Background: Prior studies have yielded conflicting results on whether or not *Helicobacter pylori* causes nonulcer dyspepsia.

Patients and Methods: We enrolled 100 consecutive patients with nonulcer dyspepsia into a randomized, double-blind, placebo-controlled trial. Patients with peptic ulcer disease, esophagitis, hepatobiliary disease, irritable bowel disease, or predominantly reflux-related symptoms were excluded by history and upper endoscopy. *Helicobacter pylori* infection was determined by biopsy and histologic examination. Serum H pylori IgG antibodies and CagA status were determined by Western blot. Enrolled patients were randomized to a 14-day regimen of omeprazole (20 mg twice daily) and clarithromycin (500 mg three times daily) or placebo. Dyspeptic symptoms were assessed by use of a visual analog scale at baseline and at 1, 3, 6, and 12 months after treatment. Follow-up upper endoscopy with biopsy was performed 4 weeks after treatment. Compliance was measured by tablet counts.

Results: At 1 year, the change in dyspeptic symptoms was −24.0 (95% confidence interval, −69.0 to 21.0) in the omeprazole and clarithromycin group and −24.2 in the placebo group (95% confidence interval, −70.0 to 21.6). Furthermore, patients with persistent *H pylori* infection demonstrated a greater, but not significant, improvement in symptoms (−40 ± 144 [mean ± SD], −65 ± 142, −45 ± 138, and −39 ± 163) than those with successful eradication (−26 ± 126, −26 ± 148, −12 ± 126, and −25 ± 151) at months 1, 3, 6, and 12, respectively.

Conclusion: Patients with nonulcer dyspepsia should not routinely be treated for *H pylori*, since it is not a cause of this condition in most patients.

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Dyspepsia is an extremely common problem in the United States. A population-based study has suggested that as many as 25% of the population have symptoms consistent with dyspepsia. These symptoms include upper midabdominal discomfort or pain, nausea, early satiety, and abdominal bloating. Prior studies have demonstrated that dyspepsia is associated with peptic ulcer disease in approximately 20% of patients, gastroesophageal reflux disease in approximately 20% of patients, and gastric cancer in approximately 1% of patients. However, the majority of patients with dyspepsia have normal findings or only minor abnormalities on upper endoscopy and are therefore said to have nonulcer dyspepsia.

The pathogenesis of nonulcer dyspepsia is not well established. Some prior studies have suggested that *Helicobacter pylori* is a cause of nonulcer dyspepsia. Certain studies have shown a higher prevalence of *H pylori* organisms in patients with nonulcer dyspepsia compared with asymptomatic controls. Furthermore, some *H pylori* eradication trials in patients with nonulcer dyspepsia have demonstrated improvement in symptoms after successful treatment, while other studies have not demonstrated a beneficial response. These studies have been faulted for failure to ensure adequate blinding of patients and investigators and for enrollment of an insufficient number of patients, as well as for other methodological problems.

The optimal clinical approach in cases of dyspepsia is controversial. Some experts advocate noninvasive serological testing for *H pylori* in patients with dyspepsia, followed by treatment of those whose test results are positive. Others recommend immediate upper endoscopy so that the cause of the dyspepsia can be determined from the outset. Because approximately 60% of patients with dyspepsia have nonulcer dyspepsia, the optimal ap-
PATIENTS AND METHODS

STUDY PATIENTS

Patients with dyspepsia and histologically proven infection with *H pylori* were eligible for this study. The dyspepsia had to have been present for a minimum of 1 month and refractory to treatment with prescription-strength histamine-receptor antagonists. The patients had not previously been treated for *H pylori* infection. The prominent symptom for enrolled patients was a dull ache or pain located predominantly in the upper midabdominal area. Patients whose symptoms were primarily reflux related (eg, heartburn) were not enrolled. Patients with symptoms suggestive of irritable bowel disease (eg, lower abdominal cramps or altered bowel habits) and those with known or suspected biliary disease were not eligible.

