CME CREDIT

ALAN F. CUTLER, MD
Associate professor of medicine, Wayne State University School of Medicine, Detroit

EDGAR ACHKAR, MD
Vice chairman, Department of Gastroenterology, Cleveland Clinic

Eradicating *H pylori* in nonulcer dyspepsia: 7 reasons for vs 7 reasons against

A spirited debate on the value of *H pylori* testing and treatment

This article is based on a debate that took place during the 35th Annual Gastroenterology Update at the Cleveland Clinic.

CASE STUDY

A 47-year-old woman comes to you seeking a second opinion regarding her 2-year history of upper abdominal discomfort. She has not been diagnosed with ulcer. The patient describes her discomfort as an aching in the epigastrium without radiation. The pain occurs three times per week and lasts approximately 15 minutes. There are no precipitating or relieving factors. She has no other associated signs or symptoms. Antacids, over-the-counter H_2 blockers, and proton pump inhibitors have failed to provide significant relief. The woman is not taking any other medications.

One month earlier, she had an upper gastrointestinal tract endoscopy; no biopsy was performed during the procedure. Endoscopic results were normal except for antral erythema. Her medical history is unremarkable, and her surgical history includes only tubal ligation. She drinks one cup of coffee per day and one cola three times per week. She does not smoke.

On physical examination, her temperature is 37.2°C (98.9°F), blood pressure 128/68 mm Hg, and heart rate 85 beats per minute. Her head, eyes, ears, nose, throat, heart, lungs, and extremities appear normal. There is tenderness to palpation at her abdomen, but no organomegaly or masses, and her bowel sounds are normal.

THE OPTIONS

- Test for the presence of *Helicobacter pylori* infection and treat it if present
- Prescribe treatment for *H pylori* empirically
- Disregard *H pylori* and prescribe an acid suppressant or motility agent, or
- Simply reassure the patient that her condition is not serious and that no further tests or treatment are necessary.

What would you do?

This question was posed to Dr. Alan Cutler, a firm advocate of eradicating *H pylori* in these circumstances, and to Dr. Edgar Achkar, who is just as adamantly opposed to doing so. In this spirited debate, each provides seven reasons for their convictions.

THE CASE FOR TREATING *H PYLORI* IN NONULCER DYSPEPSIA

DR. CUTLER: Of the four options available for this patient, I have no doubt that testing for *H pylori* and treating it if it is present is the completely appropriate choice. Consider the circumstances. An uncomfortable patient with antral erythema comes to you seeking relief. Because her endoscopy, strangely enough, did not include a biopsy, we don't know her *H pylori* status. But regardless of her specific pathology, her gastric mucosa is not normal and she is in distress. So merely reassuring her and sending her on her way is not an option. Prescribing acid suppressants and motility agents might work, but not as well as anti-*H pylori* therapy. As for empiric anti-*H pylori*

therapy, gastroenterologists agree that this is not a wise course.

What we are left with, then, is no choice at all. But there is more to this decision-making exercise than simply the process of elimination. There are seven good, independent reasons to test for and treat *H pylori* in patients with nonulcer dyspepsia.

1. Treatment sometimes works

I concede that the scientific evidence is not solid and that there are contradictory studies. But in that mix there is still enough evidence that eradicating *H pylori* in patients with nonulcer dyspepsia works often enough to be worth the effort. In 1997, Lee and O'Morain[1] published an analysis of all existing guidelines and evidence regarding *H pylori* and dyspepsia. They reported that some studies showed that eradicating the bacterium cured dyspepsia, while others showed that it didn't. But the important thing is that it did work sometimes. Therefore, it might help the patient in our case. At least it's worth a try.

Furthermore, research conducted since then has suggested that although we may not see much in the way of short-term gains in this area, there may well be benefits over the long term.

