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Tailored *Helicobacter pylori* eradication based on prior intake of macrolide antibiotics allows the use of triple therapy with optimal results in an area with high clarithromycin resistance

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CONFLICTS OF INTEREST

Julio Valle has served as speaker in Health Care centers, receiving support from Allergan.

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ABSTRACT

Background: the previous intake of macrolide antibiotics is associated with a failure to eradicate *Helicobacter pylori (H. pylori)* with clarithromycin-containing regimens. However, the standard triple therapy achieves eradication rates of over 90% in patients without a previous use of macrolides in our health area. The aim of this study was to evaluate the efficacy of an *H. pylori* eradication strategy based on the intake of macrolides by the patient during the previous years.

Methods: one hundred and sixty-nine patients with *H. pylori* infection were prospectively included in the study. The electronic medical record of each patient was reviewed at the time of inclusion. Depending on their previous intake of macrolides, patients were assigned to one of two eradication regimens: group A) patients without a previous intake of macrolides received an optimized triple therapy for 14 days; and group B) patients with a previous intake of macrolides received bismuth quadruple therapy for ten days.

Results: ninety-one patients (53.84%) without a previous intake of macrolides received an optimized triple therapy (group A) and 78 patients (46.15%) with a previous intake of macrolides received bismuth quadruple therapy (group B). In group A, the *H. pylori* eradication rates were 90.11% in the intention-to-treat and 95.35% in the per-protocol analysis. In group B, the *H. pylori* eradication rates were 85.89% in the intention-to-treat and 98.5% in the per-protocol analysis. The overall eradication rates obtained using this strategy were 88.16% (95% CI: 82.32-92.02%) in the intention-to-treat and 96.75% (95% CI: 92.59-98.94%) in the per-protocol analysis.

Conclusions: an *H. pylori* eradication strategy based on the intake of macrolides during the previous years achieves overall eradication rates close to 90% and allows the use of standard triple therapy in more than half of the patients from a health area with a high level of clarithromycin resistance.

INTRODUCTION

Helicobacter pylori (H. pylori) resistance rates to antibiotics are increasing in most parts of the world (1,2). *H. pylori* resistance to clarithromycin is the most important reason for the

decrease in the efficacy of triple therapy (3-5), which has been the recommended first-line treatment for many years (6). Clarithromycin resistance rates have reached ~30% in many countries (7), including Spain (8-11). In areas with high clarithromycin resistance (> 15%), clarithromycin-containing triple therapy without prior susceptibility testing should be abandoned (12). The recommendation of the Maastricht V/Florence Consensus Report for those areas is a first-line treatment with bismuth quadruple or non-bismuth quadruple concomitant therapies (12). Another option is to perform antibiotic susceptibility tests before treatment of *H. pylori.* Tailored eradication based on antibiotic susceptibility tests has been shown to increase eradication rates (13-15), shifting patients to bismuth-containing quadruple therapies in case they have a clarithromycin-resistant *H. pylori* strain (16).

Previous use of antibiotics is known to correlate positively with antibiotic resistance. In fact, there are studies showing that *H. pylori* isolated from previously treated patients is more often resistant to clarithromycin than *H. pylori* isolated from patients who have never received an eradication treatment (8,17). In a large multicenter European study, *H. pylori* resistance to macrolides and quinolones was positively correlated with outpatient use of those antibiotics (18). These results suggest that the consumption of antibiotics in a given region may be used to predict the efficacy of different *H. pylori* eradication regimens. If we focus on an individual patient, there is also evidence that prior use of one of the key antibiotics used in eradication therapies (macrolides and quinolones) will identify likely antibiotic resistance, despite low resistance rates in the population (12). There are two studies, one from South Korea and another from Spain, showing that prior use of macrolide antibiotics is associated with failure to eradicate *H. pylori* with clarithromycin-containing regimens (19,20).

Optimal *H. pylori* eradication rates must be over 90%, as previously suggested (21,22). Our retrospective study included 212 patients with *H. pylori* infection that were treated with clarithromycin-containing regimens. This study showed that the prior use of macrolide antibiotics significantly decreased eradication rates, both in patients treated with triple therapy (60.8% *vs* 92.9%; $p < 0.0001$) and those treated with concomitant quadruple

therapy (85.7% *vs* 98.2%; p = 0.024) (20). However, the results of this study indicate that optimal eradication rates can be achieved using triple therapy in the subgroup of patients with no macrolides used during the previous 10-12 years (20), as triple therapy achieved eradication rates over 90% in these patients. On the other hand, in the group of patients who had used macrolides during the previous years, lower eradication rates were obtained with clarithromycin-containing triple or quadruple therapies. Therefore, a bismuth-containing quadruple therapy would be a better therapeutic option for these patients.