Prior to enrollment, patients had been referred to the gastrointestinal clinic for evaluation at San Francisco General Hospital, San Francisco, Calif. Patients underwent upper endoscopy with examination of the esophagus, stomach, and duodenum (first and second portions). Patients were ineligible if gastric or duodenal ulcers were present (defined as a mucosal defect at least 2 mm in length with perceived depth), although patients with erosions alone were eligible. Patients were also not eligible if there was endoscopic evidence of reflux esophagitis or esophageal varices. Two endoscopic biopsy specimens were obtained from both the antrum and the body of the stomach of each subject. Those patients demonstrating chronic active gastritis caused by *H pylori* were eligible for enrollment. *Helicobacter pylori* status was based on the findings of examination of biopsy specimens by experienced pathologists using hematoxylin-eosin stains. Patients with clinical evidence of hepatobiliary disease, pregnancy, daily consumption of the equivalent of more than 30 mL of absolute ethanol, use of aspirin or nonsteroidal anti-inflammatory medications within the prior month, severe comorbid medical conditions, or a contraindication to treatment with either omeprazole or clarithromycin were excluded.

From March 1995 to October 1996, all patients meeting entry criteria were invited to participate. Of 111 such patients, 11 were not enrolled because of treatment of *H pylori* infection prior to enrollment, 6 concomitant medical problems, 4 and a history of bleeding gastric ulcer that required treatment for *H pylori*. The study protocol was approved by the institutional review board at the University of California, San Francisco. All patients had the opportunity to ask questions about the study, and signed informed consent was obtained at the time of enrollment.

STUDY DESIGN

Patients meeting inclusion and exclusion criteria were randomized to 2 weeks of treatment with omeprazole (Prilosec) (20 mg twice daily) and clarithromycin (Biaxin) (500 mg three times daily) or with identical-appearing placebos in a double-blind manner. They were considered compliant if they took at least 80% of both prescribed medications, as assessed by tablet counts. Patients taking histamine-receptor antagonists or proton pump inhibitors were asked to stop taking these medications at the time of enrollment. They were also instructed to avoid taking aspirin and nonsteroidal anti-inflammatory medications.

All patients underwent a follow-up upper endoscopy 4 weeks after the completion of drug therapy. The endoscopic appearance of the stomach and duodenum was scored separately based on modified criteria of Lanza27 (0, normal; 1, a single affected area with erythema or superficial erosion; 2, between 2 and 10 affected areas; 3, between

RESULTS

One hundred patients were enrolled, with 50 patients randomized to the omeprazole and clarithromycin therapy group and 50 to the placebo group. The groups were well matched for demographic and laboratory parameters, with the exception of a higher mean serum alanine aminotransferase level in the actively treated group (Table 1).

All patients had long-standing dyspepsia, with symptoms lasting longer than a mean of 5 years in both groups (range, 2-396 months). Twelve patients related a distant but unconfirmed history of peptic ulcer disease (5 in the active treatment group and 7 in the placebo group). Of 95 patients with available serum samples, 94 (99%) demonstrated IgG antibodies to *H pylori* on Western blot analysis, and 80 (84%) were CagA positive.

**H PYLORI ERADICATION**

Of 100 enrolled patients, 84 returned for follow-up endoscopy. Three (8%) of 40 patients in the placebo group and 31 (71%) of 44 patients in the omeprazole and clarithromycin group had complete eradication of *H pylori* (P < .001). In the actively treated group, *H pylori* was eradicated in 22 (65%) of 34 CagA-positive patients and in 8 (100%) of 8 CagA-negative patients (P = .08). Eradication was more successful in the compliant patients (29/29, 79%) than in the noncompliant patients or in those for whom tablet counts could not be verified (8/15, 53%) (P = .09).

