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Sequential Therapy versus Standard Triple-Drug Therapy for *Helicobacter pylori* Eradication

A Randomized Trial

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Background: Antimicrobial resistance has decreased eradication rates for *Helicobacter pylori* infection worldwide.

Objective: To determine whether sequential treatment eradicates *H. pylori* infection better than standard triple-drug therapy for adults with dyspepsia or peptic ulcers.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Two Italian hospitals between September 2003 and April 2006.

Patients: 300 patients with dyspepsia or peptic ulcers.

Measurements: ^{13}C-urea breath test, upper endoscopy, histologic evaluation, rapid urease test, bacterial culture, and assessment of antibiotic resistance.

Intervention: A 10-day sequential regimen (40 mg of pantoprazole, 1 g of amoxicillin, and placebo, each administered twice daily for the first 5 days, followed by 40 mg of pantoprazole, 500 mg of clarithromycin, and 500 mg of tinidazole, each administered twice daily for the remaining 5 days) or standard 10-day therapy (40 mg of pantoprazole, 500 mg of clarithromycin, and 1 g of amoxicillin, each administered twice daily).

Results: The eradication rate achieved with the sequential regimen was significantly greater than that obtained with the standard treatment in the intention-to-treat analysis (89% vs. 77%; $P = 0.0134$; difference, 12% [95% CI, 3% to 20%]), the modified intention-to-treat analysis (91% vs. 78%; $P = 0.0022$; difference, 13% [CI, 5% to 21%]), and the per-protocol analysis (93% vs. 79%; $P = 0.0013$; difference, 14% [CI, 6% to 21%]). Sequential therapy was significantly more effective in patients with clarithromycin-resistant strains (89% vs. 29%; $P = 0.0034$). The incidence of major and minor side effects did not differ between therapy groups (17% in both groups). One patient (0.7%) in the standard therapy group discontinued treatment because of side effects.

Limitations: Follow-up was incomplete in 4.6% and 2.7% patients in the sequential therapy and standard therapy groups, respectively. The results may not be generalizable to other countries. Sequential therapy may be more effective because it includes 1 additional antibiotic (tinidazole) that is not contained in standard therapy.

Conclusions: Sequential therapy is statistically significant compared with standard therapy for eradicating *H. pylori* infection and is statistically significantly more effective in patients with clarithromycin-resistant strains. Side effects are similar with both treatment regimens and are rarely severe enough to cause discontinuation of therapy.

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Helicobacter pylori infection causes peptic ulcers, gastric mucosa–associated lymphoid tissue lymphoma, and gastric cancer (1). Standard treatments for *H. pylori* infection that have been endorsed by U.S. and European authorities rely on clarithromycin or metronidazole in conjunction with other antibiotics and acid inhibitors (2, 3). The prevalence of clarithromycin and metronidazole resistance has increased substantially in recent years, and there has been a corresponding decrease in the eradication rate for *H. pylori* infection (4). Eradication rates in most western countries have declined to unacceptable levels. Eradication therapy fails in approximately 1 in 5 patients (5). A simple, short treatment regimen that would return eradication levels to those seen at the advent of *H. pylori* treatment is urgently needed (5). Such a regimen should have high efficacy against clarithromycin-resistant and metronidazole-resistant strains of *H. pylori* because these strains are increasingly encountered in routine clinical practice.

Novel 10-day sequential therapy consisting of 5-day dual therapy (proton-pump inhibitor plus amoxicillin) followed by 5-day triple therapy (proton-pump inhibitor, clarithromycin, and tinidazole) has had good eradication success in unblinded trials in elderly and pediatric patients (6–8). However, no double-blind, controlled trials using conventional therapy have been reported, and the effect of clarithromycin and metronidazole resistance on the outcome of sequential therapy has not been studied prospectively.

The aim of this study was to compare a 10-day sequential treatment regimen for *H. pylori* infection with standard 10-day triple therapy in a randomized, controlled trial. Secondary objectives were to determine the efficacy of the treatment regimen in patients with resistant strains of *H. pylori*, to assess treatment adherence, and to evaluate side effects.

