Assessment of first-line eradication treatment in Greece: data from the European Registry on *Helicobacter pylori* management (Hp-EuReg)

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Abstract

Background *Helicobacter pylori* (*H. pylori*) is the most common chronic bacterial infection. Its management has to rely on local effectiveness, given the geographical variability of bacterial antibiotic resistance. We evaluated treatment effectiveness in naïve patients in Greece, as part of the European Registry on the management of *H. pylori* (Hp-EuReg).

Methods Patients were registered in the AEG-REDCap Electronic Case Report Form from 2013-2020. All cases with a first-line treatment were included. Modified intention-to-treat (mITT) analysis was used.

Results A total of 547 patients from 5 medical institutions were treated with the following regimens: concomitant with proton pump inhibitors (PPIs), clarithromycin, amoxicillin and metronidazole (concomitant-C+A+M) (38%); hybrid with PPI, clarithromycin, amoxicillin and metronidazole (hybrid-C+A+M) (20%); sequential with PPI, clarithromycin, amoxicillin and tinidazole (sequential-C+A+T) (12%); sequential with PPI, clarithromycin, amoxicillin and metronidazole (sequential-C+A+M) (12%); concomitant with PPI, clarithromycin, amoxicillin and tinidazole (concomitant-C+A+T) (8%); triple with PPI, clarithromycin and amoxicillin (triple-C+A) (7%); and other (3%). Overall compliance was 99%. Triple-C+A, sequential-C+A+T, sequential-C+A+M and concomitant-C+A+T were used from 2013-2015. The respective mITT cure rates (95% confidence interval) were 92% (78-98), 87% (76-94), 67% (54-78) and 91% (79-98). Since 2015, patients were also treated with concomitant-C+A+M and hybrid-C+A+M regimens, with respective mITT cure rates of 90% (85-94) and 88% (80.5-94). Adverse events were reported by 31% of the patients, dysgeusia being the most frequent (15%).

Conclusions "Optimized" *H. pylori* therapies should achieve cure rates over 90%. In Greece, at present, only non-bismuth quadruple concomitant regimens achieve this target and can be recommended as first-line treatment.

Keywords *Helicobacter pylori*, treatment, Greece, Hp-EuReg

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Introduction

Helicobacter pylori (*H. pylori*) infection is of worldwide concern, as it has been recognized as the main cause of gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma

and gastric cancer. *H. pylori* gastritis was formally recognized as an infectious disease in 2015, leading to the recommendation that all patients should receive treatment; since then, the list of indications to test for the presence of the infection has been greatly expanded [1,2]. In 2020 the Taipei Global consensus emphasized the role of *H. pylori* eradication in accomplishing the goal of reducing or eliminating deaths from gastric cancer [3].

A number of different *H. pylori* therapies have been introduced, including triple therapies consisting of a proton pump inhibitor (PPI), amoxicillin and clarithromycin, metronidazole, a fluoroquinolone, or rifabutin; bismuth quadruple therapy; dual therapy (PPI and amoxicillin) and a group of 4-drug therapies consisting of a PPI, amoxicillin, clarithromycin and metronidazole, called sequential, concomitant, hybrid and reverse hybrid therapies, depending on the manner of administration. However, the management of *H. pylori* infection has to be tailored according to the local, geographical variability of bacterial antibiotic resistance.

A multinational and multicenter prospective ongoing registry of the clinical practice of European gastroenterologists concerning *H. pylori* infection (Hp-EuReg) has been developed, including patients from 2013 to date. Greece has been participating in the Hp-EuReg from the beginning. The aim of the present study was to analyze the data relating to first-line *H. pylori* eradication treatments in Greece during the period 2013-2020, as part of the Hp-EuReg.

Materials and methods

European Registry on *H. pylori* management

The "European Registry on *H. pylori* Management" (Hp-EuReg) is an international multicenter prospective non-interventional registry, recording information about *H. pylori* infection management (30 countries) since May 2013. It was prospectively registered in ClinicalTrials.gov (NCT02328131) and was promoted by the European Helicobacter and Microbiota

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Study Group (www.helicobacter.org) [4]. The current study is a sub-analysis focusing on a cohort of Greek *H. pylori* positive adult patients from centers actively participating in the Hp-EuReg.

