

## Long-Term Follow-Up of *Helicobacter pylori* Treatment in Non-Ulcer Dyspepsia Patients

Grace H. Elta, M.D., James M. Scheiman, M.D., Jeffrey L. Barnett, M.D., Timothy T. Nostrant, M.D., Elizabeth M. Behler, M.D., Ingrid Crause, M.D., and Henry D. Appelman, M.D.

Division of Gastroenterology, Department of Internal Medicine and Department of Pathology, University of Michigan Medical Center, Ann Arbor, Michigan

**Background/Aims:** It remains controversial whether *Helicobacter pylori* infection causes symptoms in non-ulcer dyspepsia. One hundred non-ulcer dyspepsia patients were screened for *H. pylori* infection between November 1989 and February 1994. Forty patients entered a trial where both infected and uninfected patients were treated with *H. pylori* therapy, with the uninfected group serving as controls. **Methods:** Non-ulcer dyspepsia was defined as unexplained epigastric discomfort lasting for at least 4 wk. From November 1989 until February 1992, all patients, regardless of *H. pylori* status, were treated with bismuth subsalicylate tablets (524 mg *q.i.d.*) for 4 wk and metronidazole (250 mg *q.i.d.*) for the first 2 of the 4 wk. From March 1992 until February 1994, only infected patients were treated in an attempt to obtain equal numbers in each group. *H. pylori* infection was diagnosed histologically at the index endoscopy and 1 month after completion of therapy. Symptoms were scored on a 0–5 scale for both frequency and severity. **Results:** Of 100 patients screened, 33 were infected with *H. pylori* (mean age, 42; 10 men, 23 women), and 67 were uninfected (mean age, 38; 16 men, 51 women). Thirty-six uninfected patients were not offered treatment during the latter part of the trial. Of the remaining 31 uninfected patients, 10 dropped out; of the 33 infected patients, 14 dropped out. Twenty-one uninfected patients and 19 *H. pylori*-infected patients completed treatment; in 13 of 19 patients (68%), *H. pylori* was eradicated. Symptoms improved in eight of 13 (61%) *H. pylori*-eradicated patients and in four of six (66%) *H. pylori*-persistent patients, compared with 14 of 21 (66%) uninfected patients. Long-term follow-up (mean, 34 months) showed similar symptom outcome in the two treatment groups. **Conclusions:** Thirty-three percent of our non-ulcer dyspepsia patients were infected with *H. pylori*, a number similar to the percentage of infected age-matched controls in the U.S. Treatment with bismuth subsalicylate and metronidazole resulted in symptomatic improvement in 61–66% of non-ulcer dyspepsia

patients regardless of initial or post-treatment *H. pylori* status. Long-term symptom follow-up in both the control and infected groups gave similar results. *H. pylori* infection is not related to the symptoms of non-ulcer dyspepsia.

### INTRODUCTION

It has been estimated that chronic dyspepsia affects 15% of the adult population and that 25% of these will seek medical attention (1). Most of these patients will not have peptic ulcers or other organic disease. These patients have been labeled as non-ulcer, functional, or essential dyspepsia patients (2–4). They have been shown to have a high placebo response rate and a poor response to acid suppressive therapy (5, 6). Several factors make chronic infection with *Helicobacter pylori* an attractive potential etiology of symptoms in at least a subset of these patients. First, it is known that acute infection with *H. pylori* often causes acute dyspepsia (7). Second, it is reported that the prevalence of *H. pylori* infection is higher in non-ulcer dyspepsia (NUD) patients than in controls (8). Third, *H. pylori* is the accepted cause of almost all histological chronic active gastritis (9). Fourth, *H. pylori* infection is closely associated with peptic ulcer disease. Despite these four reasons why *H. pylori* infection should cause NUD, controlled studies of symptom outcome after *H. pylori* treatment have had conflicting results (10). This has led to the conclusion that routine testing for *H. pylori* in the absence of ulcer disease is not warranted (11) and that further study of the relationship between the symptoms of NUD and *H. pylori* is needed (12).

We describe the long-term follow-up of symptoms in NUD patients who were all treated as if they had *H. pylori* infection with metronidazole and bismuth subsalicylate regardless of whether they were initially infected. The *H. pylori*-negative patients were used as controls.

