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Bismuth quadruple regimen with tetracycline or doxycycline versus three-in-one single capsule as third-line rescue therapy for *Helicobacter pylori* infection: Spanish data of the European *Helicobacter pylori* Registry (Hp-EuReg)

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Abstract

Background: Different bismuth quadruple therapies containing proton-pump inhibitors, bismuth salts, metronidazole, and a tetracycline have been recommended as third-line *Helicobacter pylori* eradication treatment after failure with clarithromycin and levofloxacin.

Aim: To evaluate the efficacy and safety of third-line treatments with bismuth, metronidazole, and either tetracycline or doxycycline.

Methods: Sub-study with Spanish data of the "European Registry on *H pylori* Management" (Hp-EuReg), international multicenter prospective non-interventional Registry of the routine clinical practice of gastroenterologists. After previous failure with clarithromycin- and levofloxacin-containing therapies, patients receiving a third-line regimen with 10/14-day bismuth salts, metronidazole, and either tetracycline (BQT-Tet) or doxycycline (BQT-Dox), or single capsule (BQT-three-in-one) were included. Data were registered at AEG-REDCap database. Univariate and multivariate analyses were performed.

Results: Four-hundred and fifty-four patients have been treated so far: 85 with BQT-Tet, 94 with BQT-Dox, and 275 with BQT-three-in-one. Average age was 53 years, 68% were women. Overall modified intention-to-treat and per-protocol eradication rates were 81% (BQT-Dox: 65%, BQT-Tet: 76%, BQT-three-in-one: 88%) and 82% (BQT-Dox: 66%, BQT-Tet: 77%, BQT-three-in-one: 88%), respectively. By logistic regression, higher eradication rates were associated with compliance (OR = 2.96; 95% CI = 1.01-8.84) and no prior metronidazole use (OR = 1.96; 95% CI = 1.15-3.33); BQT-three-in-one was superior to BQT-Dox (OR = 4.46; 95% CI = 2.51-8.27), and BQT-Tet was marginally superior to BQT-Dox (OR = 1.67; 95% CI = 0.85-3.29).

Conclusion: Third-line *H pylori* eradication with bismuth quadruple treatment (after failure with clarithromycin and levofloxacin) offers acceptable efficacy and safety. Highest efficacy was found in compliant patients and those taking 10-day BQT-three-in-one or 14-day BQT-Tet. Doxycycline seems to be less effective and therefore should not be recommended.

KEYWORDS
bismuth, doxycycline, Helicobacter pylori, metronidazole, Pylera®, tetracycline

1 | INTRODUCTION

Helicobacter pylori (*H pylori*) infection affects billions of people worldwide. This infection is the main known cause of gastritis, gastroduodenal ulcer disease, and gastric cancer. However, despite more than 30 years of experience in *H pylori* treatment, the ideal regimen to treat this infection remains undefined. The most commonly used first-line therapies fail in ≥20% of patients. A rescue therapy with levofloxacin has been recommended as one of the best options for second-line treatment.[1-3] However, this rescue regimen still fails in approximately 20%-30% of the patients, and these cases constitute a therapeutic dilemma, as patients who are not cured with two consecutive treatments including clarithromycin and levofloxacin will have at least single, and usually double antibiotic resistance.[4]

Currently, a standard third-line therapy is lacking, and some guidelines recommend performing culture in these patients to select a third-line treatment according to microbial sensitivity to antibiotics, but this strategy is currently not practical.[1-3] One possibility of empirical treatment—when antibiotic susceptibilities are unknown—is to administer a quadruple therapy including a proton-pump inhibitor (PPI), bismuth, tetracycline, and metronidazole. Since *H pylori* antibiotic resistance is almost negligible for amoxicillin and for

tetracycline, and metronidazole resistance can be, at least partially, overcome in bismuth-containing quadruple therapies,[5] there is a rational basis supporting its use as a third-line therapy without antimicrobial information.

