are less expensive than breath tests (see below), several samples may be needed in the months after therapy to confirm cure of *H. pylori*. Therefore the breath test may be a more immediate and inexpensive test to use in follow-up. If the breath test is available, then a "quick" test may be sufficient for diagnosis because comparison of baseline and convalescent serology data will not be required.

Breath Tests

Urea Breath Tests. The most important use of breath tests is to confirm cure or persistence of *H. pylori* at times when antibody tests are inaccurate, such as in the post-treatment period. This is especially useful when patients continue to have symptoms after treatment and the physician needs to know whether to perform endoscopy or simply to treat again with antimicrobials.

Breath tests can indicate cure of *H. pylori* 2–4 weeks after antibiotic therapy, at a time when antibody tests will still give a positive result. Breath tests measure the actual presence of *H. pylori* in the stomach by detecting its urease enzyme. Breath tests are highly specific and very sensitive, with accuracy rivaling that of biopsy.

Breath tests can give false-positive results in patients who have had gastric surgery or who are receiving omeprazole, because both conditions result in achlorhydria with overgrowth of urease-producing commensal organisms from the mouth. False-negative breath tests easily occur in the same situations, but especially in patients who secretly take bismuth or antibiotic in the days before the test. Some other medications that might interfere with diagnostic tests are listed in Table 1.

^{13}C Breath Tests. For the [^{13}C]urea test, patients eat a semiliquid meal and then drink urea solution. Breath is transferred from a collection bag to vacutainers. Samples are taken at intervals for about 1 h and are mailed to the lab. Various modifications exist. The ^{13}C tests are non-radioactive but more expensive, costing about $50 U.S. at the least expensive European centers.

^{14}C Breath Tests. The [^{14}C]urea test can be done in the same way as the ^{13}C test, but the isotope can also be given in water or capsule form without a meal. Time is therefore saved and the test is simpler, with less expense to the patient. The small amount of isotope (usually 3–5 μCi) is quickly excreted as urea or CO_2, so radiation exposure is very small and of no consequence to the patient.

Microdose ^{14}C Breath Test. The newest example of the ^{14}C breath test is the microdose test now under evaluation in the U.S.A. In this test, the fasting patient takes only 1 μCi of [^{14}C]urea in a capsule. Twelve minutes later a single 2-L breath sample is collected in a special balloon, and this is mailed to the laboratory for scintillation counting. Because of the short collection time, the single sample, and the presence of beta counters in most medical centers, this test is less expensive than the ^{13}C test. The radiation exposure also is extremely low. For example, a mammogram exposes a patient to an equivalent of 150 such breath tests, and a barium meal could easily exceed 1,000 breath tests (12).

TABLE 1. *Delay before biopsy diagnosis of* H. pylori

Sucralfate	2 days
Omeprazole	1 week
Antibiotics[a]	2–4 weeks
Bismuth[a]	2–4 weeks

[a] The standard for confirming cure of *H. pylori* is to wait 4 weeks after therapy before repeating histologic studies (or breath test). Some data, however, suggest that when used carefully by an experienced investigator, tests at 14 days after therapy are almost as sensitive as detecting early *H. pylori* relapse (13,14).

TABLE 2. *Summary of* H. pylori *diagnosis*

Test	Role
IgG quick serology test (usually on serum, some on whole blood)	Screening in patients with clinical suspicion of peptic ulcer disease; negative test makes other diagnosis more likely
IgG ELISA (serum)	Confirms rapid test, provides baseline titer that can be referred to later
[^{14}C] and [^{13}C]Urea breath tests	The best tests for follow-up of patients 28 days after antibiotic therapy; also used to determine true result of equivocal serology test
Biopsy rapid urease tests (e.g., CLO test)	Rapid screening for *Helicobacter pylori* in patients undergoing endoscopy
Histology	The gold standard biopsy test for patients undergoing endoscopy; provides permanent record of *Helicobacter pylori* diagnosis; far more expensive than urease test
Culture	Special role when patient fails therapy twice and antimicrobial susceptibility testing is needed

Invasive Methods (Endoscopy and Biopsy)

False-negative results occur when patients have taken medication that inhibits *H. pylori*. When patients are suspected to have taken such medication, the physician should back up initial biopsy results with serology. As with the breath test evaluation, physicians should postpone elective endoscopy for 2–4 weeks when patients have taken bismuth or antibiotics (see also Table 1).

A few false-negatives occur with all biopsy methods, mainly due to sampling error (patchy *H. pylori* distribution). The physician should also perform serology studies if the diagnosis of *H. pylori* is crucial to the patient's management. The inexpensive combination of a rapid urease test and serology could be expected to give almost 100% accuracy in patients with concordant results from both tests. Gram stains and other microscopy may give rapid results but require a technician and are not practical for most gastroenterologists. These have been replaced by the rapid urease test.

Culture does not have an important role at this time. It is useful in patients who have failed therapy and may have resistant organisms. Sensitivity to erythromycin, metronidazole, and quinolones may help to guide further therapy. A reasonable gold standard for *H. pylori* presence or absence is still histology, with tissue stained by Giemsa. Each specimen has a sensitivity of around 90%, and therefore at least two biospy samples must be taken. If the time and expense can be justified, accuracy of histology is greatest when silver stains such as Warthin Starry are used, but in most instances Giemsa is sufficient. Biopsies are usually taken from the antrum. Avoid the immediate pre-pyloric and distal lesser curve areas. For *H. pylori* diagnosis, do not biopsy lesions but take rather the samples from intact mucosa. If your pathologist is not confident with the diagnosis, you should back up histology with a urease test. Practical use of diagnostic methods is outlined in Table 2.