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METHODS

Design Overview

This was a prospective, double-blind, controlled study with a parallel-group design. At baseline, patients were evaluated for inclusion and exclusion criteria and provided written informed consent. Patients were then randomly assigned to a treatment group and had follow-up evaluations to assess the eradication rate of *H. pylori* infection, treatment adherence, and side effects. The study was performed according to good clinical practice and the Declaration of Helsinki. The ethics committees at the 2 participating centers approved the study. The consent form indicated that patients would be randomly assigned to treatment that was the current standard or a new therapy that might have higher eradication rates. Patients were told that eradication failure was possible with any therapy regimen. All patients with eradication failure were offered a rescue therapy on the basis of the results of sensitivity testing.

Setting and Participants

Between September 2003 and April 2006, consecutive patients with dyspepsia who were at least 18 years of age, who had never received treatment for *H. pylori* infection, and who had been referred to our hospitals (Bologna, Italy, and Rome, Italy) for a gastroenterology consultation were asked to participate in the study. No special recruitment techniques (such as advertisements or letters sent to primary care physicians) were used. Exclusion criteria were previous treatment for *H. pylori* infection; use of proton-pump inhibitors, H_2-receptor antagonists, bismuth preparations, or antibiotics in the previous 2 weeks; concomitant use of anticoagulants or ketoconazole (because of potential interaction with the nonsteroidal anti-inflammatory drugs) and glucocorticoids (because of association with ulcer disease); the Zollinger–Ellison syndrome; previous surgery of the esophagus or upper gastrointestinal tract (except appendectomy, polypectomy, or cholecystectomy); severe or unstable cardiovascular, pulmonary, or endocrine disease; clinically significant renal or hepatic disease or dysfunction; hematologic disorders; any other clinically significant medical condition that could increase risk; malignant disease of any kind except for successfully treated skin cancer (basal- or squamous-cell carcinoma) during the previous 5 years; Barrett esophagus or high-grade dysplasia; drug, alcohol, or medication abuse within the past year; severe psychiatric or neurologic disorders; and pregnancy or lactation, as well as sexually active women of child-bearing years who were not willing to practice medically acceptable contraception (oral or injectable contraceptives, implantable or mechanical intrauterine or vaginal devices, or vasectomy for the partner) for the study duration.

Randomization and Interventions

Patient allocation was determined with a random-number chart that was concealed from investigators and patients by using numbered blister packs of the study medication that corresponded to the random-number chart. A computer-generated randomization chart was used to determine allocation, which was stratified according to center by using a block design and a block size of 4. Allocation was concealed with an opaque envelope, which contained a number that corresponded to the numbered blister packs. The envelope was opened when the patient met the inclusion criteria and provided informed consent. Patients and investigators were blinded to treatment group. Patients were randomly allocated to receive a 10-day sequential regimen (40 mg of pantoprazole, 1 g of amoxicillin, and placebo, each administered twice daily for the first 5 days, followed by 40 mg of pantoprazole, 500 mg of clarithromycin, and 500 mg of tinidazole, each administered twice daily for the remaining 5 days); or standard therapy (40 mg of pantoprazole, 500 mg of clarithromycin, and 1 g of amoxicillin, each administered twice daily for 10 days). Medications were contained in individual blisters in the package. A placebo that was identical in color and shape to the clarithromycin capsule was administered during the first 5 days of sequential therapy to maintain blinding. This ensured that all patients took 3 medications twice a day for 10 days.

Context

Eradication rates for *Helicobacter pylori* infection are decreasing worldwide because of increasing antimicrobial resistance.

Contribution

This double-blind trial randomly assigned 300 adults with dyspepsia or peptic ulcers to a 10-day sequential regimen (pantoprazole, amoxicillin, and placebo taken for 5 days followed by pantoprazole, clarithromycin, and tinidazole taken for 5 days) or standard 10-day therapy (pantoprazole, clarithromycin, and amoxicillin). The eradication rate of *H. pylori* infection was greater with the sequential regimen (89%) than with the standard treatment (77%). Approximately 5% of patients in each group had epigastric pain and 3% to 5% had mild diarrhea.

Implication

Sequential therapy eradicates *H. pylori* infection more often than does standard therapy.

