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## SYMPTOMATIC BENEFIT FROM ERADICATING *HELICOBACTER PYLORI* INFECTION IN PATIENTS WITH NONULCER DYSPEPSIA

KENNETH MCCOLL, M.D., LILIAN MURRAY, PH.D., EMAD EL-OMAR, M.D., ANTHEA DICKSON, B.A., ADIL EL-NUJUMI, M.D.,  
ANGELA WIRZ, B.SC., ANDREW KELMAN, PH.D., CHRISTINE PENNY, M.B., CH.B., ROBIN KNILL-JONES, M.D.,  
AND THOMAS HILDITCH, PH.D.

### ABSTRACT

**Background** The eradication of *Helicobacter pylori* infection is beneficial in patients with gastric or duodenal ulcers. The value of eradicating the infection in patients with dyspepsia and no evidence of ulcer disease is not known.

**Methods** We performed a randomized, placebo-controlled trial comparing the efficacy of treatment for two weeks with 20 mg of omeprazole orally twice daily, 500 mg of amoxicillin three times daily (with 500 mg of tetracycline three times daily substituted for amoxicillin in patients allergic to penicillin), and 400 mg of metronidazole three times daily (160 patients) with that of omeprazole alone (158 patients) for resolving symptoms of dyspepsia in patients with *H. pylori* infection but no evidence of ulcer disease on upper gastrointestinal endoscopy. Symptoms were assessed with the Glasgow Dyspepsia Severity Score, with resolution of symptoms defined as a score of 0 or 1 in the preceding six months (maximal score, 20). One year later the patients were assessed to determine the frequency of the resolution of symptoms.

**Results** One month after the completion of treatment, 132 of 150 patients (88 percent) in the group assigned to receive omeprazole and antibiotics had a negative test for *H. pylori*, as compared with 7 of 152 (5 percent) in the group assigned to receive omeprazole alone. One year later, dyspepsia had resolved in 33 of 154 patients (21 percent) in the group given omeprazole and antibiotics, as compared with 11 of 154 (7 percent) in the group given omeprazole alone (95 percent confidence interval for the difference, 7 to 22 percent;  $P < 0.001$ ). Among the patients in the group given omeprazole and antibiotics, the symptoms resolved in 26 of the 98 patients (27 percent) who had had symptoms for five years or less, as compared with 7 of the 56 patients (12 percent) who had had symptoms for more than five years ( $P = 0.03$ ).

**Conclusions** In patients with *H. pylori* infection and nonulcer, or functional, dyspepsia, treatment with omeprazole and antibiotics to eradicate the infection is more likely to resolve symptoms than treatment with omeprazole alone. (N Engl J Med 1998;339:1869-74.)

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**D**YSPEPSIA affects 20 to 40 percent of the population of the Western world.<sup>1-4</sup> Upper gastrointestinal endoscopy of patients with dyspepsia reveals no abnormality in the majority; such patients are considered to have nonulcer, or functional, dyspepsia.<sup>5</sup> The cause of nonulcer dyspepsia is unclear but is thought to be heterogeneous.<sup>6-8</sup> The management of the disorder is unsatisfactory, and there are few studies showing that active treatment is superior to a placebo.<sup>7</sup>

The recognition of the pathogenic role of *Helicobacter pylori* infection in patients with peptic ulcer and the benefits of eradicating the infection<sup>9-11</sup> has led to suggestions that the infection may also be the cause of dyspepsia in some patients with nonulcer dyspepsia. A higher prevalence of *H. pylori* infection has been reported in patients with dyspepsia than in those without it, but in some of these studies the patients were not matched for age or excluded if they had underlying ulcer disease.<sup>12-14</sup> Several studies have examined the effect of eradicating *H. pylori* infection on dyspeptic symptoms in patients with nonulcer dyspepsia, but the results have been conflicting and all such studies have been criticized because of design flaws.<sup>15</sup> In a recent review of these trials, Talley and Hunt concluded that "*H. pylori* has not been established, as yet, to play a definitive role in dyspepsia."<sup>15</sup>

We report the results of a large, randomized, placebo-controlled trial that assessed the effect of eradicating *H. pylori* in patients with nonulcer dyspepsia.