Since 2004, all medication prescribed to patients by Primary Care physicians and specialists from the National Health Care institutions within our health area (Toledo) are recorded in the electronic medical record (EMR). This feature, which is available in other health areas around the world (23), allows us to review all the medication prescribed to the patient since 2004. We performed a prospective study of patients with *H. pylori* infection, in whom the first-line therapy was selected according to their prior intake of macrolide antibiotics during the previous 12 to 14 years. Patients without a prior use of macrolides were treated with optimized triple therapy and patients with a prior use of macrolides were treated with bismuth-containing quadruple therapy. The aim of the study was to evaluate the efficacy of a tailored *H. pylori* eradication strategy based on the intake of macrolides by the patient.

METHODS

Patients

This was a prospective observational study of 183 patients with *H. pylori* infection from the Complejo Hospitalario de Toledo (Spain), between August 2016 and April 2018. Only patients older than 18-years of age who had never received an eradication therapy with an accepted indication for *H. pylori* eradication according to Spanish and European guidelines (24,25) were included in the study. The initial diagnosis of *H. pylori* infection was performed by the Urease test (n = 173) or gastric biopsies (n = 4) in 177 patients who underwent an upper gastrointestinal endoscopy. *H. pylori* infection testing was performed by the Stool antigen test (*H. pylori* Ag MonlabTest®, Barcelona, Spain) in three cases who underwent an upper gastrointestinal endoscopy without gastric samples and three cases

with no upper gastrointestinal endoscopy diagnosis. Patients were invited to participate in the study by two investigators (JV and PMG) during their first outpatient visit, following the diagnosis of an *H. pylori* infection. The study protocol was approved by the Ethical Committee of the Complejo Hospitalario de Toledo and all patients gave informed consent when invited to participate.

Electronic medical record and treatment selection

The electronic medical record of each patient, which contains all of the medication prescribed to the patient since 2004, was reviewed at the time of inclusion. The intake of macrolide antibiotics (clarithromycin, azithromycin, erythromycin, roxithromycin and spiramycin), amoxicillin, metronidazole and quinolones was registered. Both the generic drug name and the brand names of each antibiotic were searched (i.e., the generic name: azitromicina; and brand names: Aratro®, Toraseptol®, Vinzam®, Zentavion®, Zitromax®). Patients were also asked about recent visits to the dentist. A combination of the macrolide spiramycin with metronidazole (Rhodogil®), which is frequently used by dentists, was considered as use of both antibiotics. Depending on their previous intake of macrolides, patients were assigned to one of two eradication regimens: group A) patients without a previous intake of macrolides who received optimized triple therapy (omeprazole, amoxicillin and clarithromycin, optimized with a double dose of omeprazole) for 14 days; and group B) patients with a previous intake of macrolides who received bismuth quadruple therapy (omeprazole and a three-in-one capsule containing bismuth subcitrate, metronidazole and tetracycline (4 pills t.i.d. of Pylera® [Allergan, Dublin, Ireland]) for ten days. An example of the EMR from one patient in each treatment group is shown in figure 1.

Eradication outcome was evaluated in all cases by the ^{13}C urea breath test (UBTest® Otsuka, Ferrer, Barcelona, Spain), which was performed at least one month after the end of the eradication therapy. Patients were instructed to avoid antibiotics one month before and proton pump inhibitors two weeks before the test (26).

Nine patients were not included in the study due to various reasons as follows. The data of the medication prescribed during the previous years was not available in five patients. The treatment was contraindicated due to severe comorbidity in two patients, another patient was excluded due to a penicillin allergy and one patient refused to participate in the study (Fig. 2). During analysis of the results, EMRs were reviewed by another investigator (CS). There was a mistake in the evaluation of prior antibiotic use in five cases. All five cases were treated with optimized triple therapy, even though they had previously used a macrolide antibiotic. These cases were considered as violations of the protocol and were excluded from the final analysis (Fig. 2).

