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)

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INTRODUCTION: **The safety of *Helicobacter pylori* eradication treatments and to what extent adverse events (AEs) influence therapeutic compliance in clinical practice are hardly known. Our aim was to assess the frequency, type, intensity, and duration of AEs, and their impact on compliance, for the most frequently used treatments in the "European Registry on *Helicobacter pylori* management."**

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METHODS: **Systematic prospective noninterventional registry of the clinical practice of European gastroenterologists (27 countries, 300 investigators) on the management of *H. pylori* infection in routine clinical practice. All prescribed eradication treatments and their corresponding safety profile were recorded. AEs were classified depending on the intensity of symptoms as mild/moderate/severe and as serious AEs. All data were subject to quality control.**

RESULTS: **The different treatments prescribed to 22,492 patients caused at least 1 AE in 23% of the cases; the classic bismuth-based quadruple therapy was the worst tolerated (37% of AEs). Taste disturbance (7%), diarrhea (7%), nausea (6%), and abdominal pain (3%) were the most frequent AEs. The majority of AEs were mild (57%), 6% were severe, and only 0.08% were serious, with an average duration of 7 days. The treatment compliance rate was 97%. Only 1.3% of the patients discontinued treatment due to AEs. Longer treatment durations were significantly associated with a higher incidence of AEs in standard triple, concomitant, bismuth quadruple, and levofloxacin triple or quadruple therapies.**

DISCUSSION: ***Helicobacter pylori* eradication treatment frequently induces AEs, although they are usually mild and of limited duration. Their appearance does not interfere significantly with treatment compliance.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B961

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INTRODUCTION

Helicobacter pylori infection affects billions of people worldwide. This infection is the main cause of gastritis, peptic ulcer disease, and gastric cancer (1). The effectiveness of the different *H. pylori* eradication regimens has been widely studied. However, to date, the frequency, severity, the type of adverse events (AEs) for the different antibiotic regimens, and the impact of these factors on therapeutic compliance in clinical practice have been poorly investigated (2).

Properly evaluation of the wide spectrum of AEs associated with the wide variety of antibiotic regimens requires the study of a very large and diverse population receiving these eradication treatments. The "European Registry on *Helicobacter pylori* management" (Hp-EuReg) brings together information on the real clinical practice of most European countries, including thousands of patients (3,4). The European Registry represents a good mapping overview of the current situation regarding *H. pylori* management, allowing not only for continuous assessment of the implementation of clinical recommendations agreed on medical consensus but also of the possible strategies for improvement. Therefore, the aim of this study was to assess the frequency, type, intensity, and duration of AEs, and their impact on compliance, for the most frequently prescribed treatments by European gastroenterologists, based on the invaluable information included in Hp-EuReg, a database systematically registering a large and representative sample of routine clinical practice in Europe.

METHODS

European Registry on *Helicobacter pylori* management

This analysis focused on the Hp-EuReg, an international multicenter prospective noninterventional registry that started in 2013 and was promoted by the European Helicobacter and Microbiota Study Group (www.helicobacter.org).

Current members of the Scientific Committee are Javier P. Gisbert (Principal Investigator), Francis Mégraud, Colm A. O'Morain, Ignasi Puig, and Olga P. Nyssen (the 2 latter are also the Scientific Directors).

Currently, 29 countries have been selected. Criteria for country selection, national coordinators, and gastroenterologist recruiting investigators are detailed in the published protocol (3). Eradication confirmation tests had to be available. Cases were managed and registered according to their routine clinical practice (this was a noninterventional registry).

The Hp-EuReg protocol (3) was approved by the Ethics Committee of La Princesa University Hospital (Madrid, Spain), which acted as reference Institutional Review Board; it was classified by the Spanish Drug and Health Product Agency and was registered at ClinicalTrials.gov under the code NCT02328131. Written informed consent was obtained from each patient included in the study.

Data were recorded in an electronic case report form and collected and managed using REDCap hosted at "Asociación Española de Gastroenterología" (www.aegastro.es) (5), a nonprofit scientific and medical society focused on gastroenterology research. The list of variables and outcomes can be found in the published protocol (3).

Study aim

The general primary aim of the Hp-EuReg was to set up an on-going database in which a large and representative sample of European gastroenterologists would systematically record their routine management of patients infected with *H. pylori*. Secondary objectives of the Hp-EuReg are further described in the protocol (3).

The aim of the current study was to assess the frequency, type, intensity, and duration of AEs, and their impact on compliance, for the most frequently used treatments in the Hp-EuReg.

Selection criteria

Adult patients treated with any therapy scheme of any treatment line were included in the analysis. Given the diversity of treatments accounting for a small number of patients treated, it was decided to establish a threshold of 100 cases by treatment. Therefore, 14 treatments were selected *a priori* for the safety analysis.

Those treatments given in combination with pro/prebiotics were excluded from the study.

Data management and analysis

A quality control check was performed on at least 10% of the records included. AEs were classified depending on the intensity

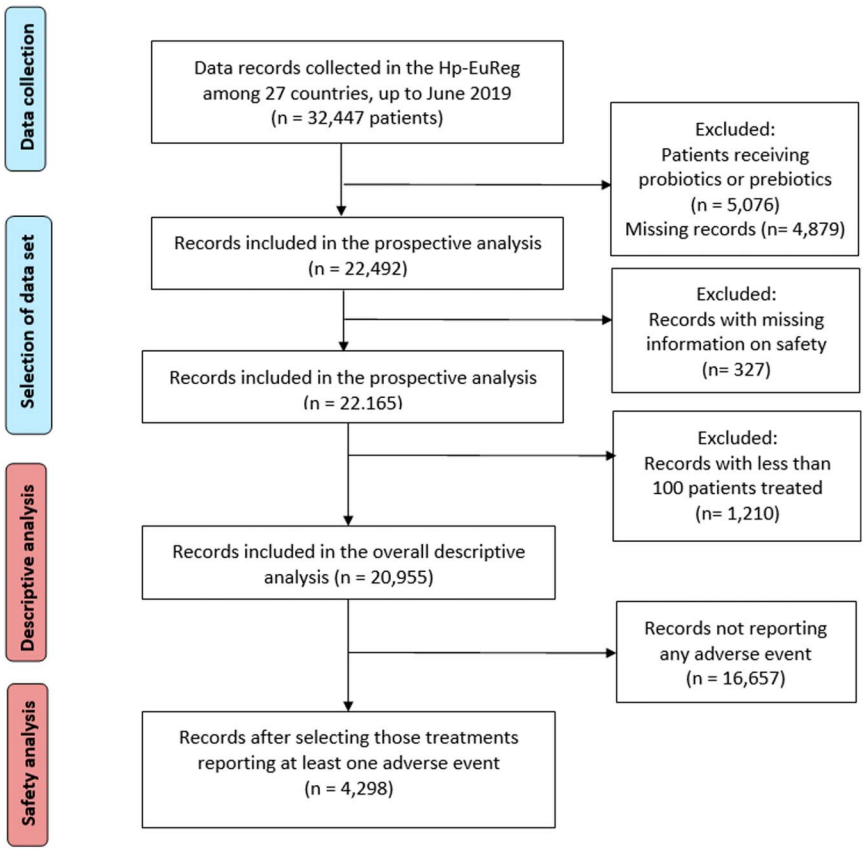

Figure 1. Study flow chart.