National coordinators

Thirty European countries were selected for this registry, with national coordinators for each country. For Greece, the National Coordinator was author TR, who was responsible for supervising data inclusion, monitoring and the drafting of this study.

Recruiting investigators

The recruiting investigators were gastroenterologists attending an adult population with a gastroenterology outpatient clinic treating patients infected with *H. pylori*. Patients were managed and registered following routine clinical practice. Greek recruiting investigators were authors TR, SG, SM, VN and CL.

Data extraction and analysis

Data were recorded in an Electronic Case Report Form (e-CRF) using a web-based application, REDCap (Research Electronic Data Capture), a platform managed and hosted by the "Asociación Española de Gastroenterología" (AEG; www.aegastro.es), a non-profit Scientific and Medical Society that focuses on gastroenterology research.

The patient's demographics, the previous eradication attempts, the treatments employed, and the outcomes: cure rates, compliance, adverse events and the follow up were recorded. All patient data were anonymized. The main outcome was confirmed eradication at least 4 weeks after treatment. Data were collected up to February 2021.

Effectiveness analysis

For the purposes of this study, a modified intention to treat (mITT) analysis was used to achieve the closest result to those obtained in clinical practice. The mITT includes all cases that had completed the follow up (i.e., had undertaken a valid confirmatory test after the eradication treatment), regardless of compliance with treatment, and excluding those cases with an incomplete follow up (lost to follow up). All patients who were empirically treated (i.e., not susceptibility-guided) were included in the effectiveness analysis. Patient compliance with treatment was defined as more than 90% drug intake.

Statistical analysis

Continuous variables were presented as arithmetic means and standard deviations. Qualitative variables were presented

as proportions and 95% confidence intervals (CIs). The statistical analyses of the results were carried out using the χ^2-Pearson test. One- and 2-sided tests were used for the analyses and the P-value cutoff for significance was set to less than 0.05. The analyses were carried out using IBM SPSS Statistics 22.0.0.

Results

Patient characteristics and regimens used

Overall, the Greek medical institutions reported data on 653 *H. pylori*-positive patients who had been treated for *H. pylori* infection; of these, 547 had received a first-line eradication treatment. The main characteristics of the cohort are shown in Table 1. Patients treated with first-line eradication treatment received the following regimens: concomitant with a PPI, clarithromycin, amoxicillin and metronidazole (concomitant-C+A+M) was received by 208 patients (38%); hybrid PPI, clarithromycin, amoxicillin and metronidazole (hybrid-C+A+M) was received by 109 patients (20%); sequential PPI, clarithromycin, amoxicillin and tinidazole (sequential-C+A+T) was received by 66 patients (12%); sequential PPI, clarithromycin, amoxicillin and metronidazole (sequential-C+A+M) was received by 66 patients (12%); concomitant PPI, clarithromycin, amoxicillin and tinidazole (concomitant-C+A+T) was received by 44 patients (8%); triple PPI, clarithromycin, amoxicillin (triple-C+A) was received by 208 patients (7%); and other treatment was received by 16 patients (3%) (Fig. 1). Triple-C+A, sequential-C+A+T, sequential-C+A+M and concomitant-C+A+T were mainly used in the period from 2013-2015. Since 2016, patients were treated with concomitant-C+A+M and hybrid-C+A+M regimens. Concerning the *H. pylori* diagnostic test, in 92% of the patients an invasive test was used, as opposed to the 8% who underwent noninvasive testing (Table 1).

