

## Research Article

# Successful Eradication of *Helicobacter pylori* with 5-Day Concomitant Treatment

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**Background.** Untreated *Helicobacter pylori* is associated with gastrointestinal conditions including peptic ulcer disease, chronic gastritis, and gastric cancer. The ACG guidelines presently call for triple therapy consisting of a PPI, clarithromycin, and amoxicillin or metronidazole for 14 days. The ACG recommends this treatment as a first-line therapy despite the recognition of growing resistance to clarithromycin, presently upwards of 15–20%. **Aims.** Studied was the effectiveness of a 5-day concomitant eradication protocol. **Methods.** This was a retrospective study of 77 *H. pylori* infected, treatment naïve patients, prescribed a 5-day concomitant therapy containing levofloxacin 500 mg b.i.d., amoxicillin 1 gm b.i.d., tinidazole 500 mg b.i.d., and esomeprazole 40 mg b.i.d. in our New Jersey community setting. Eradication was confirmed with C13 urea breath test. **Results.** In our intention-to-treat analysis of 65 patients, 54 patients (83.03%) achieved eradication confirmed by C13 urea breath testing. **Conclusions.** Highly efficacious eradication rates of 80–90% can be achieved with 5-day concomitant treatment (levofloxacin, esomeprazole, tinidazole, and amoxicillin) in a community practice. Our treatment protocol achieves comparable, if not better, clearance rates as compared to agents specified in the ACG consensus guidelines recommending a longer 10–14-day treatment. Additionally, our protocol resulted in better patient compliance, was more cost-effective, shorter, and was well-tolerated compared even to newer treatments, like rifabutin. Thus, these results successfully demonstrate that this 5-day b.i.d. therapy, originally identified over 20 years ago, continues to be an effective choice option and is likely superior as it has comparable clearance rates to traditional 10–14-day therapy.

## 1. Introduction

*Helicobacter pylori* (*H. pylori*) is a spiral-shaped bacterium typically found in the mucosal layer of the stomach and upper gastrointestinal tract. *H. pylori* is one of the most common global infections, affecting about half of the global population [1]. The prevalence of *H. pylori* in North America, specifically in the United States inclusive of New Jersey, has declined in the period between 2009 and 2018 from 11% to 9%. This data is based on community endoscopic centers which used the “Informed Diagnostics database” analyzing 1.28 M endoscopies [2]. Our percentage of *H. pylori*-positive patients found on gastric antral biopsies was 5.6% (77 of 1385 patient endoscopies) in our seven-year study period.

All endoscopy patients underwent antral biopsy for assessment of *H. pylori* as standard practice protocol.

Untreated *H. pylori* can cause dangerous and alarming complications. This bacterial infection has been proven to be associated with many gastric conditions including peptic ulcer disease, chronic gastritis, gastric cancer, and mucosa-associated lymphoid tissue lymphoma [1, 3]. *H. pylori* has been found to be the leading cause of peptic ulcer disease, associated with more than 75% of duodenal ulcer cases and 17% of gastric ulcer cases. It is now categorized as a human carcinogen, being the main cause of both distal gastric adenocarcinoma and B cell mucosa-associated lymphoid tissue lymphoma [4]. In one study of randomized trials, successful eradication of *H. pylori* was associated with about a 50%

percent decrease in sporadic gastric cancer [5]. This infection is also linked to several nongastric diagnoses such as iron deficiency anemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency [4]. *H. pylori* requires attention and eradication upon diagnosis.

*H. pylori* has been studied broadly over the past 40 years. However, at the current time, there is no optimal therapy regimen that has 100% successful eradication rates. The traditional eradication therapy regimen was triple therapy including a PPI, amoxicillin, and clarithromycin. The intention-to-treat analysis for this traditional eradication treatment program was less than 80%, an unsatisfactory result [6]. The effectiveness of this triple treatment has been declining, largely due to a growing antimicrobial resistance. In some regions of the United States, macrolide antibiotic resistance rates have exceeded 15% to 20% strongly suggesting the clarithromycin triple therapy should no longer be the primary treatment [7].

There are numerous and continuous studies exploring many alternative eradication therapies. These range from bismuth-containing quadruple therapy, concomitant therapy (CT), sequential therapy, hybrid therapy, and quinolone-based triple or quadruple therapies [8].

