Clinical Gastroenterology and Hepatology 2022;20:2243–2257

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Empirical Second-Line Therapy in 5000 Patients of the European Registry on *Helicobacter pylori* Management (Hp-EuReg)

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Abbreviations used in this paper: **Hp-EuReg, European Registry on *Helicobacter pylori* Management; mITT, modified intention-to-treat; OR, odds ratio; PPI, proton pump inhibitor.**

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2021.12.025

Most current article

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e1537. Upon completion of this CME activity, successful learners will be able to identify the best empirical second-line treatment option for eradication of *Helicobacter pylori* infection, as well as their safety profile, as part of the results' experience of the European Registry on the management of *H. pylori* (Hp-EuReg).

BACKGROUND & AIMS: **After a first *Helicobacter pylori* eradication attempt, approximately 20% of patients will remain infected. The aim of the current study was to assess the effectiveness and safety of second-line empiric treatment in Europe.**

METHODS: **This international, multicenter, prospective, non-interventional registry aimed to evaluate the decisions and outcomes of *H pylori* management by European gastroenterologists. All infected adult cases with a previous eradication treatment attempt were registered with the Spanish Association of Gastroenterology–Research Electronic Data Capture until February 2021. Patients allergic to penicillin and those who received susceptibility-guided therapy were excluded. Data monitoring was performed to ensure data quality.**

RESULTS: **Overall, 5055 patients received empiric second-line treatment. Triple therapy with amoxicillin and levofloxacin was prescribed most commonly (33%). The overall effectiveness was 82% by modified intention-to-treat analysis and 83% in the per-protocol population. After failure of first-line clarithromycin-containing treatment, optimal eradication (>90%) was obtained with moxifloxacin-containing triple therapy or levofloxacin-containing quadruple therapy (with bismuth). In patients receiving triple therapy containing levofloxacin or moxifloxacin, and levofloxacin–bismuth quadruple treatment, cure rates were optimized with 14-day regimens using high doses of proton pump inhibitors. However, 3-in-1 single capsule or levofloxacin–bismuth quadruple therapy produced reliable eradication rates regardless of proton pump inhibitor dose, duration of therapy, or previous first-line treatment. The overall incidence of adverse events was 28%, and most (85%) were mild. Three patients developed serious adverse events (0.3%) requiring hospitalization.**

CONCLUSIONS: **Empiric second-line regimens including 14-day quinolone triple therapies, 14-day levofloxacin–bismuth quadruple therapy, 14-day tetracycline–bismuth classic quadruple therapy, and 10-day bismuth quadruple therapy (as a single capsule) provided optimal effectiveness. However, many other second-line treatments evaluated reported low eradication rates. ClincialTrials.gov number: NCT02328131.**

Keywords: Bismuth; *Helicobacter pylori*; Clarithromycin; Levofloxacin; Rescue.

Helicobacter pylori infection affects more than 50% of the population worldwide and represents a significant health burden. This infection is the leading cause of gastritis, peptic ulcer disease, and gastric cancer. However, although the bacterium was discovered in 1982, the optimal eradication treatment remains undefined.[1]

The most commonly used first-line therapy contains a proton pump inhibitor (PPI) plus 2 antibiotics (usually amoxicillin and clarithromycin or metronidazole), but this regimen fails to eradicate the bacteria in at least 20% to 30% of cases.[2] Alternative regimens, such as bismuth-containing quadruple therapies (PPI, bismuth,

tetracycline, and metronidazole) or nonbismuth quadruple regimens (PPI, clarithromycin, amoxicillin, and metronidazole administered either sequentially or concomitantly) are more effective,[3,4] and generally recommended as first-line therapies when resistance to clarithromycin is greater than 15%, which is currently the case in most European countries.[5] However, even after these quadruple regimens, a considerable number of patients will have persistent *H pylori* infection.

A major reason for treatment failure is acquired antibiotic resistance, and the rate of resistance to clarithromycin or quinolones has been increasing gradually in many parts of the world.[5] Bacterial strains surviving an eradication attempt become less susceptible to subsequent therapies either through the selection of resistant bacteria or the acquisition of de novo resistance.[6] As a result, the choice of a correct rescue treatment depends largely on the previous exposure to antibiotics, especially those used in previous *H pylori* eradications attempts.[2]

Ideally, the choice of second-line treatment would be guided by the results of antimicrobial susceptibility testing, but culture generally is unavailable in routine clinical practice.[7] Moreover, access to the optimal eradication strategy based on culture and susceptibility testing also may be hampered by the need for endoscopy, higher costs, or the time required for testing and culture.[8] Thus, there is a need to optimize empiric treatment.[9]

Currently, there is no optimal strategy to cure *H pylori* infection in clinical practice, and available data, mainly for rescue therapies, often come from small studies with a limited number of patients in specific geographic locations. To address these gaps, the European Registry on *Helicobacter pylori* Management (Hp-EuReg) was designed to collect information on the real-world clinical practice among 30 European countries.[10] The philosophy of the project was to audit patient outcomes, compare current treatments with those recommended in current guidelines, detect room for improvement, and subsequently change routine clinical practice. Thus, the registry represents a valuable overview of current *H pylori* management, allowing continuous assessment for improvement through observation of treatment evolution.

The present study was a subanalysis of this large-scale international multicenter prospective registry that aimed to assess the prescription patterns, effectiveness, and safety of empiric second-line rescue therapies used in the management of *H pylori* in Europe.

Methods

The Hp-EuReg is an international, multicenter, prospective, noninterventional registry recording information about *H pylori* infection management since 2013. Detailed information on the data collection, data management,[11-13] effectiveness, safety, and compliance analyses are reported in the published protocol,[10] and are summarized in Supplementary File 2.

What You Need to Know

Background

There is still no optimal strategy to cure *Helicobacter pylori* infection in clinical practice, and first-line eradication treatment fails in approximately 20% of cases. Currently, rescue treatment strategies are the focus in overcoming this health burden.

Findings

Optimal effectiveness was reported with empiric 14-day quinolone (levofloxacin and moxifloxacin) triple therapies, 14-day levofloxacin–bismuth quadruple therapy, 14-day tetracycline–bismuth standard quadruple therapy, and 10-day bismuth quadruple therapy (as a single capsule).

Implications for patient care

The results of this study indicate that the overall effectiveness of empiric second-line *H pylori* eradication regimens was, in general, suboptimal (<90%). New therapeutic strategies should be explored by European gastroenterologists.

The principal effectiveness analysis taken into account in the current study was a modified intention-to-treat (mITT) analysis that aimed to reflect the most accurate results of the clinical practice. The mITT included all patients who had completed follow-up evaluation (ie, a confirmatory test—success or failure—available after treatment), regardless of compliance.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Baseline Characteristics

Overall, 41,562 patients were registered until February 2021. Of these, 5932 had received a second-line rescue therapy, and 5055 cases (12%) from 27 countries (Supplementary Table 1) were treated empirically and included in the present analysis (Figure 1). Further information is presented in Supplementary File 3.

