High Eradication Rates of *Helicobacter pylori* Infection with First- and Second-Line Combination of Esomeprazole, Tetracycline, and Metronidazole in Patients Allergic to Penicillin

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*H. pylori* eradication is a challenge in patients allergic to penicillin, both first-line and failures of prior therapy. We aimed to assess the eradication rate of *H. pylori* in patients allergic to penicillin, first-line and failures of prior therapy, the efficacy of healing of active duodenal ulcer disease (DUD) and erosive gastritis, and the safety and tolerability of the combination. Twenty patients with documented allergy to penicillin, DUD, and *H. pylori* infection, 17 (85%) for first-line treatment and 3 (15%) prior therapy failures, were given a 10-day regimen of esomeprazole, 40 mg qid, tetracycline, 500 mg qid, and metronidazole, 500 mg qid. Baseline and follow-up panendoscopy ≥30 days after end of treatment was performed for rapid urease test (Clotest), and four site biopsies for *H. pylori*, and to document endoscopic peptic ulcer disease. All adverse events during treatment were documented. Eradication rates by intention to treat (ITT) were 85% for first-line treatment and 100% for failures. Seventy percent of all cases had a normal endoscopy at follow-up, and 85 and 100% of patients had healed erosive gastritis and DUD, respectively, from baseline. There were histological improvements in most patients. A high eradication rate was obtained even in patients who had a shorter duration of treatment. The combination was well tolerated. A combination of esomeprazole, tetracycline, and metronidazole is effective for eradication of *H. pylori* in patients allergic to penicillin, for both first-line treatment and failures of prior treatment.

KEY WORDS: *Helicobacter pylori*; penicillin-free; esomeprazole; first-line therapy; second-line therapy.

*Helicobacter pylori* infection is estimated to be present in 50% of the world population (1). The infection will cause chronic gastritis of mild severity in most cases but, in a reduced number, will cause active chronic inflammation...
of the antrum and duodenal ulcer (2, 3). Approximately 25 millions Americans will be diagnosed with peptic ulcer disease (PUD) during their lifetime (4). Every year between 500,000–850,000 patients are diagnosed with PUD, at a significant cost in lost productivity and medical expense. Up to 95% of all duodenal ulcers and 80% of all gastric ulcers are associated with H. pylori infection (4). H. pylori infection has also been associated with gastric neoplasia and MALT lymphoma (5, 6). Since 1994, the National Institutes of Health (NIH) consensus panel on H. pylori management has recommended treatment with antimicrobial agents in combination with antisecretory drugs, either at first diagnosis of PUD or at recurrence (7). In the Maastricht 2-2000 consensus report eradication was strongly recommended for all cases of PUD, cases diagnosed with low-grade (MALT) lymphoma, patients with atrophic gastritis, patients after gastric cancer surgery, and first degree-relatives of gastric cancer patients (8). Although this consensus has been supported by clinical practice, still many patients with PUD have not been treated adequately for H. pylori eradication or have failed first-line therapy. There have been multiple regional, national, and international studies to define the treatment of choice for eradication of H. pylori (8, 9). Antimicrobial therapy for H. pylori evolved from monotherapy to the use of a proton pump inhibitor in combination with two antibiotics, of a reduced number of agents that have been demonstrated to have efficacy against H. pylori (9). Up to 20% of all patients will fail to eradicate H. pylori with therapy (10–12). Resistance to antibiotics, which can be primary (before therapy) or secondary (developed as a result of failed therapy), is mostly related to the nitroimidazoles (metronidazole or tinidazole) and macrolides (clarithromycin) (11–13). While resistance to tetracycline or amoxicillin is rare and unusual (14, 15), resistance to clarithromycin is becoming more common, and use of this antibiotic in the presence of resistance gives minimal opportunity for eradication (16–18). In the case of metronidazole resistance, in vitro resistance does not predict failure and increases in the doses of metronidazole have been shown to increase eradication (16, 17).

Clinical challenges for eradication of H. pylori are present in patients who cannot be treated with some of the antibiotic alternatives and in failures of first-line therapy. In this group are patients who cannot use amoxicillin, because of penicillin allergy, and failures on a previous combination that included clarithromycin. This study examines the efficacy, safety, and tolerability of a 10-day triple-drug regimen that spares amoxicillin and clarithromycin, for patients allergic to penicillin. The regimen selected is cost-effective, with a documented safety profile, and consists of esomeprazole, 40 mg qid, tetracycline, 500 mg qid, and metronidazole, 500 mg qid. The higher dose of metronidazole was selected in order to bypass profile resistance and increase efficacy rates.

**End Points.** The primary end point was the percentage of patients that achieve eradication of H. pylori 4 weeks after the end of treatment, in intention-to-treat (ITT) analysis. Eradication is defined as a negative urease test and negative gastric biopsies for H. pylori at all four sites, 30 days after end of treatment. The efficacy rate is also reported for patients receiving first-line therapy and prior failures (second-line therapy). Secondary end points were to determine the efficacy of treatment in the healing of active duodenal ulcer disease (DUD) and erosive gastritis and to assess the safety and tolerability of the combination therapy.

**METHODS**

**Study Population.** For participation in this study, all patients signed informed consent approved by the Institutional Review Board (IRB) of the School of Medicine of the University of Puerto Rico. Patients had to be 21 years old or more, have H. pylori infection documented by both gastric biopsy and rapid urease test (Clotest), and have a documented allergy to penicillin. Both patients for first-line therapy and failures of a prior therapy that was completed more than 1 month before enrollment were included. Patients were required to have either active DUD or a history of at least one episode of DUD documented by endoscopy in the 5 years prior to enrollment.

Patients were excluded from participation if they had a documented allergy to any of the antibiotics in the study regimen or if they had received a prior regimen that included esomeprazole. Patients were also excluded if they were unable or unwilling to provide written informed consent specific for this study, were pregnant or lactating, or were unwilling to use adequate contraception. No patients with a history of PUD complications and/or esophageal, gastric, or duodenal surgery were included. Patients were not enrolled if they were using concomitant medications with a known possible irritant effect in gastric or duodenal mucosa, such as steroids, aspirin (ASA), or nonsteroidal anti-inflammatory drugs (NSAIDS), or if, in the opinion of the investigator, they had a severe illness or any other condition that would make them unsuitable for this study.

**Study Procedures.** All consecutive patients with DUD were evaluated for participation in this study. After signing the informed consent, patients underwent a complete history and physical examination. History of DUD diagnosis, therapy and complications, and history of H. pylori treatment was obtained. All patients were required to sign another informed consent document for upper endoscopy. Patients had a complete upper endoscopy with an Olympus GIF-140 videendoscope, and biopsy of gastric mucosa at four different sites and rapid urease test (Clotest) was performed. Patients with both a positive rapid urease test (Clotest) and a biopsy showing H. pylori organisms in at least one site was enrolled in the study and underwent treatment for H. pylori within 1 week of the screening date. Patients had a telephone consultation at day 5 of treatment for safety assessments and compliance with study drugs and were reevaluated at day 10 for end of therapy. All patients were required to...