The bismuth quadruple regimen has been generally used as the optimal second-line therapy. However, the experience with this regimen as a third-line treatment is almost inexistent. On the other hand, in many parts of the world, tetracycline has become unavailable, and many pharmacies attempted to substitute doxycycline with tetracycline HCl. Doxycycline is a tetracycline analogue that has bacteriostatic properties through the inhibition of bacterial protein synthesis.[6] Doxycycline theoretically would have some advantages over tetracycline: 18-hour half-life allowing twice-daily administration instead of four times daily, better tissue penetration, better absorption with food, predominantly extra-renal excretion, and reduced gastric chelation with bismuth due to duodenal delivery and absorption.[6-9]

Although doxycycline was first demonstrated to be effective against *H pylori* in 1992, with an MIC of 0.25-8.0 μg/mL,[10] more recent evidence of doxycycline ineffectiveness comes from studies showing that this antibiotic lacks *H pylori* eradication effect when used alone[11] or even with amoxicillin.[12] Other studies prescribing doxycycline in monotherapy had previously failed to eradicate *H pylori* in most patients.[13] On the other hand, there is little to no resistance to tetracyclines,[14,15] thus supporting the use of this antibiotic class as rescue therapy. In particular, some authors have found no secondary resistance to doxycycline in *H pylori* isolates from patients who failed one or more eradication therapies,[14] while others identified a resistance of 33%[16]; however, the results of this last study were somewhat confusing because of the high resistance rate not only to doxycycline (33%), but also to tetracycline (14%) and amoxicillin (26%). Finally, a new three-in-one single capsule containing bismuth, metronidazole, and tetracycline has recently been developed, but there is still very little evidence of its effectiveness and safety in routine clinical practice, mainly as a rescue regimen.[17]

The aim of the present study was to evaluate in a large multicenter study the effectiveness of a bismuth-containing quadruple regimen with tetracycline, either in the standard form with the four components provided separately (BQT-Tet) or in the three-in-one single-capsule presentation (BQT-three-in-one) or with doxycycline (BQT-Dox), as a third-line rescue therapy in patients with two consecutive *H pylori* eradication failures.

2 | METHODS

2.1 | European registry on *H pylori* management

The "European Registry on *H pylori* Management" (Hp-EuReg) is an international multicenter prospective non-interventional registry recording information of *H pylori* infection management since May 2013 and was prospectively registered in ClinicalTrials.gov (NCT02328131). The Scientific Committee comprises Javier P. Gisbert (Principal Investigator), Francis Mégraud, Colm A. O'Morain, Ignasi Puig, and Olga P. Nyssen (the two latter are also the Scientific Directors).

The Hp-EuReg protocol[18] reported criteria for country selection, national coordinators, gastroenterologist recruiting investigators, and a list of variables and outcomes.

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 by contacting clinical researchers from non-participant European countries. Countries with compromised viability or lack of response/participation were excluded. Finally, 27 European countries were selected with over 300 recruiters. In each country, a national coordinator was invited based on its clinical and research activity and they were in charge of selecting centers and recruiting investigators and also were responsible for the follow-up and quality of the recruiting, and the compliance with national and local legislation. National coordinators remain the link between promoters and recruiter investigators, 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.

Data were recorded in an Electronic Case Report Form (e-CRF), collected, and managed using the Web-based application designed to support data capture for research studies, REDCap. Data extraction was performed in December 2019 and was subject to quality check.

The aim of this sub-analysis was to evaluate the effectiveness and safety in the eradication of *H pylori* of third-line quadruple therapies containing bismuth salts, metronidazole, and either tetracycline (standard form or with the three-in-one single capsule) or doxycycline. Thus, three bismuth quadruple regimens were analyzed in this study: traditional bismuth quadruple with a PPI, bismuth salts (120 mg/6 h or 240 mg/12 h), metronidazole (500 mg/8 h), and tetracycline (500 mg/6 h) (BQT-Tet); the same treatment substituting tetracycline with doxycycline 100 mg/12 h (BQT-Dox); and the three-in-one single-capsule commercial version (BQT-three-in-one; Pylera®). The treatment selection was performed by the recruiting gastroenterologist based on the drug accessibility at the time treatment was prescribed. Tetracycline was initially available in the market; then, when tetracycline was unavailable, it was substituted by doxycycline; and finally, the three-in-one single capsule was commercialized.

