Effectiveness of Helicobacter pylori Therapies in a Clinical Practice Setting

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Background: Whether eradication rates for Helicobacter pylori treatment regimens obtained in controlled clinical trials (efficacy) can also be obtained in clinical practice (effectiveness) is unknown because no such trials have been reported in the United States.

Objectives: To determine the eradication rates of H pylori in a community practice setting and the effects of practice variation in the choice of treatment regimen on patient outcome (H pylori infection cure) and cost.

Methods: Between February 1 and December 30, 1996, 38 community-based gastroenterologists in the Portland, Ore, metropolitan area enrolled a total of 250 patients infected with H pylori, as determined by endoscopic or noninvasive methods. Various therapeutic regimens aimed at eradicating H pylori were used by the gastroenterologists, and a posttreatment urea breath test was used to determine H pylori infection cure. Compliance and incidental effects were also measured and decision analysis was used to estimate the cost of treatment.

Results: The regimens used varied considerably. Patients receiving a 2- or 3-times-a-day treatment regimen were significantly more compliant (P = .01) than those receiving a 4-times-a-day regimen. Proton pump inhibitor–based triple-therapy regimens were significantly more effective than all other treatment regimens combined (87% vs 70%; P = .001) in eradicating H pylori. These proton pump inhibitor–based triple-therapy regimens were also more cost-effective by decision analysis for a hypothetical cohort of patients with duodenal ulcer disease.

Conclusions: The considerable variation in the choice of treatment regimens affects the clinical and economic outcomes of patients undergoing therapy for H pylori infection. Whether these data reflect the outcome in other communities is unknown but should be determined. It will be necessary to determine if the dissemination of these data results in a reduction of practice variation and improvement in clinical and economic outcomes of patients being treated for H pylori infection in clinical practice.

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Helicobacter pylori was first identified and isolated from gastric biopsy specimens in 1983 and has since emerged as an important gastroduodenal pathogen. This pathogen is unequivocally the cause of chronic active gastritis and, in addition, plays an integral role in the pathogenesis of most cases of duodenal and gastric ulcer. Therefore, the standard of care of patients with ulcer disease and associated H pylori infection is to treat the infection with antimicrobial agents. Other gastrointestinal diseases associated with H pylori include gastric cancer, gastric lymphoma, and possibly nonulcer dyspepsia. That the cure of H pylori infection may prevent gastric cancer or lessen dyspeptic symptoms is unproved; nevertheless, many patients are tested and treated for H pylori infection for conditions other than peptic ulcer disease.

The treatment of H pylori infection has been problematic, which is related to the disappointing efficacy of single antimicrobial treatments and widespread antimicrobial resistance. To overcome this suboptimal efficacy with single agents, combination therapy with 2 or more antimicrobial agents, with or without antisecretory drugs, evolved to improve the success rate of therapy. A multidrug approach to therapy has inherent disadvantages, however. Many of these regimens are complex and associated with a high incidence of adverse effects, which may result in decreased patient compliance. Decreased compliance has been shown to significantly compromise the therapeutic efficacy of some regimens.

Factors such as these have contributed to uncertainty about the optimal treatment regimen, and therapeutic regimens studied in clinical trials have demonstrated variable efficacy. Furthermore, pa-
PARTICIPANTS AND METHODS

Community gastroenterologists in the greater Portland, Ore, metropolitan area were invited to participate in this study. Most of these gastroenterologists had previously participated in other community outcomes studies17 concerning reflux disease and have constituted the Gastroenterology Outcomes Research Group in Endoscopy consortium. Subjects were entered into the study by their treating gastroenterologist following the documentation of *H pylori* infection by serological testing, urea breath testing or rapid urease testing, or histological biopsy specimen obtained at endoscopy. Any patient with *H pylori* infection, with or without ulcer disease, was eligible for the study. Because patients were enrolled at the discretion of the treating community physician, the enrollment was not necessarily consecutive, and a “characteristic” of patients enrolled vs not enrolled was not identified. This discretionary enrollment was necessitated to avoid creating bias and influencing the community basis of the study.