Most Frequent Prescriptions in Second-Line Therapy

In total, 87 second-line treatments were registered (Supplementary Table 2); however, only the most frequent ones were analyzed: PPI+amoxicillin+levofloxacin (33%), PPI+bismuth+metronidazole+tinidazole as a single capsule (17%), and PPI+amoxicillin+levofloxacin+bismuth (13%) (Table 1). These therapies were prescribed (ie, in 78% of cases) mostly after the failure of a clarithromycin-containing

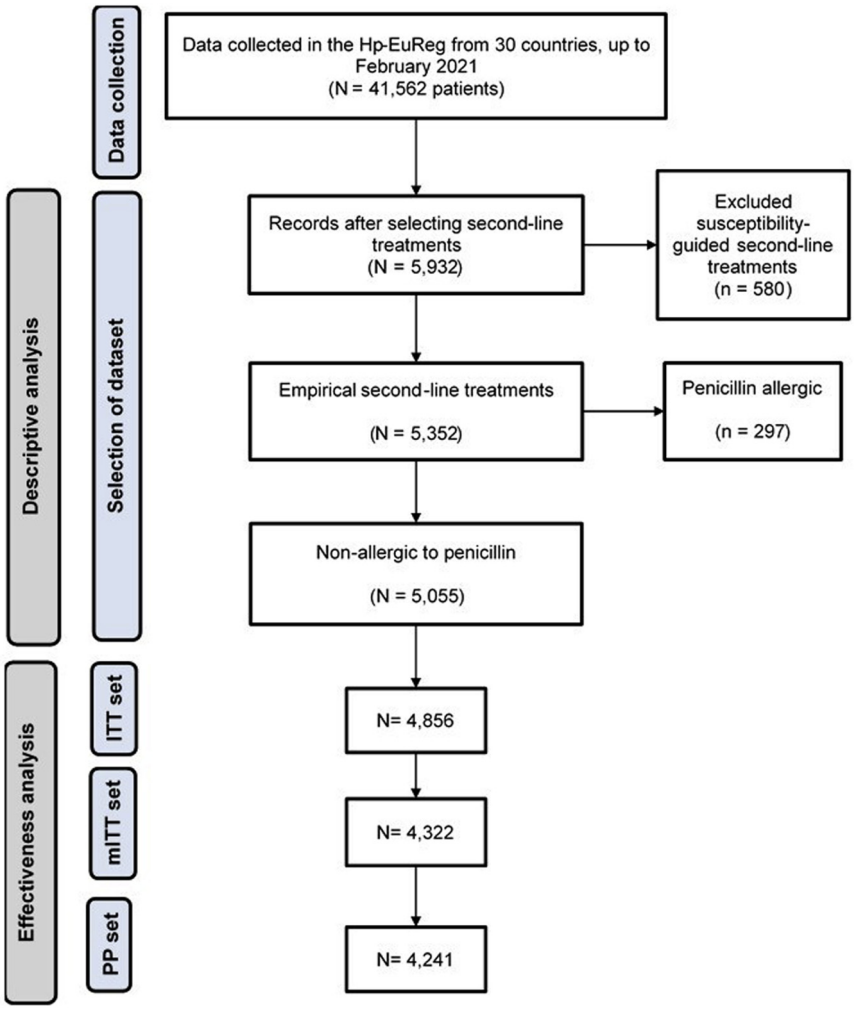

Figure 1. Study flow chart. Hp-EuReg, European Registry on *Helicobacter pylori* Management; mITT, modified intention-to-treat; PP, per protocol.

first-line regimen. The other usual antibiotics used in first-line treatment, such as amoxicillin or metronidazole, were used in 79% and 24% of the rescue therapy cases, respectively.

Evolution of Second-Line Treatment During the Study Period

A decrease in the use of triple regimens was observed in the period from 2013 to 2020: PPI+amoxicillin+levofloxacin decreased from 57% to 21%; PPI+amoxicillin+moxifloxacin was prescribed mainly between 2013 and 2016, but was not used in the past 4 years. In addition, the PPI+clarithromycin+amoxicillin standard triple therapy decreased from 12% to 9%. On the other hand, the PPI+bismuth+metronidazole+tinidazole in the standard form decreased from 9% to 6%, whereas the single-capsule therapy version increased from 0% in 2013 to 51% in 2018, and decreased again to 37% in 2020. Similarly, PPI+amoxicillin+levofloxacin+bismuth increased from 0.6% in 2013 to 20% in the 2015–2016 period, but decreased to 14% in 2017 and increased again up to 26% in 2020 (Figure 2).

A progressive increase in the duration of treatments also was noted from a mean (±SD) of 10.8 (±2.2) days in 2013, to 12.2 (±2.3) days in 2020. In addition, the use of longer treatment durations (14 days) increased from 29% in 2013 to 55% in 2020. Likewise, the highest potency of acid inhibition varied over time from an omeprazole mean (±SD) dose equivalent of 35 mg (±21 mg) in 2013 to 41 mg (±21.3 mg) in 2020; and the use of high-dose PPIs increased from 29% to 43%.

Effectiveness of Second-Line Treatment

The overall effectiveness of empiric second-line therapy was reported as 84% (95% CI, 82%–84%) by mITT. Optimal effectiveness was reached with PPI+amoxicillin+moxifloxacin (91%) and with PPI+bismuth+metronidazole+tinidazole as a single capsule (90%). PPI+amoxicillin+levofloxacin+bismuth and PPI+clarithromycin+amoxicillin+bismuth also achieved cure rates (88% and 87%, respectively) near the desired optimal threshold of 90% (Table 2).

In addition, the analysis of the evolution of the effectiveness showed that cure rates with

PPI+amoxicillin+moxifloxacin constantly remained greater than 90%. The same was true for PPI+bismuth+metronidazole+tinidazole, except in 2015, when the eradication rate was reported as 80% (only 20 patients treated) (Figure 2).

Table 1. Baseline Characteristics of Patients Receiving *H pylori* Second-Line Empiric Treatments

	N = 5055
Mean age, *y* (SD)	50 (15)
Sex, n (%)	
Female	3221 (64)
Indication, n (%)	
Dyspepsia	4184 (83)
Ulcer disease	861 (17)
Unknown	10 (0.2)
Diagnostic method, n (%)	
Noninvasive	2645 (52)
Invasive (required endoscopy)	2410 (48)
Treatment length, n (%)	
7 days	224 (4)
10 days	2648 (53)
14 days	2063 (41)
Unknown	120 (2)
Proton pump inhibitor dose, n (%)	
Low	1707 (34)
Standard	1106 (22)
High	2106 (42)
Unknown	136 (3)
Compliance, n (%)	
No, <90% drug intake	143 (3)
Yes, ≥90% drug intake	4548 (90)
Unknown	364 (7)
Most frequent first-line regimens, n (%)	
Triple therapy	3395 (67)
Conc (nonbismuth quadruple)	637 (13)
Bismuth quadruple	367 (7.3)
Seq (nonbismuth quadruple)	197 (3.9)
Single capsule[a]	162 (3.2)
Other	105 (2.1)
Dual therapy	123 (2.4)
Hybrid therapy (nonbismuth quadruple)	23 (0.5)
Unknown	46 (0.9)
Most frequent first-line antibiotics, n (%)	
Amoxicillin	3984 (79)
Clarithromycin	3936 (78)
Metronidazole	1200 (24)
Bismuth	506 (10)
Tetracycline	189 (3.7)
Levofloxacin	102 (2)
Most frequent second-line treatments, n (%)	
PPI+A+L	1631 (33)
PPI+single capsule[a]	820 (17)
PPI+A+L+B	648 (13)
PPI+C+A	350 (7.2)
PPI+C+A+B	257 (5.3)
PPI+C+A+M	227 (4.6)
PPI+M+Tc+B	221 (4.5)
PPI+A+Mx	143 (2.9)
PPI+A+M	103 (2.1)
PPI+C+M	38 (0.8)
Seq-PPI+C+A+T	32 (0.7)
Quadruple-A+M+B	30 (0.6)
Other	<30 (<0.6)

NOTE. Low-dose PPI consisted of 4.5 to 27 mg omeprazole equivalents twice daily (ie, 20 mg omeprazole equivalents twice daily), standard-dose PPI consisted of 32 to 40 mg omeprazole equivalents twice daily (ie, 40 mg omeprazole equivalents twice daily), high-dose PPI consisted of 54 to 128 mg omeprazole equivalents twice daily (ie, 60 mg omeprazole equivalents twice daily).
A, amoxicillin; B, bismuth; C, clarithromycin; Conc, concomitant administration; L, levofloxacin; M, metronidazole; Mx, moxifloxacin; PPI, proton pump inhibitor; SD, standard deviation; Seq, sequential administration; T, tinidazole; Tc, tetracycline.
[a]Three-in-1 single capsule containing bismuth, tetracycline, and metronidazole.

