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Effectiveness of first and second-line empirical treatment in Italy: Results of the European registry on *Helicobacter pylori* management

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Abstract

Background and Aims: The optimal management of naïve and not naïve *Helicobacter pylori* patients remains unclear. Therefore, it is essential to evaluate whether the actual clinical practice mirrors the indications suggested by the guidelines. This study aimed to assess the effectiveness and the safety of the empirical first- and second-line

European Helicobacter and Microbiota Study Group; Spanish Association of Gastroenterology

treatments prescribed to patients enroled at Italian centres participating in the European Registry on *H. pylori* Management (Hp-EuReg).

Methods: The Hp-EuReg is an international multicentre prospective non-interventional registry starting in 2013 aiming to evaluate the management of *H. pylori* infection by European gastroenterologists. Patients were registered in an e-CRF by AEG-REDCap. Variables assessed included demographics, previous eradication attempts, treatment regimen, effectiveness, and tolerance.

Results: Overall, 3723 patients from 2013 to February 2021 were included: 2996 and 727 received an empirical first- and second-line treatment, respectively. According to the modified ITT analysis, among the first-line regimens, only the bismuth quadruple therapy with three-in-one-single capsule (BQT-TSC), the concomitant, and the sequential treatment - all lasting 10 days - achieved an eradication rate >90%. Among the second-line regimens, only the 10-day BQT-TSC reported an effectiveness >90%. High-dose PPI twice daily also significantly increased the effectiveness of some therapies. The BQT-TSC was the regimen with the highest incidence of adverse events.

Conclusions: Only quadruple therapies lasting at least 10 days achieved over 90% eradication rates among the empirical first- and second-line regimens. It remains unclear whether high-dose PPI twice daily can improve the efficacy of quadruple treatment.

KEYWORDS
first-line treatment, *H. pylori*, Hp-EuReg, proton pump inhibitor, second-line treatment

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is one of the most common bacterial infections affecting humans,[1] causing chronic gastritis,[2] peptic ulcers, gastric mucosa-associated lymphoid tissue lymphoma and gastric cancer.[3,4] It has also been associated with some important extra-gastric diseases, such as iron deficiency anaemia or idiopathic thrombocytopenic purpura.[5]

It is recommended that only regimens with an *excellent* eradication rate (i.e., ≥95%) should be prescribed, while those with a *good* eradication rate (i.e., ≥90%) could be used where excellent results are not obtainable.[6] However, this goal is not easy to achieve in daily clinical practice. Although drug, dose, formulation, pharmacokinetics and duration of treatment are all important issues, increasing resistance to antimicrobials remains the most critical factor affecting the eradication rate.[7,8]

International scientific societies produced recommendations on treatments to use in naïve and not-naïve patients, mainly based on randomised controlled trials (RCTs) and meta-analyses of RCTs.[7,9–12] Nevertheless, these recommendations could not always be extrapolated to different geographic areas for several reasons.[13,14]

Following the publication of the Maastricht IV/Florence consensus report in 2012,[15] the European *Helicobacter* and Microbiota Study Group (EHMSG) promoted an observational study on *H. pylori* infection, "The European Registry on the Management of *H.*

Key summary

Summarise the established knowledge on this subject

- *H. pylori* infection is one of the most common bacterial infections affecting humans, but almost 40 years after its discovery, the ideal regimen to treat this infection remains unclear.

What are the significant and/or new findings of this study?

- "The European Registry on the Management of *H. pylori* infection" (Hp-EuReg), is an observational study on *H. pylori* infection promoted by the European *Helicobacter* and Microbiota Study Group to evaluate the routine of the real clinical practice of European gastroenterologists.
- In this sub-study of the Hp-EuReg, focussed on the Italian setting, we reported that among the first- and second-line regimens empirically prescribed, only quadruple therapies lasting at least 10 days were able to achieve over 90% eradication rate. It remains unclear whether high-dose PPI twice daily can improve the efficacy of quadruple treatments.
- It is essential to periodically perform studies of this type to evaluate the information acquired on regimens used, their effectiveness, and adherence to national and international guidelines.

pylori infection" (Hp-EuReg), to evaluate the routine of the real clinical practice of European gastroenterologists.[16]

The present study aimed to assess the effectiveness of first- and second-line treatments empirically prescribed to *H. pylori* positive adult patients, not allergic to penicillin and enroled by the Italian centres participating in the Hp-EuReg.

