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Twelve-day quintuple regime containing four antibiotics as a rescue therapy for *Helicobacter pylori* eradication in the central region of Portugal

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ABSTRACT

Background: *Helicobacter pylori* eradication rates with standard triple therapy in many countries are clinically unacceptable. Fluoroquinolone resistance is increasing and jeopardizing second-line regimens. There is a growing need for an effective strategy in patients who failed previous therapies.

Methods: This is a single-center, non-randomized clinical study conducted in the central region of Portugal. Sixty-four patients were included with a positive ^{13}C-urea breath test (UBT) or histology for *H. pylori,* and at least one failed eradication attempt. The patient cohort included 71.7% of females with a median of age of 52 (range 23-87). They were treated with a twelve-day regimen consisting of a proton-pump inhibitor (PPI) bid, amoxicillin at 1,000 mg 12/12h and levofloxacin at 500 mg bid during the first seven days, followed by PPI bid, clarithromycin at 500 mg 12/12 h and either tinidazole or metronidazole at 500 mg bid/tid for five days. Eradication was assessed by UBT. The local Ethics Committee approved this study.

Results: Eradication therapy was prescribed due to dyspepsia (66.7%), peptic ulcer (10%) and thrombocytopenia (8.3%). The median number of failed therapies was one (range 1-4). The eradication rate was 64.6% according to an intention-to-treat analysis (95% CI: 53-77%), and 70% by the per-protocol analysis (95% CI: 58-82%). Age, smoking, indication for eradication, previous therapies and the use of a second-generation or full-dose PPI did not affect success rates.

Conclusions: Even though treatment with four antibiotics was used, this "reinforced" therapy achieved suboptimal results. This fact highlights the lack of effective *H. pylori* antimicrobials and suggests that second-line treatment in our region should be prescribed according to susceptibility testing.

Key words: *Helicobacter pylori.* Levofloxacin. Quintuple regimen. Rescue therapy.

INTRODUCTION

Infection by *Helicobacter pylori* is one of the major public health issues worldwide. In 1994, the World Health Organization declared it as a group I human carcinogen for gastric adenocarcinoma (1). Besides well-known clinical conditions that require treatment for *H. pylori* such as peptic ulcers or MALT gastric lymphoma, there is a significant number of other diseases that may benefit from the eradication of this pathogen. These include immune thrombocytopenic purpura or iron deficiency anemia (2). In spite of the significant number of different treatment regimens used to treat this infection, there are currently no first-line therapies that cure all patients (3). Therefore, there is a growing need for an effective eradication strategy in patients who failed previous therapies. Resistance to clarithromycin is worrisome in Mediterranean countries and others worldwide (4,5), and commonly used regimens such as triple therapy with amoxicillin and clarithromycin have shown disappointing results and are considered to be obsolete (6). Despite achieving acceptable results in regions with low quinolone resistance, the currently recommended second-line levofloxacin-based triple therapy has shown unacceptable results if the *H. pylori* resistance rates to quinolones are higher than 15% (7-9). Thus, the latest Consensus in Spain with regard to *H. pylori* infection and the Maastricht V conference is to add bismuth to a levofloxacin rescue therapy, or even extend the treatment to 14 days (10,11). In the central Portugal region and in others worldwide, primary resistance rates to levofloxacin, clarithromycin and metronidazole have surpassed 15%, 25% and 35%, respectively (4,5,12,13). Furthermore, due to the current use of suboptimal first-line regimens, secondary resistance to these antibiotics has also reached the alarming figure of 60% in several countries (14,15). Unfortunately, bismuth salts, rifabutin, tetracycline and furazolidone are difficult to obtain in several countries, and doxycycline showed disappointing results (16). Thus, it is difficult to propose an effective second-line treatment regimen in these countries. The aim of this study was to test the efficacy of a strengthened quintuple regimen which included a proton-pump inhibitor (PPI) and the four most commonly used antibiotics in *H. pylori* treatment (amoxicillin, levofloxacin, clarithromycin and metronidazole) in

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patients with at least one unsuccessful eradication attempt. We also analyzed risk factors that contribute to eradication failure, such as age, gender, number of previous failed attempts, PPI dosage or generation. To our knowledge, there are no published studies documenting the efficacy of this regimen.

PATIENTS AND METHODS

Study design

This was a single-center non-randomized interventional study conducted in the central region of Portugal from January 2014 to December 2015. Patients had a persistent *H. pylori* infection defined by histology or the ^{13}C-urea breath test (UBT) despite at least one previous *H. pylori* eradication attempt. The exclusion criteria included: a) patients treated with proton-pump inhibitor (PPI), H_2 receptor antagonist or antibiotics in the four to six weeks prior to UBT; b) patients that interrupted the treatment schedule before completion for any reason; c) allergies to the drugs used in the study; and d) pregnant or breastfeeding females. Compliance and adverse events were assessed by verbal and written questionnaires. The study was approved by the Ethics Committee of our institution according to local standards and guidelines. Written informed consent of the patients included in the study was obtained. The correspondence author is in possession of these documents.