Compliance and adverse effects

Compliance and adverse effects were assessed via telephone interviews performed by one of the investigators (CS) two months after the date of inclusion and treatment prescription. Patients were asked whether they had completed the full treatment and taken all the medication. They were also asked how they felt during the treatment and whether any new signs or symptoms appeared at that time. Treatment emergent adverse effects were graded as mild (a sign or symptom that does not interfere with daily activities and does not require medical intervention), moderate (a sign or symptom that causes some limitation of daily activities and requires some treatment) and severe (symptoms that interfere with daily activities and require medical intervention) (27).

Statistical analysis

Characteristics of the patients in the triple therapy and bismuth quadruple therapy groups were compared using the Fisher's exact test (categorical data) or Student's t-test (quantitative data) as the data was normally distributed. A two-tailed p-value of < 0.05 was considered as statistically significant. The intention-to-treat and per-protocol *H. pylori* eradication rates obtained with each treatment with the exact 95% confidence interval were calculated. One hundred and sixty-nine patients who started the correct eradication treatment were included in the intention-to-treat analysis. The per-protocol analysis was

performed in 154 patients, after excluding subjects who did not attend the appointment for the post-eradication ^{13}C urea breath test and also subjects who did not complete the treatment (Fig. 2). All calculations were performed using STATA/SE version 14.0 software.

RESULTS

One hundred and sixty-nine patients with *H. pylori* infection were included in the analysis. Ninety-one patients (53.84%) without a previous intake of macrolides (55 women; median age: 51 years; range: 21-82) received optimized triple therapy (group A). Seventy-eight patients (46.15%) with a previous intake of macrolides (42 women; median age: 55 years; range: 19-80) received bismuth quadruple therapy (group B). Patients included in both groups had similar demographic characteristics with regard to sex, age and peptic ulcer prevalence (Table 1). However, the groups differed in their previous use of antibiotics. However, none of the patients included in group A and all patients in group B had previously used macrolide antibiotics, as this was the criteria used to allocate patients to one group or another. As expected, the previous use of any kind of antibiotic was significantly more frequent in patients from group B (Table 2). This difference disappeared when macrolides were excluded from the analysis. With regard to the use of antibiotics, 74/91 (81.32%) patients in group A and 69/78 (88.46%) patients in group B had previously used them (p = 0.28). However, the use of metronidazole and quinolones was significantly more common in patients allocated to the bismuth quadruple therapy than in patients allocated to optimized triple therapy (Table 2).

In group A, the *H. pylori* eradication rates obtained by optimized triple therapy were 90.11% in the intention-to-treat and 95.35% in the per-protocol analysis (Fig. 3). In group B, the *H. pylori* eradication rates obtained by bismuth quadruple therapy were 85.89% in the intention-to-treat and 98.5% in the per-protocol analysis (Fig. 3). Overall eradication rates obtained using this strategy were 88.16% (95% CI: 82.32-92.02%) in the intention-to-treat and 96.75% (95% CI: 92.59-98.94%) in the per-protocol analysis. Previous use of metronidazole or quinolones had no significant effect on eradication rates achieved by either therapy (data not shown).

Compliance and treatment emergent adverse effects were assessed in 160 patients who responded to the telephone interview. Most patients in both groups completed the treatment (Table 3). Adverse effects occurred more frequently in patients treated with bismuth quadruple therapy (group B) than in patients treated with triple therapy (group A) (Table 3). The most common adverse effect in both groups were a metallic taste and dyspepsia. One patient in group A had a severe adverse effect of vomiting and did not complete the treatment. Three patients in group B had severe adverse effects (two patients had vomiting and one patient had vomiting and diarrhea) and none of them completed the treatment. Non-compliance was due to incorrect dosage of Pylera® in two additional patients from group B.

