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Treatment of *Helicobacter pylori* in nonulcer dyspepsia: Should we or shouldn't we?

ABSTRACT

Two recent trials of treatment to eradicate *Helicobacter pylori* in infected patients with nonulcer dyspepsia seemingly came to opposite conclusions: one found such treatment to be beneficial but the other did not. My interpretation: If a patient has unexplained dyspepsia and no abnormal findings on endoscopy, blood chemistry, or the blood count, it is reasonable to test for *H pylori* and to give antibiotics if he or she tests positive. However, in no more than approximately one fourth of such patients will the problem respond to therapy. Furthermore, one should never give anti-*H pylori* treatment without first obtaining proof of infection.

In two large studies anti-*H pylori* treatment helped only a fourth of patients with nonulcer dyspepsia

GIVEN THE SUCCESS of treating peptic ulcers by eradicating *Helicobacter pylori*, physicians may be tempted to use this treatment for another disorder: nonulcer, or functional, dyspepsia (chronic or recurrent pain or discomfort in the upper abdomen, for which no cause can be found). However, two recent studies[1,2] indicate that we should temper our enthusiasm. Although one of the studies found such treatment to be beneficial in treating functional dyspepsia,[1] the other did not,[2] and in neither study did more than 27% of patients experience resolution of their symptoms.

I believe that antimicrobial therapy to eradicate *H pylori* may be reasonable for a patient with dyspepsia, but only if the physician:

- Rules out known causes of dyspepsia (notably gastric cancer);
- Knows that the patient actually is infected with *H pylori*; and
- Realizes that this treatment is not a panacea.

A COMMON COMPLAINT WITH MANY POTENTIAL CAUSES

Dyspepsia is remarkably common: approximately 25% of people in the United States report having had it in the previous 12 months, and it accounts for 2% to 5% of family practice consultations.[3] Its evaluation and treatment generate considerable direct and indirect expenses.

Dyspepsia can be a symptom of a number of diseases. Peptic ulcers account for 15% to 25% of cases, and atypical gastroesophageal reflux disease accounts for 5% to 15%. Gastric cancer accounts for less than 2%[3]; however, its incidence increases rapidly after age 45.[4]

By default, patients with no identifiable structural or biochemical cause for their symptoms—numbering up to 60%—are said to have functional or nonulcer dyspepsia.[3]

ROLE OF *H PYLORI* IN NONULCER DYSPEPSIA STILL CONTROVERSIAL

Although the cause of nonulcer dyspepsia remains elusive, a variety of abnormalities have been identified: abnormal visceral sensi-

tivity of the stomach or small intestine, delayed gastric emptying, gastric dysrhythmias, altered gastrointestinal reflexes, and altered duodenal sensitivity to acid.[3,5]

The role of *H pylori* infection in nonulcer dyspepsia is controversial. From 30% to 60% of patients with unexplained dyspepsia are infected with *H pylori*, but the percentage may be no different than in age-matched controls.[3]

Possible mechanisms whereby *H pylori* infection may cause dyspeptic symptoms include chronic inflammation, altered visceral sensitivity, increased gastric acid secretion, and abnormalities in gastric emptying.[6–8] However, there is no proof to date that *H pylori* infection causes symptoms.

TWO LARGE RECENT STUDIES YIELD CONFLICTING RESULTS

Previous trials of *H pylori* treatment in nonulcer dyspepsia have been inconclusive, in part because of inadequate size and differing outcomes measured. Two recent large, well-designed studies[1,2] yielded seemingly conflicting results.

The Glasgow trial: *H pylori* treatment beneficial

In a randomized, double-blind, placebo-controlled trial conducted in Glasgow, Scotland, McColl et al[1] examined the effect of eradicating *H pylori* in 308 patients with nonulcer dyspepsia.

Entry criteria. The investigators defined dyspepsia as intermittent or persistent pain or discomfort in the upper abdomen or lower part of the chest, heartburn, nausea, or a feeling of postprandial fullness. All patients were *H pylori*-positive and had no endoscopic evidence of peptic ulcer disease or reflux esophagitis at study entry.

Treatment regimens. All patients received omeprazole 20 mg twice a day for 2 weeks. In addition, patients were randomized to receive either placebo or the combination of amoxicillin 500 mg three times daily plus metronidazole 400 mg three times daily (patients allergic to amoxicillin received tetracycline 500 mg three times daily). Patients were permitted to take any medication necessary if they had recurrent symptoms after the initial treatment.