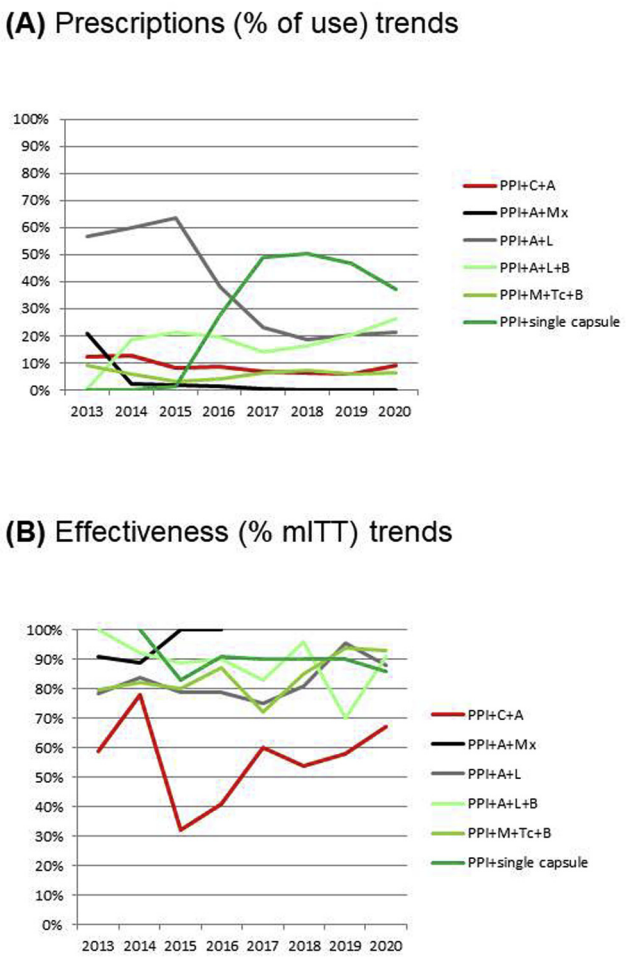

Figure 2. Evolution in (*A*) prescriptions and (B) effectiveness (mITT) of most common second-line treatments from 2013 to 2020. A, amoxicillin; B, bismuth; C, clarithromycin; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; Mx, moxifloxacin; PPI, proton pump inhibitor; Tc, tetracycline.

Table 2. Effectiveness, Safety, and Compliance of Common Empiric Second-Line Treatments

	Effectiveness, N (%)									
	ITT		mITT		PP		Adverse events		Compliance ≥90%	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
Triple regimens										
PPI+A+L	1594 (72)	70–74	1441 (81)	79–83	1421 (81)	79–83	1492 (22)	20–24	1483 (98)	97–99
PPI+C+A	332 (43)	38–48	250 (57)	51–63	244 (57)	50–63	332 (41)	36–47	332 (98)	96–100
PPI+A+Mx	141 (86)	80–92	135 (91)	86–96	135 (91)	86–96	141 (19)	12–26	140 (99)	95–100
PPI+A+M	96 (50)	39–60	87 (59)	48–69	87 (59)	48–69	94 (8.5)	2–15	93 (98)	93–100
PPI+A+Rf	29 (62)	43–81	23 (78)	56–92	23 (78)	56–92	28 (18)	6–37	28 (82)	63–94
PPI+C+L	12 (75)	43–94	10 (90)	55–99	10 (90)	55–99	12 (17)	2–12	12 (100)	74–100
Quadruple regimens										
PPI+single capsule[a]	781 (83)	80–86	750 (90)	88–92	738 (90)	88–92	780 (31)	28–34	780 (97)	96–98
PPI+A+L+B	606 (80)	77–83	560 (88)	86–91	543 (89)	86–91	569 (30)	26–33.5	12 (92)	62–100
PPI+M+Tc+B	217 (72)	66–78	192 (83)	77–88	185 (84)	79–90	221 (37)	30.5–44	212 (95)	92–99
PPI+C+A+B	243 (51)	44–57	154 (87)	81–93	149 (87)	81–93	244 (49)	42–55	248 (95)	92–98
Conc-PPI+C+A+M	217 (79)	74–85	213 (82)	77–87	208 (83)	77–88	222 (30)	24–36	220 (96)	94–99
Seq-PPI+C+A+T	32 (59)	41–78	29 (65.5)	46–84	29 (65.5)	46–84	32 (22)	6–38	31 (93.5)	79–99
Overall effectiveness										
All second-line treatments	4856 (73)	72–74	4322 (84)	82–84	4241 (84)	83–85	4559 (28)	27–29	4535 (97)	(96–97.5)
Nonevaluable cases, n	199 (4)	3.4–4.5	733 (14.5)	13–15	814 (16)	15–17	496 (10)	9–11	520 (10)	(9–11)

A, amoxicillin; B, bismuth; C, clarithromycin; CI, confidence interval; Conc, concomitant administration; ITT, intention-to-treat; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; Mx, moxifloxacin; PP, per-protocol; PPI, proton pump inhibitor; Rf, rifaximin; Seq, sequential administration; T, tinidazole; Tc, tetracycline.

[a]Single-capsule, 3-in-1 single capsule containing bismuth, tetracycline, and metronidazole.

Table 3. Effectiveness of Second-Line Therapy Stratified by First-Line Regimen

	ITT		mITT		PP	
Second-line treatments	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
After failure of clarithromycin-containing (triple or quadruple) first-line therapy						
Triple regimens						
PPI+A+L	1301 (73)	70–75	1186 (80.5)	78–83	1170 (81)	79–83
PPI+C+A	160 (16)	10–22	107 (24)	16–33	105 (24)	15–32
PPI+A+Mx	60 (84.5)	75–94	66 (91)	83–98	66 (91)	83–99
PPI+A+M	69 (51)	38–63	65 (57)	44–70	65 (60)	44–70
PPI+A+Rf	21 (71)	48–89	18 (83)	58–96	18 (83)	59–97
PPI+M+L	17 (65)	38–86	15 (73)	45–92	14 (71)	42–92
PPI+C+M	15 (67)	38–88	13 (77)	46–95	13 (77)	46–95
PPI+C+L	7 (100)	59–100	7 (100)	NA	7 (100)	59–100
Quadruple regimens						
PPI+single capsule[a]	631 (82)	79–85	609 (89)	86–91	598 (89)	87–92
PPI+A+L+B	465 (81)	77–85	432 (89)	86–92	416 (90)	86–92
PPI+M+Tc+B	116 (77)	69–85	110 (83)	75–90	106 (84)	76.5–91
PPI+C+A+B	87 (72)	62–82	78 (87)	79–95	76 (88)	80–97
Conc-PPI+C+A+M	120 (81)	73–88	121 (82)	74–89	120 (82)	74–89
Seq-PPI+C+A+T	25 (64)	43–85	23 (70)	47–87	23 (70)	47–87
Overall effectiveness of second-line regimens						
Overall	3302 (74.5)	73–76	3014 (83)	82–85	2959 (84)	82–85
Number of nonevaluable cases	234 (7)	6–7.5	522 (15)	14–16	577 (16)	16–17.5
After failure of bismuth-containing quadruple first-line therapy						
Triple regimens						
PPI+A+L	25 (60)	39–81	24 (67)	46–88	23 (65)	44–87
Quadruple regimens						
PPI+single capsule[a]	52 (88.5)	79–98	49 (94)	83–99	49 (93)	83–99
PPI+A+L+B	92 (77)	68–86	82 (88)	80–95	81 (89)	81–96
PPI+C+A+B	86 (31)	21–42	38 (76)	61–91	36 (75)	59–91
Conc-PPI+C+A+M	49 (80)	67–92	47 (85)	74–96	44 (89)	75–96
Overall effectiveness of second-line treatment						
Overall	349 (64)	59–69	275 (84)	79–88	267 (84)	80–88
Number of nonevaluable cases	30 (8)	5–11	104 (27)	23–32	112 (30)	25–34

NOTE. Statistically significant differences ($P < .001$) were obtained by the chi-square test when comparing the following schemes with and without bismuth: PPI+clarithromycin+amoxicillin vs PPI+clarithromycin+amoxicillin+bismuth and PPI+amoxicillin+levofloxacin vs PPI+amoxicillin+levofloxacin+bismuth. N shows the total number of patients receiving a treatment.