DISCUSSION

Resistance to antibiotics is the main cause of the decreasing efficacy of *H. pylori* eradication therapies (5,28). Empiric clarithromycin-containing regimens are no longer suitable in many parts of the world due to the high resistance of *H. pylori* to clarithromycin (5). One strategy used to overcome the difficulties posed by *H. pylori* resistance to antibiotics is the use of culture-guided eradication therapies (14-16). There is evidence that tailored eradication based on antibiotic susceptibility tests results in a significantly lower risk of treatment failure than empirical therapies (29). However, antibiotic susceptibility tests are rarely performed in the clinical practice (5,30,31). Recently published guidelines recommend that the choice of first-line *H. pylori* eradication therapy must consider regional antibiotic resistance patterns (30) and the previous exposure of the patient to antibiotics (31). Regional resistance to macrolides and quinolones is linked to outpatient use of these antibiotics (18) and the previous use of macrolide antibiotics is linked to a failure to eradicate *H. pylori* with clarithromycin-containing regimens (19,20). Considering this information, a tailored eradication strategy was developed, which was based on a previous use of macrolide antibiotics by the patient and not on antibiotic susceptibility tests. Our hypothesis was that patients who had never used macrolides would have a non-resistant *H. pylori* strain and would respond to optimized triple therapy. On the other hand, patients

who had used macrolides during the previous years would have a clarithromycin-resistant *H. pylori* strain. For that reason, those patients were treated with bismuth quadruple therapy, which is a recommended first-line therapy by several guidelines (12,13,30,31). Using this strategy, an intention-to-treat *H. pylori* eradication rate of 88.16% was obtained, which is very close to what is nowadays considered as optimal (21,22).

Recently published consensus reports do not recommend the use of triple therapy without antibiotic susceptibility tests in areas of high clarithromycin resistance (12,30,31). However, there is room for triple therapy in areas where the clarithromycin resistance rate is < 15% or triple therapy has shown an efficacy of > 85% (12,30,31). The results of our study show that an eradication strategy based on the previous use of macrolide antibiotics by the patient allows the use of triple therapy in areas of high clarithromycin resistance. Although we have not investigated *H. pylori* resistance to clarithromycin in our health area, all recent studies performed in northern, southern and central Spain describe *H. pylori* resistance rates to clarithromycin of well over 15% (7-10). In addition, *H. pylori* eradication rates obtained with empiric triple therapy during the past years in our area are very low, under 70% (32). Thus, indicating a high clarithromycin resistance.

High resistance of *H. pylori* to clarithromycin (> 15%) is very common in most countries of Europe and in many other parts of the world (5). In spite of international consensus report recommendations, triple therapy continues to be the most commonly used *H. pylori* eradication therapy in Europe (33). Therefore, a strategy that allows the use of triple therapy in selected patients from areas of high clarithromycin resistance would be welcomed both by gastroenterologists and general practitioners. Although our strategy of tailored eradication requires comprehensive EMR containing information on the prior use of medication by the patient, reviewing an EMR is easier than performing antibiotic susceptibility tests.

Optimal per-protocol eradication rates of over 95% were obtained in this study with optimized triple therapy in patients without prior use of macrolides (group A) and bismuth quadruple therapy in patients with a prior use of macrolides (group B). Even though antibiotic susceptibility tests were not performed, the eradication rates obtained with our

strategy indicate that *H. pylori* strains from patients in group A were sensitive to clarithromycin. We cannot say that patients in group B had a higher prevalence of clarithromycin-resistant *H. pylori* strains. However, several studies have shown that *H. pylori* isolated from patients previously treated with clarithromycin-containing therapies are more often resistant to clarithromycin than *H. pylori* isolated from patients who have never received an eradication treatment (8,17,34,35). With regard to the intention-to treat eradication rates, they were lower in group B (bismuth quadruple therapy) than in group A (triple therapy). This was due to discontinuation of treatment that was secondary to adverse effects, in a proportion similar to that reported in other studies (27,36,37).

This was a prospective study of a very homogeneous population, as most patients were recruited following a positive urease test performed during an upper gastrointestinal endoscopy. However, our study has some limitations. The main matter of concern is the fact that EMRs may not be comprehensive. As a matter of fact, we had to exclude five cases from the analysis as data on previous medication was lacking. This usually happens when a patient has recently moved to our health area, so we only have information on the medication prescribed to the patient during the last few years. Otherwise, this is a rare occurrence in Spain, where the health care system is universal and all citizens have the right of medications with a significant discount. Even in the case of patients who have a complementary private health insurance, most would visit their Primary Care physician for their prescribed medication. Another reason why EMR are not comprehensive is the fact that some antibiotics are prescribed outside the national health care systems, mainly by dentists (38). Although we asked specifically about this, patient memory as well as the EMR are not always reliable. Our study does not have the strength of a clinical trial, in which patients are randomized to receive one of two eradication therapies in order to analyze how the previous use of macrolides influences the results. Despite all these limitations, the results of our study show that the strategy works well and achieves intention-to-treat eradication rates close to 90%, which are considered as optimal.