From the Departments of Medicine and Therapeutics (K.M., L.M., E.E.-O., A.D., A.E.-N., A.W., A.K.) and Clinical Physics (T.H.), Western Infirmary; Victoria Infirmary (C.P.); and the Department of Public Health, University of Glasgow (R.K.-J.) — all in Glasgow, United Kingdom. Address reprint requests to Dr. McColl at the Department of Medicine and Therapeutics, Western Infirmary, Glasgow G11 6NT, United Kingdom.

## METHODS

## Recruitment and Evaluation of Patients

We studied patients who were referred to one dyspepsia clinic by their primary care physician because they had had dyspepsia for at least four months. All patients were found to have *H. pylori* infection but no endoscopic evidence of current or previous peptic ulcer disease. Dyspepsia was defined as intermittent or persistent pain or discomfort in the upper abdomen or lower part of the chest, heartburn, nausea, a feeling of postprandial fullness, or any other symptoms thought to be related to the upper gastrointestinal tract.<sup>16</sup> Patients were excluded if they had previously been found to have peptic ulcer disease, had endoscopic evidence of esophagitis, were taking nonsteroidal antiinflammatory drugs (other than low-dose aspirin), had undergone gastric resection, were pregnant, or had previously been treated for *H. pylori* infection.

The patients had been asked to stop taking any antisecretory drug before the initial clinic visit. At this visit, a standardized interview was used to determine each patient's symptoms and the duration of symptoms (less than 2 years, 2 to 5 years, more than 5 to 10 years, or more than 10 years) and a physical examination was conducted.

The severity of the dyspepsia during the six months preceding the visit was assessed with the Glasgow Dyspepsia Severity Score.<sup>17</sup> This scale evaluates the frequency of symptoms (maximal score, 5); the effect of dyspepsia on normal activities (2); the number of days of work missed because of dyspepsia (2); and the frequency of medical consultations (2), home visits by a physician (2), tests for dyspepsia (2), use of over-the-counter medications (2), and use of prescribed medications (3). Scores can range from 0 to 20, with higher scores indicating more severe dyspepsia. The quality of life was assessed with the 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36), which examines eight aspects of the quality of life: general and mental health, physical function, social function, physical and emotional health, pain, and vitality. Scores on each of the eight aspects can range from 0 (worst) to 100 (best).<sup>18</sup>

After the clinical assessment, the patients underwent a carbon-14 urea breath test to determine their *H. pylori* status.<sup>19</sup> The results of the test were considered positive if the value at 20 minutes was more than 30 (units equal the percentage of the dose administered per millimole of carbon dioxide expired times the body weight in kilograms times 100). A blood sample was also taken to determine whether IgG antibodies to the *CAGA* gene product of *H. pylori* were present (test kindly performed by Dr. Jean Crabtree). The presence of these antibodies indicates that patients are infected with a more virulent strain of the bacterium.<sup>20</sup>

Two weeks later the patients underwent upper gastrointestinal endoscopy. Before endoscopy, those with a positive urea breath test were invited to undergo randomization to either treatment to eradicate *H. pylori* or placebo treatment if the endoscopy showed no evidence of ulcer disease or esophagitis and to undergo studies of gastric acid secretion after the endoscopic examination. The randomization was carried out independently by the pharmacy department, which used tables of random numbers to assign half the patients to receive active treatment with omeprazole, amoxicillin, and metronidazole and half to receive omeprazole and placebo. The active and placebo tablets for each antibiotic were identical in appearance, and the trial was conducted in a double-blind fashion. The study was approved by the Western Infirmary ethics committee, and all patients gave written informed consent.

During the upper gastrointestinal endoscopy, biopsy samples were obtained from the antrum and body of the stomach. The samples were sectioned and stained with hematoxylin and eosin and examined for *H. pylori*. They were also examined for bacterial urease with a urease slide test (CLO test, Delta West, Bentley, Australia). The patients who had agreed to undergo acid secretory studies had a nasogastric tube inserted immediately after the removal of the endoscope, and they were then taken to the recovery area and allowed to rest for one hour. Acid secretion was then measured first in response to a one-hour intravenous infusion of gastrin-

releasing peptide (Calbiochem Novabiochem, Nottingham, United Kingdom) at a dose of 40 pmol per kilogram of body weight per hour and then in response to a one-hour intravenous infusion of pentagastrin (Zeneca, Macclesfield, United Kingdom) at a dose of 0.6  $\mu$ g per kilogram per hour.