For example, McColl et al[2] conducted in Scotland a randomized, double-blind, placebo-controlled, long-term study of the benefits of eradicating *H pylori* in patients with nonulcer dyspepsia. It was a well-designed study: their definition of dyspepsia was very strict, their sample size of 318 patients was adequate, their antibiotic regimens were optimal, and their definition of treatment success was appropriate. They found that 12 months after treatment, patients with nonulcer dyspepsia who had taken a proton pump inhibitor plus an antibiotic had a significantly greater rate of resolution ($P < .001$) than did those who took only a proton pump inhibitor. One point of contention with these results—one that I know hasn't escaped Dr. Achkar's attention—is that the cure rates in the two groups were only 21% and 7%, respectively. I admit that these rates are low. But remember that the definition of dyspepsia and discomfort was the strictest ever used in a study. These patients had almost no symptoms, so of course the resolution rates were low. But the bottom line is that it was a controlled study, and no matter how you slice it, 21% is greater than 7%.

No significant difference was found in the OCAY (Omeprazole plus Clarithromycin and Amoxicillin Effect One Year after Treatment) study,[3] which was published simultaneously with McColl's paper. This study was also well designed, but its criteria for dyspepsia were not quite as strict. The OCAY investigators studied 328 patients and found that 12 months after treatment the resolution rate in the group that had taken a proton pump inhibitor plus an antibiotic was 27%, while the rate in the group that took only a proton pump inhibitor was 21% ($P = .17$). In defense of these results, I will dispense with a long explanation of statistical arcana and say only that this study was designed to detect a benefit of 20%—not 10% or 15%—and perhaps it lacked adequate power.

2. Treatment will prevent ulcer recurrence

We are told that this patient does not have an ulcer, but ulcers come and go. All gastroenterologists have seen on endoscopy a site where an ulcer was but isn't now. The mucosa heals between flare-ups. On the other hand, some old ulcer sites are not apparent on endoscopy. It is possible that our patient may have had intermittent ulcer disease in the past, but the endoscopist could not see evidence of it. Footprints in the snow are not always as obvious today as they were yesterday.

'Eradicating *H pylori* cured dyspepsia sometimes'
—Dr. Cutler

Because our patient has no evidence of an ulcer now does not mean she has not had one. If so, it could recur. Therefore, we ought to look for and eradicate *H pylori* to prevent recurrence.

3. Treatment may relieve gastritis

I believe there is an association between dyspepsia and gastritis. It may be poorly defined and we may not understand it well, but I believe it exists. *H pylori* produces bacterial products that may be noxious to the mucosa and the vagus sensory system. Some patients have a visceral hypersensitivity that is activated by *H pylori* and makes them uncomfortable. Moreover, *H pylori* can affect motility and produce gas, bloating, and discomfort. Eradication

of this pathogen, therefore, should alleviate gastritis, at least in some patients.

An unpublished subgroup analysis of the OCAY study found that 32% of the patients whose gastritis had healed experienced symptom resolution, compared with only 17% of those whose gastritis went unhealed. This difference was statistically significant. Again, treating *H pylori* offers a possible symptom benefit with little risk.

4. *H pylori* is associated with cancers

H pylori has been identified as a risk factor for gastric cancer. The World Health Organization classifies it as a class I carcinogen. *H pylori* has been associated with gastric adenocarcinoma, lymphoma, and mucosa-associated lymphoid tissue (MALT) lymphoma. Again, I concede that there is a scarcity of prospective cancer studies (some studies are currently under way). In lieu of prospective studies, let us consider two other factors: event sequence and modeling.

Sequence of events. Look at the event sequence and you will see that gastritis leads to atrophy, which leads to intestinal metaplasia, which leads to dysplasia, which leads to cancer. It has been shown in multiple studies that treating *H pylori* cures gastritis. There is some question whether it can reverse atrophy, but there is evidence that it may reverse intestinal metaplasia. Therefore, it is possible that intervention can interrupt the chain of events that leads to gastric cancer.

'Detecting *H pylori* obligates us to treat it' —Dr. Cutler

In addition, a study[4] from Japan looked at 132 patients who underwent excision of gastric malignancy. Afterward, half these patients were treated for *H pylori* and none of them experienced a recurrence of their cancer. But among the 67 patients who were not treated, there were six recurrences (9%).

Modeling. In the absence of clinical trials, which we are not going to see anytime soon, we have to rely on modeling. Parsonnet et al[5] conducted what is still the best study to date analyzing the modeling of treatment efficacy and cost-effectiveness in preventing gastric cancer. They found that if you treat everyone with *H pylori* infection, you would have to prevent gastric cancer in only 20% to make the effort cost-effective. Some subgroups fared even better. For African-American and Japanese patients, the threshold is only about 10% or less. It is clear that it takes only a small degree of efficacy to prevent gastric cancer.