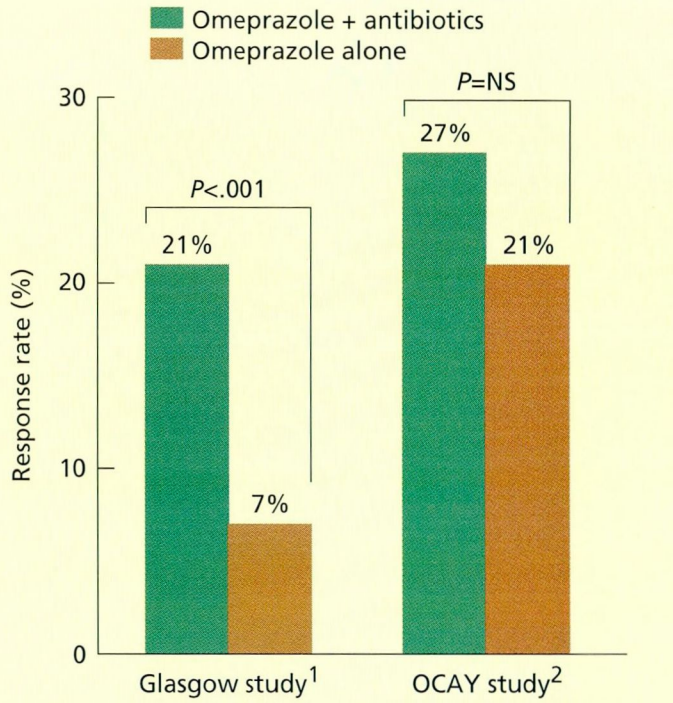

FIGURE 1. Although the Glasgow study[1] and the OCAY study[2] used different definitions, methods, and patient populations and came to seemingly different conclusions, they agreed on one point: no more than approximately one fourth of patients with nonulcer dyspepsia and *Helicobacter pylori* infection will experience symptom resolution in response to anti-*H pylori* drugs.

Assessing symptom improvement. To assess the severity of dyspepsia at baseline and at the end of the study, the investigators used an instrument called the Glasgow dyspepsia scale. This scale is based on the frequency of:

- Symptoms (maximum, 5 points)
- Medical consultations (2 points)
- Physician home visits (2 points)
- Tests for dyspepsia (2 points)
- Use of over-the-counter medications for dyspepsia (2 points)
- Use of prescription medications for dyspepsia (3 points).

In addition, patients receive points for:

- The effect of symptoms on normal activities (maximum 2 points)

- The number of days of work missed because of dyspepsia (2 points).

The highest (worst) possible Glasgow score is 20. At baseline, the median score was 11.4 in the omeprazole-plus-antibiotic group and 11.5 in the omeprazole-alone group. Symptom resolution was defined as a score of 0 or 1.

In addition, patients filled out a 36-item quality-of-life questionnaire (the Medical Outcomes Study Short-Form General Health Survey, or SF-36) at study entry and again at 1 year.[9] Clearance of *H pylori* was assessed 4 weeks after completion of therapy and at 1 year with a carbon-14 urea breath test.

Results. At 1 year, symptoms had resolved in 33 (21%) of 154 patients who received omeprazole and antibiotics, compared with 11 (7%) of 154 patients who received omeprazole alone ($P < .001$; FIGURE 1). *H pylori* was eradicated in 85% of patients given omeprazole plus antibiotics compared with only 12% of patients given omeprazole alone.

However, the groups did not differ significantly in their mean Glasgow scores, which declined from 11.4 at baseline to 5.4 in the omeprazole-plus-antibiotics group and to 6.2 in the omeprazole-plus-placebo group. Part of the apparent decrease was because all patients had received 3 points automatically at the beginning of the study for visiting their physicians, visiting the hospital, and undergoing endoscopy, which they did not receive at the end of the trial. Symptoms improved most in patients who had experienced dyspepsia for only 5 years or less.

In a similar fashion, quality-of-life scores improved in both groups and the number of prescription drugs taken for dyspepsia decreased, but the groups did not differ significantly in these measures either. (These findings point out the importance of including a control group in clinical trials.)

We have no proof that *H pylori* causes dyspepsia

The OCAY trial: *H pylori* treatment no better than placebo

In the other randomized, double-blind, placebo-controlled trial, conducted in 328 patients in Europe, Scandinavia, Canada, Iceland, Australia, and South Africa, Blum et al[2] found that eradicating *H pylori* was not effective in treating nonulcer dyspepsia. This trial was known by the acronym "OCAY" (Omeprazole plus Clarithromycin and Amoxicillin Effect One Year after Treatment).

Entry criteria for the OCAY trial were somewhat different than for the Glasgow trial. The investigators defined nonulcer dyspepsia as pain or discomfort centered in the upper abdomen that had been present for at least 6 months with no history of peptic ulcer disease or gastroesophageal reflux disease. (Note: Unlike the Glasgow investigators, they did not include heartburn in the definition.) All patients were *H pylori*-positive and, as in the first study, underwent endoscopy to exclude peptic ulcer disease and esophagitis, although patients with no more than five gastric erosions were eligible for this study.

Treatment regimens. All patients received 1 week of treatment with omeprazole 20 mg twice daily plus either placebo or the combination of amoxicillin 1,000 mg twice daily and clarithromycin 500 mg twice daily.

Assessing symptom improvement. Blum et al used a different scale to assess symptoms than did the Glasgow investigators: the Likert scale. In this scale, patients receive from 0 to 6 points, depending on symptom severity:

- 0—Absent
- 1—Minimal
- 2—Mild
- 3—Moderate
- 4—Moderately severe
- 5—Severe
- 6—Very severe.