—The Editors

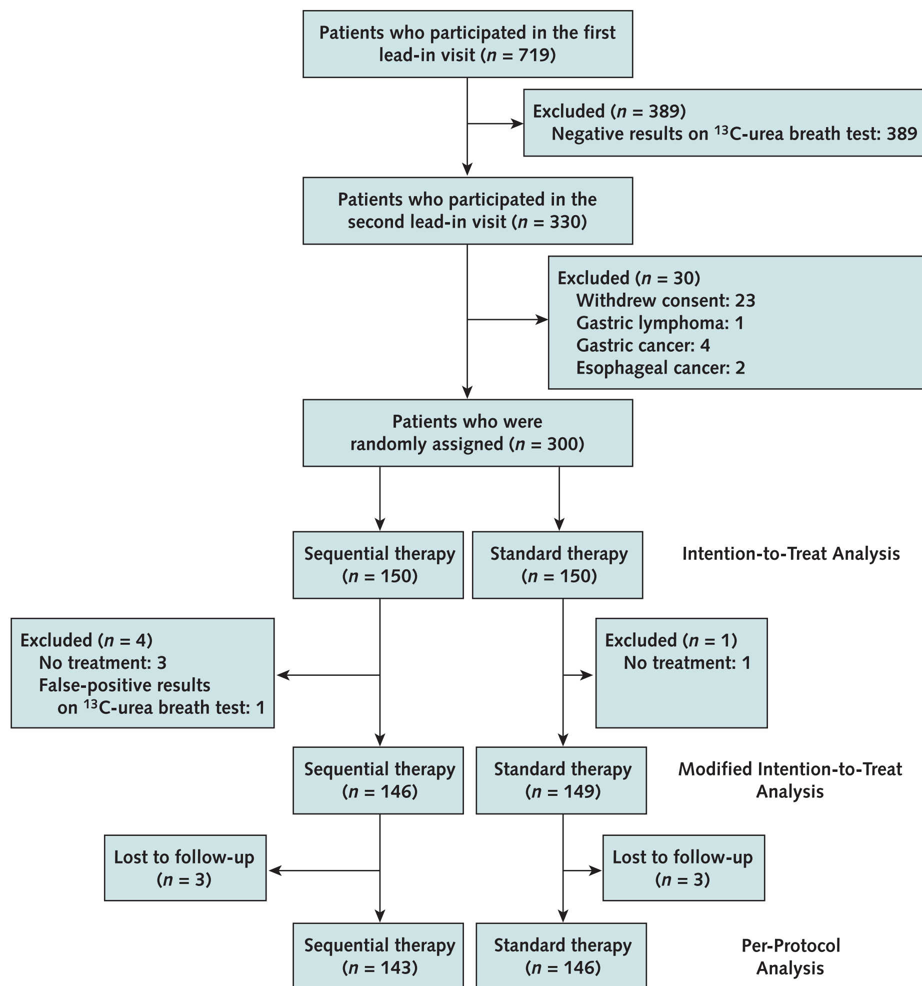
Measurements and Outcomes

The primary outcome of the study was eradication of *H. pylori* infection. Secondary outcomes were to determine the efficacy of sequential treatment against clarithromycin-resistant strains of *H. pylori*, to assess adherence to therapy, and to determine the frequency of self-reported side effects.

^{13}C-Urea Breath Test

Urea breath tests were done after an overnight fast. A baseline breath sample was obtained, and 75 mg of ^{13}C-

Figure. **Study flow diagram.**



urea with citric acid (1.5 g) was administered as an aqueous solution. Another breath sample was collected 30 minutes after the test solution was administered. The results of the test were considered positive if the difference between the baseline sample and the 30-minute sample exceeded 4.5 parts per 1000 of $^{13}CO_2$. All breath samples were analyzed in Bologna by using a single gas isotope ratio mass spectrometer (Finnigan, Bremen, Germany). The accuracy of the urea breath test was previously validated in our laboratory. We reported sensitivity and specificity values of 94.7% and 95.7%, respectively (9).