of symptoms evaluated by the corresponding physician: mild (not interfering with daily routine), moderate (affecting daily routine), intense/severe (not allowing normal daily routine), and serious (causing death, hospitalization, disability, congenital anomaly, and/or requiring intervention to prevent permanent damage).

AEs and compliance were evaluated through patient questioning with both open-ended questions and a predefined questionnaire, by face-to-face interview (see Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B961). Compliance was defined, through physician questioning, as having taken at least 90% of the prescribed drugs.

Statistical analyses

Continuous variables are presented as the arithmetic mean and respective SD. Qualitative variables are presented as percentages and 95% confidence intervals. Differences between groups were analyzed with the χ^2 test. Significance was considered at $P < 0.05$.

RESULTS

Overall

Until June 2019, 22,492 patients from 27 countries reported information on the safety of treatments (see Supplementary Table 2, Supplementary Digital Content 1, http://links.lww.com/AJG/B961). From those, 14 different treatments with at least 100 patients were analyzed, accounting for a total of 20,955 patients (Figure 1).

Mean age of patients was 51 (±17.4) years, and 61% were women. Indication for eradication was functional dyspepsia in 35% of the cases, noninvestigated dyspepsia in 20%, and peptic ulcer in 17%. Diagnosis was performed by means of histology in 39% of the patients, ^{13}C-urea breath test in 24%, rapid urease test in 31%, monoclonal stool antigen test in 6%, and culture in 5% (Table 1).

The appearance of at least 1 AE was reported in 23% of the cases overall (Table 2). There were 9 types of different AEs, and the most frequent were taste disturbance (7%), diarrhea (7%), nausea (6%), and abdominal pain (3%); most of them (57%) were mild.

The mean overall duration of AEs was 7.3 (±4.2) days, ranging from 1 to 45 days.

The incidence of AEs was 22% among the 14 different most frequent treatments evaluated (4,298 patients) (Table 3). Highest incidence of AEs was observed for the classical bismuth quadruple therapy containing a proton pump inhibitor (PPI), bismuth salts, metronidazole (M), and either tetracycline or doxycycline (37% and 33%, respectively), as well as for the bismuth quadruple with amoxicillin (A) and clarithromycin (C), levofloxacin, or josamycin (34%, 32%, and 32%, respectively).

The most frequent types of AEs by treatment were metallic taste with PPI + A + C + bismuth (16%) and with PPI + bismuth + tetracycline + M (16%); diarrhea with PPI + A + levofloxacin + bismuth (15%), and with PPI + bismuth + tetracycline + M (12%) and nausea with the bismuth quadruple therapy using either tetracycline or doxycycline (20% and 17% of the cases, respectively) (Table 4).

In addition, these AEs varied in intensity depending on the treatment (see Supplementary Table 3, Supplementary Digital Content 1, http://links.lww.com/AJG/B961). For instance, severe metallic taste was reported with PPI + A + josamycin + bismuth (15%), PPI + A + C (12%), and PPI + M + C (11%). Severe

Table 1. Demographic and clinical characteristics of patients

Total number of patients (N)	22,492
Age	
Mean (SD)	51 (17.4)
Sex (N, %)	
Male	8,818 (39)
Female	13,661 (61)
Ethnic background (N, %)	
White	20,519 (91)
Black	116 (0.50)
Asian	162 (0.70)
Others	1,370 (6.1)
Unknown/not available	317 (1.4)
Concurrent medication (N, %)	9,060 (40)
Proton pump inhibitors	5,249 (58)
Acetylsalicylic acid	1,238 (14)
NSAIDs	2,614 (18)
Statins	2,272 (25)
Indication (N, %)	
Functional dyspepsia	7,777 (35)
Duodenal ulcer	2,639 (12)
Gastric ulcer	1,167 (5)
Noninvestigated dyspepsia	4,363 (20)
Others	6,470 (29)
Most frequent prescriptions of treatments (N, %)[a]	
PPI + C + A	7,825 (35)
Concomitant (PPI + C + A + M)	3,850 (17)
PPI + three-in-one	2,519 (11)
PPI + C + A + B	1,889 (8.5)
PPI + A + L	1,741 (7.9)
PPI + C + M	1,026 (4.6)
PPI + A + L + B	599 (2.7)
PPI + A + M	381 (1.7)
Sequential (PPI + C + A + M)	278 (1.3)
PPI + M + Tc + B	233 (1.1)
PPI + A + B + J	208 (0.9)
PPI + M + D + B	190 (0.9)
Sequential (PPI + C + A + T)	115 (0.5)
Concomitant (PPI + C + A + T)	101 (0.5)
Total	20,955 (93%)

A, amoxicillin; B, bismuth; C, clarithromycin; D, doxycycline; J, josamycin; L, levofloxacin; M, metronidazole; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; T, tinidazole; Tc, tetracycline; three-in-one, three-in-one single-capsule bismuth quadruple therapy (Pylera).
[a]In > 95% of treatments, standard PPIs and antibiotic dosages were used: C 500 mg, A 1 g, M 500 mg, L 500 mg, B 240 mg, and J 500 mg were used twice daily and Tc 500 mg 4 times daily.

diarrhea occurred with PPI + M + C (11%), PPI + A + C (10%), and PPI + bismuth + doxycycline + M (10%). Severe nausea was reported in 30% of cases with PPI + A + josamycin + bismuth and occurred in 11–12% of the cases with the use of PPI + M + A and PPI + M + C or when PPI + bismuth + doxycycline + M was prescribed.