METHODS

The Hp-EuReg is an international multicentre prospective non-interventional study that began in 2013. It was approved by the Ethics Committee of La Princesa University Hospital, Madrid, Spain, and was registered at ClinicalTrials.gov under the code NCT02328131.[16,17] Comprehensive information regarding this study was already published in detail.[16,17]

Data management

The database was searched from inception to February 2021. Patients allergic to penicillin were excluded since their therapeutic management differed from the rest of the population. The length of the treatments was evaluated using three categories corresponding to the three most frequent treatment durations: 7, 10, and 14 days.[17] PPI data were standardised using the PPI acid inhibition potency as defined by Kirchheiner et al.,[18] Graham et al.,[19] and classified as low dose (ranging from 4.5 to 27 mg omeprazole equivalents *bis in die* [bid], i.e., 20 mg omeprazole equivalents bid), standard dose (ranging from 32 to 40 mg omeprazole equivalents bid, i.e., 40 mg omeprazole equivalents bid), and high dose (ranging from 54 to 128 mg omeprazole equivalents bid, i.e., 60 mg omeprazole equivalents bid).[17] The evaluation of effectiveness and safety was performed until February 2021, while the assessment of the evolution of both prescriptions and effectiveness was performed until December 2020 to account for complete years.

Data were subjected to quality control to maintain their reliability and coherence within the cohort studied.

Effectiveness and safety analyses

The effectiveness of the prescribed regimens was evaluated using three analyses: (1) intention-to-treat (ITT, including all patients registered to allow at least a 6-month follow-up, and those lost to follow-up considered treatment failures); (2) per-protocol (PP, including all patients that completed the follow-up and took at least 90% of the treatment medications); and (3) modified ITT (mITT), that included all patients who completed follow-up (i.e., patients with a confirmatory test available after eradication treatment regardless of compliance).[16,17] As per the decision of the Hp-EuReg Scientific Committee, the mITT set was defined as the principal effectiveness analysis to be taken into account since reflecting the closest results to those obtained in clinical practice.[16,17] Therefore, the mITT data were reported along with the manuscript's text, while ITT and PP analyses were reported within the tables for methodological reasons and comparison only, but not used for data evaluation. Whenever possible, the effectiveness of treatments was also evaluated by subgroup analysis considering the daily dosage of PPIs. Adverse events (AEs) were assessed only for regimens prescribed in ≥100 patients to avoid the low sample size from affecting the variation of data.[20]

Statistical analyses

Continuous variables were presented as mean and standard deviation (SD). Qualitative variables are presented as absolute or relative frequencies with percentages (%). Graphical representations were used to show the temporal trends in prescriptions. Proportions, their differences, and 95% confidence intervals (CIs) were calculated using the method recommended by Newcombe and Altman.[21] Fisher's exact test and χ^2 test was used as appropriate. A two-sided $p < 0.05$ was considered significant.

RESULTS

Patients' baseline characteristics and diagnosis

Until February 2021, 3723 patients were included in the analysis among the 9 Italian centres participating in the Hp-EuReg: 2996 and 727 received an empirical first- and second-line treatment, respectively. The characteristics of these patients are shown in Tables 1 and 2. Most of the patients underwent an upper GI endoscopy (UGI) to diagnose the infection before the first- (81.9%) and second-line therapies (77.2%). Similarly, most patients underwent an UGI for follow-up after the first- (91.3%) and -second-line (90.6%) treatments.

First-line regimens

Therapeutic regimens empirically prescribed in first-line

The five most frequently prescribed regimens are shown in Table 1.

Evolution of first-line prescriptions

Figure 1a shows the trend of prescriptions during 2013–2020 for the regimens evaluated. The sequential therapy (ST)[22] had its lowest prescription rate in 2016 (14.5%), whilst the quadruple therapy with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with a PPI[23] (i.e., bismuth quadruple therapy with a three-in-one-single capsule: BQT-TSC), never adopted

TABLE 1 Baseline characteristics of *Helicobacter pylori* first-line empirical treatments prescribed in patients not allergic to penicillin between 2013 and February 2021

Number of patients	2996
Female, N (%)	1823 (60.9)
Age, mean (SD)	51.6 (±15)
Indication	
Dyspepsia	87.5%
Ulcer disease	3.4%
Other	9.1%
Treatment length	
7 days	3.1%
10 days	90.5%
14 days	6.4%
PPI dose[a]	
Low	48.7%
Standard	1.5%
High	49.8%
Most frequent treatments[b]	
Sequential (PPI + C + A + T/M)	57.3%
BQT-TSC[c]	20.0%
Concomitant (PPI + C + A + M)	10.3%
Triple therapy: PPI + A + C	5.1%
Triple therapy: PPI + A + L	2.0%
Others	5.3%

Abbreviations: A, amoxicillin; C, clarithromycin; L, levofloxacin; M, metronidazole; N, total number of patients; PPI, proton pump inhibitor; SD, standard deviation; T, tinidazole.

