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Helicobacter pylori first-line and rescue treatments in patients allergic to penicillin: Experience from the European Registry on *H pylori* management (Hp-EuReg)

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Abstract

Background: Experience in *Helicobacter pylori* eradication treatment of patients allergic to penicillin is very scarce. A triple combination with a PPI, clarithromycin (C), and metronidazole (M) is often prescribed as the first option, although more recently the use of a quadruple therapy with PPI, bismuth (B), tetracycline (T), and M has been recommended.

Aim: To evaluate the efficacy and safety of first-line and rescue treatments in patients allergic to penicillin in the "European Registry of *H pylori* management" (Hp-EuReg).

Methods: A systematic prospective registry of the clinical practice of European gastroenterologists (27 countries, 300 investigators) on the management of *H pylori* infection. An e-CRF was created on AEG-REDCap. Patients with penicillin allergy were analyzed until June 2019.

Results: One-thousand eighty-four patients allergic to penicillin were analyzed. The most frequently prescribed first-line treatments were as follows: PPI + C + M (n = 285) and PPI + B + T + M (classic or Pylera®; n = 250). In first line, the efficacy of PPI + C + M was 69%, while PPI + B + T + M reached 91% ($P < .001$). In second line, after the failure of PPI + C + M, two rescue options showed similar efficacy: PPI + B + T + M (78%) and PPI + C + levofloxacin (L) (71%) ($P > .05$). In third line, after the failure of PPI + C + M and PPI + C + L, PPI + B + T + M was successful in 75% of cases.

Conclusion: In patients allergic to penicillin, a triple combination with PPI + C + M should not be generally recommended as a first-line treatment, while a quadruple regimen with PPI + B + T + M seems to be a better option. As a rescue treatment, this quadruple regimen (if not previously prescribed) or a triple regimen with PPI + C + L could be used but achieved suboptimal (<80%) results.

KEYWORDS
allergic, allergy, bismuth, clarithromycin, *Helicobacter pylori*, levofloxacin, penicillin

1 | INTRODUCTION

Helicobacter pylori (*H pylori*) infection affects billions of people worldwide, being the main cause of gastritis, peptic ulcer disease, and gastric cancer. Amoxicillin is one of the most effective antimicrobial agents against *H pylori*, and therefore, most eradication regimens include this antibiotic. Triple and quadruple therapies, including a proton-pump inhibitor (PPI) and two or three antibiotics, mainly amoxicillin, clarithromycin ± metronidazole, are the standard treatments for *H pylori* infection in most geographical areas.[1]

Penicillin allergy is the most common type of drug allergy, reported in about 5%-10% of individuals.[2,3] However, to date, only few studies have evaluated the efficacy of first-line *H pylori* eradication treatment specifically in patients allergic to penicillin. Furthermore, the appropriate rescue therapy when eradication therapy fails in this scenario has not been properly evaluated.

The "European Registry on *Helicobacter pylori* management" (Hp-EuReg) brings together information on the real clinical practice of a majority of European countries, including thousands of patients.[4] The Registry represents a good mapping overview of the current situation regarding *H pylori* management, allowing not only continuous assessment of the integration of clinical recommendations agreed on medical consensus, but also of the possible strategies for improvement.

The aim of the present study was to evaluate the efficacy and safety of first-line and rescue treatments in patients allergic to penicillin in the Hp-EuReg, a database registering systematically a large and representative sample of routine clinical practice in Europe.

2 | METHODS

This analysis focused on the "European Registry on *H pylori* Management" (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).

The Scientific Committee in charge of the international coordination and the approval of investigators, analyses, and manuscripts comprises: Javier P. Gisbert (Principal Investigator), Francis Mégraud, Colm A. O'Morain, and Olga P. Nyssen (Scientific Coordinator).

A first list of countries was created selecting those with at least ten *H pylori* PubMed references. Top investigators in the country were asked to perform a feasibility selection process. A subsequent more open selection process was created contacting clinical researchers from nonparticipant European countries. Countries with compromised viability or lack of response/participation were excluded. Finally, 27 European countries were selected.