First-line empiric treatment cure rates

The mITT cure rates for triple-C+A, sequential-C+A+T, sequential-C+A+M, concomitant-C+A+T, concomitant-C+A+M and hybrid-C+A+M regimens were 92% (95%CI 78-98), 87% (95%CI 76-94), 67% (95%CI 54-78), 91% (95%CI 79-98), 90% (95%CI 85-94), and 88% (95%CI 80.5-94), respectively (Fig. 2). Three regimens, i.e., triple-C+A, concomitant-C+A+T and concomitant-C+A+M achieved cure rates of more than the acceptable level of 90%. The remaining 3 regimens, i.e., sequential-C+A+T, sequential-C+A+M and hybrid-C+A+M failed to reach this level of acceptability. The sequential-C+A+M regimen was the least efficacious, and the comparisons between this and the other reported regimens yielded statistically significant results, i.e., P=0.003 vs. triple-C+A, P=0.02 vs. sequential-C+A+T, P=0.003 vs. concomitant-C+A+T, P<0.001 vs. concomitant-C+A+M and P=0.006 vs. hybrid-C+A+M. Accordingly, the best *H. pylori* therapy

Table 1 Baseline characteristics of the patients in the Greek cohort of Hp-EuReg

| Variables	Patients
Sex	
Female	52%
Male	48%
Age, mean (standard deviation)	53.21 (14.77)
Penicillin allergy	1.07%
Treatment Indication	
Dyspepsia	70.44
Peptic ulcer	13.78
Other	15.77
Culture performed	38%
Resistance	%
Clarithromycin	26.3
Nitroimidazole	20.6
Levofloxacin	6.4
Dual resistance	5.8
Triple resistance	1.1
Treatment length	
7 days	1.1%
10 days	65.2%
14 days	33.6%
Potency of PPI acid inhibition	%
Low	40.8%
Standard	0.9%
High	58.3%
Compliance	%
No (<90% drug intake)	1.2
Yes (>90% drug intake)	98.8
Diagnostic test	
Invasive	91.9%
Noninvasive	8.1%

PPI, proton pump inhibitor
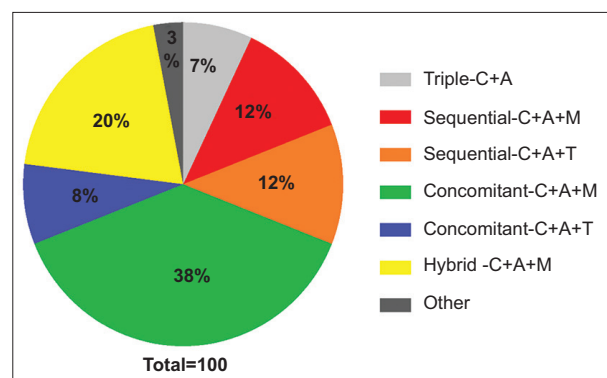
Figure 1 Percentages of regimens used as empirical first-line treatment in Greece
C, clarithromycin; A, amoxicillin; M, metronidazole; T, tinidazole

in Greece was the concomitant-C+A+imidazole (either metronidazole or tinidazole) regimen.

The treatment prescriptions by treatment length, i.e., 7, 10 and 14 days, as well as the potency of PPI acid inhibition, i.e., low, standard and high, of the regimens used in this Greek
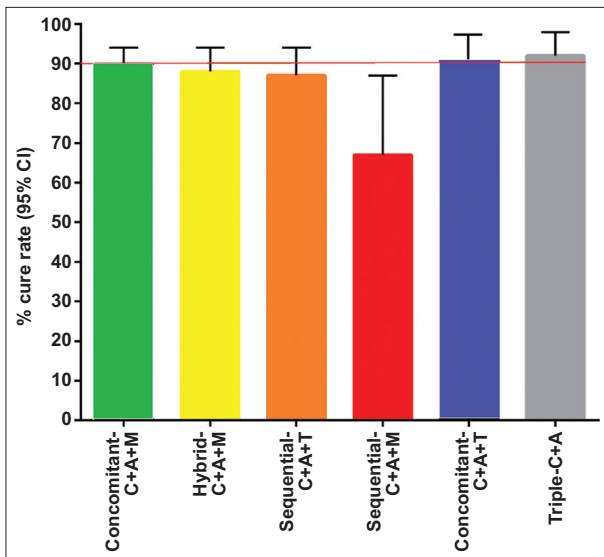
Figure 2 Effectiveness of the regimens used in the Greek cohort. Modified intention to treat results are expressed as percentages with 95% confidence intervals (CI)