[a]Low dose PPI: 4.5–27 mg omeprazole equivalents, two times per day (i.e., 20 mg omeprazole equivalents, two times per day), standard dose PPI: 32–40 mg omeprazole equivalents, two times per day (i.e., 40 mg omeprazole equivalents, two times per day), high dose PPI: 54–128 mg omeprazole equivalents, two times per day (i.e., 60 mg omeprazole equivalents, two times per day).[17]

[b]Presented in descending order of prescription.

[c]Bismuth quadruple therapy with three-in-one-single capsule.

TABLE 2 Baseline characteristics of *Helicobacter pylori* second-line empirical treatments prescribed in patients not allergic to penicillin between 2013 and February 2021

Number of patients	727
Female, N (%)	497 (68.4)
Age, mean (SD)	51 (±14.3)
Indication	
Dyspepsia	55%
Ulcer disease	4.7%
Other	40.3%
Treatment length	
7 days	1.1%
10 days	95.3%
14 days	3.6%
PPI dose[a]	
Low	47.8%
Standard	3.6%
High	48.6%
Most frequent treatments[b]	
Triple therapy: PPI + A + L	31.1%
BQT-TSC[c]	28.5%
Triple therapy: PPI + A + R	19.8%
Sequential (PPI + C + A + T/M)	10.8%
Concomitant (PPI + C + A + M)	4.1%
Others	5.7%

Abbreviations: A, amoxicillin; C, clarithromycin; L, levofloxacin; M, metronidazole; N, total number of patients; PPI, proton pump inhibitor; R, rifabutin; SD, standard deviation; T, tinidazole.

[a]Low dose PPI: 4.5–27 mg omeprazole equivalents, two times per day (i.e., 20 mg omeprazole equivalents, two times per day), standard dose PPI: 32–40 mg omeprazole equivalents, two times per day (i.e., 40 mg omeprazole equivalents, two times per day), high dose PPI: 54–128 mg omeprazole equivalents, two times per day (i.e., 60 mg omeprazole equivalents, two times per day).[17]

[b]Presented in descending order of prescription.

[c]Bismuth quadruple therapy with three-in-one-single capsule.

between 2013 and 2015, was mostly employed in 2016 (63%), and in the subsequent years, with the prescriptions ranging from 12.1% (2017) to 37.2% (2019).

The concomitant therapy (CT)[24] was mainly used between 2015 (24.7%) and 2016 (22.5), the triple therapy with PPI, amoxicillin and clarithromycin (PPI-A-C) was predominantly adopted in 2013 (22.7%), and the triple therapy with PPI, amoxicillin and levofloxacin (PPI-A-L) mostly utilised in 2020 (10.8%).

Figure 1b depicts the trends in treatment duration: overall, 10-day therapies were employed in ≥90% of cases, 14-day therapies in 6.4% of cases (ranging from 0% in 2013% and 2014% to 17% in 2016), and 7-day therapies in 3.1% of cases.

Figure S1A shows the trends of utilisation concerning the daily dose of PPI (milligrams of omeprazole equivalent). Overall, the PPI prescription rate was 48.7%, 1.5%, and 49.8% for low daily dose (LDD), standard daily dose (SDD), and high daily dose (HDD), respectively. HDDs were mainly used from 2013 to 2016 (2013: 67.2%; 2014: 79.1%; 2015: 93.4%; 2016: 88.6%). From 2017, HDDs prescriptions decreased, with an increase in LDDs (2017: 75.1%, 2018: 81%; 2019: 68.9%; 2020: 83.3%).