### MATERIALS AND METHODS

Non-ulcer dyspepsia was defined as unexplained epigastric discomfort lasting for at least 4 wk. Patients were

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excluded if their predominant symptoms were reflux-like (frequent heartburn, acid reflux) or dysmotility-like (bloating, nausea). The patients were all studied at the University of Michigan Medical Center. Most had previous thorough diagnostic evaluations and had failed prior medical therapy including H<sub>2</sub> blockers. One hundred NUD patients were screened for *H. pylori* infection by antral biopsy for histology at their normal upper endoscopies between November 1989 and February 1994, and they agreed to study participation. None had previously been treated for *H. pylori* infection. From study initiation until February 1992, all patients, regardless of their *H. pylori* status, were given the study treatment. Both the patients and the investigators were blinded to the results of the initial histological determination of *H. pylori* status until after the follow-up endoscopy. Interim review of results after entering 48 patients revealed that too few *H. pylori*-infected patients were being studied. Therefore, from February 1992 until the study close in February 1994, only *H. pylori*-infected patients were offered study entry. During this second half of the study, neither patients nor investigators were blinded to the initial presence of infection. This second portion of the study included 16 *H. pylori*-infected individuals, eight of whom completed the study.

Three antral biopsies were obtained at the entry endoscopy and at the follow-up endoscopy, which was performed 1 month after completion of therapy. The presence of *H. pylori* was determined histologically by one pathologist after review of hematoxylin and eosin stains on all biopsies and Warthin-Starry stains on the inflamed biopsies that were *H. pylori*-negative by hematoxylin and eosin staining. Biopsies were graded on the severity of plasma cell infiltration (chronic inflammation) as follows: 0, normal; 1, focal superficial involving the pit compartment; 2, diffuse superficial; 3, midmucosal extending into the middle of the mucosa; 4, transmucosal. The presence of polymorphonuclear cells in the pit epithelium was also graded as present or absent.

Patients were treated with bismuth subsalicylate tablets (524 mg *q.i.d.*) for 4 wk and metronidazole (250 mg *q.i.d.*) for the first 2 of the 4-wk treatment period. Medication compliance was determined by pill counts at the follow-up endoscopy.

At study entry, the following data were obtained: patient age and race, prior history of ulcer disease (by patient history; documentation of prior ulcer was not obtained), prior use of anti-ulcer medicines (antacids, H<sub>2</sub>-blockers, omeprazole, or sucralfate), daily use of cigarettes, at least weekly use of alcohol, and use of aspirin and nonsteroidal anti-inflammatory drugs. Symptoms were assessed at three time points: at study entry, at the follow-up endoscopy (1 month after treatment completion), and on long-term follow-up. Four symptoms were scored on a 0-5 scale for both frequency and severity: pain, nausea and vomiting, bloating/belching/gas, and anorexia. The symptom scale for frequency was graded as follows: 0, none; 1, 1 d/wk; 2, 2-3

TABLE 1  
Entry Characteristics in 100 NUD Patients

	HP-infected (n = 33)	Not infected (n = 67)
Mean age (yr)	42	38
Sex		
Male	30%	24%
Female	70%	76%
Race		
Caucasian	70%	87%
African American	21%	9%
Asian American	9%	4%
Previous ulcer history	24%	21%
Current tobacco use	27%	15%
Alcohol use ( $\geq$ 1 drink/wk)	12%	26%
Prior ulcer medications	75%	77%
Nonsteroidal anti-inflammatory drug use	18%	15%

None of these entry characteristics were statistically different in the infected versus noninfected groups.

days; 3, 4-5 days; 4, 6-7 days; 5, 4-7 days and 4-7 nights. The symptom scale for severity was graded as follows: 0, none; 1, mild and aware of symptom; 2, mild to moderate; 3, moderate and interferes with routine; 4, severe; 5, unbearable. Symptom improvement was defined subjectively as an improvement of three or more points in the pain score when the frequency and severity scores were added together. All of our patients who met this criteria felt that they had global improvement. The other symptoms (*i.e.*, nausea, bloating, and anorexia) were not used in this improvement determination, because not all patients had all of these symptoms. Patients also were asked to keep a daily diary of symptoms while taking medications and to report a single score on a 0-5 scale for overall symptoms.