The results of our study show that, in order to optimize *H. pylori* eradication, it is important to have a record of the antibiotics previously used by patients. This could be achieved

either by using comprehensive EMR or by using personal cards, similar to what is used nowadays to record vaccines. This kind of information may aid antimicrobial stewardship in Primary Care in order to prevent an increase in antibiotic-resistant bacteria (39).

In conclusion, we show for the first time in this study that the selection of the first-line therapy for *H. pylori* eradication can be based on the previous use of macrolide antibiotics. An *H. pylori* eradication strategy based on the intake of macrolides during the previous years achieves overall eradication rates close to 90%. Furthermore, it allows the use of standard triple therapy in more than half of the patients from a health area with high rate of clarithromycin resistance.

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Table 1. Characteristics of patients included in each treatment group

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Variables	**A: Triple** (n=91)	**B: Bismuth Quadruple** (n=78)	**p-value**
Age (years) Mean ± SD	50.72 ± 13.22	53.60 ± 13.99	0.17
Sex (female)	55 (60.43%)	42 (53.84%)	0.43
Upper gastrointestinal endoscopy	91 (100%)	75 (96.15%)	0.09
Peptic ulcer	4/91 (4.39%)	8/75 (10.66%)	0.14

Table 2. Intake of antibiotics during the 12 to 14 years prior to eradication therapy

Eradication therapy	*Triple therapy* (n = 91)	*Bismuth quadruple* (n = 78)	*p-value*
Any antibiotic	74 (81.31%)	78 (100%)	< 0.0001
Macrolides*	0	78 (100%)	n.a.†
Clarithromycin	0	14 (17.94%)	n.a.
Azithromycin	0	62 (79.48%)	n.a.
Other macrolides	0	23 (29.48%)	n.a.
Amoxicillin	71 (76.9%)	64 (82.05%)	0.5
Metronidazole	4 (4.39%)	15 (19.23%)	0.0029
Quinolones	24 (26.37%)	40 (51.28%)	0.0014

*Previous intake of different types of macrolides by a single patient did occur and therefore, the sum is not equal to the total number of patients who have used macrolides. † n.a.: non applicable.

Table 3. Compliance and adverse effects referred by 160 patients who answered the phone interview

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Variables	Triple therapy (n=83)	Bismuth Quadruple (n=77)	p-value
Completed treatment	82 (98.79%)	72 (93.50%)	0.10
Adverse effects	13 (15.66%)	25 (32.46%)	**0.015**
Mild	11	20	
Moderate	1	2	
Severe	1	3	