Effectiveness of first-line empirical regimens

The analysis of the effectiveness of all regimens evaluated is reported in Table 3. Among the 7-day therapies, data was available for the PPI-A-C and PPI-A-L only. The eradication rate of the PPI-A-C was of

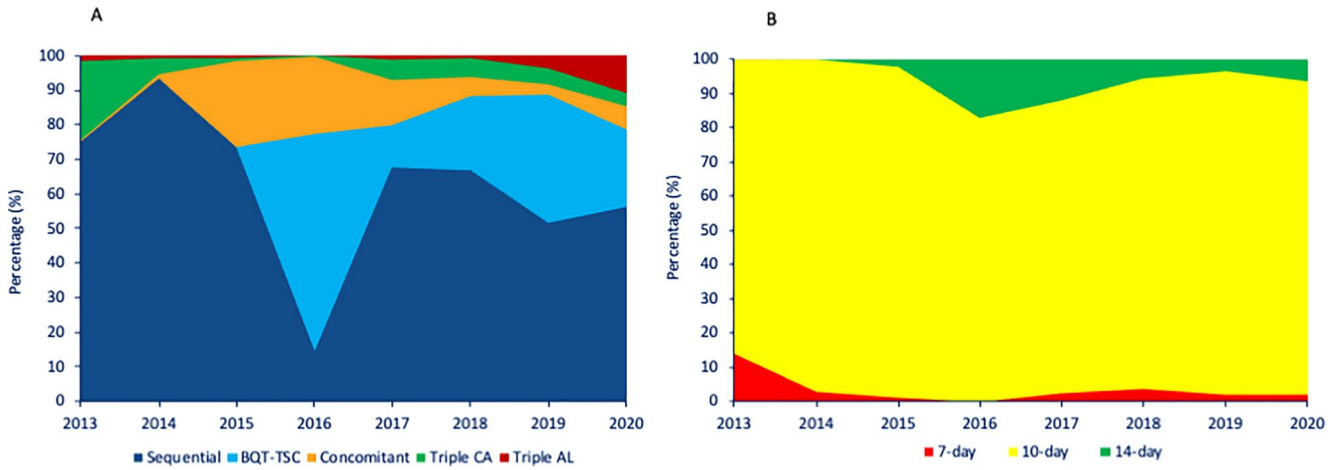

FIGURE 1 Evolution of first-line treatments between 2013 and 2020. (a) Trends in the prescriptions of the five most frequently used first-line treatments. (b) Trends in the duration of the five most frequently first-line treatments prescribed

TABLE 3 Effectiveness of first-line empirical treatments in patients not allergic to penicillin enroled in the Italian centres participating to the Hp-EuReg

		ITT		mITT		PP	
First-line treatment	**Length (days)**	***N***	**% (95% CI)**	***N***	**% (95% CI)**	***N***	**% (95% CI)**
Sequential (PPI + C-A-T/M)	10	1643	81.9 (79.9–83.7)	1495	91.4 (89.8–92.7)	1482	91.8% (90.3–93.1)
	14	1	100 (20.7–100)	1	100 (20.7–100)	1	100 (20.7–100)
BQT-TSC[a]	10	528	87.1 (84.0–89.7)	496	94.6 (92.2–96.2)	480	96.5 (94.4–97.8)
Concomitant (PPI + C-A-M/T)	10	108	87.0 (79.4–92.1)	102	92.2 (85.3–96.9)	98	94.9 (88.6–97.8)
	14	153	93.5 (88.4–96.4)	168	95.2 (90.9–97.6)	165	97.0 (93.1–98.7)
Triple PPI-C-A	7	75	77.3% (66.7–85.3)	69	84.1% (73.7–90.9)	67	85.1 (74.7–91.7)
	10	68	61.8 (49.9–72.4)	53	83.0 (70.8–90.8)	51	84.3 (72.0–91.8)
	14	5	100 (56.6–100)	5	100 (56.6–100)	5	100 (56.6–100)
Triple PPI-A-L	7	1	0 (0–79.3)	1	0 (0–79.3)	1	0 (0–79.3)
	10	42	81.0 (66.7–90.0)	50	86.0 (73.8–93.0)	48	87.5 (75.3–94.1)
	14	1	100 (20.7–100)	1	100 (20.7–100)	1	100 (20.7–100)

Abbreviations: 95% CI, 95% confidence interval; A, amoxicillin; C, clarithromycin; ITT, intention-to-treat analysis; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat analysis; N: total number of patients treated; PP, per-protocol analysis; PPI, proton pump inhibitor; T, tinidazole.

[a]Bismuth quadruple therapy with three-in-one-single capsule.

84.1% (95% CI: 73.7–90.9), while the PPI-A-L was prescribed in one patient only. For the 10-day therapies, only BQT-TSC, CT, and ST reached an eradication rate ≥90%.

Finally, regarding 14-day therapies, the CT reached an effectiveness >90%, whilst PPI-A-C, PPI-A-L, and ST were prescribed in very few patients (range: 1–5).