C, clarithromycin; A, amoxicillin; M, metronidazole; T, tinidazole

Table 2 Treatment length and potency of PPI acid inhibition of the regimens used in the Greek cohort of the Hp-EuReg

Variables	% of patients	χ^2 (Pearson test)
Treatment length		
7 days	1.1%	P < 0.001
10 days	65.2%	
14 days	33.6%	
Potency of PPI acid inhibition		
Low	40.8%	P < 0.001
Standard	0.9%	
High	58.3%	

PPI, proton pump inhibitor

cohort of the Hp-EuReg, are shown in Table 2. Thus, the percentages of treatment prescriptions for 7, 10 and 14 days were 1.1%, 65.2% and 33.65%, respectively. Concerning the potency of PPI acid inhibition, the relevant percentages were 40.8% for low, 0.9% for standard and 58.3% for high potency. The trend in the prescription of treatments (2013-2020) is shown in Fig. 3. There was a significant trend (P<0.001) towards an increase in the use of non-bismuth quadruple regimens, administered as concomitant-C+A+M and hybrid therapy.

Compliance and adverse events

The compliance of treated patients, was reported as 99% (95%CI 97.5-99.4). Concerning adverse events, they were reported in 31% of the naïve patients, dysgeusia being the most frequent (15%), followed by diarrhea (12%), nausea (6%), abdominal pain (3%), dyspepsia (3%), anorexia (2%), and vomiting (1.3%). No serious adverse events were reported.

Discussion

The Hp-EuReg was started in 2013. The idea was to collect treatment results, side effects, patients' compliance and antimicrobial susceptibility from different European countries. Thirty countries and more than 200 recruiting investigators are actively participating in the Hp-EuReg [5].

In this study, data concerning the first-line eradication treatments for the Greek cohort were analyzed and showed that 3 regimens, i.e., triple-C+A, concomitant-C+A+T and

concomitant-C+A+M, performed well in that they achieved cure rates of more than the acceptable level of 90%. Furthermore, the evolution of the prescriptions of first-line treatments over the examined period 2013-2020, showed a significant shift towards a higher use of non-bismuth quadruple regimens, mainly concomitant-C+A+M and hybrid regimens. Bismuth is not available in Greece, so regimens including this drug were not used. Triple therapy was prescribed only in the first 3 years (2013-2016), and a similar trend was found for sequential regimens. Since then, the empiric use of these regimens was abandoned and they were replaced by quadruple regimens, i.e., non-bismuth concomitant and hybrid. The reason for this shift could be attributed primarily to the fact that antibiotic resistance in Greece is increasing, which is particularly true for clarithromycin [6,7]. In 2017, the Maastricht V consensus report was published [8], which stated that when clarithromycin resistance rate exceeds 15%, triple therapy should be abandoned. Therefore, it would be possible that, as the aforementioned clinical guidelines became widely adopted in Greece, as expressed by the consensus report of the Hellenic *H. pylori* and Microbiota Study Group [9], Greek doctors became aware of the fact that when clarithromycin resistance increases, the cure rate drops to unacceptable levels [10-11]. It should be mentioned that 26% of the patients included in the present study had clarithromycin resistance, which is clearly higher than the 15% standard threshold [8]. However, there is a possibility that the cure rate achieved by triple therapy at the beginning of the Greek participation in the Hp-EuReg, might be the result of antibiotic susceptibility testing (either by culture or molecular based test), although these data are not available in this cohort. It is accepted that triple therapy is highly effective after susceptibility testing [10]. This is in agreement with the notion of antibiotic stewardship [11-14], which maintains that treatments, instead of being empirical, should be based on susceptibility testing. However, in different populations, apart from antibiotic resistance, a number of other factors should be taken into account when trying to interpret *H. pylori* cure rates, such as the relative effects of different degrees of acid suppression in relation to potency and dosage, as these markedly affect the effectiveness of the regimens [5].