A, amoxicillin; B, bismuth; C, clarithromycin; CI, confidence interval; Conc, concomitant administration; ITT, intention-to-treat; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; Mx, moxifloxacin; PP, per-protocol; PPI, proton pump inhibitor; Rf, rifaximin; Seq, sequential administration; T, tinidazole; Tc, tetracycline.

[a]Single-capsule, 3-in-1 single capsule containing bismuth, tetracycline, and metronidazole.

Effectiveness After Failure of a Clarithromycin-Containing Regimen

After a clarithromycin-containing first-line treatment attempt, optimal rates of eradication were reported with PPI+amoxicillin+moxifloxacin (91%), PPI+amoxicillin+levofloxacin+bismuth (89%), and with 10-day PPI+bismuth+metronidazole+tinidazole as a single capsule (89%) (Table 3).

In the same scenario, further post hoc analyses were performed to compare the overall effectiveness in regimens with and without bismuth in the following 2 groups: PPI+clarithromycin+amoxicillin vs PPI+clarithromycin+amoxicillin+bismuth and PPI+amoxicillin+levofloxacin vs PPI+amoxicillin+levofloxacin+bismuth. Significant differences were reported between both of the treatment schemes for each comparison; in both cases obtaining a higher mITT effectiveness when bismuth was added: 24% vs 87%, $P < .001$; and 80% vs 89%, $P < .001$; respectively.

Suboptimal effectiveness (<90%) was observed with all 7-day regimens (triple or quadruple) and most of the 10-day triple regimens; the exception was 10-day PPI+amoxicillin+moxifloxacin, which achieved a cure rate of 100%. Therapy with 14-day PPI+amoxicillin+levofloxacin also reported optimal cure rates (91%). When bismuth was added to this same 14-day combination, the effectiveness remained optimal, but no increase was reported (90%) (Table 4 and Supplementary Table 3).

Almost all second-line treatments studied (ie, with available data) were more effective when high-dose PPIs were used, ranging in overall effectiveness from 89% to 100% (Table 4). In addition, treatment with PPI+amoxicillin+moxifloxacin, PPI+clarithromycin+

amoxicillin+bismuth, and PPI+bismuth+metronidazole+tinidazole (in the standard form) reported optimal cure rates with standard-dose PPIs (100%, 100%, and 90%, respectively). Treatment effectiveness with PPI+bismuth+metronidazole+tinidazole (a single capsule) was always optimal independently of the PPI dose or the regimen (triple or quadruple) used previously (Supplementary Table 4).

In addition, the effectiveness of PPI+amoxicillin+levofloxacin, PPI+amoxicillin+levofloxacin+bismuth, and PPI+clarithromycin+amoxicillin+metronidazole was higher (>90%) when prescribed for 14 days and with high-dose PPIs (Supplementary Table 5).

Effectiveness After Failure of a Bismuth-Containing Regimen

After a first-line, bismuth-containing, quadruple-therapy (PPI+bismuth+metronidazole+tinidazole) attempt, re-treatment with 10-day PPI+bismuth+metronidazole+tinidazole (a single capsule) or with 10-day PPI+clarithromycin+amoxicillin+bismuth both achieved 94% eradication (Tables 3 and 4). The reported effectiveness of 14-day PPI+amoxicillin+levofloxacin+bismuth also was high (87%).

Optimal eradication rates were obtained with both 10-day PPI+bismuth+metronidazole+tinidazole (a single capsule), regardless of the PPI dose, and with PPI+amoxicillin+clarithromycin+metronidazole when prescribed with high-dose PPIs, reporting cure rates of nearly 90% (Table 4). In addition, 10-day PPI+clarithromycin+amoxicillin+bismuth (with low-dose PPIs) and 14-day PPI+amoxicillin+levofloxacin+bismuth (with either low- or high-dose PPIs) both reached optimal effectiveness (Supplementary Table 6); no data were available for these regimens using standard-dose PPIs.

Multivariate Analysis

Compliance was the independent factor most closely associated with higher mITT eradication rate (odds ratio [OR], 3.01; 95% CI, 1.78–5.08). A significant association with higher effectiveness also was obtained in patients with peptic ulcer disease (compared with patients who had uninvestigated or functional dyspepsia) (OR, 1.28; 95% CI, 1.01–1.61; $P < .05$); in patients receiving 14-day regimens (OR, 2.84; 95% CI, 1.94–4.08; $P < .001$); and in patients receiving high-dose PPIs (OR, 2.21; 95% CI, 1.77–2.75; $P < .001$) (Table 5).

In addition, prescribing either triple therapy with quinolones (levofloxacin or moxifloxacin) or PPI+amoxicillin+levofloxacin+bismuth quadruple therapy was associated with a higher mITT eradication rate; moreover, a higher association was found when PPI+bismuth+metronidazole+tinidazole (either in the standard form or with a single capsule) was used (OR, 6.30; 95% CI, 4.41–8.95; $P < .001$). In addition, we observed that any treatment choice (from those included in the category of other) except PPI+clarithromycin+amoxicillin also was preferable as second-line therapy; although the latter was associated with a lower eradication rate than the other reported categories.

Finally, the multivariate analysis showed that use of clarithromycin in the previous first-line treatment eradication attempt was associated with a lower eradication rate with the second-line treatment (OR, 0.60; 95% CI, 0.48–0.75; $P < .001$).

Safety of Second-Line Treatment

The overall incidence of adverse events was 28% (95% CI, 27%–29%), although the majority were mild (85%) and of short duration (mean, 6.6 d). Further information on the safety of treatments is reported in Supplementary File 4 and Supplementary Table 7.