After these tests, the patients received a two-week course of either 20 mg of omeprazole (Losec, Astra Hässle, Mölndal, Sweden) twice daily, 500 mg of amoxicillin three times daily, and 400 mg of metronidazole three times daily or 20 mg of omeprazole twice daily and placebo antibiotics. Patients with a history of allergy to penicillin were given 500 mg of tetracycline three times daily rather than amoxicillin.

The patients were given an appointment for a urea breath test and an assessment of side effects four weeks after treatment was completed and an appointment for a full reassessment one year after the start of treatment. They were also told that they could take any medication necessary, including a proton-pump inhibitor, if they had recurrent or persistent symptoms after the completion of treatment. However, their doctors were requested by letter not to prescribe any treatment to eradicate *H. pylori*. At the one-year visit, dyspeptic symptoms during the preceding six months were assessed with the Glasgow Dyspepsia Severity Score, the quality of life was assessed with the SF-36 questionnaire, and *H. pylori* status was assessed with a urea breath test. The results of the breath tests performed one month after the completion of treatment and one year after the start of treatment were not divulged to the patients or investigators until after the completion of the one-year assessment.

## Statistical Analysis

The main end point was the resolution of symptoms, defined as a score of 0 or 1 on the Glasgow Dyspepsia Severity Score, because validation studies indicated that this cutoff point was the most appropriate indication of the resolution of dyspepsia.<sup>17</sup> The analysis was based on the intention-to-treat principle. Two-sample t-tests were used to compare the mean values of variables considered continuous in the active-treatment and placebo groups. Chi-square tests were used to analyze categorical variables. A logistic-regression analysis was carried out to determine which characteristics of the patients were predictive of the resolution of symptoms. All statistical tests were two-sided.

## RESULTS

Between October 1994 and October 1996, we assessed 916 patients with dyspepsia, of whom 330 were enrolled in the study. The reasons for exclusion were endoscopic evidence of duodenal or gastric ulcer or esophagitis (209 patients), a negative test for *H. pylori* (306 patients), previous treatment for *H. pylori* (21 patients), inability to tolerate endoscopy (11 patients), use of nonsteroidal antiinflammatory drugs (9 patients), and pregnancy or a serious medical condition (21 patients). Of the eligible patients, only nine declined to participate.

Of the 330 patients who enrolled in the study, 12 were excluded from the final analysis. Eleven did not have at least two positive tests<sup>21</sup> for *H. pylori* infection, because they had entered the study immediately after the endoscopic examination when the results of the urea breath test were available but the results of the urease test and histologic analysis were not available; these subsequently proved to be negative. One patient did not meet the criteria for nonulcer dyspepsia because his base-line Glasgow Dyspepsia Severity Score in the six months preceding the study was 0.

Of the remaining 318 patients, 160 were assigned

to receive therapy to eradicate *H. pylori* (omeprazole and antibiotics) and 158 were assigned to receive omeprazole alone. The two groups were well matched with respect to age, sex, initial results on the Glasgow Dyspepsia Severity Score, prevalence of previously prescribed antisecretory-drug therapy, prevalence of smoking, predominant symptom at presentation, duration of symptoms, and quality of life (Table 1).

A total of 308 patients (97 percent) were reassessed one year after randomization, 154 in each group. Of the 154 patients in the group assigned to receive omeprazole and antibiotics, 150 had a urea breath test one month after the completion of treatment. The test was negative in 132 patients (88 percent), of whom 125 (95 percent) also had a negative test at one year. Of the 154 patients in the group assigned to receive omeprazole alone, 152 had a urea breath test one month after the end of treatment. The test was positive in 145 patients (95 percent), of whom 134 (92 percent) also had a positive test at one year.

The distribution of Glasgow Dyspepsia Severity

Scores in the two groups at one year is shown in Figure 1. On an intention-to-treat basis, the symptoms resolved (defined as a score of 0 or 1) in 33 of 154 patients (21 percent) in the group assigned to receive omeprazole and antibiotics, as compared with 11 of 154 patients (7 percent) in the group assigned to receive omeprazole alone (95 percent confidence interval for the difference between groups, 7 to 22 percent;  $P < 0.001$ ).