Overall compliance rate was 97%, and 1.3% of the patients had to discontinue the treatment because of AEs. In addition, serious AEs occurred in 20 patients (0.08%) who required hospitalization, but all of them were resolved without sequelae.

The incidence of AEs varied according to therapy length (Table 5) and their average duration (days) varied among treatment schemes (Table 6), as described in Supplementary file 2 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B961).

DISCUSSION

Usually, when choosing an antibiotic strategy for any infectious disease—including *H. pylori* infection—efficacy is the major determinant (6). However, safety is also relevant for selection of the most appropriate treatment. Generally, *H. pylori* eradication therapy is considered to be well tolerated. It is, however, associated with significant drug-induced AEs compared with acid-suppressing drugs alone (7,8). In this study, the different treatments prescribed to 22,492 patients of the Hp-EuReg caused at least 1 AE in as much as 22% of the cases. Taste disturbance (7%), diarrhea (7%), nausea (6%), and abdominal pain (3%) were the most frequent AEs. Similarly, in a Cochrane review, the most common AEs were diarrhea (8%), altered taste (7%), nausea/vomiting (5%), and abdominal pain (5%) (8). The majority of AEs in the Hp-EuReg were mild (57%), and only 0.08% were serious. In most cases, symptoms were only present while the patient was taking medication, lasting for ≤ 10 days in most of them. These results are in agreement with previous studies, where most AEs were reported to be mild and of limited duration (9–11). In particular, the safety profile of each of the most frequently prescribed regimens in the Hp-EuReg is discussed below.

Standard triple therapy

AEs are highly prevalent with PPI-based triple therapy, still one the most widely used worldwide. In our study, the incidence of AEs with PPI + C + A, PPI + C + M, and PPI + A + M was 15%, 20%, and 22%, respectively, in agreement with previous meta-analyses (12). Other studies have reported similar or higher rates of AEs, even reaching 50% (10). The most frequent types of AEs in patients receiving the standard triple regimens in the Hp-EuReg were gastrointestinal symptoms, mainly including taste disturbance, diarrhea, nausea, vomiting, and dyspepsia, in agreement with previous studies (7,9,12,13).

In the PPI + C + A and PPI + C + M regimens, the use of macrolides is probably the main cause of gastrointestinal AEs (14,15). On the other hand, the PPI + A + M regimen is also associated with a high incidence of AEs (22% in our study), despite not including C (16).

Prolonging the duration of treatments for longer than 7 days seems to significantly enhance eradication rates but may increase the rates of AEs (11,14). In our study, longer triple therapy regimens were associated with higher AE rates. Thus, for PPI + C + A regimen, the incidence of AEs was 14% for 7 days and 19% for 14 days, while for PPI + C + M, it was 21% and 25%, respectively.

Table 2. Overall frequency, intensity, and duration of the different types of adverse events

	Frequency of AE			Intensity of AE									Length of AE (d)	
Type of AE	N	%	95% CI	Mild, N	%	95% CI	Moderate, N	%	95% CI	Severe, N	%	95%CI	Mean (SD)	Min-max
Metallic taste	1,521	6.8	6.4–7.1	939	62	59–64	499	33	30–35	83	5.5	4.3–6.6	8.3 (3.3)	1–45
Diarrhea	1,541	6.9	6.5–7.2	883	57	55–60	584	38	35–40	73	4.7	3.6–5.8	6.8 (4.1)	1–45
Nausea	1,381	6.1	5.8–6.5	791	57	55–60	507	37	34–39	82	5.9	4.7–7.2	6.7 (4.0)	1–45
Abdominal pain	704	3.1	2.9–3.4	425	61	57–64	210	30	26–33	68	9.7	7.4–12	7.3 (4.4)	1–45
Dyspepsia	602	2.7	2.5–2.9	293	49	45–53	274	46	42–50	34	5.7	3.7–7.6	7.7 (4.7)	1–45
Asthenia	561	2.5	2.3–2.7	261	47	42–51	249	45	40–49	50	8.9	6.5–11	7.7 (3.8)	1–22
Vomiting	554	2.5	2.3–2.7	315	57	53–61	204	37	33–41	35	6.3	4.2–8.4	5.8 (4.2)	1–45
Anorexia	318	1.4	1.3–1.6	190	60	54–65	100	32	26–37	27	8.5	5.3–12	7.8 (3.1)	1–11
Heartburn	199	0.9	0.8–1	103	52	45–59	78	39	32–46	18	9	4.8–13	7.4 (6.5)	1–45
TOTAL	4,699	23	22–23	4,200	57	55–58	2,705	37	35–38	470	6.3	5.8–6.9	7.3 (4.2)	1–45
Serious AEs	**N**	%	95% CI											
Yes	20	0.08	0.05–0.13											
Stopped treatment due to AE	**N**	%	95% CI											
Yes	294	1.3	1.1–1.4											

AE, adverse event; CI, confidence interval; Min, minimum; Max, maximum; N, number of patients reporting an adverse event.

In a Cochrane review evaluating the optimum duration of regimens for *H. pylori* eradication, however, the proportion of patients discontinuing treatment because of AEs was not significantly different between treatment durations (9), in agreement with our results. Therefore, we can conclude that the optimal duration for standard triple therapy is 14 days, which is in agreement with recommendations of current guidelines (6).

Regarding the dose of antibiotics, most studies have prescribed A at doses of 1 g/24 hours and C at doses of 500 mg/12 hours (in the PPI + C + A regimen); therefore, the experience with lower doses in triple therapies is very limited (including also the Hp-EuReg experience) and insufficient to draw a conclusion. On the other hand, the importance of C dose in the PPI + C + M regimen remains controversial: Some systematic reviews reported that a half-dose C-based regimen is equally effective but better tolerated (17,18), which is in contrast with the results obtained in our study.

The severity of AEs of triple therapy in the Hp-EuReg was classified as mild in most cases, being serious in only <1% of them, in agreement with previous studies (9–11).

Finally, it has been recently shown that the addition of bismuth to a standard triple therapy increases its efficacy (19). Although bismuth *per se* has been reported to be well tolerated (20,21), unexpectedly, this quadruple therapy was associated with a relatively high incidence of AEs (34%) in our study, higher than that of the triple regimens in the same Hp-EuReg (see above). Nevertheless, it must be taken into account that this figure increased with longer duration of treatment (27% for 10 days and 37% for 14 days). In any case, most AEs were mild, and could be considered clinically irrelevant, in agreement with previous studies with this quadruple regimen (22).

