

# Eradication of *Helicobacter pylori* Among Patients from a Primary Care Practice

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**BACKGROUND.** The eradication of *Helicobacter pylori* is becoming the therapy of choice for peptic ulcers, if the infection is present. Published data from primary care settings are, however, limited.

**METHODS.** An open-ended, prospective study was undertaken that included 31 patients with active peptic ulcer demonstrated by endoscopy and *H pylori* infection confirmed by urease and histologic tests. After a 14-day period of treatment with omeprazole, bismuth, tetracycline, and metronidazole, healing and *H pylori* status were evaluated by repeat endoscopy done at least 28 days after the last treatment dose. Eradication is defined as absence of *H pylori* in at least four (two from the fundus and two from the antrum) samples taken from the gastric mucosa and a negative urease test. Drug side effects and patient compliance were monitored in all cases.

**RESULTS.** Twenty-eight patients completed the protocol. Healing was obtained in all cases, and eradication was accomplished in 25 (89%). Side effects were common (69%) but mild. Compliance was good. After a mean follow-up of 300 days (range, 180 to 400), one ulcer recurrence was observed in an *H pylori*-positive patient and none in *H pylori*-negative patients.

**CONCLUSIONS.** The treatment of *H pylori* infection is an effective way of healing peptic ulcers, and can be applied in primary care settings. Further studies with more patients and with shorter and easier therapies should be undertaken to confirm our findings.

**KEY WORDS.** *Helicobacter pylori*; peptic ulcer; treatment protocols; treatment outcome. (*J Fam Pract* 1996; 43:551-555)

Since Warren and Marshall published their original findings in 1983,<sup>1</sup> cumulative evidence has increasingly linked infection by *Helicobacter pylori* to various gastric diseases.<sup>2-4</sup> Multiple studies have shown that the natural history of peptic ulcer changes after the infection<sup>5-8</sup> has been eradicated, and, in fact, most patients seem to be cured of the disease.<sup>9,10</sup> Although recent reviews<sup>11-13</sup> acknowledge that the eradication of *H pylori* from the gastric mucosa should be the first line of treatment for peptic ulcers with infection, many physicians do not use this treatment, and few data have been reported from

primary care settings. Therapy to eradicate *H pylori* is often considered too complex, and it is difficult to choose among the various alternatives.<sup>14,15</sup>

Triple therapy with a combination of bismuth, metronidazole, and tetracycline is considered the reference therapy<sup>4,13,15,16</sup> because it achieves high rates (>80%) of eradication, is inexpensive, and the results are consistent in studies from diverse geographical areas.<sup>17</sup> H<sub>2</sub>-receptor antagonist therapy is frequently added when the ulcer is active to control symptoms and accelerate healing.<sup>13</sup> Triple therapy and other regimens directed at eradicating *H pylori* are acknowledged by experts as the therapy of choice for peptic ulcer when *H pylori* infection is present.<sup>18</sup> However, expert authors also note that their results were achieved in highly motivated patients, and question whether similar results can be achieved in practice.<sup>18</sup> The study reported here was designed to evaluate results from clinical practice.

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## METHODS

An endoscopy-controlled, prospective study was undertaken with patients whose symptoms suggested peptic ulcers at a primary care center in Zaragoza, Spain. The study period was from May 1994 to February 1995.

Patients of either sex were considered eligible for the study if they were 18 to 70 years old and were willing to undergo endoscopy as a diagnostic test. Many patients were chronic ulcer patients who were requesting a prescription of H<sub>2</sub>-receptor antagonists because of flare-up of symptoms. After endoscopy, inclusion criteria were: active peptic (duodenal or gastric) ulcer with >5 mm in diameter and a positive urease test of an antral sample at <60 minutes (Jatrox-Test). In all cases four additional samples were obtained (two from the antrum and two from the fundus) for histologic confirmation of *H pylori* infection. All samples were evaluated by the same pathologist and were stained with H&E and Giemsa. Exclusion criteria were pregnancy, allergy to drugs in protocol, any other treatment for *H pylori* in the previous 6 months, malignancy, and severe (grades III or IV according to Savary-Miller criteria) esophagitis. Informed consent was obtained in all cases.

After a diagnosis of active peptic ulcer was made, the patient was seen at a primary care center by his or her primary care physician, who explained the treatment, prescribed all the medications, and completed a questionnaire in which symptoms and other clinically relevant data (eg, smoking history) were noted. The importance of compliance was reinforced by oral explanations, and a written information form was given to all patients. Treatment consisted of a combination of four drugs: omeprazole 20 mg orally daily, tetracycline hydrochloride 2 g divided in four 500-mg doses, colloidal bismuth subcitrate 480 mg in four 120-mg doses, and metronidazole 750 mg in three doses of 250 mg. All the drugs were taken during a 14-day period, and no further treatment was permitted until the results of the follow-up endoscopy were known.