Therapeutic regimens

Patients were treated for twelve days with a regimen consisting of a proton-pump inhibitor (PPI), amoxicillin at 1,000 mg 12/12 h and levofloxacin at 500 mg 24/24 h for the initial seven days, followed by a proton-pump inhibitor, clarithromycin at 500 mg 12/12 h and tinidazole at 500 mg 12/12 h or metronidazole at 500 mg 8/8 h for another five days. The choice between different PPI's and nitroimidazole antibiotics was made by the prescribing physician. First-generation PPI's (omeprazole, pantoprazole and lansoprazole) were used in 75% of the patients, whereas 25% were prescribed second-generation drugs (rabeprazole, esomeprazole). Full-dose PPI was used in 78.3% of the patients, whereas the remaining 21.7% received a double-dose (Table I).

Statistical analysis

Eradication rates were calculated by the intention-to-treat (ITT) and per-protocol (PP) analyses. All patients enrolled in the study were included in the ITT analysis. With regard to the PP analysis, patients that deviated from the protocol were excluded (i.e., non-compliant and patients lost to follow-up). Statistical analysis of the results was performed using the Chi-squared test, Student's t-test and Fisher's exact test, as well as binomial logistic regression for multivariate analysis. p values < 0.05 were considered as significant in all analyses. The 95% confidence intervals (CI) were calculated by normal approximation. Statistical analysis was performed using SPSS for Windows (version 21; SPSS Inc.).

Table I. Patients' demographic and clinical characteristics

	Quintuple rescue therapy
Mean age (years)	52.4 ± 14.9 (23-87)
Gender	
Female	43 (71.7%)
Male	17 (28.3%)
Smoking habits	2 (3.3%)
Alcohol consumption	8 (13.3%)
Indication(s) for H. pylori eradication	
Non-ulcer dyspepsia	40 (66.7%)
Peptic ulcer	6 (10%)
Others	6 (10%)
Thrombocytopenia	5 (8.3%)
Anemia	3 (5%)
Nitroimidazole antibiotic	
Tinidazole	53 (88.3%)
Metronidazole	7 (11.7%)
PPI 1st or 2nd generation	
Omeprazole/pantoprazole/lansoprazole	45 (75%)
Esomeprazole/rabeprazole	15 (25%)
PPI dosage	
Full-dose	47 (78.3%)
Double-dose	13 (21.7%)
Prescribing physician	
Gastroenterologist	56 (93.3%)
Non-gastroenterologist	4 (6.7%)

Figures are number and (percentage) or mean ± standard deviation. PPI: Proton-pump inhibitor; GERD: Gastroesophageal reflux disease.

RESULTS

Study population

Sixty-four patients with proven infection by *H. pylori* were included in the study; 71.7% were females with a mean age of 52.4 years (standard deviation [SD]: 14.9; range: 23-87); 3.3% were smokers; and 13.3% were alcohol consumers (> 20 g/day). Indications for *H. pylori* eradication included dyspepsia (66.7%), peptic ulcer (10%), other diseases (10%), thrombocytopenia (8.3%) and anemia (5%). Only one patient was over eighty years of age and was treated with a second-line eradication regimen after being admitted to hospital due to a bleeding peptic ulcer.

The patients underwent at least one and a maximum of three previous unsuccessful attempts of eradication (one attempt: 70%; two attempts: 25%; and three attempts: 5%). The median number of attempts was one. The most commonly prescribed regimens before the rescue therapy in the study were the 14-day triple therapy with clarithromycin (66%), 10-day sequential therapy (28%) and 14-day dual therapy with amoxicillin and esomeprazole four times a day (6%).

Tinidazole was prescribed in the majority of cases (88.3%) while metronidazole was used in the remaining patients (11.7%). A full-dose of PPI was preferred in 78.3% of prescribed regimens. A double-dose reinforced dosage of PPI was used (e.g., omeprazole 40 mg bid) in the remaining regimens. Three-quarters of the patients received first-generation PPI's (omeprazole, pantoprazole, lansoprazole), and the remaining were prescribed with second-generation PPI's (rabeprazole, esomeprazole). The majority of the physicians that prescribed this adapted regimen were gastroenterologists (93.3%). The demographic and clinical characteristics of the patient cohort are described in table I.