Despite the interesting findings, this study has some limitations. The main limitation is the relatively small number of recruiting centers. This is expected to improve with the recruitment of more centers from various parts of Greece.
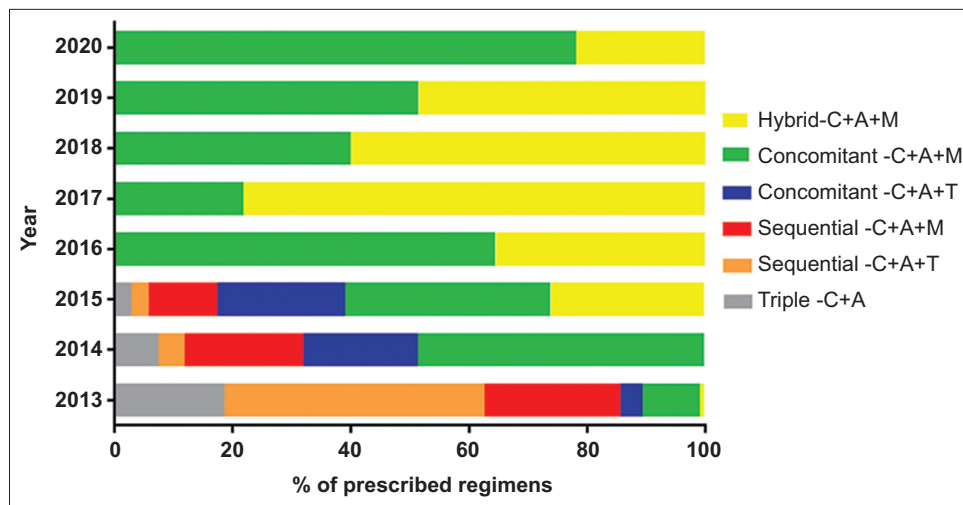
Figure 3 Treatment prescription trends (2013-2020) in Greece
C, clarithromycin; A, amoxicillin; M, metronidazole; T, tinidazole

An additional limitation is the fact that not all recruited patients underwent culture testing. It is obvious that the promotion and creation of large databases to record local antibiotic resistance information could improve effectiveness. Nonetheless, the current study was performed to evaluate the routine empirical practice of gastroenterologists in Greece concerning first-line treatment. Therefore, the present study provides a comprehensive overview of current local empirical first-line *H. pylori* treatment in Greece; consequently, the conclusions drawn are easily applicable in routine clinical practice, i.e., the use of non-bismuth quadruple concomitant regimens (with a PPI, clarithromycin, amoxicillin and a nitroimidazole) can achieve over 90% cure rates and therefore can be recommended as empirical first-line treatment in Greece.

Nonetheless, *H. pylori* treatment continues to be a challenge, as bacterial antibiotic resistance continues to emerge and impair clinicians' ability to cure *H. pylori* infection. Recently, a consensus report recommended that clarithromycin, metronidazole, and levofloxacin should not be used empirically unless proven to be reliably effective locally [2]. Under these circumstances, a new approach concerning *H. pylori* treatment is needed, and towards this end there are views supporting the notion that it is now time to transition from trial and error to antimicrobial stewardship, as in other infectious diseases [15]. This approach requires therapy to be restricted to optimized therapies that have been proven to be reliably highly effective in the local population (e.g., cure rate of more than 90%), and therefore comparisons should be restricted to regimens that meet these criteria.

In conclusion, in recent years in Greece, only non-bismuth quadruple concomitant regimens (with a PPI, clarithromycin, amoxicillin and a nitroimidazole) can achieve over 90% cure rates and therefore can be recommended as empirical first-line treatment.

Summary Box

What is already known:

- A multinational and multicenter prospective ongoing registry of the clinical practice of European gastroenterologists concerning *Helicobacter pylori* (*H. pylori*) infection (Hp-EuReg) has been developed, including patients from 2013 to date
- Greece has been participating in the Hp-EuReg from the beginning

What the new findings are:

- In this study we analyzed the data of first-line *H. pylori* eradication treatments in Greece during the 2013-2020 period, as part of the Hp-EuReg
- "Optimized" *H. pylori* therapies should achieve over 90% cure rates
- In Greece, at present, only non-bismuth quadruple concomitant regimens achieve this target and can be recommended as first-line treatment

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