A follow-up visit was scheduled at day 15, and at this visit another questionnaire on symptoms was completed by the primary care physician. Drug side effects were prospectively determined by prompting the patient with the general question: "Have you noticed any new symptom during the last two

weeks?" and by specific questions on the most common expected side effects (eg, metallic taste, nausea, vomiting, diarrhea, abdominal pain, and headache). Compliance was checked by a standardized interview and a pill count of the unused portion of the prescriptions.

At day 45 (range, 44 to 50) from the start of treatment, a follow-up endoscopy was scheduled. Healing was defined as complete epithelialization of the ulcer crater, and at least five samples (three from the antrum, one for urease test, and two from the fundus) were obtained. Eradication was defined as complete absence of *H pylori* in the four histologic samples (stained with H&E and Giemsa in all cases) and a negative urease test at 1, 4, and 24 hours.

With the exception of the endoscopies that were undertaken at the reference hospital (in all cases by the same gastroenterologist), all patient care was done by family physicians during routine office visits.

Data were retrieved using DataBase III (Asthon-Tate, 1987), and statistical analysis was conducted using the SPSS package. Student *t* tests for paired data were used for comparison of means before and after treatment for some variables (eg, smoking expressed in number of cigarettes/day). Comparison of clinical data before and after the treatment were made using the Wilcoxon ranks sum test for paired data. Possible differences between patients with effective treatment as opposed to patients with non-effective treatment were evaluated with the Mann-Whitney test for quantitative variables and the chi-square test of Fisher's exact test for qualitative ones. In all cases, significance was defined as  $P < .01$ .

## RESULTS

Sixty-five patients were considered as candidates for endoscopy because of symptoms suggesting peptic ulcer. This determination was made by family physicians, based on clinical data and previous history. On endoscopy, 31 patients had active peptic ulcer, and all of them fulfilled inclusion criteria; the endoscopic diagnosis of the other 34 patients are summarized in Table 1. *H pylori* infection was demonstrated by a positive urease test at 30 minutes in 30 cases and at 1 hour in one case, and confirmed by histologic findings in all cases. Treatment was administered to all patients.

Thirty-one patients returned for follow-up, but

TABLE 1

## Endoscopic Confirmed Diagnoses in 65 Patients

Diagnosis	No.
Active peptic ulcer	31
Scar of previous ulcer	8
Peptic esophagitis	6
Gastric MALT lymphoma	1
Normal endoscopy	19

MALT denotes mucosa-associated lymphoid tissue.

only 28 (90.3%) agreed to the second endoscopy. The three patients who refused a second endoscopy were all patients with chronic ulcers, who previously received frequent courses of H<sub>2</sub>-receptor antagonists and remained asymptomatic (for the first time in years) during at least 180 days. They are not included in the analysis.

Clinical data of the 28 evaluable patients are available in Table 2. Healing of the ulcer was complete at follow-up endoscopy in all 28 (100%) evaluable patients, and symptoms were absent or mild in all cases. *H pylori* infection was eradicated in 25 patients (89.3%). In the three remaining patients, both the urease test and biopsy samples were positive for *H pylori* infection. Compliance was good in all cases (>80% of prescribed doses taken). As only three patients had refractory infections, comparisons were difficult, but no significant difference was found. Compliance was adequate (>90% doses taken) even in the three patients with refractory *H pylori* infection.

Side effects were common: 19 (67%) patients reported some problem (Table 3). Side effects were most commonly scored as mild by 73% of patients, and only in 22% were they considered moderate. No patients had side effects severe enough to stop them from taking the medication. Diarrhea (25%), metallic taste (17.8%), and headache (11%) were the most common symptoms reported.

Follow-up at 180 days (mean 300 days, range 180 to 400) was completed in all cases at the time the authors were writing the paper. No patient received any form of maintenance anti-ulcer treatment, except for one patient with noneradicated *H pylori*, who received a 6-week course of ranitidine. After being questioned specifically, 92% of patients were

completely satisfied with the results of treatment at follow-up.