**SYMPTOM RESPONSE**

While there was some improvement in the dyspepsia score of the patients who were treated with omeprazole and clarithromycin throughout the observation period, similar improvement occurred in those who received pla-
10 and 25 affected areas; 4, more than 23 affected areas; and 5, frank ulceration). Two biopsy specimens were obtained from both the antrum and the body of the stomach. The biopsy specimens were examined by experienced pathologists who were blinded to the clinical treatment received by the patients. The presence or absence of *H pylori* was determined using hematoxylin-eosin stains.

Gastrointestinal symptoms were assessed at baseline and at 1, 3, 6, and 12 months after the *H pylori* treatment was completed. The patients completed a visual analog scale covering 11 symptoms relating to the digestive system. For each symptom, a score ranging from 0 to 100 was recorded daily over 3 consecutive days. The mean score for each symptom during the 3-day period was recorded for each patient. The dyspepsia score was calculated by summing the mean scores for 3 symptoms (nausea, abdominal pain, abdominal bloating, abdominal burning, and pain after eating). The maximum dyspepsia score was 500, while the minimum was 0. The change in dyspepsia score was calculated by taking the difference in the score at baseline from the score at 1, 3, 6, and 12 months (negative changes in the dyspepsia score indicated improved symptoms, while positive changes indicated worsened symptoms).

The primary end point was an intention-to-treat analysis of symptomatic response after treatment. Because some patients randomized to receive omeprazole and clarithromycin therapy did not have successful eradication of *H pylori* organisms, there was the possibility that a lack of symptomatic response in these patients would mask a beneficial response in those who had successful eradication of *H pylori*. Therefore, a second analysis compared the symptomatic response in the patients with persistent *H pylori* infection with that in the patients with successful eradication.

**DETECTION OF IgG ANTIBODIES TO H PYLORI**

Serum samples were drawn at baseline and at 1 month after completion of drug therapy and were frozen at −10°C until time of analysis. The detection of IgG antibodies to *H pylori* was carried out by Western immunoblot analysis. Briefly, a nitrocellulose strip blot (Helico Blot 2.0; Genelabs Diagnostics Pte Ltd, Singapore) with *H pylori* antigens was incubated with 2 mL of patient’s serum, diluted 100-fold, for 1 hour at room temperature. The blot was washed 3 times with 2 mL of wash buffer for 5 minutes and incubated with 2 mL of conjugate solution (goat anti–human IgG alkaline phosphatase conjugate), diluted 1000-fold, for 1 hour at room temperature. The blot was washed 3 times, and the color was developed by substrate solution (nitroblue tetrazolium reduction plus 5-bromo-4-chloro-3-indolyl phosphate [BCIP]) for 15 minutes. Results meeting the manufacturer’s criteria (any single band at 116, 89, or 35 kd or any 2 bands at 30, 26.5, or 19.5 kd), were considered positive for *H pylori*. Two of the criterion proteins on the blot, the 116- and the 89-kd protein band, are CagA and Vaca, respectively.

**STATISTICAL ANALYSIS**

We estimated that the long-term response in the placebo group would be approximately 30%. To detect improvement in 60% of the actively treated group, 42 patients would need to be enrolled in each group, with 80% power and a 5% level of significance (2-sided test). Allowing for a drop-out rate of approximately 10%, we enrolled 50 patients in each arm of this study.

A t test was used to analyze the dyspepsia score. A χ² test with a Fisher exact test was used for comparison between proportional data. All tests were 2-tailed, and P values less than .05 were considered statistically significant. Continuous variables are presented as mean ± SD.

**Figure 1, Table 2**. After 1 year, the mean change in symptom score in the placebo group was −24.2 (95% confidence interval, −70.0 to 21.6) and −24.0 (95% confidence interval, −69.0 to 21.0) in the actively treated group (Figure 2). When only the CagA-positive patients were considered, there was no difference in the change in symptom score at months 1, 3, 6, and 12 between those in the actively treated group (−37 ± 153, −50 ± 163, −19 ± 140, and −4 ± 168) and those in the placebo group (−33 ± 136, −59 ± 112, −54 ± 139, and −29 ± 149).