Endoscopy

All patients with positive results on the urea breath test had upper endoscopy, and 5 biopsy specimens were obtained during the procedure. Two specimens were taken from the antrum and 2 were taken from the corpus for histologic evaluation. The specimens were stained with hematoxylin and eosin and Giemsa stains, and gastritis was scored by using the updated Sydney System (10). The pathologist who performed the histologic examination was blinded to the results of all other tests. One biopsy specimen was obtained from the antrum for the rapid urease test (*Campylobacter pylori* test, Yamanouchi Pharma S.p.A, Corrugate, Milan, Italy). Two additional biopsy samples from the antrum were collected for bacterial culture and susceptibility testing. We performed cultures without knowing the other test results. For this purpose, biopsy specimens were sent to a single microbiological laboratory in Bologna within 24 hours and were stored at −70 °C. Isolated strains were tested for primary clarithromycin and metronidazole resistance by using an agar dilution method, which was defined as a minimal inhibitory concentration greater than 1 mg/L and greater than 8 mg/L for clarithromycin and metronidazole, respectively (11). Strains were classified as having isolated resistance to clarithromycin or metronidazole if the organisms were only resistant to 1 antibiotic. Dual resistance was defined as resistance to clarithromycin and metronidazole.

At baseline, patients were classified as having *H. pylori* infection if the results on the urea breath test were positive and if the results on at least 2 of the following 3 tests were positive: rapid urease test, histologic examination, and culture. An expert panel recommended these criteria for use in clinical trials of *H. pylori* infection (12).

Follow-up Procedures

Treatment Adherence and Side Effects

Patients were asked to return at the completion of therapy for a physical evaluation and to assess adherence to therapy and side effects. We first asked open-ended questions on side effects and then asked specific questions on anticipated side effects. Adherence was defined as consumption of more than 90% of the prescribed drugs and was determined by pill counts. One investigator at each center assessed self-reported side effects during an interview. No questionnaires were used. Causality was assessed by using the temporal relationship of the symptom to the start of therapy. All new symptoms and exacerbations of preexisting symptoms were considered to be treatment-related and are included in the analysis. Any symptom that began after treatment was assumed to be related to the drug. We had no a priori hypothesis on differences in side effects between the 2 treatment groups.

Confirmation of Eradication

The urea breath test was repeated 4 and 8 weeks after treatment was stopped. The infection was considered to have been successfully eradicated when the results on both urea breath tests were negative.

Cost Calculations

The cost of each treatment was estimated by using retail U.S. costs obtained from a large commercial Internet pharmacy (13). The retail cost of the medications in the United States was as follows: 1 g of amoxicillin, $0.80; 500 mg of clarithromycin, $4.75; 500 mg of tinidazole, $2.95; and 40 mg of pantoprazole, $3.96. The calculated costs for 10-day sequential therapy and standard therapy were $164.20 and $190.20, respectively.

Statistical Analysis

We calculated the differences between the proportion of eradicated infections and the 95% CIs for the 2 treatments by using the method recommended by Newcombe and Altman (14). The level of significance was assessed by using Fisher exact test (Intercooled Stata, version 8, Stata Corp., College Station, Texas). For all other variables, the chi-square and *t*-test were used as appropriate, and *P* values less than 0.05 were considered significant.

We calculated a sample size of 123 to detect a 13% difference in the eradication rate between the standard triple therapy for 10 days (assumed to have an eradication rate of 80%) and the new 10-day regimen (estimated to have an eradication rate of 93%) with a power of 0.80 and a significance level of 0.05 (2-sided α level = 0.05). When we assumed a withdrawal rate of 20%, at least 148 patients were required in each group. Assumptions regarding the eradication rates were based on our preliminary studies (6). The results are reported in an intention-to-treat analysis. A modified intention-to-treat analysis (all patients who took at least 1 dose of medication) is also reported to allow comparison with other trials that report data using this end point (15–17). A per-protocol analysis is also reported and is limited to patients who took more than 90% of their medications and completed follow-up. We determined the proportion of patients in each center and group who had successful eradication of infection. Before pooling the results from the 2 centers, we used a chi-square test to investigate heterogeneity between centers. Pooling of data was planned a priori if eradication rates did not statistically significantly differ between centers. The statistician who performed the analyses was blinded to patient group assignment (standard therapy or sequential therapy).