## DISCUSSION

Our report confirms that the eradication of *H pylori* can be successfully accomplished in primary care practices. Although the number of patients in our study was small, the use of endoscopy as the reference test confirms the diagnosis and outcome. A short and inexpensive therapy of 14 days' duration heals peptic ulcers effectively, and recently it was reported that effective treatment has been achieved even with a 7-day course.<sup>19</sup> A high rate of eradication can be obtained even in a geographical area with a high level of metronidazole-resistant strains (30% to 50% in Spain). Efficacy of these treatments seems to be very good, can be achieved at reasonable cost, and can be done in the primary care setting.

Limitations to our study are that it is was not

TABLE 2

## Clinical and Demographic Data on 28 Evaluable Patients

Characteristic	Outcome
Age, mean±SD	39.1 (±6.9)
Sex, n (%)	
Male	24 (85.7)
Female	4 (14.3)
Smokers, n (%)	
Yes	18 (64.3)
No	10 (35.7)
Family history, n (%)	
Yes	11 (39.3)
No	17 (60.7)
Personal history, n (%)	
Yes	22 (78.6)
No	6 (21.4)
Previous complication, n (%) <sup>*</sup>	
Yes	5 (17.8)
No	23 (82.2)
Ulcers, n (%)	
Duodenal	26 (92.7)
Gastric	2 (7.1)

\* 4 cases of bleeding, and one of perforation treated with suture.

TABLE 3

## Common Drug Side Effects Reported by Study Subjects

Side Effect	No. (%) of Patients
Diarrhea	7 (25)
Metallic taste	5 (17.8)
Headache	3 (10.7)
Constipation	2 (7.1)
Nausea	2 (7.1)
Dermatitis	0 (0)
Photosensitivity	0 (0)
Emesis	0 (0)
Dilsulfiram effect	0 (0)
Other	6 (21.5)

blinded and it included a relatively small number of subjects. Our patients, however, were unselected patients from a primary care practice, without those sometimes stringent and restrictive criteria used in formal double-blind research trials.<sup>18</sup> In fact, most cases were patients with chronic ulcers who required maintenance treatment or at least frequent prescriptions of H<sub>2</sub>-receptor antagonists. Medications were routinely prescribed, and no additional incentive was offered to patients. In our view, and as stated in a recent editorial,<sup>18</sup> these types of data from clinical practice are needed to complete the picture of *H pylori* infection and peptic ulcer. Our data do confirm that results in the "real world" are not very different from those obtained in research studies.

Drug side effects were common but mild, and such side effects have been reported previously in detail in other studies.<sup>20</sup> The high rate of side effects reported by our patients may be attributed to the specific methods for ascertaining symptoms. In no case were the side effects severe enough for the patients to stop treatment. In our opinion side effects of classic triple therapy have been magnified in the literature. We agree with DeBoer and Tytgat<sup>15</sup> that side effects are common but mild with this regimen, and efficacy outweighs the importance of side effects. In more recent therapies directed at eradicating *H pylori*, the side effects were less common, but few direct comparative data are available.

Compliance was good in our study (>80%). We feel, yet we cannot prove, that the physician-patient relationship was an important reason for success in patient compliance. Detailed oral and written information have probably also played an

important role.

Endoscopy was used in this study to confirm the diagnosis, ulcer healing, and *H pylori* eradication. Although we used endoscopy for the study, the cost of the procedure may limit its availability in clinical practice. A recent and detailed decision analysis<sup>21</sup> confirms, however, that only modest savings may result from empiric therapy, and endoscopy as a first strategy seems preferable. Endoscopy by family physicians has been found to be accurate,<sup>22</sup> and charges can be reduced because hospital costs are avoided. These arguments favor endoscopy as the key test in the evaluation of these patients. Rapid urease tests provide a quick, specific, and inexpensive method to confirm *H pylori* infection if endoscopy is performed.

In our opinion, a treatment with high efficacy both in healing and eradication does not require a follow-up test in the majority of patients, as has been previously suggested by DeBoer et al.<sup>23</sup> Only in selected cases, such as in patients with previous bleeding or recurrence of symptoms, will proof of eradication, perhaps with a carbon 13 breath test (when available), be indicated.<sup>24</sup> Follow-up endoscopy should be reserved for selected cases with persistent or recurrent symptoms.

The treatment of *H pylori* infection has a major impact on the natural history of peptic ulcers.<sup>25</sup> An inexpensive, short, and effective way of treatment can be accomplished in the primary care setting. New, shorter, and better tolerated therapies should make the treatment of *H pylori* infection even easier.<sup>15,18,19,26,27</sup> The treatment of infection should be our primary goal to make peptic ulcer an extinct, or at least rare, disease in the near future.

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