Effectiveness evaluating the daily PPI dose (milligrams of omeprazole equivalent)

The analysis of the effectiveness according to the daily dose of PPI was possible for three regimens only, and is fully reported in Table S1. Among patients treated with the 10-day ST, LDDs and HDDs were prescribed in 56.3% and 42.7% of cases, respectively. Patients prescribed HDDs reported an eradication rate of ≥94%, significantly higher than those prescribed LDDs ($p = 0.001$).

Among patients treated with the 10-day BQT-TSC, 28.5% and 69.8% of cases received an LDD and an HDD, respectively: no significant differences in effectiveness were found between the two different dosages ($p = 0.288$).

Over 90% of patients treated with 10- or 14-day CT received HDDs, not making therefore possible the comparison with those who received LDDs. The eradication rate using the DDs was 94.8% (95% CI: 88.4–97) with the 10-day CT, and 97% (95% CI: 93.1–98.7) with the 14-day CT.

Safety in first-line empirical treatment

The overall incidence of AEs was 23.1% (95% CI: 21.6–24.7; Table S2). The AEs of 10-day ST were significantly lower than those observed with the 10-day BQT-TSC (difference: 11.8%; 95% CI: 7.4–16.4; $p < 0.001$), and with the 10-day CT (difference: 8.2%; 95% CI: 2.7–14.2; $p = 0.002$, Table S3). No difference was found between the BQT-TSC and the CT ($p = 0.304$). Finally, it was not possible to evaluate the safety of the 14-day CT due to missing records.

SECOND-LINE REGIMENS

Therapeutic regimens empirically prescribed in second-line

The five most frequently prescribed second-line regimens are shown in Table 2.

Evolution of second-line prescriptions

Figure 2a shows the trend of prescriptions during 2013–2020 for the regimens considered. Two patterns of prescription were identified. When the period 2013–2015 was evaluated, the PPI-A-L was the most frequent treatment used (41%), followed by the triple therapy with PPI, amoxicillin and rifabutin (PPI-A-R)[25] (27%), ST (20%), and CT (12%). On the other hand, when the period 2016–2020 was considered, the BQT-TSC was the first most adopted regimen (46%), followed by the PPI-A-L (32%), PPI-A-R (15%), and ST (7%), whilst CT had no prescription.

Figure 2b depicts the trends in treatment duration: overall, 10-day therapies were used in ≥95% of cases, 14- day therapies in 3.6% of cases (range: 0% in 2013%–13.9% in 2020), and 7-day therapies in only 1.1%.

Figure S1B shows the trends of utilisation concerning the daily dose of PPI (milligrams of omeprazole equivalent). Overall, the prescription rate was 47.8%, 3.6%, and 48.6% for LDDs, SDDs, and HDDs, respectively. HDDs were mainly used from 2013 to 2016 (2013: 68.9%; 2014: 75.9%; 2015: 89.0%; 2016: 66.2%). From 2017, the use of HDDs decreased, with a corresponding increase for LDDs (2018: 89.4%, 2018: 70.8%; 2019: 72.4%; 2020: 75%).

Effectiveness of second-line empirical regimens

The complete analysis of the effectiveness of all regimens evaluated is reported in Table 4. Among the 7-day therapies, there was no data for ST and CT, whilst PPI-A-L and BQT-TSC were prescribed in one and two patients only, respectively.

Considering the 10-day therapies, the eradication rate was 91.9% (95% CI: 86.5–95.3), and 84.8 (95% CI: 78.6–89.5) for the BQT-TSC and the PPI-A-L respectively. ST and CT achieved an eradication rate of <80%.

For the 14-day therapies, no data was available for the CT, whilst PPI-A-L, BQT-TSC, and ST were prescribed in very few patients (range: 1–6).

Finally, for the PPI-A-R, it was not possible to perform a stratification by the treatment duration as data were unavailable. However, the overall eradication rate was 85.2% (95% CI: 77.3–90.7).

Effectiveness of evaluating the daily PPI dose (milligrams of omeprazole equivalent)

The analysis of the effectiveness according to the daily dose of PPI was possible only for the 10-day PPI-A-L: LDDs and HDDs were used in 56% and 39% of cases, respectively (Table S1). The eradication rate was higher (89.6%) with HDDs when compared to LDDs (80.2%), although the difference was not statistically significant ($p = 0.091$).