Role of the Funding Sources

Medications were provided by Altana Pharma (now Nicomed, Oslo, Norway); Pharmacia, Milan, Italy (pantoprazole); and Pharmacia & Upjohn (now Pfizer), Milan, Italy (tinidazole and amoxicillin). Clarithromycin was purchased with university foundation research funds. Identical-appearing placebos were made by the pharmacy at S. Orsola Hospital, Bologna, Italy. We received no other financial support for this study. The funding sources had no role in the analysis or interpretation of the data, in the preparation of the manuscript, or in the decision to submit the manuscript for publication.

RESULTS

Patients

The **Figure** shows the flow of patients through the study. The baseline demographic and clinical characteristics of patients were similar in the 2 groups (**Table 1**). Of the 300 patients randomly assigned, 5 were excluded from

Table 1. **Baseline Characteristics**

Variable	Sequential Therapy (*n* = 150)	Standard Therapy (*n* = 150)
Mean age (SD), *y*	48.6 (14)	49.2 (15)
Patients, %		
Men	39	34
Women	61	66
Mean body mass index, *kg/m²*	24.8	23.9
Patients who smoke, %	23	26
Patients who drink alcohol, %	28	23
Peptic ulcer, %	11	10
Antral gastritis, %	4.6	6.6
Pangastritis, %	95.3	93.3
Intestinal metaplasia, %	16	11
Bacterial culture available, %	88	81

Table 2. **Helicobacter pylori Eradication Rates with Sequential and Standard Therapy**

Variable	Sequential Therapy		Standard Therapy		Difference (95% CI), %	*P* Value
	Patients, *n*	Eradication Rate, %	Patients, *n*	Eradication Rate, %		
Standard intention-to-treat analysis	150	89	150	77	12 (3–20)	0.0134
Modified intention-to-treat analysis*	146	91	149	78	13 (5–21)	0.0022
Per-protocol analysis	143	93	146	79	14 (6–21)	0.0010

* All patients who took at least 1 dose of medication are included.

the modified intention-to-treat analysis. One of the patients did not meet the criteria for *H. pylori* infection at baseline (the results on urea breath test and rapid urease test were positive and those on histologic evaluation and cultures were negative). The other 4 did not receive any study medication (1 patient developed severe abdominal pain and had cholecystectomy the day after the baseline visit, 1 patient discovered that she was pregnant before commencing therapy, 1 patient elected not to take study medications after randomization, and 1 patient moved out of the country and forgot to take the medications). Six patients were excluded from the per-protocol analysis (5 were lost to follow-up and 1 discontinued therapy after 1 day because of side effects). Thus, 295 patients were included in the modified intention-to-treat analysis and 289 in the per-protocol analysis (**Figure**). Excluded patients were equally distributed between sequential and standard treatment groups (4.6% vs. 2.7%; $P = 0.56$).

Eradication of *Helicobacter pylori* Infection

Tests to investigate heterogeneity regarding eradication rates for the intention-to-treat analysis between the 2 centers were not statistically significant (for the sequential regimen, 90.7% vs. 91.8% [$P = 0.923$] and for the standard regimen, 80.8% vs. 72.0% [$P = 0.189$]), and we therefore pooled the data. The eradication rate achieved with the sequential regimen was statistically significant compared with that obtained with standard treatment in the intention-to-treat analysis (89% vs. 77% [$P = 0.0134$]; difference, 12% [CI, 3% to 20%]), in the modified intention-to-treat analysis (91% vs. 78% [$P = 0.0022$]; difference, 13% [CI, 5% to 21%]), and in the per-protocol analysis (93% vs. 79% [$P = 0.0013$]; difference, 14% [CI, 6% to 21%]) (**Table 2**).

Role of Primary Resistance on Eradication of *Helicobacter pylori* Infection

Bacterial culture was successful in 255 (85%) patients (80% and 87.5% of patients enrolled in Rome and Bologna, respectively). Isolated clarithromycin resistance was present in 32 (12.5%) strains, isolated metronidazole resistance was present in 61 (23.9%) strains, and resistance to both drugs was present in 11 (4.3%) strains. Therefore, clarithromycin resistance was detected in 43 (16.9%) patients and metronidazole resistance was detected in 72 (28.2%) patients. Bacterial resistance did not statistically significantly differ between the 2 centers for clarithromycin (17.5% vs. 16.6%; $P = 0.789$) and metronidazole (33.7% vs. 25.7%; $P = 0.183$).