2.1 | Ethics

The Hp-EuReg protocol 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 prospectively registered at ClinicalTrials.gov under the code NCT02328131. An addendum for a 10-year extension of the project was also approved. The protocol has been recently published.[4]

2.2 | National coordinators

In each country, a National Coordinator was invited based on its clinical and research activity. The National Coordinators constitute the monitoring and drafting committee of the registry. The National Coordinators were in charge of selecting recruiting investigators in each country and are responsible for the follow-up and quality of the recruiting, and the compliance with national and local legislation; they are the link between promoters and recruiter investigators.

2.3 | Recruiter investigators

The Recruiter Investigators were required to be gastroenterologists serving an adult population with a gastroenterology outpatient clinic that routinely manages *H pylori*-infected patients with *H pylori* diagnosis and treatment indication. Eradication confirmation tests had to be available. Cases were managed and registered according to their routine clinical practice.

2.4 | Study aim

The general primary aim of the Hp-EuReg was to set up an ongoing 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.[4]

The aim of the current study was to evaluate the efficacy and safety of first-line and rescue treatments in patients allergic to penicillin in the "European Registry of *H pylori* management" (Hp-EuReg).

2.5 | Data extraction and management

In order to perform the present analysis, a programmed data extraction was developed in June 2019 selecting those cases registered in Europe until January 2019, thus allowing a minimum of 6-month follow-up. All countries were accounted for in the analysis.

Study data were collected and managed using REDCap electronic data capture tools hosted at "Asociación Española de Gastroenterología" (AEG; www.aegastro.es).[5] REDCap is a secure, web-based application designed to support data capture for research studies. The characteristics of the electronic case report form (e-CRF) were detailed in the protocol publication describing the tools created for data collection. The AEG is a nonprofit Scientific and Medical Society focused on Gastroenterology, which provided this service free of charge, with the sole aim of promoting independent investigator-driven research.

2.6 | Monitoring and quality of data

At least a 10% of the total of the included records were monitored in each country and each hospital. Monitoring was performed within the e-CRFs using REDCap applications. The process of data review was meant to evaluate whether the study selection criteria were met, the information was correctly registered and ultimately, to ensure the study was conducted according to the highest scientific and ethical standards. Data discordances were resolved by querying the investigators and through group e-mailing.

Additionally, after data extraction and prior to statistical analysis, the database was reviewed for inconsistencies and subsequently subjected to data cleaning. As part of the process, a quality index tool was developed to select the records that met a minimum of data quality. Such quality was defined by the amount of relevant data completion within the e-CRFs. Data completion was assessed based on three pivotal items pooling a group of variables each. The three quality items were as follows: "baseline characteristics," "treatment," and "follow-up". Each item grouped relevant clinical variables that were considered essential to evaluate *H pylori* management. Each variable was allocated a weighted coefficient, thereby enabling a quality index for each item. The quality index scale, ranging between 0 and 1, was calculated as the ratio between the sum of the registered variables and the sum of all the variables assessed for a given item. Thereafter, all three quality indexes obtained were added into an overall quality index used for the final quality assessment. The threshold of the overall quality index of a record for "having a good quality" and "being eligible for analysis" was set to a minimum of 0.9.

2.7 | Variables and outcomes

The e-CRF registered 290 variables including demographics, history and comorbidity, data on infection and diagnosis, previous eradication attempts, current treatment, compliance, adverse events, and effectiveness. All personal data were anonymized. The main outcome was eradication of *H pylori* confirmed at least 4 weeks after treatment using locally accepted/validated diagnostic methods. Compliance was defined as having taken at least 90% of the prescribed drugs. Adverse events and compliance were evaluated through patient questioning with both open-ended questions and a predefined questionnaire. A detailed list of variables and outcomes is shown in the protocol publication.[4]

2.8 | Effectiveness analysis

The intention-to-treat (ITT) analysis included all patients that had been registered up to January 2019, to allow at least a 6-month follow-up as mentioned before, and lost to follow-up cases were considered treatment failures. Per-protocol (PP) analysis included all cases that finished follow-up and had taken at least 90% of the treatment drugs, as defined in the approved protocol. A modified ITT (mITT) was designed aiming to reach the closest result to those obtained in clinical practice. This mITT included for analyses all cases that had completed follow-up (that is, a confirmatory test—success or failure—was available after the eradication treatment). In the current study, mITT and PP effectiveness results are provided.