Safety in second-line empirical regimens

The overall incidence of AEs was 23.3% (95% CI: 20.3–26.6; Table S2), and AEs reported with 10-day PPI-A-L were significantly

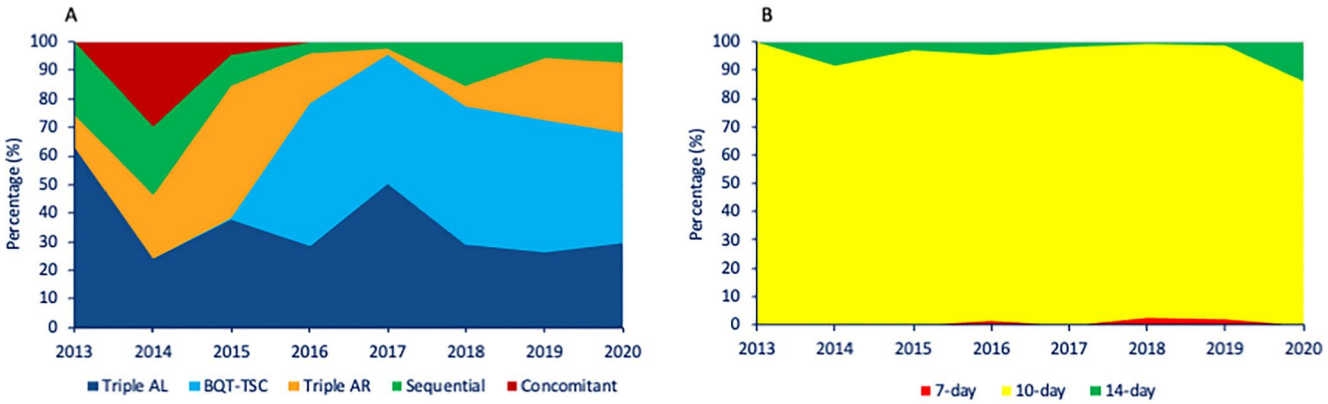

FIGURE 2 Evolution of second-line treatments between 2013 and 2020. (a) Trends in the prescriptions of the five most frequently used second-line treatments. (b) Trends in the duration of the five most frequently second-line treatments prescribed

TABLE 4 Effectiveness of second-line empirical treatments in patients not allergic to penicillin enroled in the Italian centres participating to the Hp-EuReg

		ITT		mITT		PP	
Second-line treatment	**Length (days)**	***N***	**% (95% CI)**	***N***	**% (95% CI)**	***N***	**% (95% CI)**
Triple PPI-A-L	7	2	100 (34.2–100)	2	100 (34.2–100)	2	100 (34.2–100)
	10	188	74.5 (67.8–80.2)	165	84.8 (78.6–89.5)	165	84.8 (78.6–89.5)
	14	6	100 (61.0–100)	6	100 (61.0–100)	6	100 (61.0–100)
BQT-TSC[a]	7	1	0 (0.0–79.3)	1	0 (0.0–79.3)	1	0 (0.0–79.3)
	10	159	83.6 (77.1–86.6)	149	91.9 (86.5–95.3)	147	92.5 (87.1–95.8)
	14	1	100 (20.7–100)	1	100 (20.7–100)	1	100 (20.7–100)
Triple PPI-A-R	NA	122	73.8 (65.3–80.8)	108	85.2 (77.3–90.7)	106	85.8 (78.0–91.2)
Sequential (PPI + C-A-T/M)	10	66	71.2 (59.4–80.7)	61	78.7 (66.9–87.1)	70	78.3 (66.4–86.9)
	14	1	100 (20.7–100)	1	100 (20.7–100)	1	100 (20.7–100)
Concomitant (PPI + C-A-M/T)	10	26	69.2 (50.0–83.5)	25	72 (52.4–85.7)	25	72 (52.4–85.7)

Abbreviations: 95% CI, 95% confidence interval; A, amoxicillin; C, clarithromycin; ITT, intention-to-treat analysis; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat analysis; N, total number of patients treated; NA, not available; PP, per-protocol analysis; PPI, proton pump inhibitor; R, rifabutin; T, tinidazole.

[a]Bismuth quadruple therapy with three-in-one-single capsule.

lower than those observed with the 10-day BQT-TSC (difference: 16.7%; 95% CI: 7.2–26.0; $p < 0.001$; Table S3).