Statistical analysis was performed using the Student's *t* test and the  $\chi^2$  test with Yates correction. This study was approved by the Institutional Review Board at the University of Michigan.

## RESULTS

Entry characteristics for the 100 patients screened are listed in Table 1. Thirty-three patients were infected with *H. pylori*, and 67 had no histological evidence for infection. The mean age of the infected patients, 42 yr, was slightly higher than the uninfected patients, 38 yr, although this did not reach statistical significance ( $p = 0.19$ ). Seventy percent of the *H. pylori*-infected NUD patients were women compared with 76% of the uninfected patients. African Americans and cigarette smokers were more likely to be *H. pylori*-infected, although this was not statistically significant by  $\chi^2$ . Other entry characteristics—including a history of prior ulcer disease and the use of alcohol, nonsteroidal anti-inflammatory drugs, and prior ulcer medications—were similar between the *H. pylori*-infected and uninfected groups. The prevalence of types of symptoms was also not different between the infected and uninfected groups (Table 2).

TABLE 2

Mean Symptom Scores at Study Entry: Sum of Frequency and Severity Scores

Symptoms	HP-infected (n = 33)	Not infected (n = 67)
Epigastric pain	6.4	6.9
Nausea/vomiting	2.6	3.9
Bloating/belching/gas	4.5	4.9
Poor appetite	2.6	2.7

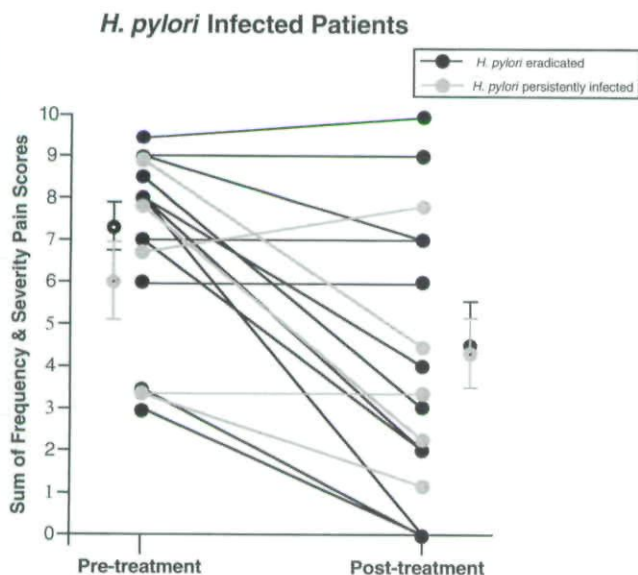


FIG. 1. Individual and mean ( $\pm$  SE) pain scores at study entry and 1 month after treatment completion in *H. pylori*-infected NUD patients.

At interim study analysis, it became clear that NUD patients without *H. pylori* infection outnumbered infected NUD patients 2:1. To obtain equal numbers of treated infected and uninfected patients, 36 uninfected patients were not offered treatment in the second part of the study. Of the remaining 31 uninfected patients, 10 dropped out, and of the 33 infected patients, 14 dropped out. Reasons for drop-out included drug side effects in eight patients, lost or refused follow-up in 12 patients, and unrelated medical problems in four patients. Nineteen infected patients and 21 uninfected patients completed treatment and returned for the follow-up endoscopy. *H. pylori* was eradicated in 13 of 19 patients (68%).

Symptom improvement was defined as an improvement in the sum of the frequency and severity pain score of at least three points at the time of follow-up endoscopy, which was performed 1 month after completion of therapy. An improvement in pain occurred in eight of 13 (61%) *H. pylori*-eradicated patients and in four of six (66%) persistently infected patients versus 14 of 21 (66%) noninfected patients (Figs. 1 and 2). Long-term follow-up (26–51 months; mean, 40 months) of 21 noninfected patients showed that nine patients were lost, six remained improved, three became symptomatic again, and three got better de-