2.9 | Statistical analyses

Continuous variables are presented as the arithmetic mean and respective standard deviation. Qualitative variables are presented as percentages and 95% confidence intervals (95%CI). The chi-square test was applied to compare qualitative variables. Significance was considered at $P < .05$.

3 | RESULTS

3.1 | Overview

A final dataset including 1084 patients allergic to penicillin was used, representing 3.3% of the total cases registered in the Hp-EuReg until June 2019.

Mean age of patients was 53 (±15.1) years, 70% were women and 92% Caucasian. Indication for eradication was functional dyspepsia in 40% of the patients, noninvestigated dyspepsia in 18%, and peptic

ulcer in 17%. Diagnosis was performed by means of histology in 40% of the cases, ^{13}C-urea breath test in 28%, rapid urease test in 28%, monoclonal stool antigen test in 6%, and culture in 5% of the cases. Overall, 65% of the patients underwent an invasive endoscopic procedure. The results corresponding to each of the treatment lines evaluated are reported below.

3.2 | First-line treatment in patients allergic to penicillin

The triple therapy with PPI-clarithromycin-metronidazole was the most commonly prescribed first-line therapy (n = 285, 48%); followed by the bismuth quadruple therapy with a PPI-bismuth-tetracycline-metronidazole (n = 250, 42%) and the triple PPI-clarithromycin-levofloxacin (n = 54, 9%). The highest effectiveness in first-line treatment was reported with the bismuth quadruple therapy, achieving on average 91% eradication rate (93% with Pylera®, 92% with PPI + bismuth + tetracycline + metronidazole, and 78% with PPI + bismuth + doxycicline + metronidazole) in the mITT population. Differences between most frequently used first-line treatments were statistically significant (chi-square test, $P < .001$). However, differences between the use of doxycycline and tetracycline in the bismuth first-line quadruple therapy were nonstatistically significant (Fisher's exact test, $P > .05$). Compliance was >90% in all three therapies, and the triple PPI-clarithromycin-levofloxacin showed the lowest rate of adverse events (19% of the cases). Results (effectiveness, compliance, and adverse events) of the first-line eradication treatments evaluated in patients allergic to penicillin are presented in Table 1.

3.3 | Second-line treatment in patients allergic to penicillin

After a failed triple therapy with PPI-clarithromycin-metronidazole, the classic bismuth quadruple therapy (given as a PPI-bismuth-tetracycline-metronidazole, PPI-bismuth-doxycycline-metronidazole, or the single three-in-one capsule Pylera® plus a PPI) was the most commonly prescribed second-line treatment (n = 70, 53%), followed by the triple therapy with a PPI-clarithromycin-levofloxacin (n = 20, 16%) and the triple therapy with a PPI-metronidazole-levofloxacin (n = 13, 11%). The highest effectiveness in second-line treatment was reported for the bismuth quadruple therapy, achieving on average 78% eradication rate (92% with PPI + bismuth + tetracycline + metronidazole, 81% with Pylera®, and 50% with PPI + bismuth + doxycicline + metronidazole) in the mITT population. Differences between second-line treatment schemes were nonstatistically significant (chi-square test, $P > .05$); however, statistically significant differences (Fisher's exact test, $P < .05$) were reported with the use of doxycycline vs. tetracycline in second-line bismuth quadruple treatment after failure of triple therapy with PPI-clarithromycin-metronidazole. Compliance was >90% after one failed therapy attempt; however, adverse events occurred in higher proportion when bismuth quadruple therapy was used (34% of the cases). Results (effectiveness, compliance, and adverse events) of the second-line eradication treatments evaluated in patients allergic to penicillin are presented in Table 2.