Efficacy of therapy and factors associated with eradication failure

Helicobacter pylori was eradicated in 70% of patients according to the PP analysis (95% CI: 58-82%) and in 65.6% (95% CI: 53-77%) by ITT analysis. Several factors were evaluated as potential risk factors for eradication failure, including age, gender, alcohol consumption and smoking, indication for therapy, number of previous eradication attempts, use of tinidazole *vs* metronidazole, PPI generation or dosage, and prescription by gastroenterologists or non-gastroenterologists (Table II). None of these factors were significantly associated with the eradication rate in the univariate and multivariate analysis.

Compliance, tolerability and adverse events

Adverse events were recorded in order to evaluate the tolerability of this regimen. Thirteen patients experienced adverse events (21.6%). The most common adverse events were dysgeusia (nine patients) and self-limited diarrhea (three patients). Only four patients (6.3%) were considered as non-adherent to the protocol (failure to take at least one dose of medication) and, therefore, excluded from PP analysis (Fig. 1).

DISCUSSION

The results of this study revealed an unacceptable success rate obtained by the "reinforced" sequential therapy with four antibiotics. The eradication rate obtained was well below the 90% threshold defined by the latest Spanish Consensus on *H. pylori* infection (10), underlining the problem of *H. pylori* resistance to several classes of antibiotics including macrolides, quinolones and nitroimidazoles. The combination of four different classes of antibiotics does not lead to an acceptable eradication rate. To our knowl-

Table II. Potential risk factors associated with eradication failure

	Quintuple rescue therapy		
	Success	*Failure*	*Statistical significance (p value)*
Age	54 ± 14.8	48.6 ± 14.6	0.202
> 65 years	10 (23.8%)	2 (11.1%)	0.317
Female	31 (51.7%)	12 (66.7%)	0.328
Smoking habits	1 (2.4%)	1 (5.6%)	0.514
Alcohol consumption	4 (9.5%)	4 (22.2%)	0.225
Indication for therapy			
Non-ulcer dyspepsia	26 (61.9%)	14 (77.8%)	0.165
Peptic ulcer disease	6 (100%)	0	0.341
Others	4 (9.5%)	2 (11.1%)	0.981
Thrombocytopenia	4 (9.5%)	1 (5.6%)	0.829
Anemia	2 (4.8%)	1 (5.6%)	0.756
Tinidazole *vs* metronidazole	37 (88.9%) 5 (11.1%)	16 (88.1%) 2 (11.9%)	0.986
1st generation PPI *vs* 2nd generation	32 (76.2%) 10 (23.8%)	13 (72.2%) 5 (27.8%)	0.106
Full-dose PPI *vs* double-dose	33 (78.6%) 9 (21.4%)	14 (77.8%) 4 (22.2%)	0.892
Number of previously failed therapies (mean)	1.36 ± 0.45	1.33 ± 0.57	0.756
Prescription by non-gastroenterologist *vs* gastroenterologist	3 (7.1%) 39 (92.9%)	1 (5.6%) 17 (94.4%)	0.821

Figures are number and (percentage) or mean ± standard deviation. PPI: Proton-pump inhibitor; GERD: Gastroesophageal reflux disease.

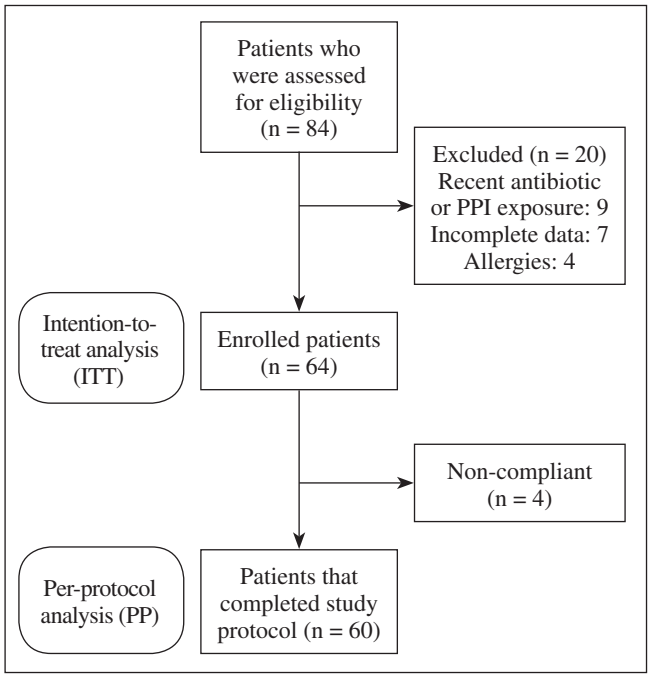

Fig. 1.