The mean ( $\pm$ SD) dyspepsia score at one year was  $5.4 \pm 4.0$  in the group treated with omeprazole and antibiotics, as compared with  $6.2 \pm 3.6$  in the group treated with omeprazole alone ( $P = 0.07$ ) (Table 2). The scores in both groups were lower than those at

TABLE 1. BASE-LINE CHARACTERISTICS OF 318 PATIENTS WITH NONULCER DYSPEPSIA.\*

CHARACTERISTIC	OMEPRAZOLE AND ANTIBIOTICS (N=160)	OMEPRAZOLE ALONE (N=158)
Male sex (%)	51	47
Age (yr)		
Mean $\pm$ SD	$42 \pm 12$	$42.2 \pm 13$
Range	18–70	17–70
Glasgow Dyspepsia Severity Score†		
Mean $\pm$ SD	$11.4 \pm 2.2$	$11.5 \pm 2.5$
Range	6–17	4–18
Quality-of-life score‡		
Mean $\pm$ SD	$520 \pm 176$	$507 \pm 164$
Range	25–786	93–764
Duration of symptoms (%)§		
<2 yr	39	38
2–5 yr	25	21
>5–10 yr	11	16
>10 yr	24	25
Predominant symptom (%)		
Epigastric pain	57	54
Retrosternal pain	21	16
Reflux	12	13
Other	10	17
History of smoking in past 6 mo (%)	34	33
Medication prescribed in past 6 mo (%)	84	80
Histamine H <sub>2</sub> -receptor antagonists	59	54
Proton-pump inhibitors	13	11
Both	8	11
Other	4	4
Medication prescribed for >3 of the past 6 mo (%)	44	45

\*There were no significant differences between the two groups.

†Scores can range from 0 (no symptoms or limitations) to 20 (severe symptoms most days, requiring regular medication).

‡Quality of life was measured with the SF-36; scores can range from 0 (worst) to 800 (best).

§Because of rounding, percentages may not total 100.

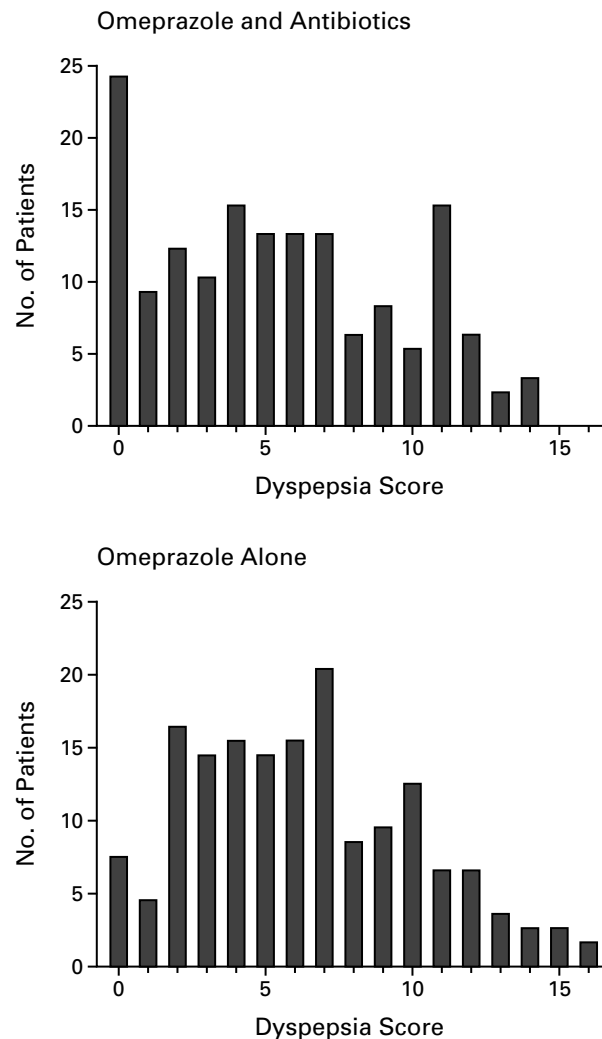


Figure 1. Distribution of Glasgow Dyspepsia Severity Scores One Year after the Start of Treatment.

The resolution of symptoms (defined as a score of 0 or 1) was significantly more common in the group assigned to receive omeprazole and antibiotics ( $P < 0.001$ ). Data were missing for one patient in the omeprazole-alone group.