DISCUSSION

This study found that ST, BQT-TSC, and CT lasting ≥10 days were empirically prescribed in over 87% of naïve patients. These prescriptions mostly mirror the indications of Italian and international guidelines available during the years evaluated (i.e., from 2013 to February 2021).[7,26] According to the mITT analysis, the four quadruple regimens lasting 10 days provided a *good* eradication rate, while the 14-day CT reached an *excellent* effectiveness.[6] Indeed, the updated Italian and European guidelines, recently published in 2022, recommended that the duration of CT has to be 14 days.[12,27] The eradication rates found in our study were also comparable to those reported in a review evaluating the effectiveness of empirical first lines in Italy, suggesting the reproducibility of our results.[28] Similarly, a Hp-EuReg study performed over 21,000 treatment-naïve patients encompassing 27 European countries and assessing the prescriptions and effectiveness trends of first-line empirical therapy reported that only quadruple therapies lasting at least 10 days were able to achieve over 90% eradication rates, in line with current study results.[17] Furthermore, a similar Hp-EuReg sub-study focussing on the Spanish cohort, found that the highest first-line effectiveness outcomes were obtained with the 10-day BQT-TSC (95% cure rate by intention-to-treat), with the 14-day bismuth-clarithromycin quadruple therapy (PPI-bismuth-clarithromycin-amoxicillin: 91%) and the 14-day non-bismuth CT therapy (PPI-clarithromycin-amoxicillin-metronidazole: 92%), findings that were also in line with present study conclusions.[29] In our study, only a small percentage of physicians prescribed the triple therapy for 14 days, despite the recommendation given by the national and European guidelines.[10,26] This lack of adherence to guidelines might be due to the common practice of prescribing triple therapy for 7 or 10 days.

The second-line regimens used in our study mostly also reflect the Italian and international recommendations existing during those years.[7,26] Even in this case, the effectiveness found was somewhat comparable to that reported in a study assessing the performance of empirically rescue treatments in Italy.[30] Also, an Hp-EuReg study performed on 5000 cases evaluating second-line empirical therapy stated that regimens including 14-day quinolone triple therapies, 14-day levofloxacin–bismuth quadruple therapy, 14-day classic BQT, and 10-day BQT-TSC, provided optimal effectiveness; the latter supporting current study results.[31] Furthermore, in the Hp-EuReg sub-study previously mentioned, second-line therapy provided the highest cure rates with the 14-day triple quinolone (PPI-amoxicillin-levofloxacin/moxifloxacin, 92% and 89%, respectively), the 14-day bismuth-levofloxacin quadruple schemes (PPI-bismuth-levofloxacin-amoxicillin: 90%), and the 10-day BQT-TSC (88.5%), this latter regimen supporting as well current study findings.[29]

We found that triple therapy with rifabutin was prescribed in almost 20% of patients as empiric second-line therapy. Previous and recent guidelines do not recommend this treatment as second-line but as third- or fourth-line.[7,12,26,27] Rifabutin displays several characteristics that make it eligible for eradicating *H. pylori*,[8,25,32] but recommendations raise some concerns about its use.[7,30]

The evaluation of the trends of prescriptions of the daily dose of PPI used with the first- and second-line regimens showed that HDDs were mainly used from 2013 to 2016, whilst LDDs from 2017 to 2020. LDDs were frequently used in our study, and we are unaware of the reasons for this lack of adherence to the guidelines. Our study was observational and, therefore, not designed to catch the rationale behind the physicians' prescriptions. It would be worth highlighting as Maastricht VI emphasised that the use of high-dose PPI twice daily increases the efficacy of triple therapy,[12]. However, they also stated that it was unclear whether high-dose PPI twice daily could improve the efficacy of quadruple therapies.[12]

Among the first-line regimens, it was found that 10-day ST used with an HDD significantly improved its effectiveness. This finding was consistent with the overall results reported from the Hp-EuReg study for the ST,[17] and corroborates the results of a meta-analysis assessing the efficacy of esomeprazole or rabeprazole versus first-generation PPIs, where only therapies using esomeprazole 40 mg bid had significantly higher eradication rates compared to first-generation PPIs.[33] On the contrary, we found that the effectiveness of the BQT-TSC was not affected by the HDDs, being the results, even in this case, consistent with the general results reported from the Hp-EuReg study for this regimen.[33]

Evaluating the second-line regimens, only data concerning the 10-day PPI-A-L could be assessed, reporting no significant statistical differences between HDDs and LDDs, even if there was a clear trend in favour of HDDs. Conversely, no significant difference in effectiveness was found between LDDs and HDDs with the 10-day BQT-TSC.

Our study reported an overall incidence of AEs of 23.1% and 23.3% for the first- and second-line regimens, respectively. These findings were not different from those reported in the pioneering RCTs of the different treatments evaluated.[22–24,34] However, in our study, the BQT-TSC had the highest incidence of AEs when used as a first- or second-line regimen.