3.4 | Third-line treatment in patients allergic to penicillin

After a first failed eradication attempt with the triple therapy PPI-clarithromycin-metronidazole and a second-line treatment failure with the triple therapy PPI-clarithromycin-levofloxacin, the third-line treatment used in all cases was the bismuth quadruple therapy (13 patients). Eradication rate was 75% in the mITT population, compliance was 90%, but adverse events occurred in 58% of the patients. Results (effectiveness, compliance, and adverse events) of the third-line eradication treatments evaluated in patients allergic to penicillin are presented in Table 3.

3.5 | Safety of treatments in patients allergic to penicillin

Overall, in first-line treatment, adverse events were higher when the bismuth quadruple therapy was used (29% of the cases), followed by the triple therapy PPI-clarithromycin-metronidazole (23%) and the PPI-clarithromycin-levofloxacin triple therapy (19%). Taste disturbance, diarrhea, and nausea were the most frequent adverse events. The duration of the adverse events ranged from 5 to almost 10 days. The intensity of the adverse events was higher when the triple therapy with a PPI-clarithromycin-metronidazole was administered (26% of severe adverse events); however, discontinuation of treatment due to the occurrence of an adverse event was frequent in patients treated with the bismuth quadruple therapy (17% stopped treatment). The type of adverse event, average duration, severity, and rate of treatment discontinuation due to an adverse event are reported by treatment in Table S1.

4 | DISCUSSION

The treatment of *H pylori* in patients with penicillin allergy—a relatively frequent scenario—represents a significant challenge, as amoxicillin is one of the most effective antibiotics against this infection, and acquired resistance is rare.[6] Only few studies, including very low number of patients, have evaluated *H pylori* first-line eradication treatments in patients with penicillin allergy (summarized in Table 4).[7-21] Triple therapy including a PPI and two antibiotics, mainly amoxicillin and clarithromycin, still remains the standard treatment for *H pylori* infection in some countries. However, when penicillin allergy is present, replacing amoxicillin with metronidazole has been recommended.[1] In fact, this was the most common strategy in the Hp-EuReg, prescribed in 48% of the cases (285 patients). However, although this regimen was relatively well tolerated (23% adverse events, mostly mild), the

TABLE 1 First-line *H pylori* eradication treatments in patients with penicillin allergy in the "European Registry of *H pylori* management"

First-line regimen	Use, n (%)	mITT, n/N (%)	95% CI	PP, n/N (%)	95% CI	Compliance, n/N (%)	Adverse events, n/N (%)
PPI + C + M[a]	285 (48)	158/228 (69)	63-75	157/227 (69)	63-75	231/236 (98)	55/243 (23)
PPI + C + L	54 (9.2)	40/50 (80)	68-92	40/49 (82)	70-93	51/52 (98)	10/52 (19)
PPI + B + T + M[a]	250 (42)	207/228 (91)	87-95	203/221 (92)	88-96	224/234 (96)	68/233 (29)

Abbreviations: B, bismuth; C, clarithromycin; CI, confidence interval; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; PP, per-protocol; PPI, proton-pump inhibitor; T, tetracycline.

PPI + B + T + M: classic bismuth quadruple or Pylera®.

[a]Chi-square test statistical comparisons were performed with most frequently prescribed first-line treatments, and differences between treatments were statistically significant ($P < .001$).