Nonbismuth quadruple therapies

Nonbismuth quadruple therapy (i.e., the combination of a PPI with A, C, and a nitroimidazole), either in sequential or concomitant regimen, is at present one of the most widely used (23,24). Sequential regimen was associated with a 7–19% incidence of AEs in this study, a similar figure to that reported with triple therapy, in accordance with previous systematic reviews and meta-analyses (25,26). As it was the case with triple therapy, most AEs were mild, and none was serious. Furthermore, the use of tinidazole instead of M was associated with a lower rate of AEs (7% vs 19%) in our study, while the efficacy seems to be similar (23).

Although it has been suggested that concomitant treatment (PPI + A + C + M) has a similar safety profile than standard triple or sequential therapies (24,27), the incidence of AEs with concomitant therapy in our study (25%) seemed to be slightly higher, which is in agreement with previous systematic reviews and meta-analyses (11,28). The use of tinidazole instead of M seemed to be associated with a lower incidence of AEs (17% vs 25%), as was previously reported for sequential therapy. Anyhow, the overall safety profile with concomitant regimen (either with M or tinidazole) was quite favorable: most AEs were mild, and only <1% were serious, in agreement with previous meta-analyses (29).

Prolonging the duration of concomitant treatment seems to significantly enhance eradication rates but, at the same time, may increase the rates of AEs (24). Accordingly, the incidence of AEs in our patients receiving concomitant therapy increased from 19% (7 days) to 27% (14 days).

Bismuth quadruple therapies

Although a similar incidence of AEs has been previously reported for classic bismuth quadruple therapy (PPI + bismuth + tetracycline + M) and triple therapy (30,31), in the Hp-EuReg, AEs with the bismuth regimen were more frequent, reaching the highest rate of AEs (37%), although most of them were mild and only <1% were serious. This relatively high proportion of AEs

Table 3. Adverse events of most frequent *H. pylori* eradication treatments

Treatment regimen[a,b]	N	%[b]	95% CI
PPI + C + A	1,037	15	14–16
PPI + C + M	184	20	18–23
PPI + A + M	79	22	17–26
PPI + C + A + B	627	34	34–37
Concomitant (PPI + C + A + M)	926	25	23–26
Concomitant (PPI + C + A + T)	16	17	9.1–26
Sequential (PPI + C + A + M)	50	19	14–24
Sequential (PPI + C + A + T)	5	6.8	2.2–15
PPI + B + Tc + M	84	37	30–43
PPI + B + D + M	62	33	26–40
PPI + three-in-one	642	28	26–30
PPI + A + L	339	21	19–23
PPI + A + L + B	180	32	28–36
PPI + B + A + J	67	32	26–39
Total	4,298	22	22–23

N, number of patients with at least 1 adverse event; CI, confidence interval; PPI, proton pump inhibitor; A, amoxicillin C, clarithromycin; M, metronidazole; T, tinidazole; D, doxycycline; L, levofloxacin; B, bismuth; Tc, tetracycline; J, josamycin; three-in-one, three-in-one single-capsule bismuth quadruple therapy (Pylera).

[a]Nonstatistically significant ($P > 0.05$) differences were found in the safety of treatments when comparing first-line *vs* rescue treatment.

[b]Percentage relative to the information on safety available on each treatment category.

could be due, at least in part, to the long duration of treatment (14 days) in a high proportion of the patients included in the Hp-EuReg. Thus, in a recent meta-analysis, increased duration from 7 to 14 days was associated with an increase in the proportion of AEs (9).

In many parts of the world, tetracycline has become unavailable, and many pharmacies attempted to substitute doxycycline for tetracycline HCl (32). It has also been suggested that doxycycline may be better tolerated than tetracycline, although our results could not confirm this hypothesis, in agreement with previous studies (33).

Finally, the three-in-one single-capsule bismuth quadruple therapy (Pylera) was associated with a lower incidence of AEs (28%), compared with the classic bismuth quadruple regimen, which could be due to the lower dose of tetracycline in the three-in-one single presentation as compared to the classic quadruple regimen. This figure was lower than that previously reported in the literature, although the results have been highly heterogeneous (34).

Levofloxacin-based triple and quadruple therapies

Levofloxacin-based triple therapies have been demonstrated to be at least equally effective for *H. pylori* eradication than bismuth quadruple regimens (35). AEs related to levofloxacin are generally mild and related to the gastrointestinal system, including nausea and diarrhea (36). In this line, the incidence of AE with the PPI + A + levofloxacin regimen was 21% in our study, with a very low (0.1%) percentage of serious AEs. These results are fully coincident with those reported by the largest series of levofloxacin-based treatments (37) and with a previous systematic review (38). Several meta-analyses have confirmed a lower incidence of AEs with levofloxacin-based regimens than with the bismuth quadruple combination (38–40). Finally, in a network meta-analysis comparing tolerance of treatments for *H. pylori*, all regimens were considered tolerable, but 7 days of levofloxacin-based triple treatment ranked best in terms of the proportion of AEs reported (14). Nevertheless, the risk of suffering from AEs increased with longer durations of the treatment in our study, from 21% for 7 days to 39% for 14 days.

More recently, it has been demonstrated that combining bismuth and levofloxacin may enhance the efficacy of eradication regimens (35). AEs associated with the PPI + A + levofloxacin + bismuth treatment were relatively frequent in our study (32%), but none of them was classified as serious AEs. In fact, in a comparative study, there was no significant difference in the incidence of AEs when comparing a levofloxacin-based triple therapy with or without the addition of bismuth (41).

Impact of AEs on treatment compliance

It has been shown that decreased compliance is significantly associated with side effects (42). Thus, even more important than the incidence of AEs is their impact on compliance. In our study, the compliance rate was as high as 97% (which was applicable to virtually all treatment regimens). Furthermore, although AEs associated with all therapy regimens were quite common, only 1.3% of the patients discontinued treatment due to these AEs (figures varied depending on the treatment, but were <5% for all regimens). Several other studies have confirmed that the percentage of patients who stop medication because of AEs is very low, only approximately 1%–5% (9–12,22). Together with antibiotic resistance, compliance with therapy is the most important factor predicting *H. pylori* eradication; therefore, this represents a clinically relevant aspect of all regimens (43–47). The most common AEs recorded in all studies are bothersome digestive symptoms such as diarrhea, nausea, and vomiting, which have significant physical and social impact. Thus, doctors should explain to their patients that AEs might occur but that these are temporary and very often harmless (48).