2.2 | Statistical analyses

Continuous variables are presented as mean and standard deviation (SD). Qualitative variables are presented as absolute and relative frequencies with percentages (%). In the multivariate analysis,

the effect was evaluated by calculating odds ratios (OR) and 95% confidence intervals (CI). Statistical significance was considered at $P < .05$. The variable treatment length was assessed using three categories, corresponding with the most frequent treatment durations: 7, 10, and 14 days. The variable proton-pump inhibitor (PPI) dose was grouped into three categories as reported by Graham[19] and Kirchheiner[20]: low dose, when the potency of acid inhibition was between 4.5 and 27 mg omeprazole equivalents given twice a day; standard dose, between 32 and 40 mg omeprazole equivalents given twice a day; and high dose, between 54 and 128 mg omeprazole equivalents given twice a day.

2.3 | Effectiveness, safety, and compliance analysis

Treatment eradication rate was studied in three sets of patients: Intention-to-treat (ITT) analysis included all patients registered up to December 2019, to allow at least a 6-month follow-up, 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 protocol. A modified ITT (mITT) analysis was designed aiming to reach the closest result to those obtained in clinical practice. This mITT included all cases that had completed follow-up (ie, a confirmatory test—success or failure—was available after eradication treatment).

Logistic regression was performed using mITT eradication as dependent variable. The independent factors were treatment group (BQT-Tet, BQT-Dox, or BQT-three-in-one), age, gender, compliance with treatment (through physician questioning, > or <90% drug intake), PPI dose, length of treatment, and prior metronidazole use. Safety and compliance were evaluated through patient interrogation by the physician. Compliance was defined as having taking at least 90% of the prescribed drugs.

3 | RESULTS

3.1 | Baseline characteristics

In Spain, 454 treatments fitting the studied regimens (BQT-Tet or BQT-Dox, or BQT-three-in-one) were registered, and 443 were valid for inclusion (outcome was registered). The flowchart diagram is shown in Figure 1.

Ages ranged from 18 to 81 years, with a mean age of 53 years and a SD of 13; 68% of the cases were women. The *H pylori* infection was diagnosed by ^{13}C-urea breath test in 51% of the cases, histology in 41%, rapid urease test in 22%, and monoclonal stool antigen test in 8%. In 79% of the cases, one single diagnostic method was used; in 18%, two; and in over 2%, three.

Indications for treatment were as follows: dyspepsia in 68% (non-investigated 29%, functional 37%), peptic ulcer in 19.8% (duodenal 15%, gastric 4.8%), and others in 14% [of which the most common were related to cancer prevention such as first-degree relative of a gastric cancer patient (6%) and precancerous gastric lesions (6%)]. Demographics and concomitant drug use for each treatment group are presented in Table 1.