TABLE 2 Second-line *H pylori* eradication treatments in patients with penicillin allergy in the "European Registry of *H pylori* management"

1st-line	2nd-line	mITT, n/N (%)	95% CI	PP, n/N (%)	95% CI	Compliance, n/N (%)	Adverse events, n/N (%)
PPI + C + M	PPI + C + L[a]	12/17 (71)	44-90	11/16 (69)	41-89	17/19 (89.5)	3/19 (16)
	PPI + M + L	10/13 (77)	46-95	10/13 (77)	46-95	13/13 (100)	3/13 (23)
	PPI + B + T + M[a]	50/64 (78)	67-89	50/61 (82)	71-92	62/65 (95.3)	14/42 (34)
PPI + C + L	PPI + B + T + M	4/5 (80)	28-99	4/5 (80)	28-99	5/5 (100)	1/5 (20)
PPI + B + T + M	PPI + C + L	3/3 (100)	29-100	3/3 (100)	29-100	3/4 (75)	2/4 (50)
	PPI + M + L	3/4 (75)	19-99	3/4 (75)	19-99	4/4 (100)	0/4 (0)

Abbreviations: B, bismuth; C, clarithromycin; CI, confidence interval; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; PP, per-protocol; PPI, proton-pump inhibitor; T, tetracycline.

PPI + B + T + M: classic bismuth quadruple or Pylera®.

[a]Chi-square test statistical comparisons were performed with most frequently prescribed second-line treatments. Nonstatistically significant differences ($P > .05$) were reported between second-line therapies after failure of PPI + C + M.

TABLE 3 Third-line *H pylori* eradication treatments in patients with penicillin allergy in the "European Registry of *H pylori* management"

1st-line	2nd-line	3rd-line	mITT, n/N (%)	95% CI	PP, n/N (%)	95% CI	Compliance, n/N (%)	Adverse events, n/N (%)
PPI + C + M	PPI + C + L	PPI + B + T + M	9/12 (75)	43-94	9/100 (82)	2.9-15	11/12 (92)	7/12 (58)
	PPI + M + L	PPI + B + T + M	5/5 (100)	48-100	5/5 (100)	48-100	5/5 (100)	0/5 (0)
	PPI + B + T + M	PPI + C + L	1/2 (50)	1.3-99	1/2 (50)	1.3-99	2/2 (100)	0/2 (0)
PPI + C + L	PPI + B + T + M	PPI + B + T + M	0/1 (0)	—	0/1 (0)	—	1/1 (100)	0/1 (0)
PPI + B + T + M	PPI + M + L	PPI + C + M + L	1/1 (100)	1.3-99	1/1 (100)	1.3-99	1/1 (100)	0/1 (0)

Abbreviations: B, bismuth; C, clarithromycin; CI, confidence interval; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; PP, per-protocol; PPI, proton-pump inhibitor; T, tetracycline.

PPI + B + T + M: classic bismuth quadruple or Pylera®.

compliance rate was very high (98%), and the cure rate was clearly insufficient (69%). These results are in agreement with those previously reported (six studies evaluating the PPI-clarithromycin-metronidazole regimen, Table 4), with a mean eradication rate of only 60%.[9-14] Although most studies prescribed these regimens for only 7 days, a length which is at present considered as clearly insufficient, one study achieved similar disappointing results with 14 days of treatment.[14] Another study showed that using high-dose metronidazole in this triple combination was unable to achieve higher cure rates.[14]

The disappointing cure rates in the Hp-EuReg and in the aforementioned studies with this triple combination (PPI-clarithromycin-metronidazole) might be related, at least in part, to increasing resistance rates to both clarithromycin and metronidazole.[22-24] It may be speculated that the resistance rate to nonbeta-lactamic antibiotics could be even higher in patients allergic to penicillin; this may be due to the fact that these patients have probably been previously treated with these antibiotics.

A possible strategy to increase the efficacy of this triple regimen could be to add bismuth. Long et al, in a randomized study including patients allergic to penicillin, demonstrated that the addition of bismuth to a triple therapy with a PPI, clarithromycin, and metronidazole dramatically increased the eradication rates (from 64% to 85%).[14] Another option to improve the efficacy of the standard triple therapy is to increase the anti-secretory potency. Vonoprazan is a novel potassium-competitive blocker that inhibits the gastric H + K+-ATPase, and it has a quicker and stronger acid-inhibitory effect than PPIs.[25] Two studies, including only 33 patients, have evaluated a triple regimen with vonoprazan,

TABLE 4 Studies evaluating *H pylori* first-line eradication treatments empirically prescribed (without susceptibility testing) in patients with penicillin allergy