Limitations and strengths of this study

The major drawback of our study is that it seems difficult to compare AE profiles between different investigators (the Hp-EuReg includes 300 investigators from 27 countries) and between different therapies (only comparative randomized controlled trials could reliably how side-effect profiles really differ between regimens). This limitation affects any comparison with published studies as the terminologies and definitions of AEs (and of their intensity and severity) used to represent safety vary among studies and, unfortunately, there is no uniform grading system (49,50). As a result, for example, most meta-analyses are unable to provide a comprehensive analysis of AEs (51). Nevertheless, it should be noted that in our study, AEs were well defined and *a priori* classified as mild (not interfering with daily routine), moderate (affecting daily routine), intense/severe (not allowing normal daily routine), and serious (causing death, hospitalization, disability, congenital anomaly, and/or requiring intervention to prevent permanent damage), which we think facilitates an homogeneous interpretation of the safety profile by all investigators.

Table 4. Incidence of the different types of adverse events by treatment

	PPI + C + A	PPI + C + M	PPI + A + M	PPI + C + A + B	PPI + C + A + M conco	PPI + C + A + T conco	PPI + C + A + M seq	PPI + C + A + T seq	PPI + B + Tc + M	PPI + B + D + M	PPI + three-in-one	PPI + A + L	PPI + A + L + B	PPI + B + A + J
Metallic taste, N	338	75	28	308	380	2	23	0	38	19	125	27	43	13
%	4.3	7.3	7.2	16	9.9	2	8.3	0	16	10	5	1.6	7.2	6.3
95% CI	3.9–4.8	5.7–9.0	4.6–10	15–18	8.9–11	0.24–7.0	4.9–12	0.0–3.2	11–21	5.5–15	4.1–5.8	0.94–2.2	5.0–9.3	2.7–9.8
Diarrhea, N	235	28	28	210	400	6	4	0	29	10	204	144	95	24
%	3	2.7	7.3	11	10	5.9	1.4	0	12	5.3	8.1	8.3	15	12
95% CI	2.6–3.4	1.7–3.8	4.6–10	9.7–13	9.4–11	0.84–11	0.39–3.6	0.0–3.2	8.0–17	1.8–8.7	7.0–9.2	6.9–9.6	13–19	7.0–16
Nausea, N	331	41	27	154	256	6	13	1	47	33	200	106	51	13
%	4.2	4	7.1	8.2	6.6	5.9	4.7	0.9	20	17	7.9	6.1	8.5	6.3
95% CI	3.8–4.7	2.7–5.2	4.4–9.8	6.9–9.4	5.8–7.4	0.84–11	2.0–7.3	0.02–4.8	15–26	12–23	6.9–9.0	4.9–7.2	6.2–11	2.7–9.8
Vomiting, N	90	11	13	80	85	2	3	1	17	8	110	74	20	1
%	1.2	1.1	3.4	4.2	2.2	2	1.1	0.9	7.3	4.2	4.4	4.3	3.3	0.5
95% CI	0.91–1.4	0.39–1.8	1.5–5.4	3.3–5.2	1.7–2.7	0.24–7.0	0.22–3.1	0.02–4.8	3.7–11	1.1–7.3	3.5–5.2	3.3–5.2	1.8–4.9	0.01–2.6
Dyspepsia, N	141	49	16	39	97	1	6	0	13	16	93	55	16	7
%	1.8	4.8	4.2	2.1	2.5	1	2.2	0	5.6	8.4	3.7	3.2	2.7	3.4
95% CI	1.5–2.1	3.4–6.1	2.1–6.3	1.4–2.7	2.0–3.0	0.03–5.4	0.27–4.0	0.00–3.2	2.4–8.7	4.2–13	2.9–4.4	2.3–4.0	1.3–4.0	0.67–6.1
Heartburn, N	79	5	15	9	24	1	0	0	3	2	22	26	2	2
%	1	0.5	3.9	0.5	0.6	1	0	0	1.3	1.1	0.9	1.5	0.3	1
95%CI	0.78–1.2	0.16–1.1	1.9–6.0	0.14–0.81	0.36–0.89	0.03–5.4	0.00–1.3	0.00–3.2	0.27–3.7	0.13–3.8	0.5–1.3	0.90–2.1	0.04–1.2	0.12–3.3
Abdominal pain, N	112	12	21	131	162	4	4	0	14	20	125	26	25	6
%	1.4	1.2	5.5	6.9	4.2	4	1.4	0	6	11	5	1.5	4.2	2.9
95% CI	1.2–1.7	0.46–1.9	3.1–7.9	5.8–8.1	3.6–4.9	1.1–9.8	0.39–3.6	0.00–3.2	2.7–9.3	5.9–15	4.1–5.8	0.90–2.1	2.5–5.9	0.37–5.4
Asthenia, N	127	12	4	33	110	0	5	2	11	9	145	35	11	5
%	1.6	1.2	1	1.7	2.9	0	1.8	1.7	4.7	4.7	5.8	2	1.8	2.4
95%CI	1.3–1.9	0.46–1.9	0.29–2.7	1.1–2.4	2.3–3.4	0.00–3.6	0.59–4.1	0.21–6.4	1.8–7.7	1.5–8.0	4.8–6.7	1.3–2.7	0.68–3.0	0.79–5.5
Anorexia, N	74	8	16	10	38	0	3	1	10	1	59	56	4	2
%	0.9	0.8	4.2	0.5	1	0	1.1	0.9	4.3	0.5	2.3	3.2	0.7	1
95% CI	0.73–1.2	0.19–1.4	2.1–6.3	0.18–0.88	0.66–1.3	0.00–3.6	0.22–3.1	0.02–4.8	1.5–7.1	0.01–2.9	1.7–3.0	2.4–4.1	0.18–1.7	0.12–3.4
TOTAL	1,527	241	168	974	1,552	22	61	5	182	118	1,083	549	267	73
%	22.38%	3.53%	2.46%	14.28%	22.75%	0.32%	0.89%	0.07%	2.67%	1.73%	15.88%	8.05%	3.91%	1.07%

N, number of patients with an adverse event; CI, confidence interval; PPI, proton pump inhibitor; A, amoxicillin C, clarithromycin; M, metronidazole; T, tinidazole; D, doxycycline; L, levofloxacin; B, bismuth; Tc, tetracycline; J, josamycin; three-in-one, three-in-one single-capsule bismuth quadruple therapy (Pylera); conco, concomitant; seq, sequential.