Patients were treated for *H pylori* infection with a regimen that was left to the discretion of the treating physician. The physicians, however, were encouraged before the start of the study to use 1 of 6 treatment regimens (Table 1). These regimens were (1) bismuth subsalicylate (Pepto Bismol) (2 tablets 4 times a day), metronidazole hydrochloride (250 mg 4 times a day), and tetracycline hydrochloride (500 mg 4 times a day) for 2 weeks (BMT); (2) omeprazole sodium (20 mg twice a day) and amoxicillin (1 g twice a day) for 2 weeks; (3) omeprazole (40 mg/d) and clarithromycin (500 mg 3 times a day) for 2 weeks (OC); (4) metronidazole (500 mg twice a day), omeprazole (20 mg twice a day), and clarithromycin (500 mg twice a day) for 1 week (MOC); (5) omeprazole (20 mg twice a day), amoxicillin (1 g twice a day), and clarithromycin (500 mg twice a day) for 1 week (OAC); and (6) omeprazole (20 mg/d) with BMT for 1 week. The actual regimen used and its duration were left to the treating physician's discretion.

Following the completion of therapy, patients were contacted for the first time by a research assistant (N.M.), and a standardized questionnaire relating to adverse effects and degree of compliance was administered. Compliance was arbitrarily defined as taking 80% or more of the medications. Four or more weeks following the completion of therapy, patients underwent a standard carbon 13–labeled urea breath test ($\text{^{13}C}$UBT) (Meretek Inc, Houston, Tex) to document *H pylori* eradication. The $\text{^{13}C}$UBT was administered according to the manufacturer's guidelines, and breath specimens were collected and mailed to the manufacturer for analysis. Patients were off antibiotic therapy for 4 weeks and proton pump inhibitors (PPIs) for 2 weeks before testing. A positive test result was defined as an increase of 2.4 U or greater above baseline on the second breath specimen.

Decision analysis was used to determine the cost-effectiveness of the regimens prescribed in this study for a hypothetical cohort of patients with duodenal ulcer disease. A detailed description of the model and the assumptions used for this analysis have previously been published.18 Intention-to-treat eradication rates for *H pylori* infection treatment groups observed in this study were used in the calculations, and pharmaceutical costs were calculated from the published average wholesale price (1996 *Red Book* update). The duration of therapy for each treatment was that recommended above. The model is limited to duodenal ulcer disease because of the paucity of data on the clinical outcome of *H pylori* eradication in dyspepsia and other conditions. The model assumes the viewpoint of the third-party payer and is developed for a 2-year time frame.

The study subjects were categorized for statistical analysis according to the antimicrobial therapy they received. Summary descriptive statistics, including mean, SEM, range, and proportions, were computed for all groups. Per-protocol (those taking ≥80% of medication and completing a posttreatment $\text{^{13}C}$UBT) and intention-to-treat (all patients entered, including those taking <80% of their medication and/or without a follow-up $\text{^{13}C}$UBT who were considered treatment failures) effectiveness between therapy groups was compared using a χ² analysis and the 2-tailed Fisher exact test. We calculated 95% confidence intervals (CIs) using the standard formula for the estimation of Z. *P* < .05 was considered statistically significant.

Consent for the study was obtained from each patient by their private physicians. The study was approved by the institutional review board at Oregon Health Sciences University, Portland.

RESULTS

This study accrued patients from February 1 to December 30, 1996, and a total of 250 patients were enrolled by 38 gastroenterologists. The demographics of this group largely reflect those of the Portland metropolitan area: 72.8% were white, 7.2% African American, 6.0% Asian American, 4.8% Hispanic, and 8.8% other. One hundred forty-three patients (57.2%) were men, and 107 (42.8%) were women. The mean age was 56 years.
The following clinical indications were used to treat patients for *H pylori* infection:

<table>
<thead>
<tr>
<th>Indication</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer disease</td>
<td>140 (56.0)</td>
</tr>
<tr>
<td>Erosion or inflammation</td>
<td>45 (18.0)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>47 (18.8)</td>
</tr>
<tr>
<td>Gastroesophageal reflux symptoms</td>
<td>19 (5.2)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (2.0)</td>
</tr>
</tbody>
</table>

Of the 140 patients with ulcer disease, 106 were treated for an active ulcer. Forty-four percent of patients were treated for other indications, despite the recommendations by the 1994 National Institutes of Health consensus conference that these regimens be used to treat ulcer disease only.