Having a regimen able to reach an eradication rate ≥95% is not an easy goal to achieve in daily clinical practice, as resistance to antimicrobials remains the most critical factor.[35] Susceptibility testing might ideally determine no eradication failure by tailoring the therapy for each patient. Nonetheless, a recent comprehensive review of this topic concluded that the evidence is too limited to support the generalised use of susceptibility-guided therapy in routine clinical practice, either as first-line or rescue treatment.[36]

When considering the results of this study, some limitations should be acknowledged. Firstly, this was not a RCT, and the comparison of effectiveness among different regimens should be prudent due to the likely presence of unidentified biases.

Secondly, the number of recruiting centres was low ($n = 9$), and they were mainly in tertiary care. It might be possible that different results could have been found if general practitioners and secondary care centres were also included.

Thirdly, as one of the aims of the Hp-EuReg was to evaluate the European gastroenterologists in their real clinical practice, implying registering as many regimens as possible, this increased the heterogeneity, but sometimes reduced the amount of data obtainable for each treatment, limiting, therefore, the analysis and the interpretation of results.[17]

Due to the increasing use of antibiotics worldwide,[37] the World Health Organization and the European Union Council both advocated cautious use of antibiotics to avoid the increase of bacterial resistance,[38] as if strategies to improve their use are not put in place, it will be increasingly difficult to treat infectious diseases in the future.[37] This applies to *H. pylori* infection too. Indeed, it would be epidemiological desirable to perform regular monitoring of primary resistance on a regional/local basis within each country to assist physicians in choosing the optimal eradication regimen.[39]

In conclusion, the Hp-EuReg focussed on the Italian setting found that, among the first-line empirical regimens, only BQT-TSC, CT, and ST, all lasting ≥10 days, had a good or excellent eradication rate. Among the second-line empirical regimens, only 10-day BQT-TSC achieved an effectiveness ≥90%. We also found that HDDs might significantly increase the effectiveness of some therapies (e.g., 10-day ST). Finally, it would be useful to periodically perform studies like this to obtain information on adherence to the national and international guidelines as well as on old and new regimens used.

AUTHOR CONTRIBUTIONS

Luigi Gatta, Dino Vaira, Antonio Gasbarrini, Olga P. Nyssen, and Javier P. Gisbert initiated and led the development of the manuscript with the active input of all the authors mentioned above. Olga P. Nyssen, Hp-EuReg Scientific Director, also performed the data extraction, the monitoring and the quality check, analysed the data, reviewed the manuscript draft, and approved the submitted manuscript. Dino Vaira, Giulia Fiorini, Ilaria Maria Saracino, Matteo Pavoni, Marco Romano, Antonietta Gerarda Gravina, Lucia Granata, Rinaldo Pellicano, Alfredo Di Leo, Giuseppe Losurdo, Francesco Franceschi, Gerardo Nardone, Alba Rocco, Maria Pina Dore, Fabio Farinati and Matteo Ghisa acquired data, critically reviewed the manuscript draft and approved the submitted manuscript; Massimo Bellini, John Holton, and Claudio Borghi critically reviewed the manuscript draft and approved the submitted manuscript. Colm O'Morain, Francis Mégraud, Olga P. Nyssen and Ignasi Puig, as Members of the Hp-EuReg Scientific Committee, assisted with data interpretation, critically reviewed the manuscript's drafts, and approved the submitted manuscript. Javier P. Gisbert, Principal investigator, directed the project, obtained funding, designed the protocol and planned the study, analysed and interpreted the data, recruited patients, critically reviewed the manuscript drafts, and approved the final submitted manuscript.

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CONFLICT OF INTEREST

Olga P. Nyssen received research funding from Mayoly and Allergan; Antonio Gasbarrini served as consultant for Abbvie, Actial, Alpha-Sigma, Eisai, Gilead, Malesci, Maria Pina Dore, Sanofi, Takeda; Alfredo Di Leo served as a consultant for THD SpA; Gerardo Nardone received research grant from Sofar S.p.a and Alfasigma; Francis Mégraud received research grant from Allergan, bioMerieux, Mobidiag (to the institution), and as speaker from Biocodex and Mayoly; Claudio Borghi served as served as speaker, consultant, and advisory member for Servier, Novo-Nordisk, Astra-Zeneca, Sanofi; Javier P. Gisbert served as speaker, consultant, and advisory member for or received research funding from Mayoly, Allergan, Diasorin, Gebro Pharma, and Richen. All the remaining Authors have nothing to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the privacy/ethical restrictions corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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