5. Because it's there

We must treat *H pylori* simply because we're doctors and it's a disease. Keep in mind that the decision to treat must be made before any tests are run. It makes little sense to look for *H pylori* and then do nothing if you find it.

Medical considerations aside, there are legal ramifications. Detecting *H pylori* obligates us both medically and legally to treat it.

6. Treatment is cost-effective

Many studies have shown that eradication rates following *H pylori* treatment exceed 90%. If the pathogen is eradicated, symptoms of dyspepsia and gastritis may disappear as well. And don't discount the placebo effect, which I gratefully accept. Second, if you don't treat *H pylori*, you will have to do something else that probably will not be cost-effective. If you can treat the patient early, you will save money because you will avoid a lot of other workup.

The case study we are discussing here is unusual for two reasons: the referring physician had performed an endoscopy, and he did not perform a biopsy while doing so. He not only conducted the most expensive test first, he did not allow himself the opportunity to obtain any information from it. Obviously, this was not a cost-effective approach.

Ofman et al[6] found that a cure rate of only 5% would be necessary to make serologic testing of all patients with dyspepsia symptoms cost-effective. Such is not the case with initial endoscopy. It is not wise to front-load your costs by running an expensive test first.

7. Treatment will help future generations

Eradicating *H pylori* will prevent a child from inheriting it from a parent. Thus, the child will not be exposed to the increased risks of ulcer and gastric cancer. Treating *H pylori* benefits more than the individual patient.

In summary, the decision to treat *H pylori* in this patient is obvious. It will relieve her symptoms with little risk. It will prevent ulcer recurrence, gastritis, and gastric cancer. It will also reduce the need for further diagnosis and

treatment, thereby saving money. It is the natural order of things.

THE CASE FOR NOT TREATING *H PYLORI* IN NONULCER DYSPEPSIA

DR. ACHKAR: I want to make three things clear before I explain my position on this case. First, my arguments pertain to dyspepsia, not peptic ulcer disease. I firmly believe that peptic ulcer disease demands that we look for and treat *H pylori*. Second, I agree that if you order a test, you must deal with the result. Otherwise, there is no point in ordering the test. Finally, I am not impressed with the concept of endoscopic gastritis. I don't believe that gastric erythema is very relevant clinically.

As far as this case is concerned, I would not treat this patient's dyspepsia by looking for or eradicating *H pylori*. Such a strategy is not appropriate for the following reasons.

1. There is no clear association between dyspepsia and *H pylori*

Both dyspepsia and *H pylori* are very common. Twenty-five percent of all Americans have reported dyspepsia to their physicians in the past year, and dyspepsia and dyspepsia-like symptoms account for 2% to 5% of all family practice consultations. Likewise, *H pylori* is very common. Yet only a small proportion of persons infected with *H pylori* experience dyspepsia, and a large number of patients with dyspepsia do not harbor *H pylori*, according to a recent study from the Netherlands.[7]

2. The cause of dyspepsia is ill-defined

The common definition of dyspepsia is "a persistent or recurrent abdominal pain or discomfort centered in the upper abdomen in patients who have no definite structural or biochemical explanation for their symptoms." Dozens of conditions fit this definition, so when we attempt to treat dyspepsia, we don't know exactly what we're treating. At best, we can narrow the possibilities and place patients into two general categories:

- Those who complain of acidity-like symptoms—heartburn and epigastric distress—for whom antacids sometimes work and sometimes don't, and
- Those who complain of bloating, nausea, and discomfort after eating. These two categories of symptoms require different medications. Even so, about half of the patients have a little of both.

Dyspepsia is a syndrome that overlaps other functional syndromes. Many patients with dyspepsia also have irritable bowel syndrome, fibromyalgia, psychiatric problems, depression, anxiety, etc. Also, even though we now know that stress doesn't cause ulcer, that doesn't mean it can't cause dyspepsia. In fact, I am convinced that stress and dyspepsia go hand and hand.