The diagnosis of *H pylori* infection was largely made by endoscopy (213 patients [85.2%]), reflecting the enrollment of patients only by gastroenterologists. Of patients whose *H pylori* infection was diagnosed endoscopically, 117 (54.9%) had the diagnosis made by an endoscopic rapid urease test. For 37 patients, the diagnosis was made by a serological test in 16 patients (6.4% of total) and by 13C UBT in 21 patients (8.4%).

The time from the completion of therapy to the survey was a mean of 14 days (range, 0-53 days) and for the 13C UBT, a mean of 37 days (range, 26-79 days).

The regimens used in these 250 patients are shown in Table 1. Fifty-nine percent of the regimens consisted of a twice-a-day triple therapy, MOC or OAC. Regimens approved by the Food and Drug Administration (FDA) for that period (OC and BMT) were used in only 45 patients (18.0%). The number of physicians prescribing each regimen is also shown in Table 1. Twenty-nine physicians (76.3%) used a PPI-based twice-a-day regimen at least once. Twenty-one physicians (55.3%) used only 1 regimen, 4 physicians (10.5%) used 2 regimens, and 13 physicians (34.2%) used 3 or more regimens. Two thirds used 1 regimen more than 75% of the time. By protocol analysis (≥80% compliant [233 patients] and follow-up 13C UBT performed), there was a significant difference (P = .02) between MOC and OAC vs all other therapies (of 135 patients, 88.9% [95% CI, 83.6%-94.2%] were effectively treated vs 77.3% [95% CI, 68.4%-86.1%] of patients). By intention-to-treat analysis (all those entered into the study), treatment with MOC and OAC (146 patients) was significantly more effective (P = .001) than all other therapies: 87.0% with *H pylori* cure (93% CI, 81.6%-92.4%) vs 70.2% (95% CI, 61.4%-79.0%). The MOC and OAC regimens were also significantly more effective (P < .001) than the then-FDA-approved BMT and OC regimens. Of 137 patients treated with MOC or an MOC-equivalent regimen (6 received lansoprazole instead of omeprazole), 76, 42, and 19 were prescribed therapy for 7, 10, and 14 days, respectively. *Helicobacter pylori* was eradicated in 70 (92.1%) of those treated for 7 days, 36 (85.7%) of those treated for 10 days, and 16 (84.2%) of those treated for 14 days by intention-to-treat analysis, which was not significantly different (P = .38). Of the 34 patients receiving omeprazole with BMT, 25 received therapy for 14 days and 9 received therapy for 7 days. The difference in efficacy of these 2 durations of therapy was not statistically significant (P = .93 for per protocol, P = .43 for intention to treat).

Patients receiving a 2- or 3-times-a-day regimen (MOC, OAC, OC, and omeprazole and amoxicillin) were significantly more compliant (took ≥80% of medication) (P < .02) than those receiving a 4-times-a-day regimen (BMT and omeprazole with BMT) (Table 2). Compliance of 80% or greater in taking their medication was also significantly better (P < .002) in those without vs those with adverse effects (98.9% vs 87.9%). Patients receiving a 4-times-a-day regimen were significantly more likely to be noncompliant (P = .01) than those receiving a 2- or 3-times-a-day regimen, but there were no significant differences in compliance between individual regimens (P = .12).

Incidental effects were noted in 38% to 71% of the regimens, but most were classified as mild, and few pa-

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**Table 1. Therapeutic Regimens Used by 38 Physicians to Treat 250 Patients With *Helicobacter pylori* Infection**

<table>
<thead>
<tr>
<th>Drug Combinations</th>
<th>No. (%) of Patients</th>
<th>No. of Physicians Prescribing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth subsalicylate, metronidazole hydrochloride, and tetracycline hydrochloride</td>
<td>21 (8.4)</td>
<td>11</td>
</tr>
<tr>
<td>Omeprazole sodium, bismuth, metronidazole, and tetracycline</td>
<td>34 (13.6)</td>
<td>11</td>
</tr>
<tr>
<td>Omeprazole and amoxicillin</td>
<td>17 (6.8)</td>
<td>7</td>
</tr>
<tr>
<td>Omeprazole and clarithromycin</td>
<td>25 (10.0)†</td>
<td>9</td>
</tr>
<tr>
<td>Metronidazole, omeprazole, and clarithromycin</td>
<td>137 (54.8)†</td>
<td>29</td>
</tr>
<tr>
<td>Omeprazole, amoxicillin, and clarithromycin</td>
<td>9 (3.6)</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>7 (2.8)</td>
<td>4</td>
</tr>
</tbody>
</table>