Discussion

H pylori treatment failure can occur as a result of diverse factors, but mainly owing to primary or acquired bacterial antibiotic resistance (specifically to clarithromycin and metronidazole, and, more recently, also to levofloxacin).[5,6] Antibiotic resistance (which varies between countries in relation to antibiotic use) has become an important hurdle to overcome, particularly in rescue therapy, in which 90% effectiveness also is demanded.[14,15]

In our study, the overall effectiveness of second-line empiric treatment was less than 90%. Treatment with PPI+amoxicillin+levofloxacin was the most widely prescribed (33%) in Europe after a failed attempt with clarithromycin; however, its overall effectiveness was clearly suboptimal (81%), unless prescribed for 14 days, which provided acceptable cure rates (91%). A triple regimen with 10- or 14-day PPI+amoxicillin+moxifloxacin (although prescribed in just 3% of cases) reported an encouraging rate of 90% effectiveness. Thus, only 14-day triple regimens with quinolones (either levofloxacin or moxifloxacin) showed acceptable cure rates (91% and 96%, respectively). In fact, several studies have shown optimal results with extended, optimized, 14-day PPI+amoxicillin+levofloxacin,[16,17] and so 14-day regimens currently are recommended, unless shorter therapies are proven effective locally.[1,5,14]

Furthermore, effectiveness increased to more than 90% when high-dose PPIs were used in combination with longer treatment durations (ie, 14 days), in accordance with previously published research.[1,8,9,15,18]

Bismuth was added to levofloxacin+amoxicillin triple therapy in 13% of our patients, as recommended in the last European Consensus guidelines,[1] and reported effectiveness indeed was significantly higher as compared with triple therapy with levofloxacin (without

Table 4. Effectiveness of Second-Line Therapy According to the Duration and Dose of the Proton Pump Inhibitor, Stratified by First-Line Therapy

		First-line: clarithromycin-containing triple or quadruple therapy						First-line: bismuth quadruple therapy					
Second-line treatment	Length, *d*	ITT, N (%)	95% CI	mITT, N (%)	95% CI	PP, N (%)	95% CI	ITT, N (%)	95% CI	mITT, N (%)	95% CI	PP, N (%)	95% CI
Triple regimens													
PPI+A+L	7	32 (50)	31–69	24 (71)	49–87	24 (71)	49–87	NA	NA	NA	NA	NA	NA
	10	799 (69)	66–72.5	737 (76)	72–79	728 (76)	73–79	15 (67)	38–88	14 (71.5)	42–92	13 (69)	39–91
	14	461 (81)	77–84	416 (91)	88–93	409 (91)	88–94	NA	NA	NA	NA	NA	NA
PPI+C+A	7	23 (30)	13–53	15 (47)	21–73	15 (47)	21–73	NA	NA	NA	NA	NA	NA
	10	95 (15)	7–22	61 (23)	12–34	59 (22)	11–33	NA	NA	NA	NA	NA	NA
	14	39 (13)	4.3–27	31 (16)	5.4–34	31 (16)	5.4–34	NA	NA	NA	NA	NA	NA
PPI+A+Mx	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	10	23 (96)	78–100	22 (100)	85–100	22 (100)	85–100	NA	NA	NA	NA	NA	NA
	14	48 (79)	67–92	44 (87)	76–98	44 (86)	75–98	NA	NA	NA	NA	NA	NA
PPI+A+M	7	26 (35)	14–55	28 (32)	13–51	28 (32)	13–51	NA	NA	NA	NA	NA	NA
	10	34 (65)	47–82	30 (77)	60–93	30 (77)	60–93	NA	NA	NA	NA	NA	NA
	14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PPI+A+Rf	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PPI+M+L	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	10	10 (70)	35–93	10 (70)	35–93	10 (70)	35–93	NA	NA	NA	NA	NA	NA
	14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PPI+C+M	7	10 (60)	26–88	9 (67)	30–92	10 (70)	30–92	NA	NA	NA	NA	NA	NA
	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PPI+C+L	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Quadruple regimens													
PPI+single capsule[a]	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	10	614 (83)	79.5–86	593 (84)	87–92	584 (90)	87–92	52 (88.5)	79–98	49 (94)	83–99	49 (94)	83–99
	14	11 (82)	48–98	11 (82)	48–98	11 (82)	48–98	NA	NA	NA	NA	NA	NA
PPI+A+L+B	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	10	23 (57)	34–79	18 (78)	52–94	18 (78)	52–94	NA	NA	NA	NA	NA	NA
	14	442 (82)	79–96	414 (90)	86–92	398 (90)	87–93	88 (76)	67–86	78 (87)	79–95	77 (88)	80.5–96

Table 4. Continued

Second-line treatment	Length, *d*	First-line: clarithromycin-containing triple or quadruple therapy						First-line: bismuth quadruple therapy					
		ITT, N (%)	95% CI	mITT, N (%)	95% CI	PP, N (%)	95% CI	ITT, N (%)	95% CI	mITT, N (%)	95% CI	PP, N (%)	95% CI
PPI+M+Tc+B	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	10	48 (71)	57–85	47 (72)	58.5–86	45 (76)	62–89	NA	NA	NA	NA	NA	NA
	14	61 (84)	73.5–94	57 (93)	83–98	55 (93)	82–98	NA	NA	NA	NA	NA	NA
PPI+C+A+B	7	NA	NA	NA	NA	NA	NA	9 (11)	0.3–48	5 (20)	0.5–72	5 (20)	0.5–72
	10	41 (78)	64–92	37 (86)	71–95.5	37 (86)	71–95.5	33 (51.5)	33–71	18 (94)	73–100	17 (94)	71–100
	14	45 (69)	54–83.5	41 (88)	74–96	39 (90)	76–97	42 (21)	8-35	14 (79)	49–95	13 (77)	46–95
Conc-PPI+C+A+M	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	10	38 (76)	61–91	13 (54)	25–81	36 (78)	63–93	NA	NA	NA	NA	NA	NA
	14	77 (84.5)	76–93	79 (85)	76–93	79 (85)	76–93	44 (77)	64–91	42 (83)	71–96	39 (87)	73–96
Seq-PPI+C+A+T	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	10	25 (64)	43–85	23 (70)	47–87	23 (70)	47–87	NA	NA	NA	NA	NA	NA
	14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

	PPI dose	First-line: clarithromycin-containing triple or quadruple therapy						First-line: bismuth quadruple therapy					
		ITT, N (%)	95% CI	mITT, N (%)	95% CI	PP, N (%)	95% CI	ITT, N (%)	95% CI	mITT, N (%)	95% CI	PP, N (%)	95% CI
Triple therapy combinations													
PPI+A+L	Low	437 (67)	62–71	401 (73)	68–77	395 (74)	69–78	14 (50)	23–77	13 (54)	25–81	13 (54)	25–81
	Standard	307 (71)	66–76	289 (76)	71–81	284 (77)	72–82	NA	NA	NA	NA	NA	NA
	High	551 (78)	75–82	491 (89)	86–92	486 (89)	86–92	NA	NA	NA	NA	NA	NA
PPI+C+A	Low	91 (21)	12–30	67 (28)	17–40	66 (29)	17–40	NA	NA	NA	NA	NA	NA
	Standard	50 (8)	2–19	28 (14)	4–33	27 (11)	2.3–29	NA	NA	NA	NA	NA	NA
	High	16 (19)	4–46	12 (25)	5.5–57	12 (25)	5.5–57	NA	NA	NA	NA	NA	NA
PPI+A+Mx	Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Standard	18 (94)	73–100	17 (100)	80–100	17 (100)	80–100	NA	NA	NA	NA	NA	NA
	High	51 (80)	68–92	47 (87)	77–98	47 (87)	77–98	NA	NA	NA	NA	NA	NA
PPI+A+M	Low	49 (47.5)	31–64	41 (51)	35–68	41 (51)	35–68	NA	NA	NA	NA	NA	NA
	Standard	12 (50)	21–79	9 (67)	30–92	9 (67)	30–92	NA	NA	NA	NA	NA	NA
	High	17 (59)	33–81	15 (67)	38–88	15 (67)	38–88	NA	NA	NA	NA	NA	NA