The most current ACG [9] update recommends three different first-line treatments, cautioning the importance of asking patients about previous antibiotic exposure and allergies to help guide their specific treatment regimen. One recommendation is clarithromycin triple therapy consisting of a PPI, clarithromycin, and amoxicillin or metronidazole for 14 days [9]. However, the eradication rates with this drug regimen have been disappointing, historically reporting a 77-85% success rate for clearance [10-14, 19]. The ACG consensus is that *H. pylori* may be resistant to clarithromycin and suggests that this regimen should be avoided in regions where resistance exceeds 15% or where a patient has had any previous macrolide exposure. Bismuth quadruple therapy, consisting of a PPI, bismuth, tetracycline, and nitroimidazole for 10-14 days, is also recommended. The ACG states that this should be considered as first-line treatment where clarithromycin resistance is high or in patients with penicillin allergies and/or previous macrolide exposure. An additional primary treatment regimen the ACG recommends is concomitant therapy consisting of PPI, clarithromycin, amoxicillin, and nitroimidazole (tinidazole or metronidazole) for 10-14 days. Many studies have been able to prove the effectiveness of this regimen as compared to clarithromycin triple therapy [9].

A study published in 2012 performed a noninferiority randomized trial to explore the efficacy of a 5-day concomitant therapy containing levofloxacin, esomeprazole, tinidazole, and amoxicillin instead of the suggested 10-day sequential regimen in eradicating *H. pylori* in previously untreated patients. The results showed only a 1.1% difference in the intention-to-treat-analysis between sequential and concomitant therapy (95% confidence interval; -7.6% to 9.8%). This 2012 study demonstrated concomitant therapy to result in greater than 80% eradication rates with 5-day therapy [15].

Utilizing the protocol outlined in this 2012 study, our New Jersey community gastroenterology practice was interested in the effectiveness of our *H. pylori* clearance rate. Twenty years since this study first appeared in the literature, our practice wanted to demonstrate that despite frequent patient exposure to antibiotic therapies, this 2012 protocol is as beneficial in achieving effective *H. pylori* clearance rates to the traditional 10- or 14-day programs. Equivalent eradication rate could be achieved using fewer days of treatment in a more cost-effective, patient-compliant manner.

During the period of our study, other accepted treatment regimens used commonly in the United States inclusive of New Jersey have been reviewed [16]. Reported clearance rates for clarithromycin-based triple therapy 7-14-day treatment duration ranged from 76-78.1% success, and bismuth quadruple therapy 14-day regimen has 71-88% clearance success. Rifabutin triple therapy for 14 days reports a 83.8% eradication rate. Levofloxacin-based regimens of 10-14 days reflect 64-90% success (Shah, 2022). Of note, no reported treatment program in the published literature boasts treatment efficacy exceeding 90%.

Proposed was an intention-to-treat paradigm with 5-day concomitant b.i.d. therapy containing levofloxacin, esomeprazole, tinidazole, and amoxicillin. It was the purpose of the study to demonstrate equivalent efficacy rates to the traditional program with this 5-day, 10 pill protocol. This treatment, if as effective as traditional programs, would offer a superior treatment option in both patient compliance and drug out-of-pocket costs.

## 2. Methods

Over the timeframe of 2015 to 2021, our New Jersey community practice identified a total of 77 symptomatic and asymptomatic treatment naive *H. pylori*-positive patients. Sequentially, all of these patients were given a 5-day concomitant therapy containing levofloxacin 500 mg b.i.d., amoxicillin 1 gm b.i.d., tinidazole 500 mg b.i.d., and esomeprazole 40 mg b.i.d. In the office, counseling was provided at the time of issuing the prescriptions to reinforce the treatment protocol. Patients were given standard written instructions. Post the 5-day treatment period, patients were asked to stay off PPI therapy for 4 weeks. At the conclusion of 4 weeks, they were asked to repeat a breath test to ascertain eradication of *H. pylori* infection. Eradication was confirmed with a C13 urea breath test performed at a commercial reference lab of either LabCorp or Quest in accordance with standard laboratory protocol guidelines.