*See the “Participants and Methods” section for the specific drug regimens.
†Nine of these patients received lansoprazole instead of omeprazole.

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**Table 2. Regimen Compliance in 250 Patients by Frequency of Dosing and Adverse Effects**

<table>
<thead>
<tr>
<th>Regimen (No. of Patients)</th>
<th>% of Patients With ≥80% Compliance (n = 233)</th>
<th>Any Adverse Effects (n = 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four times a day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bismuth subsalicylate, metronidazole hydrochloride, and tetracycline hydrochloride</td>
<td>85 (50)</td>
<td>64 (46)</td>
</tr>
<tr>
<td>Omeprazole sodium, bismuth, metronidazole, and tetracycline (20)</td>
<td>85 (50)</td>
<td>64 (46)</td>
</tr>
<tr>
<td>Omeprazole and amoxicillin (14)</td>
<td>100 (57)</td>
<td>67 (40)</td>
</tr>
<tr>
<td>Omeprazole and clarithromycin (24)</td>
<td>96 (67)</td>
<td>60 (40)</td>
</tr>
<tr>
<td>Metronidazole, omeprazole, and clarithromycin (134)</td>
<td>95 (60)</td>
<td>60 (40)</td>
</tr>
<tr>
<td>Omeprazole, amoxicillin, and clarithromycin (8)</td>
<td>100 (57)</td>
<td>67 (40)</td>
</tr>
<tr>
<td>Other (7)</td>
<td>86 (57)</td>
<td>71 (40)</td>
</tr>
</tbody>
</table>

*Compliance is significantly greater than with 4-times-a-day regimens (P < .02).*

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tients discontinued therapy due to incidental effects. In patients receiving MOC or OAC, 57% reported incidental effects vs 56% receiving other regimens. Most common side effects with a metronidazole-containing regimen were nausea (40%) and upset stomach (45%), whereas with a clarithromycin-containing regimen, it was nausea (38%) and foul taste (18%).

The estimated average 2-year cost of treating a hypothetical cohort of patients with *H pylori*-related peptic ulcer disease for each of the treatment regimens is shown in the Figure. The principal determinant of the cost of each strategy is the cost of recurrence rather than the cost of the therapy. Whereas the BMT regimen had the lowest acquisition cost, because of its lower efficacy, the regimen was not cost-effective. Sensitivity analysis demonstrated that the model was not sensitive to the costs of endoscopy or office visits required for the treatment of patients whose regimen failed to eradicate *H pylori*. It was highly sensitive to the eradication rate with each regimen. One-way sensitivity analysis demonstrated that the omeprazole-with-BMT regimen became cost-effective if it had an eradication rate of 89% or higher. The BMT regimen became cost-effective if the eradication rate obtained with this regimen was more than 82%.

This study reveals substantial practice variation in the clinical indications for the treatment of *H pylori* infection, the method of diagnosing *H pylori* infection, the choice of anti-*H pylori* therapeutic regimens, the effectiveness of the regimens, and the cost-effectiveness of *H pylori* infection treatments in a subspecialty community practice setting. These data, however, refute the hypothesis of the study that the effectiveness of *H pylori* infection treatment in a community setting is less than that obtained in research trials. Eradication rates observed in this study are similar to those reported in published clinical trials and reported to the FDA (PPI-based triple therapy, 85%-95%; BMT, 77%-82%; and OC, 70%-75%). This study also indicates that a non–FDA-approved regimen, MOC (although 2 PPI-based triple therapies, lansoprazole, amoxicillin, and clarithromycin and OAC, have since been approved by the FDA) is more effective than FDA-approved regimens in community settings. The MOC regimen was also the most cost-effective therapy because of its superior clinical efficacy. In addition, in this study, PPI-based therapy for 7 days was as effective as longer courses of therapy. This is at variance with the experience in controlled clinical trials, which show lower efficacy with shorter courses (7 or 10 vs 14 days) of therapy. Whether these findings are generalizable to other community settings is unknown. This patient population was largely white, male, and older and does not demographically reflect many other practice environments.