Table 4. Continued

		First-line: clarithromycin-containing triple or quadruple therapy						First-line: bismuth quadruple therapy					
	PPI dose	ITT, N (%)	95% CI	mITT, N (%)	95% CI	PP, N (%)	95% CI	ITT, N (%)	95% CI	mITT, N (%)	95% CI	PP, N (%)	95% CI
PPI+A+Rf	Low	9 (78)	40–97	9 (78)	40–97	9 (78)	40–97	NA	NA	NA	NA	NA	NA
	Standard	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	High	12 (67)	35–90	9 (89)	52–100	9 (89)	52–100	NA	NA	NA	NA	NA	NA
PPI+M+L	Low	8 (62.5)	24–91	7 (71)	29–96	7 (71)	29–96	NA	NA	NA	NA	NA	NA
	Standard	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PPI+C+M	Low	11 (64)	31–89	10 (70)	35–93	10 (70)	35–93	NA	NA	NA	NA	NA	NA
	Standard	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PPI+C+L	Low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Standard	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Quadruple therapy combinations													
PPI+single capsule[a]	Low	306 (80)	75–85	291 (86)	82–90	286 (86)	82–90	9 (89)	52–100	8 (100)	63–100	8 (100)	63–100
	Standard	101 (79)	71–88	92 (90)	84–97	914 (90)	83–97	19 (89.5)	67–99	17 (100)	80.5–100	17 (100)	80–100
	High	222 (86.5)	82–91	224 (92)	88–96	219 (92)	88–96	24 (87.5)	67–97	24 (87.5)	67–97	24 (87.5)	67–97
PPI+A+L+B	Low	44 (61)	46–77	39 (72)	56–87	39 (72)	56–87	16 (68)	41–89	12 (92)	61.5–100	12 (92)	61–100
	Standard	42 (69)	54–84	36 (83)	67–94	35 (83)	66–93	NA	NA	NA	NA	NA	NA
	High	378 (85)	81–89	356 (92)	88–94	341 (92)	89–95	73 (79.5)	69.5–89	67 (86)	78–96	66 (88)	79–97
PPI+M+Tc+B	Low	44 (68)	53–83	39 (77)	62–91	38 (79)	65–93	NA	NA	NA	NA	NA	NA
	Standard	48 (73)	59–86	45 (78)	64–91	42 (79)	65–92	NA	NA	NA	NA	NA	NA
	High	23 (100)	85–100	25 (100)	86–100	25 (100)	86–100	NA	NA	NA	NA	NA	NA
PPI+C+A+B	Low	14 (50)	23–77	11 (64)	31–89	11 (64)	31–89	29 (38)	19–57	14 (79)	49–95	13 (77)	46–95
	Standard	50 (82)	70–94	47 (96)	85–99	47 (96)	85–99	20 (35)	15–53	11 (64)	31–89	11 (64)	31–90
	High	22 (64)	41–86	19 (79)	54–94	17 (82)	56–96	33 (27)	11–44	12 (92)	62–100	11 (91)	59–100
Conc-PPI+C+A+M	Low	39 (69)	53–85	39 (69)	53–85	38 (68)	52–84	18 (89)	65–99	19 (84)	60–97	18 (89)	65–99
	Standard	25 (80)	59–93	25 (80)	59–93	25 (80)	59–93	9 (56)	21–86	6 (83)	36–99	5 (100)	48–100
	High	56 (89)	80–98	57 (91)	81–97	57 (91)	81–97	22 (82)	60–95	22 (86)	66–98	21 (86)	64–97
Seq-PPI+C+A+T	Low	16 (56)	30–80	15 (60)	32–84	15 (60)	32–84	NA	NA	NA	NA	NA	NA
	Standard	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

NOTE. Low-dose PPI consisted of 4.5–27 mg omeprazole equivalents twice daily (ie, 20 mg omeprazole equivalents twice daily), standard-dose PPI consisted of 32–40 mg omeprazole equivalents twice daily (ie, 40 mg omeprazole equivalents twice daily), high-dose PPI consisted of 54–128 mg omeprazole equivalents twice daily (ie, 60 mg omeprazole equivalents twice daily).

A, amoxicillin; B, bismuth; C, clarithromycin; CI, confidence interval; Conc, concomitant administration; ITT, intention-to-treat; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; Mx, moxifloxacin; NA, not available; PP, per protocol; PPI, proton pump inhibitor; Rf, rifaximin; Seq, sequential administration; T, tinidazole; Tc, tetracycline.

[a]Single-capsule, 3-in-1 single capsule containing bismuth, tetracycline, and metronidazole.

Table 5. Multivariate Analysis in Empiric Second-Line Treatment

	OR (95% CI)	P value
Indication [ref. dyspepsia]	1.280 (1.014–1.616)	.038
Treatment length [ref. 7 days]		
10 days	2.089 (1.476–2.957)	.000
14 days	2.814 (1.942–4.079)	.000
PPI dose [ref. low dose]		
Standard	1.507 (1.215–1.869)	.000
High	2.208 (1.774–2.748)	.000
Use of clarithromycin first-line	0.600 (0.479–0.751)	.000
Second-line treatment [ref. PPI+C+A]		
PPI+A+L or PPI+A+Mx	3.112 (2.276–4.255)	.000
PPI+A+L+B	3.638 (2.395–5.525)	.000
Bismuth quadruple[a]	6.284 (4.411–8.951)	.000
Other (remaining therapies)	2.944 (2.130–4.069)	.000
Compliance [ref. no, <90% drug intake]	3.013 (1.788–5.077)	.000

NOTE. Low-dose PPI consisted of 4.5 to 27 mg omeprazole equivalents twice daily (ie, 20 mg omeprazole equivalents twice daily); standard-dose PPI consisted of 32 to 40 mg omeprazole equivalents twice daily (ie, 40 mg omeprazole equivalents twice daily); and high-dose PPI consisted of 54 to 128 mg omeprazole equivalents twice daily (ie, 60 mg omeprazole equivalents twice daily).

A, amoxicillin; B, bismuth; C, clarithromycin; CI, confidence interval; L, levofloxacin; Mx, moxlifloxacin; OR, odds ratio; PPI, proton pump inhibitor; ref, reference category.

[a]Accounting for PPI+metronidazole+tetracycline+bismuth and a single capsule.

bismuth), achieving 89% vs 80% ($P < .001$) cure rates, in line with previous studies.[9,19–21]

After failure of a first-line regimen (triple or quadruple) with clarithromycin, another recommended rescue treatment is a bismuth-based quadruple therapy with metronidazole and tetracycline.[1,22] In our study, 10-day PPI+bismuth+metronidazole+tinidazole as a single capsule was the second most frequently used treatment (17% of cases), and reported approximately 90% effectiveness, regardless of the PPI dose. A recent update on this 10-day treatment with a single capsule in more than 5000 patients in the Hp-EuReg confirmed excellent cure rates, not only in first-line but also in second-line treatment, achieving 90% eradication.[23] In addition, a previous meta-analysis showed similar results with a single capsule of bismuth quadruple therapy, reporting high effectiveness in naïve patients and in subsequent rescue treatment lines (including those with bacterial resistance to clarithromycin or metronidazole, or both).[24]

The bismuth compound shows an antibacterial effect that prevents *H pylori* colonization and adherence to the gastric mucosa, reducing the bacterial load.[9] This compound, therefore, has a synergistic effect with antibiotics, with no resistance described.[25] Adding bismuth to either triple or quadruple therapy may further enhance effectiveness and overcome bacterial antibiotic resistance.[19,26,27] Such a strategy of adding bismuth to different antibiotic combinations may explain the increase in the eradication rates of rescue treatments used in our cohort, despite first-line treatment failure with clarithromycin. Such was the case with quadruple therapy with 14-day PPI+clarithromycin+amoxicillin+bismuth, in which a cure rate of 87% was reported, which was significantly higher compared with a standard 14-day PPI+amoxicillin+clarithromycin regimen (which obtained a 24% eradication rate only). This latter example showed greater differences (with respect to other with vs without bismuth comparisons, such as PPI+amoxicillin+levofloxacin vs PPI+amoxicillin+levofloxacin+bismuth), probably as a result not only of the beneficial effect of adding bismuth to the regimen, but also the repeated use of clarithromycin in second-line treatment after a failed first-line use.[2]

Also, in our study, re-treatment with 10-day PPI+bismuth+metronidazole+tinidazole (a single capsule) achieved 94% eradication. It has been stated elsewhere[24] that re-treating with the single capsule is feasible given that the potential acquired bacterial resistance to tetracycline or bismuth would be minor (<3%),[28] and that resistance to metronidazole can be easily overcome.