When the dyspepsia score was analyzed according to whether or not *H pylori* was successfully eradicated, those patients with persistent *H pylori* infection (−40 ± 144, −65 ± 142, −45 ± 138, and −39 ± 163) actually demonstrated a better, but nonsignificant, clinical response than those in whom *H pylori* was successfully eradicated (−26 ± 126, −26 ± 148, −12 ± 126, and −25 ± 151). Among the CagA-positive patients, there was no difference in the change in dyspepsia score between those with successful eradication (−27 ± 131, −25 ± 143, −5 ± 142, and 3 ± 145) and those with persistent infection (−50 ± 145, −81 ± 137, −53 ± 141, and −47 ± 151) at any time. Furthermore, within the actively treated group, the CagA-positive patients (−38 ± 128, −29 ± 147, −10 ± 147, and −7 ± 133) and the CagA-negative patients (−22 ± 120, −79 ± 132, −37 ± 18, and −129 ± 138) with successful *H pylori* eradication had a similar improvement in mean dyspepsia scores.

No individual symptom within the dyspepsia score was significantly different between those in the omeprazole and clarithromycin therapy group and those in the placebo group. There was no consistent difference in 6 additional gastrointestinal symptoms during the course of this study (Table 2), nor was there consistent improvement in any individual symptom in the patients with successful *H pylori* eradication compared with those with persistent infection.

Patients in both groups were equally likely to have taken histamine₂-receptor antagonists or proton pump inhibitors throughout the study period. In fact, at the 12-month follow-up visit, it was found that a majority of patients were receiving acid-reduction therapy, despite a confirmed diagnosis of nonulcer dyspepsia (Figure 3).

**ENDOSCOPIC EVALUATION**

Three patients demonstrated new gastric ulcers at follow-up endoscopy (1 in the active therapy group in whom *H pylori* eradication was not successful and 2 in the placebo group), while another patient in the placebo group
developed a duodenal ulcer. These patients were treated for *H pylori* infection.

The mean endoscopic gastric score in patients with successful *H pylori* eradication was 1.8 ± 1.4 at baseline and 1.6 ± 1.2 at follow-up, compared with a score of 1.6 ± 1.4 at baseline and 1.5 ± 1.6 at follow-up for those with persistent *H pylori* infection. The mean duodenal endoscopic score was 0.5 ± 1.1 in the successfully treated group and 0.3 ± 0.8 in the persistently infected group at baseline, with no change in either group after treatment.

**COMPLIANCE AND ADVERSE EFFECTS**

In the actively treated group, 95.2% of the omeprazole capsules were consumed, compared with 100% of the capsules in the placebo group (*P* = .07), and an estimated 94.5% of the clarithromycin tablets were ingested, compared with 99.5% of the tablets in the placebo group (*P* = .06). In the actively treated group, 31 patients were confirmed to be compliant by pill counts, compared with 34 in the placebo group (*P* = .68). Mild adverse effects, including nausea (n = 4), dysgeusia (n = 3), thrush (n = 2), headache (n = 1), fatigue (n = 1), vomiting (n = 1), dizziness (n = 1), lower extremity edema (n = 1), and a self-limited rash (n = 1), were reported by 11 of 50 patients who received omeprazole and clarithromycin. Only 2 of 50 patients in the placebo group reported nausea (*P* = .01).