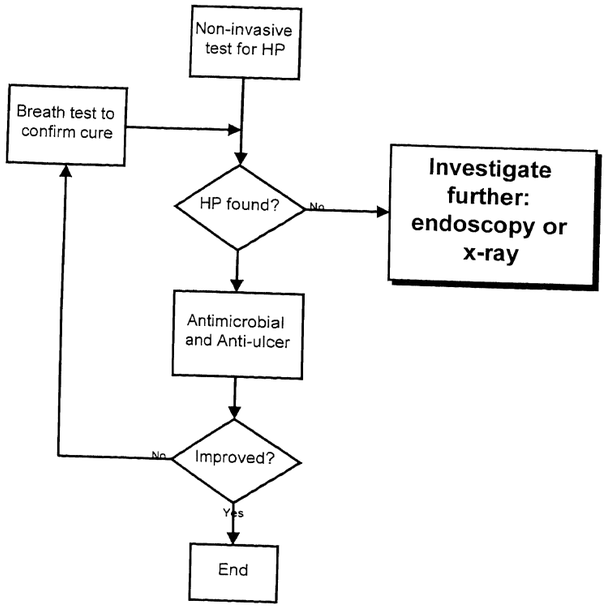

FIG. 1. Algorithm for management of *Helicobacter pylori* infection.

METHODS OF TREATMENT

Inexpensive Therapies for Initial Treatment

The least expensive therapy to use in most countries is triple therapy with bismuth, tetracycline, and metronidazole. The cure rate is slightly lower if amoxicillin is used instead of tetracycline, but the regimen can be given to children below the age of 12 years. Triple therapy may be associated with diarrhea in about 30% of patients, but several investigators have reported excellent efficacy with a 7-day therapy, so that 14-day treatment can be curtailed to 7 days if side effects are severe.

When ulcer patients are already taking ranitidine, it is very inexpensive to add amoxicillin and metronidazole to their therapy for 14 days. This therapy was advocated by Hentschel et al. (5), with excellent results. In Brazil, bismuth, furazolidone, and metronidazole have been used with similarly high cure rates (>70%).

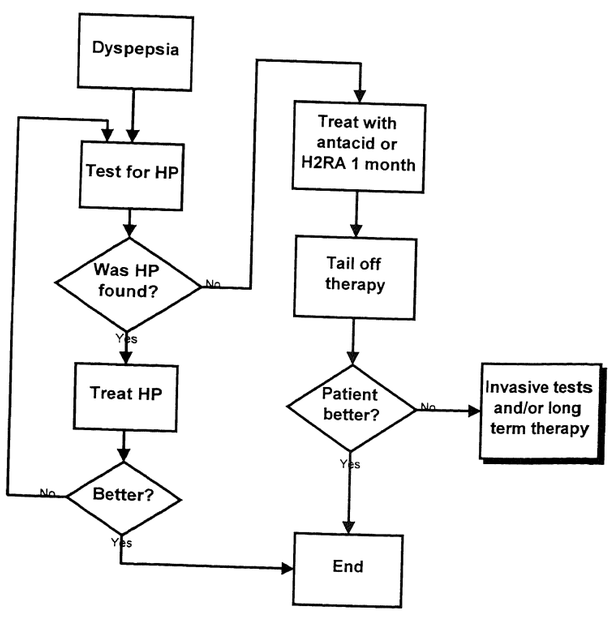

FIG. 2. Algorithm for the management of dyspepsia in the *Helicobacter pylori* era.

More Expensive Therapies for Recurrences

Without doubt, the therapies with the fewest side effects are those in which omeprazole 20 mg b.i.d. is combined with amoxicillin 2 g q.d. or clarithromycin 1–1.5 g q.d. Both give cure rates of greater than 80% over 14 days and require only a few tablets per day, thus increasing compliance. If metronidazole 1 g q.d. is added to these therapies, then cure rates of greater than 90% can be achieved.

When patients fail therapy, the physician should use a different therapy for retreatment. For example, if the initial therapy contained metronidazole, then retreatment should be done with an amoxicillin or clarithromycin combination.

FINAL ALGORITHM FOR TREATMENT OF INFECTION

Figure 1 shows an algorithm for ordinary treatment of *H. pylori*. All patients should have diagnosis confirmed before therapy and symptomatic patients should not be treated again without confirmation of persistent infection. The trigger for a noninvasive test should be the need for any chronic therapy for symptoms of dyspepsia. Therefore, serology might easily be requested at the time a patient receives the first prescription for an H_2-receptor antagonist.

FINAL ALGORITHM FOR MANAGEMENT OF DYSPEPSIA

Figure 2 shows an algorithm for management of dyspepsia in the *H. pylori* era. Patients are tested for *H. pylori* and are treated if positive. If they are still symptomatic after therapy, further diagnosis and possible therapy are considered (left-hand loop). Once *H. pylori* has been eradicated, patients who feel well undergo no further investigation or treatment. Luckily, double-blind data predict that most patients with ulcers will fall into the group rendered asymptomatic.

Patients who are *H. pylori*-negative initially, or who are still symptomatic after eradication of *H. pylori*, are unlikely to have peptic ulcer disease and may have a more severe or even malignant condition. Therefore, endoscopy or barium study is indicated (right-hand loop). On the other hand, good response to acid-reducing therapy or clear clinical evidence of benign disease, such as mild esophageal reflux, might encourage the physician to postpone any invasive investigation and continue H_2 receptor antagonists.

In areas where gastric cancer is more common, such as Japan and Latin America, inexpensive endoscopy or a barium meal would tend to encourage earlier investigation, perhaps after an initial clinical treatment failure. In the United States, however, initial therapy for *H. pylori* is likely to provide major cost savings, since invasive testing might then be unnecessary in a proportion of patients.

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