Regarding the influence of resistance, data for 246 patients, including 127 who were treated with sequential therapy and 119 who were treated with the standard regimen, were available for the per-protocol analysis. **Table 3** shows that the infection was eradicated in 88.9% of patients with isolated clarithromycin resistance who received sequential therapy compared with 28.6% of patients who received standard therapy (difference, 60.3% [CI, 28.2% to 75.9%]; $P = 0.0034$). Clarithromycin resistance reduced the cure rate by 65.9% in the standard treatment group ($P < 0.001$), whereas the efficacy of the sequential regimen was reduced by 5.8% ($P = 0.889$) compared with susceptible strains. Patients receiving the sequential regi-

Table 3. **Effect of Clarithromycin and Metronidazole Resistance on *Helicobacter pylori* Eradication Rates in the Per-Protocol Analysis**

Variable	Sequential Therapy, *n/n (%)*	Standard Therapy, *n/n (%)*	*P* Value
Clarithromycin			
Resistant	8/9 (88.9)	6/21 (28.6)	0.0034
Susceptible	108/114 (94.7)	86/91 (94.5)	0.8065
Metronidazole			
Resistant	34/35 (97.1)	20/22 (90.9)	0.5526
Susceptible	83/88 (94.3)	72/90 (80)	0.009
Clarithromycin and metronidazole			
Resistant	0/4 (0)	2/7 (28.6)	0

men achieved a statistically significantly higher cure rate in metronidazole-susceptible strains than those receiving standard treatment (94.3% vs. 80%; difference, 14.3% [CI, 6.1% to 22.6%]; $P = 0.009$). However, the difference was not statistically significant in patients with metronidazole-resistant strains (97.1% vs. 90.9%; difference, 6.2%; $P = 0.613$). None of the 4 patients with double-resistant strains achieved eradication after sequential therapy compared with 2 of 7 patients treated with the standard regimen.

Treatment Adherence

A total of 135 (94%) patients in the sequential therapy group and 135 (93%) patients in the standard therapy group adhered to the treatment (>90% of medication taken).

Adverse Events

Both treatments were well tolerated, and only 1 (0.7%) patient who was randomly assigned to the standard regimen group discontinued treatment (because of vomiting on the second day). A total of 25 (17.5%) patients who received sequential therapy and 25 (17.1%) patients who received standard treatment reported minor side effects (**Table 4**). The most frequent side effects in both groups were epigastric pain (5.6% vs. 4.8%; $P = 0.902$) and mild diarrhea (4.8% vs. 2.8%; $P = 0.54$). **Table 4** shows all the side effects reported by the patients.

Table 4. **Patients with Self-Reported Adverse Events during Therapy**

Adverse Event	Sequential Therapy (*n* = 143)	Standard Therapy (*n* = 146)
Epigastric pain, *n*	8	7
Diarrhea, *n*	7	4
Heartburn, *n*	1	4
Vomiting, *n*	3	1
Glossitis, *n*	1	3
Bloating, *n*	2	2
Headache, *n*	1	1
Constipation, *n*	0	2
Candidiasis, *n*	1	0
Itching, *n*	1	0
Taste alteration, *n*	0	1
Total, *n (%)*	25 (17.5)	25 (17.1)
Patients who withdrew, *n (%)**	0 (0)	1 (0.7)
Adherence <90%, *n (%)**	3 (2)	2 (1.4)

* Because of side effects.

DISCUSSION

The results of this study show that sequential therapy is superior to triple therapy for the eradication of *H. pylori* infection. The study also demonstrates that triple therapy, which is the current standard treatment, has low eradication rates. Both treatments were well tolerated and had similar rates of side effects and low rates of patients who withdrew from the study.