Only patients with moderate to very severe pain for at least 3 of the 7 days before the study were eligible. The mean score at baseline was 3.2. Treatment was considered successful if patients scored 0 or 1 (no symptoms or only minimal pain) in any of the 7 days preceding the final visit at 12 months.

Patients were followed up at 1 week, and then at 1, 3, 6, 9, and 12 months after completing treatment. Endoscopy and biopsy were performed at baseline and again at 3 and 12 months. *H pylori* infection at 3-month and 12-month follow-up visits was defined as a positive urea breath test, abnormal histology, or both.

Results: At 1 year, symptoms had resolved in comparable numbers of patients in the two groups: 45 (27%) of 164 patients given omeprazole and antibiotics compared with 34 (21%) of 164 given omeprazole alone (FIGURE 1). While the mean symptom score decreased in both groups at 12 months compared with baseline, there was no difference between the two groups: 1.73 in the omeprazole-plus-antibiotics group vs 1.74 in the omeprazole-only group.

As would be expected, eradication of *H pylori* infection was more frequent in the omeprazole-plus-antibiotics group than in the omeprazole-only group (79% vs 2%), as was healing of gastritis (75% vs 3%). However, in the group given omeprazole plus antibiotics, there was no difference in symptom response in those in whom *H pylori* infection was eradicated (31%) compared with those in whom *H pylori* infection was not eradicated (26%). Both treatment groups experienced an improvement in quality of life as measured by both the Psychologic General Well-Being Index and the Gastrointestinal Rating Scale, although these differences were not statistically significant.

RESOLVING THE CONTRADICTIONS

What accounts for the differences in the results of these two well-designed studies? What are the implications for clinical practice?

Differences between the two studies

Actually, the studies reported a remarkably similar efficacy: approximately one fourth of patients with unexplained dyspepsia and *H pylori* infection improved after a course of eradication therapy. The difference between the studies was the response rate in the control groups (7% vs 21%). In fact, the low placebo response rate in the Glasgow trial is atypical for almost any study of a presumed functional disorder such as nonulcer dyspepsia; typically, the placebo response is closer to 30%. What accounts for this?

The answer may be found by taking a closer look at differences in the design of the two studies. The Glasgow investigators conducted their study at a single site in Scotland, whereas the OCAY study was global and therefore perhaps included a more homogeneous population. Also, dyspepsia was defined differently in the two studies; the OCAY study used the classic definition, while the Glasgow study used a different definition that included heartburn. Furthermore, the studies used different scales to assess symptoms and response to therapy. In both studies, response to therapy was based on absent or minimal symptoms; however, it is unknown if these scales are comparable.

Finally, the Glasgow investigators buttressed their conclusion by noting that there was no difference in response in the subset of patients treated with omeprazole and antibiotics who were still infected with *H pylori* compared with those in whom eradication was achieved.

Similarities between the two studies

Taken together, the studies both point to a similar conclusion: approximately one fourth of patients with nonulcer dyspepsia infected with *H pylori* will get better if *H pylori* is eliminated. They also tell us that the other three fourths of patients will not improve. This is not a surprising finding, as the cause of nonulcer dyspepsia is not known.

Never treat *H pylori* without proof of infection

Possible adverse effects of indiscriminately treating *H pylori*

Before empirically treating *H pylori* in patients with dyspepsia, the clinician should keep in mind the potential downside. Widespread antibiotic use increases bacterial resistance of an organism that is already difficult to treat and can lead to adverse effects such as *Clostridium difficile* colitis.

Furthermore, eradicating *H pylori* may also cause gastroesophageal reflux disease. Although most studies to date found no relationship between *H pylori* infection and gastroesophageal reflux disease, Labenz et al[10] reported that erosive esophagitis developed in 26% of patients with duodenal ulcers 3 years after they were successfully treated for *H pylori*. Other recent studies also suggested that *H pylori* infection protects against gastroesophageal reflux disease.[11,12]

WHAT IS THE BEST APPROACH TO PATIENTS WITH DYSPEPSIA?

What then should the physician do for a patient with dyspepsia? Here is my advice.

Obtain an endoscopic evaluation early on, without a trial of empiric antisecretory or *H pylori* eradication therapy, if the patient has any of the following, which might indicate a more serious cause:

- Weight loss
- Bleeding
- Nausea and vomiting
- New-onset dyspepsia after age 45 to 50 (owing to the possibility of gastric neoplasia).

Obtain an initial noninvasive test for *H pylori*, if the patient is under age 45 and has uncomplicated dyspepsia, and give antimicrobial therapy if the patient tests positive. This approach is cost-effective,[3] and will heal any ulcer disease if present. Unfortunately, epidemiologic studies indicate that most of such patients in developed countries do not have *H pylori* infection.

Do not obtain a barium radiograph. This test has poor sensitivity and specificity and thus no longer has any role in the evaluation of dyspepsia.

Do not treat for *H pylori* without proof of infection. No theoretical model to date supports such empiric treatment. In patients with unexplained dyspepsia and a negative evaluation (endoscopy, blood chemistry, and blood count), it is reasonable to determine *H pylori* status and to treat patients who test positive for *H pylori*. However, expect no more than a 20% to 25% response in these patients.

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