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Alimentary Tract

# Two-week, high-dose proton pump inhibitor, moxifloxacin triple *Helicobacter pylori* therapy after failure of standard triple or non-bismuth quadruple treatments

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ABSTRACT

*Background:* Aim was to evaluate the efficacy and tolerability of a moxifloxacin-containing second-line triple regimen in patients whose previous *Helicobacter pylori* eradication treatment failed.
*Methods:* Prospective multicentre study including patients in whom a triple therapy or a non-bismuth-quadruple-therapy failed. Moxifloxacin (400 mg qd), amoxicillin (1 g bid), and esomeprazole (40 mg bid) were prescribed for 14 days. Eradication was confirmed by $^{13}$C-urea-breath-test. Compliance was determined through questioning and recovery of empty medication envelopes.
*Results:* 250 patients were consecutively included (mean age 48 ± 15 years, 11% with ulcer). Previous (failed) therapy included: standard triple ($n$ = 179), sequential ($n$ = 27), and concomitant ($n$ = 44); 97% of patients took all medications, 4 were lost to follow-up. Intention-to-treat and per-protocol eradication rates were 82.4% (95% CI, 77–87%) and 85.7% (95% CI, 81–90%). Cure rates were similar independently of diagnosis (ulcer, 77%; dyspepsia, 82%) and previous treatment (standard triple, 83%; sequential, 89%; concomitant, 77%). At multivariate analysis, only age was associated with eradication (OR = 0.957; 95% CI, 0.933–0.981). Adverse events were reported in 25.2% of patients: diarrhoea (9.6%), abdominal pain (9.6%), and nausea (9.2%).
*Conclusion:* 14-day moxifloxacin-containing triple therapy is an effective and safe second-line strategy in patients whose previous standard triple therapy or non-bismuth quadruple (sequential or concomitant) therapy has failed, providing a simple alternative to bismuth quadruple regimen.


## 1. Introduction

*Helicobacter pylori* infection is the main known cause of gastritis, gastroduodenal ulcer disease, and gastric cancer [1]. However, despite more than 30 years of experience in *H. pylori* treatment, the ideal regimen to treat this infection remains undefined. Consensus conferences have recommended therapeutic regimens that achieve cure rates higher than 80% on an intention-to-treat basis [2]. However, large clinical trials and meta-analyses have shown that the most commonly used first-line therapies – a proton pump inhibitor (PPI) plus 2 antibiotics – can fail in ≥20% of patients, and, in clinical practice, this rate might be even higher [1,3]. Moreover, during the last few years, the efficacy of standard triple regimens has been decreasing, and several studies have reported

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intention-to-treat eradication rates lower than 75% and even lower than 50% [4]. Antibiotic resistance to clarithromycin has been identified as one of the major factors affecting our ability to cure *H. pylori* infection, and the rate of resistance to this antibiotic seems to be increasing in many geographic areas [5].

A rescue regimen comprising a quadruple combination of a PPI, bismuth, tetracycline, and metronidazole has been used as the optimal second-line approach based on the relatively good results reported [6,7]. However, administration of the regimen is complex and adverse events are relatively common [6,7]. Furthermore, the quadruple regimen still fails to eradicate *H. pylori* in approximately 20–30% of cases. Finally, bismuth salts are no longer available worldwide. Therefore, management of first-line eradication failures is becoming challenging.

Non-bismuth quadruple "sequential" and "concomitant" regimens, including a PPI, amoxicillin, clarithromycin and a nitroimidazole, are increasingly used as first-line treatments for *H. pylori* infection [8,9]. However, eradication with rescue regimens may be challenging after failure of key antibiotics such as clarithromycin and nitroimidazoles.

Recent findings indicate that fluoroquinolones such as levofloxacin could prove to be an efficacious alternative to standard antibiotics, not only as first-line therapies but also, and more interestingly, as second-line regimens [10–12]. We previously obtained "intermediate" results (74% eradication rate) with a combination of a PPI, amoxicillin, and levofloxacin given for 10 days in multicenter studies performed in Spain [13,14]. On the other hand, recent studies suggest that the efficacy of levofloxacin-containing therapy is decreasing, most likely due to increased primary quinolone resistance [15].