Table 5. Incidence of adverse events in most frequent treatments by length (7, 10, or 14 d)

	7 d		10 d		14 d	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
PPI + C + A**	2,003 (14)	12–15	2,904 (14)	13–15.5	1,699 (19)	17–21
PPI + C + M	723 (21)	18–24	112 (16)	8.8–23	67 (25)	14–36
PPI + A + M	83 (14.5)	6.3–23	227 (26)	20–31	44 (18)	5.6–31
PPI + C + A + B	NA	NA	569 (27)	23–31	1,233 (37)	35–40
Concomitant (PPI + C + A + M)*	NA	NA	2,031 (23)	21–25	1,649 (27)	25–29
Concomitant (PPI + C + A + T)	NA	NA	69 (17)	7.7–27	18 (17)	3.6–41
Sequential (PPI + C + A + M)	1 (100)	1.3–99	254 (18.5)	13–23	10 (10)	0.2–44
Sequential (PPI + C + A + T)	NA	NA	65 (8)	2.5–17	NA	NA
PPI + B + Tc + M**	24 (21)	7.1–42	120 (25)	17–33	85 (56.5)	45–68
PPI + B + D + M**	6 (0)	0–46	70 (17)	7.6–27	110 (45.5)	36–55
PPI + three-in-one	4 (0)	0–60	2,279 (28)	26–30	NA	NA
PPI + A + L**	218 (21)	15–26	887 (12)	9.5–14	483 (39)	34–43
PPI + A + L + B**	NA	NA	20 (30)	12–54	538 (32)	28–36
PPI + B + A + J	10 (20)	2.5–56	86 (39.5)	29–50	106 (24.5)	16–33

N, number of patients with an adverse event, CI, confidence interval; PPI, proton pump inhibitor; A, amoxicillin C, clarithromycin; M, metronidazole; T, tinidazole; D, doxycycline; L, levofloxacin; B, bismuth; Tc, tetracycline; J, josamycin; three-in-one, three-in-one single-capsule bismuth quadruple therapy (Pylera); NA, not available. The χ^2 test showed statistically significant differences (*$P < 0.05$ and **$P < 0.001$) between treatment lengths for some treatment schemes, as reported in the table.

We believe that our study, based on the invaluable information of the Hp-EuReg, has a number of strengths. Several clinical trials report high compliance rates suggesting a negligible impact of medication AEs, which may not necessarily reflect real-life compliance and adherence. Outcomes in clinical trials are often favored because of the homogeneous nature of the study population, close patient follow-up, the presence of well-defined protocols, adherence controls (e.g., pill counts and phone calls), financial incentive (free drug supplies, tests, and follow-up), and patient motivation. However, the open inclusion criteria of the Hp-EuReg ensure that our data represent the real clinical practice of the participant centers and corresponding European gastroenterologists. Moreover, the large number of recruiters and countries has provided, to the best of our knowledge, the largest study evaluating the safety of *H. pylori* eradication treatment, including more than 22,000 patients.

Table 6. Average duration (days) of adverse events by treatment

Days, mean (SD)	Metallic taste	Diarrhea	Nausea	Vomiting	Dyspepsia	Heartburn	Abdominal pain	Fatigue	Anorexia
PPI + C + A	7.2 (3.7)	5.4 (3.6)	5.2 (3.7)	5.2 (4.0)	7.2 (5.3)	5.7 (5.9)	5.4 (4.1)	5.9 (3.4)	6.5 (3.2)
PPI + C + M	6.5 (1.8)	8.7 (8.6)	6.2 (2.6)	5.2 (3.5)	6.5 (2.5)	7.4 (5.0)	7.0 (3.1)	8.3 (5.0)	7.0 (3.7)
PPI + A + M	7.6 (3.3)	7.4 (3.9)	7.4 (3.9)	6.0 (4.0)	8.4 (3.1)	8.9 (3.1)	9.5 (4.6)	5.0 (1.7)	10 (2.5)
PPI + C + A + B	9.2 (2.8)	7.6 (4.5)	7.6 (4.2)	7.6 (4.2)	9.7 (5.1)	7.6 (3.5)	8.4 (3.3)	8.7 (3.9)	6.3 (2.9)
Concomitant (PPI + C + A + M)	8.4 (3.2)	7.0 (3.6)	7.1 (3.5)	5.5 (3.7)	7.3 (3.7)	9.9 (6.4)	6.8 (3.7)	7.6 (3.7)	7.1 (3.2)
Concomitant (PPI + C + A + T)	11 (0.00)	6.7 (4.1)	3.7 (3.7)	1.5 (0.71)	NA	NA	3.8 (2.2)	NA	NA
Sequential (PPI + C + A + M)	5.5 (1.9)	3.0 (1.4)	4.5 (2.4)	3.0 (2.0)	6.3 (3.7)	NA	4.8 (4.5)	5.6 (3.2)	5.0 (0.00)
Sequential (PPI + C + A + T)	NA	NA	NA	NA	NA	NA	NA	NA	NA
PPI + B + Tc + M	9.0 (2.7)	7.0 (3.9)	8.9 (2.7)	5.8 (3.1)	8.8 (3.6)	8.0 (5.2)	8.0 (2.9)	7.6 (3.7)	9.2 (3.0)
PPI + B + D + M	8.3 (1.9)	7.6 (2.7)	7.8 (3.3)	5.0 (1.9)	7.3 (2.4)	28 (24)	7.6 (3.7)	8.8 (2.1)	NA
PPI + three-in-one	9.2 (3.4)	7.2 (3.9)	7.1 (3.6)	6.1 (4.0)	7.9 (3.2)	9.2 (8.5)	8.6 (6.1)	9.0 (4.1)	9.0 (2.3)
PPI + A + L	8.0 (2.8)	5.4 (2.4)	7.1 (4.6)	4.3 (2.1)	7.0 (3.4)	6.5 (3.1)	5.4 (2.9)	8.2 (2.9)	8.2 (2.7)
PPI + A + L + B	10 (2.9)	8.8 (5.2)	9.3 (6.1)	7.7 (9.9)	14 (13)	6.0 (1.4)	7.6 (2.8)	7.5 (3.1)	8.5 (3.0)
PPI + B + A + J	9.7 (2.6)	7.5 (4.5)	8.2 (4.9)	NA	8.4 (3.6)	6.5 (6.4)	10 (6.1)	8.6 (3.4)	11 (0.00)

PPI, proton pump inhibitor; A, amoxicillin C, clarithromycin; M, metronidazole; T, tinidazole; D, doxycycline; L, levofloxacin; B, bismuth; Tc, tetracycline; J, josamycin; three-in-one, three-in-one single-capsule bismuth quadruple therapy (Pylera); NA, not available.