However, after a first failed eradication attempt with PPI+bismuth+metronidazole+tinidazole, the recommended treatment is PPI+amoxicillin+levofloxacin+bismuth[1] because it has been suggested not to repeat antibiotics[2] (the overall effectiveness was always <90% when repeating antibiotics[29]). In line with this, in our study, 14-day PPI+amoxicillin+levofloxacin+bismuth reported approximately 90% effectiveness.

In addition, prescribing clarithromycin in a quadruple regimen (with amoxicillin and bismuth) also might be an option, although there still is limited experience as a rescue treatment.[9,30] In the studied cohort, 10-day PPI+clarithromycin+amoxicillin+bismuth was used in a relatively small proportion of patients (5%), achieving 94% effectiveness, and confirming previous encouraging results.[30]

These results were reinforced in the multivariate analysis, in which longer treatment durations and higher PPI acid inhibition were associated significantly with higher effectiveness, as previously reported.[2,9] In addition, in our study, previous use of clarithromycin in first-line therapy was associated with a risk of second-line treatment failure; in fact, those prescribing clarithromycin after a clarithromycin failure reported cure rates far less than 90%. Indeed, repeating antibiotics was not adequate, as confirmed both in Europe and in the United States.[2,5,31] Better outcomes also were confirmed with 14-day quinolone triple therapies (also when combined with bismuth into quadruple regimens) and 10-day bismuth quadruple therapy (either in the classic form or as a single capsule).

Regarding safety, our data reported at least 1 adverse event in a relatively high proportion of patients (28%). The most frequent adverse events, including diarrhea (10%), nausea (9%), or metallic taste (5%), were of mild intensity and short duration (self-limited). These results

were in accordance with those recently published in the study on the safety of *H pylori* treatments in more than 22,000 patients from the Hp-EuReg.[2]

In general, the tolerability of quadruple therapies was less than that of triple therapies, in agreement with previous research.[32,33] Quadruple therapies, especially PPI+clarithromycin+amoxicillin+bismuth, but also PPI+bismuth+metronidazole+tinidazole (either in the standard version or with a single capsule), were the most poorly tolerated. Regimens containing bismuth and levofloxacin were associated with a poorer tolerance compared with triple therapy containing levofloxacin or moxifloxacin, also in accordance with the Hp-EuReg safety study.[34]

The major limitation of our study was that the empiric regimens in the studied cohort were heterogeneous; many treatments (>50) were prescribed to fewer than 40 patients each, and therefore, these regimens could not be used for the subanalyses by treatment duration or PPI dosage. To some extent, this reduced the amount of information available. Nonetheless, the current analysis was performed on the 10 most frequently used treatments, representing more than 90% of the study sample. Heterogeneity was inherent to the study design of the Hp-EuReg (ie, observational, noninterventional) and therefore difficult to avoid, because wide selection criteria initially were established to reflect real clinical practice as much as possible. As an example, 85% of patients came from only 5 countries, and the majority of patients (54%) were from a single country (Spain), and this might have introduced some selection bias. Therefore, comparisons of treatments should be interpreted with caution because allocation biases may affect effectiveness.

Another point to highlight is that we did not include patients with culture testing, and therefore information on *H pylori* antibiotic resistance was lacking; thus, no definite conclusions could be drawn about the effect of resistance on the choice and effectiveness of second-line therapy. However, this reflects real routine gastroenterology practice in Europe, where antibiograms are not performed on a routine basis and treatments mainly are empirically prescribed.[8]

However, we believe that our study had a number of strengths based on the invaluable information of the Hp-EuReg. The present study comprised a large cohort of patients treated with second-line *H pylori* eradication treatment. The large number of patients and wide range of treatment strategies maximized the distribution and the representativeness of the population, which may counterbalance the potential heterogeneity. Finally, a high-quality method has been used to register, store, manage, and monitor the data by using the Online Platform for Collaborative Research Spanish Association of Gastroenterology–Research Electronic Data Capture, which provides robustness and coherence to the data with programmed and real-time quality controls, queries, reports, and statistics.

In conclusion, the overall effectiveness of empiric second-line *H pylori* eradication treatment was, in general, below the desired threshold. Therefore, the use of some regimens should be reconsidered and new therapeutic strategies explored by European gastroenterologists. In this respect, the empiric second-line regimens providing optimal effectiveness included 14-day quinolone triple therapies, 14-day levofloxacin–bismuth quadruple therapy, 14-day tetracycline–bismuth classic quadruple therapy, and 10-day bismuth quadruple therapy as a single capsule.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.12.025.

References

1. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. Gut 2017;66:6–30.
2. Nyssen OP, Vaira D, Tepes B, et al. Room for improvement in the treatment of *Helicobacter pylori* infection: lessons from the European Registry on H. pylori management (Hp-EuReg). J Clin Gastroenterol 2022;56:e98–e108.
3. Gisbert JP, Calvet X. Update on non-bismuth quadruple (concomitant) therapy for eradication of *Helicobacter pylori*. Clin Exp Gastroenterol 2012;5:23–34.
4. Nyssen OP, McNicholl AG, Megraud F, et al. Sequential versus standard triple first-line therapy for *Helicobacter pylori* eradication. Cochrane Database Syst Rev 2016;6:CD009034.
5. Megraud F, Bruyndonckx R, Coenen S, et al. Helicobacter pylori resistance to antibiotics in Europe in 2018 and its relationship to antibiotic consumption in the community. Gut 2021;70:1815–1822.
6. Megraud F. *Helicobacter pylori* and antibiotic resistance. Gut 2007;56:1502.
7. Gisbert JP. Empirical or susceptibility-guided treatment for *Helicobacter pylori* infection? A comprehensive review. Therap Adv Gastroenterol 2020;13:1756284820968736.
8. Caldas M, Perez-Aisa A, Castro-Fernandez M, et al. European Registry on *Helicobacter pylori* management: effectiveness of first and second-line treatment in Spain. Antibiotics (Basel) 2020;10:13.
9. Gisbert JP, McNicholl AG. Optimization strategies aimed to increase the efficacy of *H. pylori* eradication therapies. Helicobacter 2017;22:e12392.
10. McNicholl AG, O'Morain CA, Megraud F, et al. Protocol of the European Registry on the management of *Helicobacter pylori* infection (Hp-EuReg). Helicobacter 2019;24:e12630.
11. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–381.