TABLE 2. OUTCOMES OF THE PATIENTS AT ONE YEAR.\*

CHARACTERISTIC	OMEPRAZOLE AND ANTIBIOTICS (N=154)	OMEPRAZOLE ALONE (N=154)	P VALUE
Resolution of symptoms (%)	21	7	<0.001
Glasgow Dyspepsia Severity Score†			
Mean ±SD	5.4±4.0	6.2±3.6	0.07
Range	0–14	0–16	
Quality-of-life score‡			
Mean ±SD	566±179	556±175	0.61
Range	50–786	113–776	
<i>H. pylori</i> -negative (%)	85	12	<0.001
Medication prescribed in past 6 mo (%)	43	53	0.09
Histamine H <sub>2</sub> -receptor antagonists	25	28	
Proton-pump inhibitors	16	22	
Both	1	3	
Medication prescribed for >3 of the past 6 mo (%)	20	30	0.05
Eradication therapy prescribed during follow-up (no.)	3	9	0.08

\*Ten patients were lost to follow-up: six patients in the group assigned to omeprazole and antibiotics and four patients in the group assigned to omeprazole alone.

†Total scores can range from 0 (no symptoms or limitations) to 20 (severe symptoms most days, requiring regular medication).

‡Quality of life was measured with the SF-36; scores can range from 0 (worst) to 800 (best).

base line; however, the higher scores at entry were due in part to the fact that all patients received a total of three points for visits to their general practitioner, visits to the hospital, and undergoing endoscopy.

At base line, 84 percent of the patients in the group given omeprazole and antibiotics and 80 percent of those in the group given omeprazole alone had been taking prescription drugs for dyspepsia during the preceding six months (Table 1). At one year, the respective values were 43 percent and 53 percent (Table 2). At base line, among patients who were taking prescription drugs for dyspepsia, 53 percent of the patients in the group given omeprazole and antibiotics had taken such a drug for more than three of the preceding six months, as compared with 55 percent of the patients in the group given omeprazole alone; at one year the respective values were 47 percent and 57 percent. There was no significant difference between groups in the quality of life after treatment (Table 2).

We used univariate logistic-regression analysis to examine whether any characteristics of the patients at base line could be used to predict a response to treatment. Only the duration of symptoms was predictive ( $P=0.03$ ). None of the following factors were predictive: age ( $P=0.81$ ), sex ( $P=0.20$ ), smoking status ( $P=0.80$ ), initial Glasgow Dyspepsia Severity Score ( $P=0.35$ ), predominant symptom at presentation ( $P=0.50$ ), *H. pylori* CagA status ( $P=0.78$ ), acid secre-

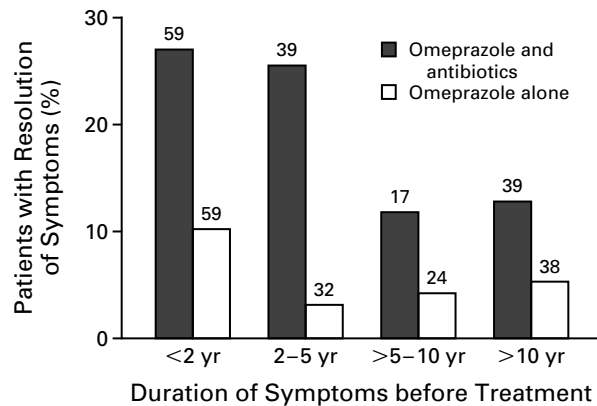


Figure 2. Percentages of Patients with Resolution of Symptoms in Relation to the Duration of Symptoms before Treatment.

The resolution of symptoms was defined as a Glasgow Dyspepsia Severity Score of 0 or 1. The numbers of patients in each group are shown above the bars.

tion in response to pentagastrin ( $P=0.92$ ), or acid secretion in response to gastrin-releasing peptide ( $P=0.35$ ). In a multivariate model, treatment ( $P<0.001$ ) and the duration of symptoms ( $P=0.03$ ) were independently related to the resolution of symptoms. There was no evidence of an interaction between treatment and the duration of symptoms ( $P=0.90$ ). The odds ratio for the resolution of symptoms in the group assigned to receive omeprazole and antibiotics, as compared with the group assigned to receive omeprazole alone, was 3.9 (95 percent confidence interval, 1.8 to 8.3). The percentage of patients with resolution of symptoms decreased with increasing duration of symptoms (Fig. 2). Among the patients who had had symptoms for five years or less, 7 of 91 patients (8 percent) in the group given omeprazole alone had a response to treatment, as compared with 26 of 98 patients (27 percent) in the group given omeprazole and antibiotics. Among the patients who had had symptoms for more than five years, 3 of 62 patients (5 percent) in the group given omeprazole alone had a response to treatment, as compared with 7 of 56 patients (12 percent) in the group given omeprazole and antibiotics.