Author	Country	Design	Regimen	Duration	Number or patients	Eradication rate (%)	Adverse events (%)
Prach[7]	UK	P	PPI + C	14	3	100	–
Tavakoli[8]	UK	P	PPI + C	14	3	100	–
Gisbert[9]	Spain	P	PPI + C + M	7	12	58	17
Gisbert[10]	Spain	P	PPI + C + M	7	50	54	10
Gisbert[11]	Spain	P	PPI + C + M	7	112	57	14
Ono[12]	Japan	R	PPI + C + M	7	10	50	–
Sue[13]	Japan	R	PPI + C + M	7	30	83	–
Long[14]	China	P	PPI + C + M	14	33	64	45
Ono[12]	Japan	R	V + C + M	7	13	92	–
Sue[13]	Japan	R	V + C + M	7	20	100	–
Rodriguez[15]	Puerto Rico	R	PPI + T + M	10	17	82	–
Matsushima[16]	Japan	R	PPI + T + M	7-14	5	80	–
Gisbert[11]	Spain	P	PPI + B + T + M	10	50	74	14
Gao[17]	China	R	PPI + B + T + M	14	120	87	47
Ono[12]	Japan	R	PPI + M + S	7	20	100	–
Furuta[18]	Japan	R	PPI + M + S	7-14	11	100	64
Mori[19]	Japan	P	PPI + M + S	10	33	100	32
Ono[12]	Japan	R	V + M + S	7	14	93	–
Osumi[20]	Japan	R	PPI + M + Mi	7	5	100	–
Long[14]	China	P	PPI + C + M + B	14	33	85	48
Song[21]	China	P	PPI + B+L + Ce	14	152	85	21

Abbreviations: B, bismuth; C, clarithromycin; Ce, cefuroxime; L, levofloxacin; M, metronidazole; Mi, minocycline; PPI, proton-pump inhibitor; S, sitafloxacin; T, tetracycline; V, vonoprazan.

Design: P (prospective), R (retrospective).

Eradication rate: by intention-to-treat analysis.

clarithromycin, and metronidazole, and have achieved a remarkable mean cure rate of 97%[12,13] (Table 4).

On the other hand, two research groups prescribed a regimen of PPI, tetracycline, and metronidazole to five and 17 patients with documented allergy to penicillin and reported an 80% eradication rate[15,16] (Table 4). These encouraging results suggest that this triple combination (or even better, with the addition of bismuth, resulting in a quadruple regimen, see later) may be a better alternative for first-line treatment in the presence of penicillin allergy (mainly in areas with high metronidazole and/or clarithromycin resistance), probably because the negative effect of metronidazole resistance is mostly overcome by the co-administration of bismuth[26,27] and because the efficacy of this regimen is not influenced by clarithromycin resistance.[28] In this respect, the classic bismuth-based quadruple therapy (PPI, bismuth, tetracycline, and metronidazole) was the second most common strategy in the Hp-EuReg, prescribed in 42% of the cases (250 patients). This regimen was relatively well tolerated (29% adverse events, mostly mild), the compliance rate was very high (96%), and it was clearly more effective than the standard triple therapy, achieving 91% cure rate, in agreement with the very limited data from the literature (two studies, 170 patients, Table 4)[11,17] and also consistent with the reported mITT effectiveness (95%) in nonallergic patients in the Hp-EuReg. Therefore, we think it may be concluded that, although in areas of low clarithromycin resistance a PPI-clarithromycin-metronidazole combination could be prescribed, the classical bismuth-based quadruple therapy should be preferred for treating patients allergic to penicillin in areas of high (or unknown) clarithromycin resistance, which is in agreement with Maastricht IV consensus recommendations.[1]

Finally, some authors have used a combination of a PPI, metronidazole, and sitafloxacin, and achieved *H pylori* eradication in 100% of the patients, although the experience is still very limited (only three studies and 64 patients, Table 4).[12,18,19] These encouraging results may be explained by the fact that sitafloxacin has a lower minimum inhibitory concentration than levofloxacin and could be effective in patients infected with strains with mutations in *gyrA*, a genetic marker for resistance to levofloxacin.[29]