edge, there is only one other study evaluating the efficacy of quintuple regimens as a second-line or rescue therapy (17). An Iranian study compared two short-term bismuth-based therapies with three antibiotics that achieved a borderline acceptable eradication rate in one treatment group and an unacceptable rate in the second group (intention-to-treat: 86.5% and 75.5%, and per-protocol: 86.7 and 76%, respectively). The eradication rate in this study, although disappointing, was higher than that obtained with the triple levofloxacin-based second-line therapy. In fact, as reported by Cerqueira et al. (18), the efficacy of levofloxacin-based triple as a second-line therapy fell from 71% in 2006-2008 to 55.1% during in 2009-2010 (PP results). This was later confirmed by Almeida et al. (7), who reported a per-protocol eradication rate of 55.1%. These two studies were conducted in regions with resistance patterns similar to ours, especially with regard to levofloxacin.

The epidemiologic and clinical factors analyzed did not influence eradication rate, this was probably due to the limited size of our study. A higher number of previous eradication attempts was not associated with eradication failure. This would be expected considering the high secondary and tertiary resistance rates to *H. pylori*. With regard to the use of different nitroimidazole antibiotics, there was no advantage with tinidazole or metronidazole use. As previously demonstrated, metronidazole resistance can be overcome if high-doses of this antibiotic are used (19). Demographic variables such as age, gender and smoking or alcohol consumption did not influence eradication rates.

The main limitation of our study is the lack of data with regard to antibiotic resistance, even though resistance rates may be extrapolated from regional data (4,5). A very high resistance rate is expected in studies that analyze rescue regimens as these patients have already been treated with several antibiotics. The relatively small size of our sample is also a limitation. Nonetheless, this study shows that even the combination of four antibiotics is useless as a second-line regimen in our region.

Considering the growing problem of ineffective second-line and rescue therapy for *H. pylori* eradication, a significant effort should be made to improve these results. Recent exposure to antibiotics is one of the most important risk factors for eradication failure, as shown in multiple studies (20,21), and the secondary resistance rates often surpass 60% (22). Therefore, the best available first-line empirical regimen should be chosen taking into account local resistance patterns, cost and tolerability. Another strategy to improve the efficacy of currently used regimens could be the implementation of a national program to restrict antibiotic consumption, especially macrolides and nitroimidazoles. In Taiwan, this policy has probably contributed to a low primary clarithromycin and metronidazole resistance of *H. pylori* (23).

In several countries there is currently a scarcity of effective second-line therapies. We avoid using levofloxacin-based triple therapy due to the fact that the eradication rates are under 60% (7). The new "three-in-one" formulation including bismuth, metronidazole and tetracycline (Pylera®) is useful in countries with increasing resistance patterns (24,25). Furthermore, the use of a second-line quadruple therapy containing levofloxacin and bismuth achieved an eradication rate of around 90% in Spain and China (26,27). Unfortunately, bismuth salts are currently unavailable in our region and also in other countries. Tetracyclines may be an option if included in bismuth-based therapies, but they have achieved poor results as part of a triple therapy with amoxicillin and a high-dose of PPI (16). Rifabutin is considered as a fourth-line treatment in Spain but requires a strict control and follow-up of the patient, whereas in other countries it is reserved for the treatment of tuberculosis. Furazolidone is quite difficult to obtain in several countries due to commercial constraints.

Therefore, we propose that a second-line regimen should be personalized according to recent antibiotic exposure and guided by susceptibility testing. Although recommended only as a third-line strategy in the Maastricht V consensus (11), and considering the problems of multidrug resistance, there is no place for empiric second-line treatment regimens in our region. However, this proposal should be limited to regions with similar resistance patterns.

In spite of the immediate costs associated with susceptibility-guided prescription, this strategy will probably achieve better results and improve secondary resistance rates to most antibiotics in the long term. Northern Spain is a region that also harbors high rates of multidrug resistance. However, a study has shown that antimicrobial susceptibility-guided therapy is more effective than empiric concomi-

tant therapy with fewer adverse effects (28). The superiority of a tailored therapy as a second-line approach was also demonstrated by a South-Korean prospective study (29). Furthermore, it may also prove to be a cost-effective strategy in high clarithromycin resistance regions (30,31).

In conclusion, this modified sequential therapy achieved a suboptimal eradication rate in the central region of Portugal in spite of the use of four antibiotics. Our findings highlight the lack of effective *H. pylori* antimicrobials and suggest that second-line treatments in our region should be tailored according to susceptibility testing and also taking into account recent antibiotic exposure, instead of the "one therapy fits all" methodology used in recent years.

PROTECTION OF HUMAN AND ANIMAL SUBJECTS

The authors declare that no experiments were performed on humans or animals for this study.

CONFIDENTIALITY OF DATA

The authors declare that they have followed the protocols of their institute with regard to the publication of patient data.

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