Routine repeated endoscopy was not part of the study protocol. However, nine patients were referred for endoscopy by their primary care physician during the year after randomization because of severe, persistent dyspepsia. Three of the patients were in the group given omeprazole and antibiotics, and all three had normal findings on endoscopy. In contrast, six of the patients were in the group given omeprazole alone, and four had ulcers. Three of these four patients subsequently received therapy to eradicate *H. pylori*; the symptoms resolved in only one.

## DISCUSSION

We found that therapy to eradicate *H. pylori* resulted in more frequent resolution of symptoms than did placebo in patients with nonulcer dyspepsia and documented *H. pylori* infection. Treatment with antibiotics and omeprazole resulted in the resolution of dyspepsia in 21 percent of patients; in contrast, symptoms resolved in 7 percent of patients who were treated with omeprazole alone. These results confirm and extend those of an earlier randomized trial showing symptomatic benefit from eradicating *H. pylori* in nonulcer dyspepsia.<sup>22</sup> The beneficial effect of this approach is also reflected by the findings in our study of a trend toward reduced use of prescription-drug therapy for dyspepsia ( $P=0.09$ ) and a shorter duration of such therapy ( $P=0.05$ ) in the group given omeprazole and antibiotics.

We found no evidence that factors associated with duodenal ulcer disease, including smoking, epigastric pain as the predominant symptom, male sex, a high acid output, or a positive test for *H. pylori* CagA,<sup>19,23-25</sup> were predictive of the success of treatment with omeprazole and antibiotics. Only the duration of dyspeptic symptoms before treatment was predictive of the response. The longer the history of dyspepsia, the less likely the benefit from this therapy. The mechanism of this association is not clear. It is possible that prolonged, symptomatic *H. pylori*-associated gastritis induces changes that become irreversible, or only slowly reversible, resulting in persistent dyspepsia despite eradication of the infection.

Our study also suggests that patients with *H. pylori* infection and nonulcer dyspepsia are at risk for ulcers. Of the six patients in the group given omeprazole alone who were referred for further evaluation because of severe, persistent dyspepsia, four had peptic ulcers. More ulcers might have been detected if all the patients in this group who had persistent symptoms had undergone follow-up endoscopy. A high incidence of peptic ulcers in patients with *H. pylori* infection and nonulcer dyspepsia has been reported in other studies. In one randomized study, ulcers developed in 14 percent of 50 *H. pylori*-positive patients with nonulcer dyspepsia in the placebo group during the one-year follow-up period.<sup>22</sup> In another, similar study, peptic ulcers developed in 21 percent of 41 patients during a mean follow-up period of three years.<sup>26</sup>

It is tempting to assume that the subgroup of patients with nonulcer dyspepsia in whom dyspepsia resolved on treatment of *H. pylori* corresponds to the subgroup of patients in the group given omeprazole alone in whom peptic ulcers developed. However, of the three patients in this group in whom ulcers developed and who subsequently underwent treatment for *H. pylori*, only one had resolution of dyspepsia. This finding is consistent with previous reports that the

symptomatic response to the eradication of *H. pylori* varies in patients with peptic ulcers.<sup>27-29</sup>

Our findings have clinical implications for the treatment of patients with dyspepsia. Previous studies have shown that eradicating *H. pylori* is beneficial in patients with confirmed peptic ulcers; thus, eradication of the infection has been recommended only in such patients. We found that this approach was beneficial in a proportion of *H. pylori*-infected patients with dyspepsia who had no evidence of current or previous ulcers at the time treatment was initiated. Because it is not yet possible to identify prospectively patients whose symptoms will resolve with such treatment, it will be necessary to treat all patients with *H. pylori* infection and nonulcer dyspepsia in order to cure a minority. However, the potential benefit — curing a chronic disorder with a single course of antibiotic treatment — would seem to justify this approach.

Our study also has implications for the use of endoscopy in younger patients with uncomplicated dyspepsia. Endoscopy has been used to identify patients with *H. pylori* infection and associated peptic ulcer disease and thus to identify those who should be treated for this infection. Our findings that the eradication of *H. pylori* is also beneficial for patients with no peptic ulcers and that negative endoscopic results do not rule out the possibility of an ulcer in the future raise questions about the appropriateness of endoscopy in determining management. They support a strategy that includes noninvasive testing of patients with dyspepsia for *H. pylori* and eradicating *H. pylori* infection in those with evidence of infection.

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