**Table 1. Baseline Data**

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (n = 50)</th>
<th>Omeprazole and Clarithromycin Group (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, No.</td>
<td>32</td>
<td>37</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>46.7 ± 13.3</td>
<td>46.2 ± 14.3</td>
</tr>
<tr>
<td>Race, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Asian</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>White</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Duration of dyspepsia, y</td>
<td>5.4 ± 6.5</td>
<td>6.3 ± 6.9</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.2-33.0</td>
<td>0.2-21.0</td>
</tr>
<tr>
<td>History of ulcer, No.</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Alcohol users, %</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>Laboratory data, mean ± SD</td>
<td>0.41 ± 0.04</td>
<td>0.42 ± 0.04</td>
</tr>
<tr>
<td>Hematocrit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, µmol/L (mg/dL)</td>
<td>7 ± 5 (0.4 ± 0.3)</td>
<td>9 ± 3 (0.5 ± 0.2)</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>71 ± 20</td>
<td>79 ± 26</td>
</tr>
<tr>
<td>Aspartate</td>
<td>21 ± 6</td>
<td>25 ± 11</td>
</tr>
<tr>
<td>Aminotransferase, U/L</td>
<td>19 ± 7</td>
<td>26 ± 15*</td>
</tr>
<tr>
<td>Alanine</td>
<td>59 ± 17</td>
<td>68 ± 22</td>
</tr>
<tr>
<td>Amylase, U/L</td>
<td>90</td>
<td>79</td>
</tr>
<tr>
<td>CagA present, %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P = .02.

Our study demonstrates that treatment for *H pylori* is no better than placebo in improving symptoms in patients with nonulcer dyspepsia. These data argue strongly that *H pylori* is not a cause of nonulcer dyspepsia in most patients infected with the organism. We were not able to identify any known subgroups that responded to *H pylori* therapy. In contrast, patients with peptic ulcer disease demonstrate ulcer healing and improvement in symptoms after *H pylori* eradication.22,23,26

Prior studies on the role of *H pylori* in nonulcer dyspepsia have shown mixed results. Recent reviews have highlighted the methodological problems of these studies.18,19 Major problems include a lack of a placebo group, failure to ensure blinding, small study size, and inadequate exclusion of patients with reflux disease. Three recent studies have suggested improvement after eradication of *H pylori* in patients with nonulcer dyspepsia. In 2 of these studies, however, there were only about 20 patients randomized to each study arm, with even fewer completing the study.5,6 Another study did not have a control group and had an extremely high reinfection rate, suggesting that *H pylori* was not truly eradicated.4 Most importantly, none of these 3 studies had a true untreated, placebo group, and none provided data on an intention-to-treat basis. Because of the well-established placebo response in nonulcer dyspepsia, any patient awareness of treatment randomization may significantly alter the results. We used a treatment regimen that
specifically did not include bismuth, given the difficulty in establishing secure patient blinding with bismuth.

Clinical criteria are not perfect in distinguishing nonulcer dyspepsia from reflux disease, biliary disease, or irritable bowel. However, we used clinical and endoscopic criteria to carefully exclude patients with predominant reflux symptoms or other definable diseases such as irritable bowel. The possibility remains that some patients were included in the present study and were inappropriately classified as having nonulcer dyspepsia, although this problem is not unique to our study.

In the present study, 4 patients had active ulcer disease on follow-up endoscopy. The presence of ulcers in these patients highlights the observation that ulcers may be transient and that patients diagnosed as having nonulcer dyspepsia after endoscopy may in actuality have ulcer disease. Therefore, we cannot exclude the possibility that certain subsets of patients with nonulcer dyspepsia might benefit from treatment. At present, there is no way to determine which, if any, of these patients should be treated for H pylori.39 Preliminary evidence suggests that the presence of CagA in patients with H pylori infection predicts a more virulent strain that is more likely to lead to dyspeptic symptoms and ulcer disease than are strains without CagA.30 However, subset analysis of CagA status did not influence the main results of this study. As our understanding of the pathogenesis of H pylori infection improves, it may be possible to select appropriate patients with nonulcer dyspepsia for H pylori treatment, based on the presence or absence of bacterial virulence factors.