Many patients who were tested and treated for *H pylori* infection did not meet the National Institutes of Health consensus guidelines of that period. Furthermore, only a few patients were treated with FDA-approved regimens. The use of a twice-a-day PPI-based regimen in most patients may have reflected gastroenterologists’ “exposure” to emerging PPI-based regimens during that period.

The second hypothesis of the study was also disproved because self-reported compliance was high. The study demonstrated, however, that simpler regimens (2 or 3 times a day) were associated with significantly better compliance than 4-times-a-day regimens. If the self-reported data are accurate, it is unlikely that compliance was an important factor in treatment failure because compliance did not affect a regimen’s efficacy. The accuracy of self-reporting, however, is less than optimal because pill counts were not used in this study to avoid “testing bias”—ie, if patients are aware of oversight, compliance may be artificially enhanced by study participation. Thus, in a community study such as this, the accuracy of compliance data is unknown. Another factor that may have contributed to treatment failure is antimicrobial resistance, which was not measured in this study. Thus, the effect of antimicrobial resistance on observed effectiveness is speculative. Given the limitations of this study, we cannot be certain of the reasons for treatment failures because the study was designed to detect differences in community-based treatment effectiveness, not their cause.

Other possible weaknesses of the study are the nonblinding of the study, the use of a single diagnostic test for determining *H pylori* eradication, and the use of a variety of diagnostic methods to detect infection. The community basis of this outcome study necessitates its being unblinded, and the objective measure of outcome—[13C]UBT—should not be affected by blinding. Many studies have previously used a “gold standard” of 2 separate negative test results to determine “cure” of infection; however, the use of a single test, particularly the [13C]UBT, can be justified as indicative of treatment cure. The posttreatment [13C]UBT has excellent sensitivity and specificity and has been used and validated by others as a single test after treatment to document cure. Furthermore, a simple noninvasive test is most compatible with the standard of practice in community settings.

Finally, decision analysis indicates that for a hypothetical cohort of patients with *H pylori*–related peptic
ulcer in this community, a regimen of MOC or OAC is the most cost-effective therapy. This model illustrates that the most cost-effective therapy is the one that has the greatest efficacy of cure and is not dependent on treatment cost. As indicated in the Figure, the cost of the \( H \) pylori treatment accounts for little of the total costs of managing a patient with peptic ulcer disease. Whether these data are applicable and relevant to other communities is unknown. Given the availability of an office-based post-treatment test to noninvasively document the effectiveness of a treatment regimen and because this is the most important determinant of cost-effectiveness, local effectiveness rates are clinically relevant and should be measured. The less effective the regimen, the greater the cost, ie, the most expensive therapy is the one that does not work. Thus, in Portland, a PPI-based triple-therapy regimen (MOC or OAC) is clinically and economically the most cost-effective therapy.

**CONCLUSIONS**

To our knowledge, this is the first study in the United States to measure the outcome of treating \( H \) pylori infection in community practice settings. There was considerable variation in the choice of treatment regimens and, in most patients, physicians in practice selected regimens based on more recent published reports, rather than on older, but still active, FDA-approved guidelines. The study confirms that many of the new emerging regimens were superior to the FDA-approved treatments in older, but still active, FDA-approved guidelines. The PPI-based triple therapy MOC is the most clinically effective and cost-effective \( H \) pylori treatment regimen in Portland. Further study is needed to determine if there is regional variation in drug treatment outcomes due to antimicrobial resistance or other factors. Finally, this study provides some insight into individual practice patterns and the effects these behaviors have on patient outcomes, including bacterial eradication and costs. This investigation should be considered part of an iterative process in which this new information will be disseminated to community physicians. Further study should be conducted to determine if the dissemination of these data will result in a reduction in practice variation and improvement in outcomes.

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**REFERENCES**