Helicobacter pylori eradication is a challenge in patients allergic to penicillin in general, and especially in those who have failed a first-eradication attempt with key antibiotics such as clarithromycin and/or metronidazole. Only very few studies, including very low number of patients, have evaluated *H pylori* rescue eradication treatments in patients with penicillin allergy (summarized in Table 5).[9-12,15,18,19] Among patients failing clarithromycin triple therapy with

TABLE 5 Studies evaluating *H pylori* rescue eradication treatments empirically prescribed (without susceptibility testing) in patients with penicillin allergy

Author	Country	Design	Rescue therapy	Regimen	Duration	Number of patients	Eradication rate (%)	Adverse events (%)
Ono[12]	Japan	R	2nd & 3rd	PPI + C + M	7	3	33	—
Ono[12]	Japan	R	2nd & 3rd	V + C + M	7	1	100	—
Rodriguez[15]	Puerto Rico	R	2nd	PPI + T + M	10	3	100	—
Gisbert[9]	Spain	P	2nd	RBC + T + M	7	17	47	53
Gisbert[11]	Spain	P	2nd	PPI + B + T + M	10	24	37	58
Gisbert [10]	Spain	P	2nd	PPI + C + L	10	15	73	20
Gisbert[11]	Spain	P	2nd	PPI + C + L	10	64	64	25
Furuta[18]	Japan	R	2nd	PPI + M + S	7-14	10	100	40
Mori[19]	Japan	P	2nd	PPI + M + S	10	19	84	32
Gisbert[11]	Spain	P	3rd	PPI + B + T + M	10	3	100	67
Gisbert[11]	Spain	P	3rd	PPI + C + L	10	3	33	67
Gisbert[9]	Spain	P	3rd	PPI + C + R	10	9	11	89
Gisbert[11]	Spain	P	3rd	PPI + C + R	10	7	14	71
Furuta[18]	Japan	R	3rd	PPI + M + S	7-14	7	100	71
Mori[19]	Japan	P	3rd	PPI + M + S	10	5	40	32
Gisbert[9]	Spain	P	4th	PPI + C + L	10	2	100	50
Gisbert[11]	Spain	P	4th	PPI + C + L	10	2	100	67
Gisbert[11]	Spain	P	4th	PPI + C + R	10	2	50	100

Abbreviations: B, bismuth; C, clarithromycin; L, levofloxacin; M, metronidazole; PPI, proton-pump inhibitor; R, rifabutin; RBC, ranitidine bismuth citrate; S, sitafloxacin; T, tetracycline; V, vonoprazan.

Design: P (prospective), R (retrospective).

Eradication rate: by intention-to-treat analysis.

metronidazole, a bismuth-based quadruple therapy may still be considered as second-line therapy, as has been demonstrated in our study (eradication rate of 78%, relatively good tolerance, and very high compliance).

However, due to a number of shortcomings (eg, relatively complicated administration, and bismuth and tetracycline unavailability in many regions), the clinical application of bismuth quadruple therapy has been restricted. In this scenario, levofloxacin-based rescue regimens (together with clarithromycin or metronidazole) may represent possible options, as has been suggested by our results (eradication rates >70%, with relatively good tolerance and very high compliance) and is in agreement with Maastricht IV consensus recommendations.[1] Some studies have demonstrated that levofloxacin has remarkable in vitro activity against *H pylori*, and it has been shown that levofloxacin retains its activity when the strains are resistant to clarithromycin and metronidazole.[30] These favorable results have been confirmed in vivo, indicating that most of the patients with both metronidazole and clarithromycin resistance are cured with the levofloxacin-containing regimen.[30] Several studies have tested a combination of a PPI, amoxicillin, and levofloxacin in patients without penicillin allergy and with a previous eradication failure, reporting encouraging results.[30] Furthermore, several meta-analyses have demonstrated that after *H pylori* eradication failure, levofloxacin-based rescue regimen is at least as effective, and better tolerated, than the generally recommended bismuth-based quadruple therapy.[31] However, resistance to quinolones is acquired easily, and in countries with high consumption of these drugs, the resistance rate is relatively high.[30] As previously mentioned, sitafloxacin could be effective in patients infected with *H pylori* strains resistant to levofloxacin.[29] Thus, two studies have obtained a mean eradication rate of 89% with a combination of a PPI, metronidazole, and sitafloxacin[18,19] (Table 5).