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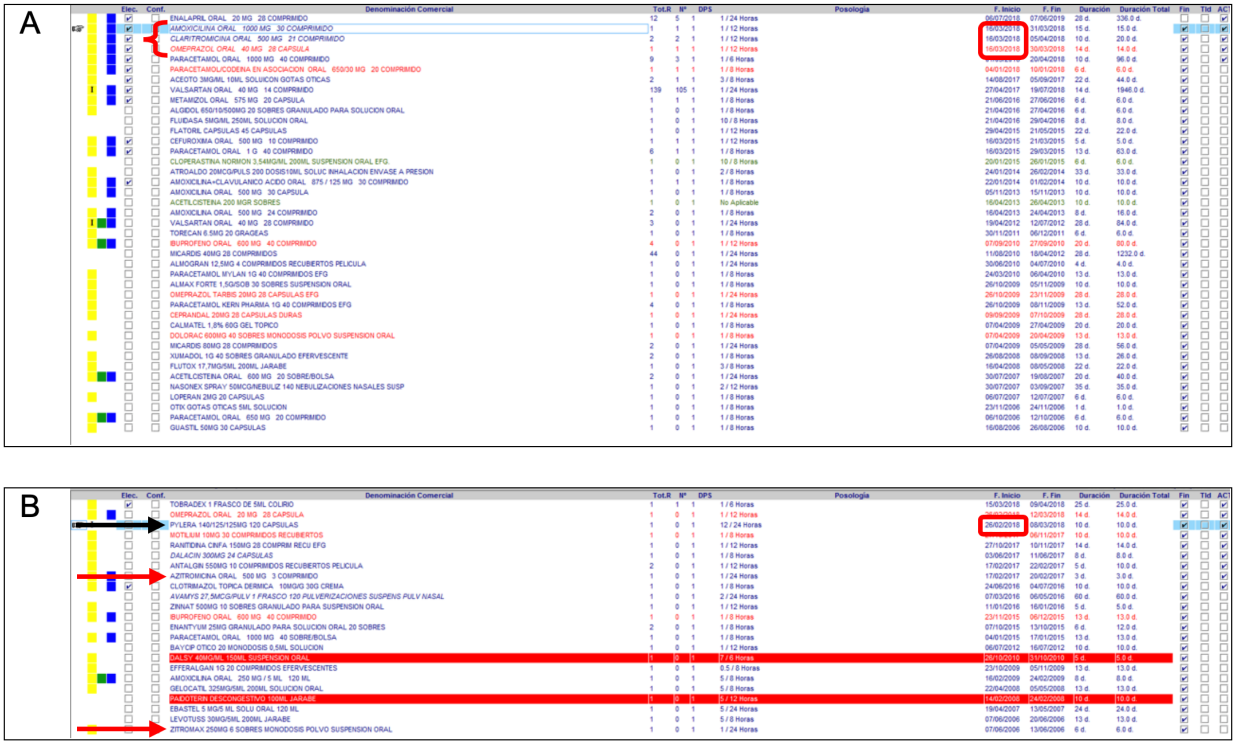

Fig. 1. Two examples of electronic medical records. A. A patient without a previous intake of macrolides. Triple therapy was administered in March 2018 (brackets). B. A patient with a previous intake of macrolides (red arrows). Bismuth quadruple therapy was administered in February 2018 (black arrow).

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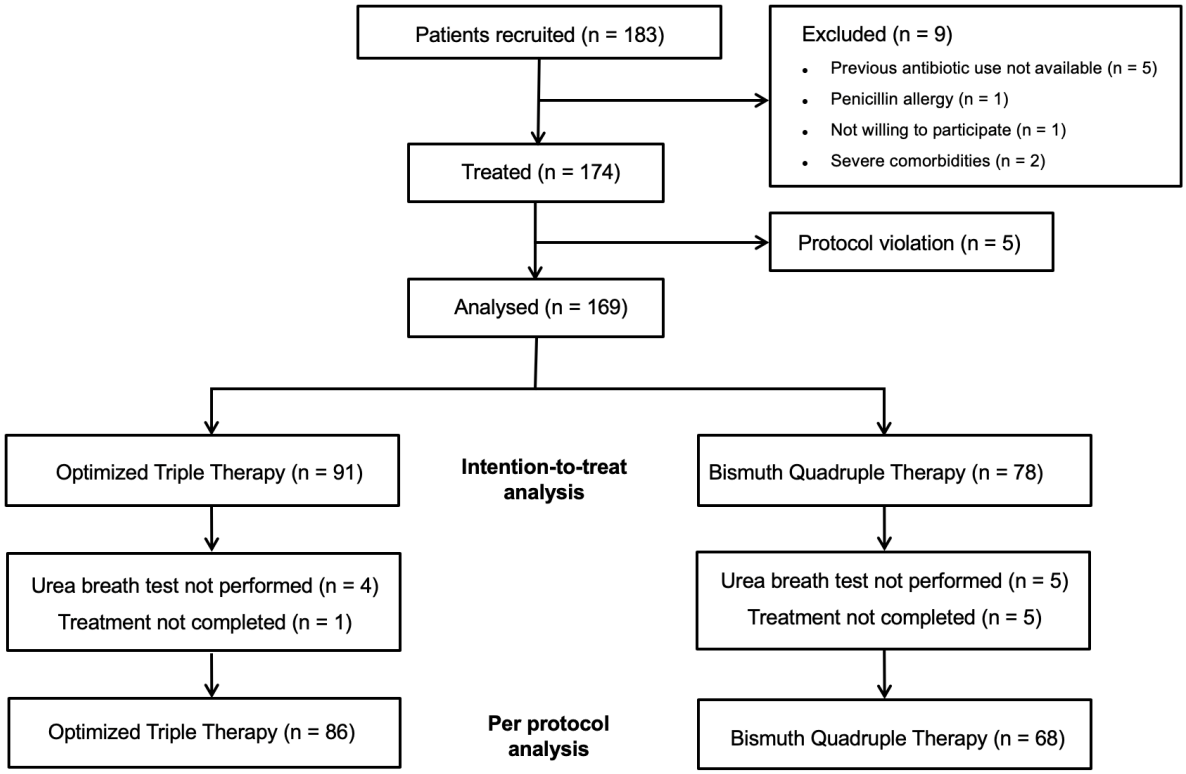

Fig. 2. Flow chart of the subjects included in the study.