In summary, from the valuable experience of the Hp-EuReg, we can conclude that *H. pylori* eradication treatment tends to be safe in real clinical practice (as it occurs in randomized clinical trials). Although it quite frequently induces AEs, these are mostly mild and limited to the duration of treatment. Furthermore, these AEs do not have a negative impact on treatment compliance.

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CONFLICTS OF INTEREST

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Specific author contributions: O.P.N.: Scientific Director, member of the project's Scientific Committee, coordinated the study, designed, and programmed the electronic case report form, reviewed, analyzed, and interpreted the data, drafted the manuscript, and approved the submitted manuscript. A.P.-A., B.T., M.C.-F., L.J., L.B., A.L., N.B.J., J.P.-L., G.F., J.M.H., Z.K., I.V., M.A., L.F.-S., L.R., S.A., J.B., J.O., M.P., L.V., P.M.R., O.Z., S.G., R.P., I.M., B.J.G.R., C.S., M.R.L., T.I., J.G.C., M.D.-C., V.N., N.N.D., and O.N.: collected and helped interpret data, critically reviewed the manuscript, and approved the submitted manuscript. J.K., O.S., D.B., M.L., J.C.M., T.R., G.M.B., I.S., P.P., F.L., M.V., and F.H.: acted as National Coordinators and as recruiters. They selected national recruiters, collected and helped interpret data, critically reviewed the manuscript, and approved the submitted manuscript. M.C.: supervised, coordinated, and monitored the data collection, interpreted the data, critically reviewed the manuscript, and approved the submitted manuscript. I.P.: Scientific Director and member of the project's Scientific Committee, critically reviewed the manuscript draft, and approved the submitted manuscript. F.M.: member of the project's Scientific Committee, designed the protocol, planned the study, critically reviewed the manuscript, and approved the submitted manuscript. C.O'M.: member of the project's Scientific Committee, designed the protocol, planned the study, critically reviewed the manuscript, and approved the submitted manuscript. J.P.G.: director of the project and member of the project's Scientific Committee, obtained funding, designed the protocol and planned the study, acted as the National Spanish Coordinator, recruited patients, analyzed and interpreted the data, critically reviewed the manuscript, and approved the submitted manuscript.

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Study Highlights

WHAT IS KNOWN

- ✓ The frequency, severity, and type of adverse events (AEs) for the different *H. pylori* eradication regimens, and the impact of these factors on therapeutic compliance, have been poorly investigated.
- ✓ Properly evaluation of the wide spectrum of AEs associated with the wide variety of antibiotic regimens requires the study of a very large and diverse population receiving these eradication treatments.
- ✓ The "European Registry on *Helicobacter pylori* management" brings together information on the real clinical practice of most European countries.

WHAT IS NEW HERE

- ✓ *Helicobacter pylori* eradication treatment tends to be safe in real clinical practice (as it occurs in randomized clinical trials).
- ✓ The different treatments prescribed to 22,492 patients caused at least 1 AE in 23% of the cases. Taste disturbance (7%), diarrhea (7%), nausea (6%), and abdominal pain (3%) were the most frequent.
- ✓ The majority of AEs were mild (57%), and only 0.08% were serious, with an average duration of 7 days.
- ✓ The appearance of AEs does not interfere significantly with treatment compliance.

REFERENCES

1. Crowe SE. Helicobacter pylori infection. N Engl J Med 2019;380:1158–65.
2. Chey WD, Leontiadis GI, Howden CW, et al. ACG clinical guideline: Treatment of Helicobacter pylori infection. Am J Gastroenterol 2017;112:212–39.
3. McNicholl AG, O'Morain CA, Megraud F, et al. As scientific committee of the Hp-Eureg on Behalf of the national C. Protocol of the European registry on the management of Helicobacter pylori infection (Hp-EuReg). Helicobacter 2019;24:e12630.
4. 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.
5. 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;42:377–81.
6. 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.
7. Kwok A, Lam T, Katelaris P, et al. Helicobacter pylori eradication therapy: Indications, efficacy and safety. Expert Opin Drug Saf 2008;7:271–81.
8. Ford AC, Delaney BC, Forman D, et al. Eradication therapy in Helicobacter pylori positive peptic ulcer disease: Systematic review and economic analysis. Am J Gastroenterol 2004;99:1833–55.
9. Yuan Y, Ford AC, Khan KJ, et al. Optimum duration of regimens for Helicobacter pylori eradication. Cochrane Database Syst Rev 2013:CD008337.
10. de Boer WA, Tytgat GN. The best therapy for Helicobacter pylori infection: Should efficacy or side-effect profile determine our choice? Scand J Gastroenterol 1995;30:401–7.
11. Yeo YH, Hsu CC, Lee CC, et al. Systematic review and network meta-analysis: Comparative effectiveness of therapies for second-line Helicobacter pylori eradication. J Gastroenterol Hepatol 2019;34:59–67.
12. Gong EJ, Yun SC, Jung HY, et al. Meta-analysis of first-line triple therapy for helicobacter pylori eradication in korea: Is it time to change?. J Korean Med Sci 2014;29:704–13.