Primary care physicians and gastroenterologists in the United States and Europe commonly prescribe triple therapy with a proton-pump inhibitor, clarithromycin, and either amoxicillin or metronidazole to cure *H. pylori* infection (18–20). The success of eradication therapy is often reported as a modified intention-to-treat rate (patients who do not take a single dose of the medication are excluded from the analysis), which should be kept in mind when our study is compared with other studies. Two recent double-blind, U.S. multicenter studies found disappointingly low eradication rates with standard therapy. A total of 75.6% of 402 patients in one study (21) and 77.2% of 307 patients in the other study (22) achieved eradication of *H. pylori* infection by using a modified intention-to-treat analysis after a 10-day standard regimen. Low eradication rates have also been reported with standard therapy in Europe, Australia, and Asia (23). Our study confirms these reports on the poor success rates of infection eradication with standard therapy and suggests that this may be largely due to clarithromycin resistance.

The outcome of therapy for *H. pylori* infection substantially depends on adherence to the regimen and the presence of antibiotic resistance (24). Clarithromycin resistance is a major problem in many western countries. Prevalence is 12.9% (range, 6.1% to 14.5%) in the United States and may be as high as 24% in some European countries (12, 25, 26). A systematic review of therapy for *H. pylori* reported a 53% decrease in eradication rates if clarithromycin resistance was present and if a clarithromycin-containing regimen was used (24). In our study, the prevalence of primary clarithromycin resistance was 17%, which confirms data recently reported in Italy (27, 28). In our study, approximately 90% of patients with clarithromycin-resistant strains were cured after sequential therapy: An eradication rate that is 3 times higher than that of the standard regimen in this subgroup was obtained. The sequential treatment regimen may be preferable when the prevalence of clarithromycin-resistant *H. pylori* infection is high, which is the case in many developed countries.

The precise mechanism for the success of the sequential therapy is not known; however, bacteria can develop efflux channels for clarithromycin, which rapidly transfer the drug out of the bacteria cell, preventing the antibiotic from binding to the ribosome (29). Because amoxicillin acts on the bacterial cell wall and weakens it, the initial phase of treatment may prevent the development of efflux channels by weakening the cell wall of the bacterium (29). This may improve the efficacy of clarithromycin in the second phase of treatment. The higher efficacy of the sequential regimen may be related to the larger number of antibiotics (3 drugs) to which the organism is exposed with this regimen or to the use of tinidazole, which is not contained in the standard triple-drug regimen. Sequential therapies are relatively new, and few data on these regimens are

in the literature. A MEDLINE search to December 2006 by using the keywords "sequential therapy" and "*H. pylori*" yielded 62 citations, 7 of which were trials that involved a sequential treatment regimen. All of these studies have substantial limitations: small sample sizes, lack of blinding, and failure to evaluate resistance and prospectively measure its effect (6–8, 30–32). Our study is an improvement on the design of our earlier studies on this field (6, 7, 33). In contrast, our study is double-blinded and prospectively evaluates the effect of resistance in all patients. Our previous studies have been unblinded or nonrandomized or have evaluated the effect in a post hoc analysis (6, 7, 33).

Cost is a major consideration in many countries. In Europe, the cost of the sequential regimen is similar to that of the standard regimen, which makes it an attractive alternative to triple therapy. Tinidazole has recently become available in the United States, and the cost of sequential therapy based on retail prices is lower than that of standard therapy. Sequential therapy may therefore be a reasonable alternative to standard therapy.

Our trial has limitations. The results may not be applicable to other countries and populations. The low rate of withdrawal may not be reproducible outside the trial setting, especially if the prescribing physician does not explain the temporary nature of most side effects and the importance of completing the regimen as prescribed. Finally, although sequential therapy is an improvement over current therapies, it does not decrease the duration of therapy. Our study design does not tell us whether the improved effect with sequential therapy is due to the sequential administration or to the additional antibiotic (tinidazole) that is not contained in the standard regimen.

In conclusion, our large, prospective, double-blind, controlled study shows the superiority of sequential treatment for eradicating *H. pylori* infection compared with conventional triple therapy. The sequential regimen is less expensive and is more effective than conventional therapy for patients with clarithromycin-resistant organisms. Side effects with both regimens were similar and consisted mostly of diarrhea and abdominal discomfort. Our data suggest that sequential therapy may have a role as a first-line treatment for *H. pylori* infection.

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