Finally, for third-line treatment in patients allergic to penicillin, after the failure of a standard triple therapy (PPI, clarithromycin, and metronidazole) and a levofloxacin triple therapy (PPI, levofloxacin, and clarithromycin), the bismuth-based quadruple regimen was successful in 75% of the Hp-EuReg cases. Another theoretical alternative could be to prescribe a rifabutin-based regimen, which represents an option after multiple previous eradication failures.[32] However, in the literature, third-/fourth-line treatment with a PPI, rifabutin, and clarithromycin in penicillin-allergic patients achieved *H pylori* eradication in only 12% of the cases, although it should be highlighted that this regimen was empirically evaluated in only 16 patients[9,11] (Table 4).

The present study has several limitations. The major drawback is that culture was not performed, and consequently, information on the prevalence of antibiotic resistances is lacking. Culture is not generally performed in clinical practice, and therefore, the empirical treatment has been prescribed in most of the patients included in

the Hp-EuReg and in the literature (Tables 4 and 5), reflecting what is usually done by gastroenterologist in their daily clinical practice. Although susceptibility-guided treatment has been proposed as a way to improve *H pylori* eradication rates, evidence on its efficacy is very scarce.[33,34] Furthermore, some empirical treatments, especially bismuth quadruple therapy (which should be recommended for penicillin-allergic patients based on our results), can lead to excellent eradication rates, thanks to bismuth salts and tetracycline for which no resistance is usually found and can therefore be an alternative to the tailored treatments after antimicrobial susceptibility testing. However, after failure of the bismuth quadruple therapy, as all of the second-line regimens assessed in our study achieved suboptimal results, susceptibility testing (using either culture or molecular methods) should be considered in order to prescribe a susceptibility-guided treatment.

Another limitation of the present study is that penicillin allergy was not systematically confirmed by adequate penicillin allergy testing. A history of penicillin allergy reported by the patient or general practitioner is common, often based on remote recollection without documentation. Moreover, the term "allergy" may be used by patients to denote any past adverse drug reaction.[6,35] Thus, it has been suggested that formal penicillin allergy testing may be done for the patients with a remote or unlikely history of allergy to determine whether they may be able to tolerate a penicillin or amoxicillin challenge.[6,35] Nevertheless, the aim of our study was to evaluate the efficacy of different treatments in patients allergic to penicillin, and not to assess the real frequency of this kind of antibiotic allergy.

In contrast to these limitations, we believe that our study, based on the invaluable information of the Hp-EuReg, has a number of strengths. The open inclusion criteria 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 our knowledge, the largest study evaluating *H pylori* eradication treatment in patients allergic to penicillin, including more than 1000 patients with this antibiotic allergy (while most studies from the literature included just a few patients, with only three of them including more than 100 patients, Tables 4 and 5).

The conclusion of our study is that in *H pylori*-infected patients allergic to penicillin, a first-line treatment with a bismuth-based quadruple therapy (PPI, bismuth, tetracycline, and metronidazole) seems to be a better option than the generally recommended triple therapy with a PPI, clarithromycin, and metronidazole. On the other hand, after *H pylori* eradication failure, this quadruple regimen (if not previously prescribed) or a levofloxacin-based triple regimen (PPI, levofloxacin, and clarithromycin) represents second-line rescue options in the presence of penicillin allergy, although they achieved suboptimal (<80% cure rate) results.

DISCLOSURES OF INTERESTS

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX A1

Contribution log

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