Is the presence of *H pylori* a rational explanation for dyspepsia? Or is it just a convenient one? I believe it is the latter. Because of our inability to identify a specific cause of dyspepsia, it is difficult to justify *H pylori* treatment on a large scale. Our desire to do *something* to help our patients must be realistically balanced against the consequences of doing nothing.

3. The evidence is not convincing

This is the age of evidence-based medicine. We are told by peers, policy-makers, and insurers that they will not support any finding without definitive proof. Where is the proof? Dr. Cutler mentioned the McColl[2] study, in which only 21% of patients with nonulcer dyspepsia improved after treatment for *H pylori* and the response rate in the control group was only 7%. Despite the statistically significant difference, neither figure is impressive. Should we tell our patient that she has only a 21% chance of improving, but she shouldn't be discouraged because the *P* value is significant?

Dr. Cutler also admitted the results of the OCAY[3] study were not statistically significant. He did not mention the ORCHID (Optimal Regimen Cures Helicobacter-Induced Dyspepsia)[8] study from Australia. In that study, 278 patients with dyspepsia and *H pylori* infection were treated with either omeprazole plus two antibiotics or with placebo. One year following treatment, the resolution rates for dyspepsia were 24% and 22%, respectively. So there is no evidence that treating dyspepsia by eradicating *H pylori* is effective. In fact, what evidence we do have is to the contrary.

'Is *H pylori* a rational explanation for dyspepsia or just a convenient one?'
—*Dr. Achkar*

4. There is no evidence that eradicating *H pylori* will prevent other diseases

There is no evidence that eradicating *H pylori* will prevent peptic ulcer, antral gastritis, gastric cancer, or MALT lymphoma.

There is no correlation between the frequency of *H pylori* infection and peptic ulcer disease. In the United States, *H pylori* rates among women and men are equal, yet men develop ulcer twice as often. India has one of the highest incidences of *H pylori* in the world, but the incidence of ulcer disease there is one of the lowest. Furthermore, it is not rational to treat dyspepsia in the hope of preventing ulcer when we already have effective treatments for ulcer when it does arise. Finally, the incidence and virulence of ulcer has already been declining for many years.

The importance of antral gastritis is not well understood, so any attempt to prevent it at such a high cost is not justified.

The connection between *H pylori* and gastric cancer is well established, but there is no evidence that eradicating the former will prevent the latter. Finally, MALT lymphomas are rare, and they respond quite well to treatment when they are discovered.

'Before a treatment can be cost-effective, it must first be effective'
—Dr. Achkar

5. Indiscriminate eradication of *H pylori* may be harmful

The dangers of antibiotic resistance are well known. Some physicians who would not dream of prescribing doxycycline prophylaxis against diarrhea for an overseas traveler have no qualms about prescribing two antibiotics for a common disorder such as dyspepsia. I believe that is not responsible.

Second, a great number of people on any antibiotic combination develop *Clostridium difficile* colitis. I'd rather have dyspepsia.

Finally, it is possible that *H pylori* eradication may predispose patients to gastroesophageal reflux disease, although I concede that the evidence for this is highly speculative.

6. Indiscriminate treatment is not cost-effective

It would seem logical that treating dyspepsia with a drug regimen for 1 or 2 weeks is less costly than submitting patients to a variety of tests such as endoscopy, serology, and histology over a long period of time. However, the initial cost savings have to be measured against the potential side effects of the drugs. One must also consider the fact that many of these patients will still eventually need further testing.

Dr. Cutler mentioned the study by Ofman et al[6] which, in addition to reporting that initial serology for all patients with dyspepsia was cost-effective, also found that initial anti-*H pylori* drug therapy was more cost-effective than initial endoscopy. They wrote, "The financial effect of a 252% increase in the use of antibiotics for initial *H pylori* therapy is more than offset by reducing the endoscopy workload by 53%." Of course drug treatment is less costly. But what bothers me is that, relative economy notwithstanding, costs are still running amok. We are spending money without evidence that our expenditures are worthwhile. For example, Dr. Cutler cited the study by Parsonnet et al[5] that showed that preventing cancer by treating *H pylori* is cost-effective, but there still is no proof that treating *H pylori* does indeed prevent cancer. Before a treatment can be cost-effective, it must first be effective. I fail to see that this treatment is.