## 3. Results

Of the original 77 *H. pylori*-positive patients, 16 patients were excluded from analysis as they were lost to follow-up or were unable to obtain medications due to insurance issues. 65 patients fell into an intention-to-treat group. This group included patients intolerant to the treatment protocol and all patients with eradication test results. In this intention-to-treat group, 54 patients demonstrated eradication of the *H. pylori* infection confirmed by way of the C13

urea breath test analysis. Additionally, 4 patients were intolerant to the treatment protocol, and 7 patients remained positive, all requiring salvage therapy. The eradication rate in this intention-to-treat group was 83.08%. An *N* of 61 patients were classified as per-protocol group as they successfully completed the treatment program as prescribed. The eradication rate in the per-protocol group was 88.52%.

Of the four patients who were intolerant to the treatment protocol, none underwent salvage therapy; three left practice care and one was deceased prior to offering salvage therapy. Of the seven patients who failed to eradicate the *H. pylori* infection, all were offered salvage therapy but only two underwent new treatment. Based on previous antibiotic exposure, two different treatments were offered. One patient received a seven day protocol of levaquin 500 mg b.i.d., doxycycline 100 mg b.i.d., nitazoxanide 500 mg b.i.d., and pantoprazole 40 mg b.i.d. This treatment also failed to eradicate the infection, and the patient had elected not to undergo any more treatment. The second patient on salvage therapy received a 14-day course of omeprazole 20 mg b.i.d., amoxicillin 1000 mg b.i.d., and clarithromycin 500 mg b.i.d. This triple therapy did eradicate the *H. pylori* infection as confirmed by C-13 urea breath testing.

#### 4. Discussion

Our study results with 5-day concomitant therapy containing levofloxacin, amoxicillin, tinidazole, and esomeprazole, b.i.d. dosing demonstrates that effective eradication rates can be achieved in the community setting with a very short duration of treatment and without the need of clarithromycin therapy. The results from our community practice demonstrated clearance eradication rates well above 80% in both intention-to-treat and per-protocol groups. Our results showed intention-to-treat at 83% and per-protocol at 88% clearance. Our study with this choice of drug treatment regimen demonstrated highly efficacious eradication rates. The ACG consensus guidelines recommend a longer 10–14-day treatment with similar clearance rates ranging between 80 and 90%. Our protocol demonstrates similar or superior eradication rates in a standard community practice. Patients were more likely to be compliant with this cost-effective, shorter, easier to follow, and well-tolerated protocol. The side effects reported were trivial and transient. Fewer than 30% of our patients reported side effects on our treatment protocol. The most frequently reported symptoms included dysgeusia, headache, diarrhea, nausea, and abdominal pain. The most common reason patients gave for intolerance and discontinuation of the treatment was abdominal pain. This drug regimen on wholesale average cost (WAC) was \$72.00 to provide eradication. Thus, these results successfully demonstrate that this 5-day b.i.d. therapy, originally identified over 20 years ago, continues to be an effective choice option and likely superior as it has comparable clearance rates to traditional 10–14-day therapy.

Additionally, this protocol addresses the problem of antibiotic resistance which is well described in the literature. The effectiveness of triple-drug therapy has been declining, largely due to a growing antimicrobial resistance. The ACG

guidelines have been strongly suggesting the clarithromycin triple therapy should no longer be the primary treatment. Newer agents like rifabutin are available. However, the FDA-approved treatment protocol with this agent still requires 14 days of therapy. The approximate WAC for a standard 14-day course of triple therapy treatment is \$74.80 [17]. Newer agents like rifabutin have a WAC of \$650 for the treatment protocol [18]. As compared to these two regimens, our estimated WAC of \$72.00 [17] for our study protocol is no more expensive and most likely cheaper for the patient and/or insurance company. Our study affirms superior and effective clearance of *H. pylori* infection can be achieved with a well-tolerated, simple, cost-effective, five-day program.

#### Data Availability

The data used to support the findings of this study are restricted by Westfield Gastro Associates in order to protect PATIENT PRIVACY. Data are available from Thomas Amrick, MD, westfieldgastro@comcast.net for researchers who meet the criteria for access to confidential data.

#### Disclosure

Guarantor of the article is Thomas Amrick, MD, FACG.

#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

#### Authors' Contributions

Thomas J. Amrick, MD was the treating physician, counseled patients, prescribed medication, reviewed, certified results, and performed review of publication. Lia Goldberg did the literature research and review and authorship of all sections of publication. Thomas Amrick, MD, FACG and Lia Goldberg, BS approve the final version of the manuscript and the integrity of the work as a whole, from inception to published article.

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