Moxifloxacin is a second-generation fluoroquinolone with a wide antibacterial spectrum [16]. Studies in vitro have shown that moxifloxacin has an improved coverage of Gram-positive and anaerobic bacteria while retaining good activity against Gram-negative bacteria [16]. Moxifloxacin has a higher in vitro activity against gram-positive and anaerobic pathogens compared with levofloxacin [17]. In vitro studies have shown excellent susceptibility of *H. pylori* strains to moxifloxacin [18], and clinical trials have confirmed its higher effectiveness – as a first-line therapy – compared with standard clarithromycin-based triple therapy [19]. Furthermore, few studies have suggested that the emergence of bacterial resistance appears to be less common for moxifloxacin than for other fluoroquinolones, and that moxifloxacin may be less affected by quinolone resistance than levofloxacin in *H. pylori* [18] and other bacterial infections [20,21].

Therefore, the aim of the present study was to evaluate the efficacy and tolerability of a second-line triple regimen containing moxifloxacin in patients whose previous *H. pylori* eradication treatment failed.

## 2. Methods

### 2.1. Patients

This was a prospective multicenter study (21 Hospitals, 19 Spanish and 2 Italian) including consecutive patients in whose first-line therapy [standard triple therapy (PPI, clarithromycin, and amoxicillin) or a non-bismuth quadruple therapy (PPI, clarithromycin, amoxicillin and metronidazole), either sequentially or concomitantly] had failed to eradicate *H. pylori* infection. Previous failure was defined as a positive $^{13}$C-urea breath test result 4–8 weeks after completion of treatment. The exclusion criteria were as follows: (1) age under 18 years, (2) presence of clinically significant associated conditions (insulin-dependent diabetes mellitus, neoplastic diseases, coagulation disorders, and hepatic, cardiorespiratory, or renal diseases), (3) previous gastric surgery, and (4) allergy to any of the drugs used in the study. The protocol was approved by the local ethics committee, and written informed consent was obtained from all patients.

### 2.2. Therapy

A second eradication regimen with moxifloxacin (400 mg o.d.), amoxicillin (1 g b.i.d.), and esomeprazole (40 mg b.i.d.) was prescribed for 14 days. Esomeprazol and amoxicillin were administered together after breakfast and dinner, and moxifloxacin after dinner. Patients were informed about potential side events (mainly metallic taste, nausea, vomiting, abdominal pain and diarrhoea) during the treatment period. Compliance with therapy was defined as intake of 100% of the medication prescribed and was determined from a questionnaire and recovery of empty envelopes of medications. The incidence of adverse events was evaluated by means of a specific questionnaire administered at the time the success or failure of *H. pylori* eradication treatment was confirmed.

### 2.3. Diagnostic methods to confirm eradication

Eradication of *H. pylori* was defined as a negative $^{13}$C-urea breath test result (with citric acid and 100 mg of urea, using a previously reported protocol [22]) performed 4–8 weeks after completion of re-treatment in each centre. The test was carried out by nurses who were unaware of the therapy administered and the patients' *H. pylori* status. As endoscopy – and consequently culture – was not performed after therapy, antibiotic susceptibility was unknown and, therefore, the moxifloxacin eradication regimen was chosen empirically.

### 2.4. Outcomes

Primary outcome was eradication rate, measured as percentage of confirmed eradicated patients as reported in the previous section, by intention-to-treat analysis. Secondary outcomes were compliance (percentage of patients taking 100% of medications), safety (percentage of appearance, type and severity of adverse events), and per-protocol eradication rate. Eradication rates were stratified according to the first-line failed therapy, and the geographical region. Adverse events were classified depending on the intensity of symptoms evaluated by the corresponding physician. Adverse events were classified as mild (not interfering with daily routine), moderate (affecting daily routine), intense/severe (not allowing normal daily routine), and serious (death, hospitalization, disability, congenial anomaly, and/or requires intervention to prevent permanent damage).

### 2.5. Statistical analysis

The 95% confidence interval (95% CI) was calculated for categorical variables and the mean ± standard deviation for quantitative variables. Analysis of the efficacy of *H. pylori* eradication was performed on an intention-to-treat basis (including all eligible patients enrolled in the study regardless of compliance with the study protocol; patients with non-evaluable data were assumed to have been unsuccessfully treated) and on a per-protocol basis (excluding patients whose compliance with therapy was poor and patients with non-evaluable data after therapy).

A multiple logistic regression analysis was performed. The dependent variable was eradication of *H. pylori*, and the independent variables were age, sex, smoking (smokers and non-smokers), diagnosis (peptic ulcer or functional/uninvestigated dyspepsia), and type of first-line (failed) therapy. We used a backward modelling strategy, and the log-likelihood ratio was the statistic for model comparison.