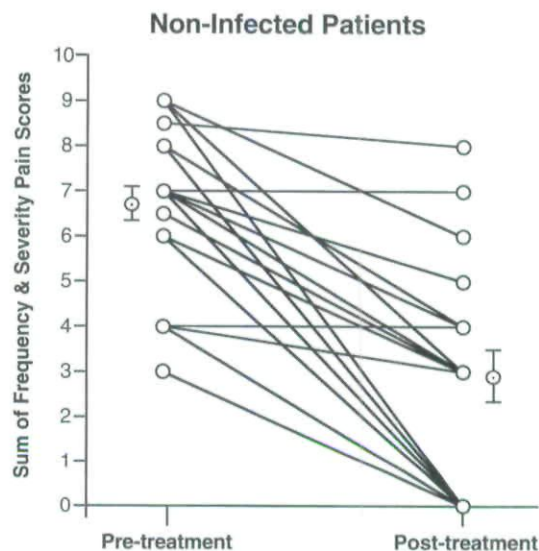


FIG. 2. Individual and mean ( $\pm$  SE) pain scores at study entry and 1 month after treatment completion in noninfected NUD patients.

spite initial treatment failure. Of the 19 *H. pylori*-infected patients, 13 had eradication of *H. pylori* with a follow-up of 12–45 months (mean, 26 months). Three patients were lost, three continued well, two relapsed, three who had failed initial treatment improved over time, and two continued symptomatic. Of the six persistently infected patients, two were lost, one continued well, one relapsed, and two continued symptomatic. The response to treatment of the non-pain symptoms (nausea/vomiting, bloating/belching/gas, and anorexia), which were not present in all patients at study entry, is listed in Table 3.

The mean pretreatment gastritis score (scale of 0–4) for the *H. pylori*-infected patients was 2.7, and 17 of 19 had evidence for activity (polymorphonuclear cell infiltration). The mean follow-up gastritis score in the eradicated patients was 1.8, and none had persistent activity. The persistently infected patients had a mean score of 2.8, and all had activity. In contrast, the mean pretreatment gastritis score in the noninfected patients was 0.1, and none had activity. Their post-treatment score was 0.8, again without activity.

## DISCUSSION

Although the role of *H. pylori* infection in peptic ulcer disease is now well established, controversy continues regarding its relationship to non-ulcer dyspepsia (13, 14). One of the epidemiologic links of *H. pylori* to NUD is the high prevalence (50%) of infection in these patients (15, 16). However, in this study, we demonstrate a 33% infection rate in a group of NUD patients with a mean age of 40. This is in agreement with Greenberg (17), who reports a 37% infection rate in NUD patients with a mean age of 49. These prevalence rates are identical with those reported in age-matched asymptomatic volunteers in the U.S. (18). The higher prevalence reported earlier may be a result of the type of patients studied, [*i.e.*, patients with erosive gastritis or

TABLE 3  
Treatment Response of Symptoms Other Than Pain

Symptom	HP-infected patients total (HP eradicated) [n = 19 (13)]			Noninfected patients (n = 21)		
	Not present at entry	Improved	Not improved	Not present at entry	Improved	Not improved
Nausea/vomiting	9 (7)	6 (4)	4 (2)	3	15	3
Bloating/belching/gas	3 (3)	8 (5)	8 (5)	2	10	9
Anorexia	10 (7)	5 (4)	4 (2)	12	3	6

duodenitis (19), some of whom may simply have a mild form of peptic ulcer disease]. Alternately, because the prevalence of *H. pylori* infection varies with nationality, race, and socioeconomic class, prior data may be from populations known to have higher infection rates (20).