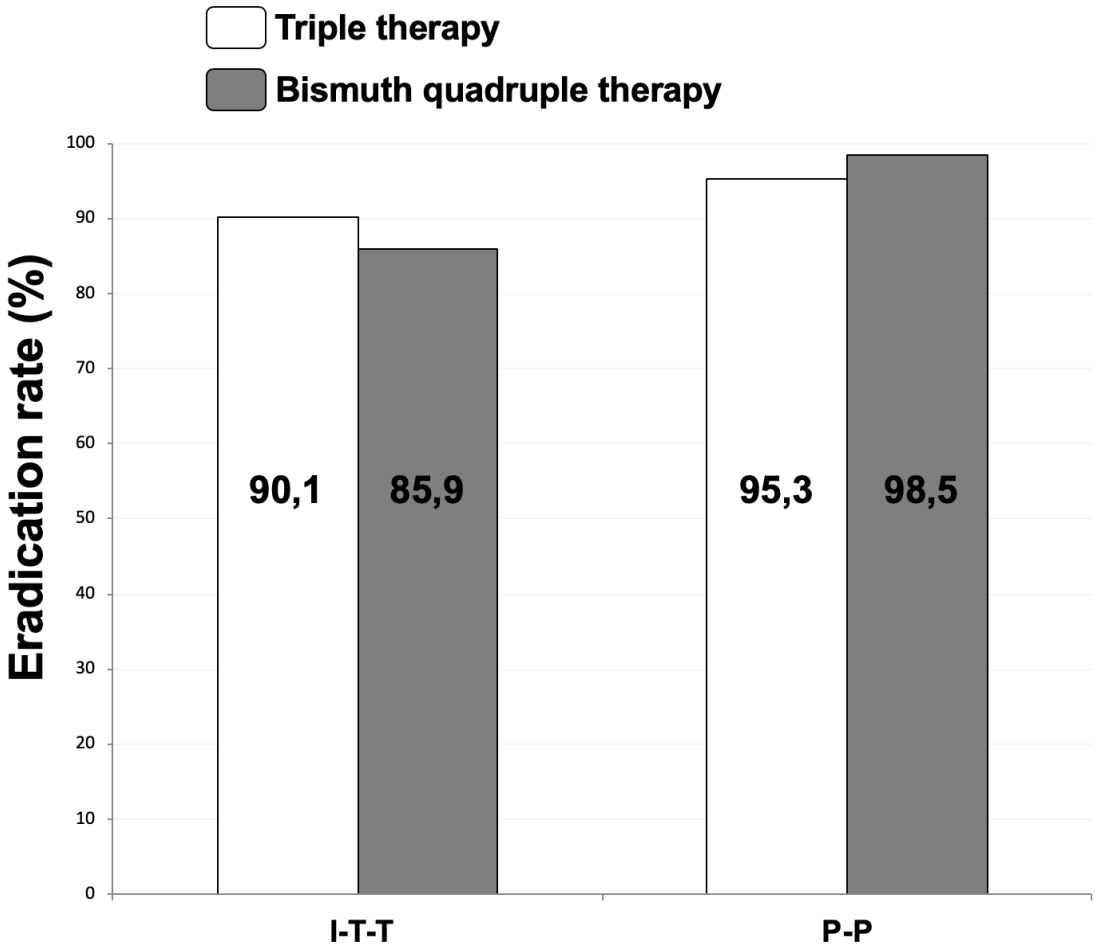

Fig. 3. Eradication rates obtained with optimized triple therapy in patients without a previous intake of macrolides (group A) and with bismuth quadruple therapy in patients with a previous intake of macrolides (group B). I-T-T: intention-to-treat; P-P: per-protocol.