13. Fuccio L, Minardi ME, Zagari RM, et al. Meta-analysis: Duration of first-line proton-pump inhibitor based triple therapy for Helicobacter pylori eradication. Ann Intern Med 2007;147:553–62.
14. Li BZ, Threapleton DE, Wang JY, et al. Comparative effectiveness and tolerance of treatments for Helicobacter pylori: Systematic review and network meta-analysis. Bmj 2015;351:h4052.
15. Hansen MP, Scott AM, McCullough A, et al. Adverse events in people taking macrolide antibiotics versus placebo for any indication. Cochrane Database Syst Rev 2019;1:CD011825.
16. Puig I, Baylina M, Sanchez-Delgado J, et al. Systematic review and meta-analysis: Triple therapy combining a proton-pump inhibitor, amoxicillin and metronidazole for Helicobacter pylori first-line treatment. J Antimicrob Chemother 2016;71:2740–53.
17. Huang J, Hunt RH. The importance of clarithromycin dose in the management of Helicobacter pylori infection: A meta-analysis of triple therapies with a proton pump inhibitor, clarithromycin and amoxycillin or metronidazole. Aliment Pharmacol Ther 1999;13:719–29.
18. Harb AH, Chalhoub JM, Abou Mrad R, et al. Systematic review and meta-analysis: Full- vs. half-dose anti-microbials in clarithromycin-based regimens for Helicobacter pylori eradication. Aliment Pharmacol Ther 2015;42:131–41.
19. 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.
20. Ford AC, Malfertheiner P, Giguere M, et al. Adverse events with bismuth salts for Helicobacter pylori eradication: Systematic review and meta-analysis. World J Gastroenterol 2008;14:7361–70.
21. Hillemand P, Palliere M, Laquais B, et al. [Bismuth treatment and blood bismuth levels]. Sem Hop 1977;53:1663–9. French.
22. Gisbert JP, McNicholl AG. Optimization strategies aimed to increase the efficacy of H. pylori eradication therapies. Helicobacter 2017;22:e12392.
23. Gisbert JP, Calvet X, O'Connor A, et al. Sequential therapy for Helicobacter pylori eradication: A critical review. J Clin Gastroenterol 2010;44:313–25.
24. Gisbert JP, Calvet X. Review article: Non-bismuth quadruple (concomitant) therapy for eradication of Helicobater pylori. Aliment Pharmacol Ther 2011;34:604–17.
25. Nyssen OP, McNicholl AG, Megraud F, et al. Sequential versus standard triple first-line therapy for Helicobacter pylori eradication. Cochrane Database Syst Rev 2016:CD009034.
26. Liou JM, Chen CC, Lee YC, et al. Systematic review with meta-analysis: 10- or 14-day sequential therapy vs. 14-day triple therapy in the first line treatment of Helicobacter pylori infection. Aliment Pharmacol Ther 2016;43:470–81.
27. Wang Y, Zhao R, Wang B, et al. Sequential versus concomitant therapy for treatment of Helicobacter pylori infection: An updated systematic review and meta-analysis. Eur J Clin Pharmacol 2018;74:1–13.
28. Chen MJ, Chen CC, Chen YN, et al. Systematic review with meta-analysis: Concomitant therapy vs. Triple therapy for the first-line treatment of Helicobacter pylori infection. Am J Gastroenterol 2018;113:1444–57.
29. Essa AS, Kramer JR, Graham DY, et al. Meta-analysis: Four-drug, three-antibiotic, non-bismuth-containing "concomitant therapy" versus triple therapy for Helicobacter pylori eradication. Helicobacter 2009;14:109–18.
30. Fischbach LA, van Zanten S, Dickason J. Meta-analysis: The efficacy, adverse events, and adherence related to first-line anti-Helicobacter pylori quadruple therapies. Aliment Pharmacol Ther 2004;20:1071–82.
31. Luther J, Higgins PD, Schoenfeld PS, et al. Empiric quadruple vs. triple therapy for primary treatment of Helicobacter pylori infection: Systematic review and meta-analysis of efficacy and tolerability. Am J Gastroenterol 2010;105:65–73.
32. Niv Y. Doxycycline in eradication therapy of Helicobacter pylori—a systematic review and meta-analysis. Digestion 2016;93:167–73.
33. Borody TJ, George LL, Brandl S, et al. Helicobacter pylori eradication with doxycycline-metronidazole-bismuth subcitrate triple therapy. Scand J Gastroenterol 1992;27:281–4.
34. 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.
35. 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;77:765–76.
36. Croom KF, Goa KL. Levofloxacin: A review of its use in the treatment of bacterial infections in the United States. Drugs 2003;63:2769–802.
37. Gisbert JP, Perez-Aisa A, Bermejo F, et al. Second-line therapy with levofloxacin after failure of treatment to eradicate helicobacter pylori infection: Time trends in a Spanish multicenter study of 1000 patients. J Clin Gastroenterol 2013;47:130–5.
38. Gisbert JP, Morena F. Systematic review and meta-analysis: Levofloxacin-based rescue regimens after Helicobacter pylori treatment failure. Aliment Pharmacol Ther 2006;23:35–44.
39. Saad RJ, Schoenfeld P, Kim HM, et al. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent Helicobacter pylori infection: A meta-analysis. Am J Gastroenterol 2006;101:488–96.
40. Li Y, Huang X, Yao L, et al. Advantages of moxifloxacin and levofloxacin-based triple therapy for second-line treatments of persistent Helicobacter pylori infection: A meta analysis. Wien Klin Wochenschr 2010;122:413–22.
41. Liao J, Zheng Q, Liang X, et al. Effect of fluoroquinolone resistance on 14-day levofloxacin triple and triple plus bismuth quadruple therapy. Helicobacter 2013;18:373–7.
42. Henry A, Batey RG. Enhancing compliance not a prerequisite for effective eradication of Helicobacter pylori: The HelP study. Am J Gastroenterol 1999;94:811–5.
43. Wermeille J, Cunningham M, Dederding JP, et al. Failure of Helicobacter pylori eradication: Is poor compliance the main cause?. Gastroenterol Clin Biol 2002;26:216–9.
44. Lee M, Kemp JA, Canning A, et al. A randomized controlled trial of an enhanced patient compliance program for Helicobacter pylori therapy. Arch Intern Med 1999;159:2312–6.
45. Graham DY, Lew GM, Malaty HM, et al. Factors influencing the eradication of Helicobacter pylori with triple therapy. Gastroenterology 1992;102:493–6.
46. Kotilea K, Mekhael J, Salame A, et al. Eradication rate of Helicobacter pylori infection is directly influenced by adherence to therapy in children. Helicobacter 2017;22:e12383.
47. 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 2021. [Epub ahead of print January 5, 2021.] (doi: 10.1097/MCG.0000000000001482).
48. O'Connor JP, Taneike I, O'Morain C. Improving compliance with helicobacter pylori eradication therapy: When and how? Therap Adv Gastroenterol 2009;2:273–9.
49. Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: An evaluation of 7 medical areas. JAMA 2001;285:437–43.
50. de Boer WA, Thys JC, Borody TJ, et al. Proposal for use of a standard side effect scoring system in studies exploring Helicobacter pylori treatment regimens. Eur J Gastroenterol Hepatol 1996;8:641–3.
51. Golder S, Loke Y, McIntosh HM. Room for improvement? A survey of the methods used in systematic reviews of adverse effects. BMC Med Res Methodol 2006;6:3.