Clearly, conclusions concerning an association between *H. pylori* infection and NUD must come from clinical outcome trials. Most studies to date have been flawed by inadequate *H. pylori* therapy to achieve eradication (21-23), by inclusion of patients with gastroesophageal reflux (24, 25), or by difficulty in achieving a true placebo because of the black stools and tongue caused by bismuth treatment. We treated our patients with 2 wk of metronidazole and 4 wk of bismuth and demonstrated eradication in 68% at 1 month after completion of therapy. The superior treatment regimens now known were not used in this study because it was started in 1988. Although 24-hr pH studies were not performed on all patients, the incidence of gastroesophageal reflux disease was minimized by the exclusion of patients with "reflux-like" symptoms, by the lack of prior response to acid suppression therapy in more than 75% of our patients, and by the normal esophageal findings at endoscopy. Instead of trying to devise an effective placebo, we treated uninfected patients with the identical regimen without their knowledge of the presence or absence of infection. Although eight infected patients who were recruited in the second part of the study were aware of the presence of infection, their outcome was not different from those who were recruited in the first half of the study. By treating uninfected patients with the same regimen, we controlled for the possibility that bismuth and antibiotic therapy may have beneficial effects other than antibacterial action for NUD. Uninfected patients seem to be an ideal control, although as expected from previous epidemiological studies, infected patients tended to be older and had a higher incidence of being African American. We also found a higher incidence of smoking in the infected patients (27% vs 15%), a result that has been noted in previous studies (20). None of the differences in entry characteristics between infected and uninfected patients reached statistical significance.

The mean symptom scores at study entry listed in Table 2 show that the infected and uninfected NUD patients had a similar frequency and severity of chronic epigastric pain. Other symptoms that were monitored throughout the study included nausea/vomiting, bloating/belching/gas, and an-

orexia. These were not present in all patients but were of similar severity and frequency in the infected and uninfected patients, suggesting that *H. pylori* infection is not associated with any "type" of NUD that has been previously suggested (8). Our failure to identify subgroups of NUD patients based upon *H. pylori* status is in agreement with a recent report of 180 healthy blood donors (26). The treatment responses of these symptoms (Table 3) were also similar between the infected (both eradicated and persistently infected patients) and noninfected patients. One possible exception was nausea and vomiting, which seemed to be more common in the uninfected patients and seemed to improve more with treatment. The small number of patients with these other symptoms, however, prevents any firm conclusions.

A 61-67% symptom response rate, regardless of the presence of infection before treatment or of the success of eradication, strongly implies that *H. pylori* infection does not play a role in causing the symptoms of NUD. Although this seems to be a very high placebo response rate, other functional dyspepsia trials have had similar placebo response rates (27, 21). The high drop-out rate in our study was disappointing but was similar in the infected and uninfected patients and therefore was unlikely to affect our results. Similar problems have plagued prior NUD studies and probably reflect characteristics of this patient population (28). Although it has been stated that the diagnosis of NUD greatly outnumbers peptic ulcer disease, obtaining a detailed history to rule out patients with probable gastroesophageal reflux disease or irritable bowel syndrome significantly decreases the number of patients diagnosed with NUD. This led to slow recruitment and a prolonged trial allowing us to obtain long-term follow-up in many patients. It has been suggested that symptomatic improvement may be delayed for 6-12 months (29) after *H. pylori* eradication as has been shown for normalization of gastric histology (9). A recent report of 1-yr follow-up in *H. pylori*-infected NUD patients showed lower mean symptom scores in patients remaining clear of infection versus those who were persistently infected or re-infected (30), although no control group was studied. Our similar rate of eventual disappearance of symptoms in both the infected and uninfected patients argues against this hypothesis. The strongest criticism of our study is the relatively small number of patients studied, clearly insufficient to rule out a  $\beta$ -type error in our conclusions. It has been estimated that a sample size of 100

patients in each group would be needed (10). When patients with symptoms suggestive of gastroesophageal reflux disease or irritable bowel syndrome are carefully excluded, a multicenter study would be required to obtain such a large number of patients.

Our controlled study with careful inclusion criteria, follow-up for eradication, and long-term symptom outcome results strongly suggests that chronic *H. pylori* infection is not associated with the symptoms of NUD. The absence of an association between chronic *H. pylori* infection and dyspepsia despite the association of dyspeptic symptoms with acute infection has previously been reported (31). There appears to be no justification for routinely obtaining random antral biopsies at endoscopy to identify *H. pylori* in patients with non-ulcer dyspepsia. Larger controlled studies with enough power to rule out a small but potentially clinically significant benefit from *H. pylori* treatment in NUD are still needed.

Reprint requests and correspondence: Dr. Grace H. Elta, 3912 Taubman Center, Box 0362, University of Michigan, Ann Arbor, MI 48109-0362.

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