A popular, although unproved, management strategy has been to screen dyspeptic patients with a serum enzyme-linked immunosorbent assay for H pylori.31-33 Patients with positive results are then treated for H pylori and are followed up clinically. Those with persistent dyspepsia after H pylori treatment undergo endoscopy. Although this approach may appear attractive from a management standpoint, it must be recognized that this strategy should lead to improvement in those patients with peptic ulcer disease (approximately 20% of patients with dyspepsia), but would not be likely to improve symptoms in the 80% of dyspeptic patients with nonulcer dyspepsia, acid-reflux disease, or gastric cancer. Thus, ap-

Table 2. Differences in Symptom Score at Months 1, 3, 6, and 12, Compared With Baseline

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC</td>
<td>Placebo</td>
<td>OC</td>
<td>Placebo</td>
<td>OC</td>
</tr>
<tr>
<td>Nausea</td>
<td>-7</td>
<td>-9</td>
<td>-5</td>
<td>-3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>-9</td>
<td>-2</td>
<td>-13</td>
<td>-7</td>
</tr>
<tr>
<td>Abdominal bloating</td>
<td>0</td>
<td>-4</td>
<td>-15</td>
<td>-18</td>
</tr>
<tr>
<td>Abdominal burning</td>
<td>-5</td>
<td>-11</td>
<td>-4</td>
<td>-15</td>
</tr>
<tr>
<td>Pain after eating</td>
<td>-12</td>
<td>-1</td>
<td>-9</td>
<td>-3</td>
</tr>
<tr>
<td>Dyspepsia Score</td>
<td>-32</td>
<td>-25</td>
<td>-44</td>
<td>-45</td>
</tr>
<tr>
<td>Vomiting</td>
<td>-4</td>
<td>-3</td>
<td>-5</td>
<td>-1</td>
</tr>
<tr>
<td>Belching</td>
<td>-10</td>
<td>-1</td>
<td>-11</td>
<td>-4</td>
</tr>
<tr>
<td>Heartburn</td>
<td>-9</td>
<td>-8</td>
<td>-7</td>
<td>-13</td>
</tr>
<tr>
<td>Pyrosis</td>
<td>-7</td>
<td>-2</td>
<td>-9</td>
<td>-8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-41</td>
<td>-6</td>
<td>-3</td>
<td>-1</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>-18</td>
<td>-8</td>
<td>-20</td>
<td>-12</td>
</tr>
</tbody>
</table>

*Comparison of scores of patients randomized to treatment with omeprazole and clarithromycin (OC) with those of patients randomized to treatment with placebo. Negative numbers indicate improvement.

Figure 2. Mean change in dyspepsia scores, compared with baseline values. Negative numbers represent improved symptoms. Values are expressed as mean ± SD.

Figure 3. Combined use of histamine-receptor antagonists and proton pump inhibitors.
proximately 5 patients with dyspepsia will be treated for *H pylori* so that the 1 patient with peptic ulcer disease will be treated appropriately. Also, when embracing this strategy, one must take into consideration the possible adverse effects of antibiotic therapy as well as issues of drug resistance.

An alternative approach that has been recommended by some authors is to perform upper endoscopy immediately in patients with newly diagnosed dyspepsia before initiating trials with histamine₂-receptor antagonists or screening for *H pylori*.²³ Endoscopy is necessary for accurate diagnosis in patients with dyspepsia, as clinical symptoms alone are unreliable.³⁴ The attraction of this management strategy is that treatment can be tailored more precisely when the cause of dyspepsia is known for each patient. The patient outcomes and cost benefits of these differing strategies are controversial. Further clinical studies are needed to clarify the optimal treatment of patients with dyspepsia.

In the present study, we enrolled patients in whom an empirical trial of a histamine₂-receptor antagonist had failed and in whom peptic ulcer disease and gastroesophageal reflux disease had been excluded. Both *H pylori* infection and dyspepsia are common, and many patients with dyspepsia are infected with *H pylori*. However, the present study demonstrates that *H pylori* is not likely to be the cause of dyspepsia and that treatment for *H pylori* is therefore not likely to improve symptoms better than placebo. At the present time, based on our study findings, we recommend that patients with nonulcer dyspepsia not be treated for *H pylori*.

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REFERENCES