12. Graham DY, Lu H, Dore MP. Relative potency of proton-pump inhibitors, *Helicobacter pylori* therapy cure rates, and meaning of double-dose PPI. Helicobacter 2019;24:e12554.
13. Kirchheiner J, Glatt S, Fuhr U, et al. Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. Eur J Clin Pharmacol 2009;65:19–31.
14. Morehead MS, Scarbrough C. Emergence of global antibiotic resistance. Prim Care 2018;45:467–484.
15. Graham DY, Lu H, Yamaoka Y. Therapy for *Helicobacter pylori* infection can be improved: sequential therapy and beyond. Drugs 2008;68:725–736.
16. Chuah SK, Tai WC, Hsu PI, et al. The efficacy of second-line anti-*Helicobacter pylori* therapy using an extended 14-day levofloxacin/amoxicillin/proton-pump inhibitor treatment–a pilot study. Helicobacter 2012;17:374–381.
17. Cao Z, Chen Q, Zhang W, et al. Fourteen-day optimized levofloxacin-based therapy versus classical quadruple therapy for *Helicobacter pylori* treatment failures: a randomized clinical trial. Scand J Gastroenterol 2015;50:1185–1190.
18. Arama SS, Tiliscan C, Negoita C, et al. Efficacy of 7-day and 14-day triple therapy regimens for the eradication of *Helicobacter pylori*: a comparative study in a cohort of Romanian patients. Gastroenterol Res Pract 2016;2016:5061640.
19. Gisbert JP, Romano M, Gravina AG, et al. *Helicobacter pylori* second-line rescue therapy with levofloxacin- and bismuth-containing quadruple therapy, after failure of standard triple or non-bismuth quadruple treatments. Aliment Pharmacol Ther 2015;41:768–775.
20. Kahramanoglu Aksoy E, Pirincci Sapmaz F, Goktas Z, et al. Comparison of *Helicobacter pylori* eradication rates of 2-week levofloxacin-containing triple therapy, levofloxacin-containing bismuth quadruple therapy, and standard bismuth quadruple therapy as a first-line regimen. Med Princ Pract 2017;26:523–529.
21. Song Z, Zhou L, Zhang J, et al. Levofloxacin, bismuth, amoxicillin and esomeprazole as second-line *Helicobacter pylori* therapy after failure of non-bismuth quadruple therapy. Dig Liver Dis 2016;48:506–511.
22. Shah SC, Iyer PG, Moss SF. AGA Clinical Practice update on the management of refractory Helicobacter pylori infection: expert review. Gastroenterology 2021;160:1831–1841.
23. Nyssen OP, Perez-Aisa A, Castro-Fernandez M, et al. European Registry on *Helicobacter pylori* management: single-capsule bismuth quadruple therapy is effective in real-world clinical practice. United European Gastroenterol J 2021;9:38–46.
24. Nyssen OP, McNicholl AG, Gisbert JP. Meta-analysis of three-in-one single capsule bismuth-containing quadruple therapy for the eradication of *Helicobacter pylori*. Helicobacter 2019;24:e12570.
25. Megraud F. The challenge of *Helicobacter pylori* resistance to antibiotics: the comeback of bismuth-based quadruple therapy. Therap Adv Gastroenterol 2012;5:103–109.
26. Liang X, Xu X, Zheng Q, et al. Efficacy of bismuth-containing quadruple therapies for clarithromycin-, metronidazole-, and fluoroquinolone-resistant *Helicobacter pylori* infections in a prospective study. Clin Gastroenterol Hepatol 2013;11:802–807 e1.
27. Malfertheiner P. Infection: bismuth improves PPI-based triple therapy for *H. pylori* eradication. Nat Rev Gastroenterol Hepatol 2010;7:538–539.
28. Graham DY, Lee YC, Wu MS. Rational *Helicobacter pylori* therapy: evidence-based medicine rather than medicine-based evidence. Clin Gastroenterol Hepatol 2014;12:177–186 e3, discussion e12–e13.
29. Nyssen OP, Bordin D, Tepes B, et al. European Registry on *Helicobacter pylori* management (Hp-EuReg): patterns and trends in first-line empirical eradication prescription and outcomes of 5 years and 21 533 patients. Gut 2021;70:40–54.
30. McNicholl AG, Bordin DS, Lucendo A, et al. Combination of bismuth and standard triple therapy eradicates *Helicobacter pylori* infection in more than 90% of patients. Clin Gastroenterol Hepatol 2020;18:89–98.
31. Argueta EA, Alsamman MA, Moss SF, et al. Impact of antimicrobial resistance rates on eradication of Helicobacter pylori in a US population. Gastroenterology 2021;160:2181–2183 e1.
32. Chen Q, Zhang W, Fu Q, et al. Rescue therapy for *Helicobacter pylori* eradication: a randomized non-inferiority trial of amoxicillin or tetracycline in bismuth quadruple therapy. Am J Gastroenterol 2016;111:1736–1742.
33. Marin AC, Nyssen OP, McNicholl AG, et al. Efficacy and safety of quinolone-containing rescue therapies after the failure of non-bismuth quadruple treatments for *Helicobacter pylori* eradication: systematic review and meta-analysis. Drugs 2017;77:765–776.
34. Nyssen OP, Perez-Aisa A, Tepes B, et al. Adverse event profile during the treatment of *Helicobacter pylori*: a real-world experience of 22,000 patients from the European registry on H. pylori management (Hp-EuReg). Am J Gastroenterol 2021;116:1220–1229.

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Acknowledgments
The authors want to thank the Spanish Association of Gastroenterology for providing the electronic case report form service free of charge. The authors also thank Catherine Rees of Springer Healthcare Communications for providing assistance with the English editing of the manuscript before submission.

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Olga P. Nyssen, Hp-EuReg Scientific Director, designed the protocol and planned the study, performed the data extraction, the monitoring and the quality check, analyzed and synthesized the data, wrote the manuscript draft, and approved the submitted manuscript. Dino Vaira, Ángeles Pérez Aísa, Luis Rodrigo, Manuel Castro-Fernandez, Laimas Jonaitis, Bojan Tepes, Liudmila Vologzhanina, María Caldas, Angel Lanas, Alfredo Lucendo, Luis Bujanda, Juan Ortuño, Jesús Barrio, Jose M. Huguet, Irina Voynovan, Jorge Perez Lasala, Aiman Silkanovna Sarsenbaeva, Luis Fernandez-Salazar, Javier Molina-Infante, Natasa Brglez Jurecic, Miguel Areia, Antonio Gasbarrini, Juozas Kupčinskas, Dmitry Bordin, Ricardo Marcos Pinto, Frode Lerand, Marcis Leja, Gyorgy M. Buzas, Yaron Niv, Theodore Rokkas, Perminder Phull, Sinead Smith, Oleg Shvets, Marino Venerito, Vladimir Milivojevic, Ilkay Simsek, Vincent Lamy, Peter Bytzer, Lyudmila Boyanova, Lumír Kunovský, Christoph Beglinger, Michael Doulberis, Wojciech Marlicz, Adrian Goldis, Ante Tonkić, and Lisette Capelle collected data and assisted with data interpretation, critically reviewed the manuscript's drafts, and approved the submitted manuscript. Colm O'Morain, Francis Mégraud, Olga P. Nyssen and Ignasi Puig are Members of the Hp-EuReg Scientific Committee; they 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, analyzed and interpreted the data, recruited patients, critically reviewed the manuscript drafts, and approved the final submitted manuscript.

The full list of authors, their affiliations, and contributions are listed in Supplementary File 1.

Conflicts of interest

These authors disclose the following: Javier P. Gisbert has served as a speaker, consultant, and advisory member, or has received research funding from Mayoly, Allergan, Diasorin, Gebro Pharma, and Richen; Olga P. Nyssen has received research funding from Mayoly and Allergan; Ángeles Pérez Aísa has received compensation from Allergan and Mylan for formative actions; Laimas Jonaitis has served as speaker for KRKA; and Angel Lanas has served as a consultant to Bayer A.G. The remaining authors disclose no conflicts.

Funding

This project was promoted and funded by the European Helicobacter and Microbiota Study Group, the Spanish Association of Gastroenterology, and the Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas.

Data Transparency Statement

Raw data were generated by the Spanish Association of Gastroenterology–Research Electronic Data Capture. Derived data supporting the findings of this study are available from the first author and senior corresponding author (O.P.N. and J.P.G.) upon request.

Data Sharing Statement

The data that support the findings of this study are not publicly available given that the information could compromise the privacy of research participants. However, previously published data on the Hp-EuReg study, or de-identified raw data referring to the current study, as well as further information on the methods used to explore the data, could be shared with no particular time constraint. Individual participant data will not be shared.