7. The medical establishment is not sure

In 1994, a National Institutes of Health consensus group clearly recommended that we not look for or treat *H pylori* in patients with dyspepsia.[9] But in 1998, the American Gastroenterological Association (AGA) recommended that a trial of eradication therapy be initiated in these patients when *H pylori* infection is documented.[10] However, the AGA's rationale for such treatment does not seem to have anything to do with dyspepsia. The AGA wrote, "The rationale is that ulcer disease will heal, and the ulcer diathesis will be abolished." Apparently unable to make a persuasive case for its recommendation, the AGA fell back on the ulcer argument.

What's more, the AGA's position paper was accompanied by an exhaustive technical review of the entire issue, in which the authors addressed all aspects of treatment.[11] In their summation, they wrote that the decision whether to treat *H pylori* should be based not only on cost, but on "other considerations

such as patient and physician attitudes toward uncertainty [and] the ethics of not identifying a curable disease…[G]uidelines may therefore easily endorse any of these management approaches, depending on the weight of circumstances in different regions." I don't consider this very strong advice. It is obvious to me that the experts and policy-makers in the field are still not sure which course of action is best.

When I see a patient with dyspepsia, first I rule out disease, and then I prescribe either an acid suppressant or a motility agent, which I sometimes alternate.

REBUTTALS: ANTIBIOTIC RESISTANCE, ULCER, AND REFRACTORY DYSPEPSIA

AUDIENCE QUESTION: Dr. Cutler, how do you counter Dr. Achkar's arguments about the potential risks of treatment?

DR. CUTLER: With respect to antibiotic resistance, remember that *H pylori* is passed from parent to child genetically. It is not a contagious infection that spreads like pneumonia. So in this regard, antibiotic resistance is not a community issue, it's an individual matter. Second, the incidence of *C difficile* colitis following *H pylori* treatment is exceedingly low. I've seen it only once so far in the hundreds of patients I've treated.

AUDIENCE QUESTION: One of the arguments in favor of aggressive therapy for *H pylori* is that it might prevent other diseases, particularly ulcer. Dr. Achkar, why don't you support this line of reasoning?

DR. ACHKAR: I just don't see the point of trying to prevent ulcer in patients with dyspepsia, because the group of patients you would have to treat is so large that it's not practical. We are quite capable of treating ulcer when we know it's there.

AUDIENCE QUESTION: Dr. Cutler, you said ulcers come and go. A patient has symptoms, he comes to see you, and you perform gastroscopy. If you don't find any lesion, then his symptoms have nothing to do with ulcer. So why treat that patient?

DR. CUTLER: There are two fallacies inherent in the question. The first is that patients have symptoms only when their ulcer is active. I know that ulcers are transient. I have had patients come to me with symptoms, and I've found dormant duodenal scars. I do not believe that all patients present only when their ulcer is active.

The second fallacy is that we are able to perform endoscopy right away when a patient comes to the office. We can't, of course. In the Detroit area, the lag between the time you see a patient and the time you obtain authorization from an HMO to perform the procedure is 21 days. So we ordinarily have to schedule the procedure for 28 days from the office visit.

If you look at all the studies published in the past 5 years, you will see that patients don't always have symptoms when they have active ulcers, and they don't always have active ulcers when they have symptoms.

AUDIENCE QUESTION: Dr. Achkar, what do you do for refractory dyspepsia? Say you see a patient who has unremitting epigastric pain, who has had endoscopy numerous times, and who has been on every possible medication. Would you still refuse to prescribe *H pylori* eradication therapy just because the evidence doesn't meet your standards?

DR. ACHKAR: I do see patients like this, and by the time I do, most of them have already been treated for *H pylori*. In such patients, we have to look at other functional disorders. Many of these patients have a serious psychological problem in their background. Some have had their gallbladders removed even though no stones were found. Some have had a half-dozen endoscopies and CT scans, and are grossly overweight. What I do for these patients is something that is difficult, time-consuming, and not very well received. I shift my focus to their other functional disorders and I encourage them to follow through on my referral to someone who can help them on that level.

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ADDRESSES: *Alan F. Cutler, MD, Digestive Health Consultants, 31500 Telegraph Road, Suite 220, Bingham Farms, Michigan 48205. Edgar Achkar, MD, Department of Gastroenterology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195.*