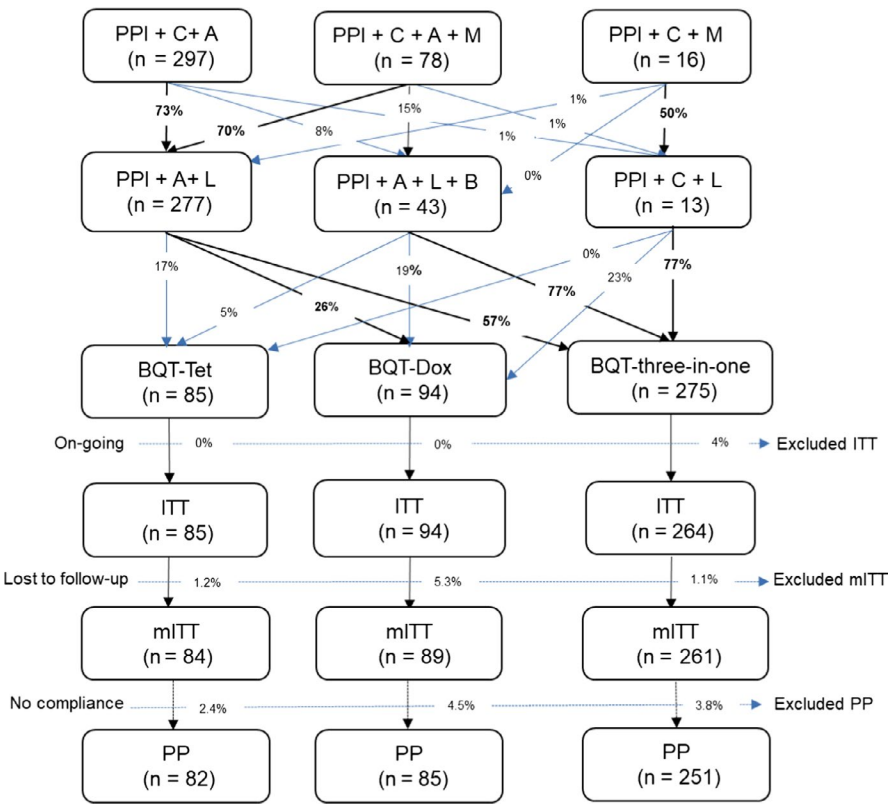

FIGURE 1 Flowchart of included patients. A, amoxicillin; B, bismuth salts; BQT-Dox, doxycycline-containing bismuth quadruple therapy; BQT-Tet, tetracycline-containing bismuth quadruple therapy; BQT-three-in-one, three-in-one single-capsule bismuth quadruple therapy; C, clarithromycin; ITT, intention-to-treat; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; n, number of patients; PP, per-protocol; PPI, proton-pump inhibitor

TABLE 1 Demographic characteristics of patients and drug use

Demographics, N (%)		All, N = 454	BQT-Tet, N = 85	BQT-Dox, N = 94	BQT-three-in-one, N = 275	*P*-value
Age	Years, mean (SD)	53 (13)	50 (12)	53 (13)	54 (13)	NS
Gender	Female	310 (68%)	50 (59%)	74 (80%)	186 (68%)	$P < .05$
Ethnic background	Caucasian	429 (95%)	81 (98%)	92 (98%)	256 (93%)	NS
	Black	4 (0.9%)	1 (1.2%)	1 (1.1%)	2 (0.7%)	
	Others	8 (1.8%)	1 (1.2%)	1 (1.1%)	6 (2.2%)	
Drug allergy	Penicillin	22 (4.8%)	3 (3.5%)	5 (5.3%)	14 (5.1%)	NS
Indication	Non-investigated dyspepsia	131 (29%)	18 (21%)	31 (33%)	82 (30%)	$P < .05$
	Functional dyspepsia	170 (37%)	36 (42%)	31 (33%)	103 (37.5%)	
	Duodenal ulcer	67 (15%)	19 (22%)	8 (8.5%)	40 (14.5%)	
	Gastric ulcer	22 (4.8%)	2 (2.4%)	3 (3.2%)	17 (6.2%)	
	Others	64 (14%)	10 (12%)	21 (22%)	33 (12%)	
Concomitant drug use						
PPI	Daily	85 (38%)	11 (31%)	20 (48%)	54 (37%)	$P < .05$
	On demand	83 (37%)	16 (44%)	6 (14%)	61 (41.5%)	
	Not taking	56 (25%)	9 (25%)	16 (38%)	31 (21%)	
ASA	Daily	22 (9.8%)	1 (2.8%)	1 (2.4%)	20 (14%)	$P < .05$
	On demand	10 (4.4%)	1 (2.8%)	0 (0%)	9 (6%)	
	Not taking	190 (84%)	34 (94%)	41 (98%)	115 (78%)	
NSAIDs	Daily	10 (4.4%)	0 (0%)	4 (9.5%)	6 (4.1%)	$P < .05$
	On demand	72 (32%)	12 (33%)	3 (7.1%)	57 (39%)	
	Not taking	141 (63%)	24 (67%)	35 (83%)	82 (56%)	
Statins	Daily	77 (34%)	6 (17%)	10 (24%)	61 (41.5%)	$P < .05$
	Not taking	147 (65%)	30 (83%)	32 (76%)	85 (58%)	
Previous treatments[a]						
First line	PPI + C + M	17 (3.7%)	3 (3.5%)	3 (3%)	11 (4%)	NS
	PPI + C + A	298 (66%)	33 (39%)	70 (23.5%)	195 (71%)	
	PPI + C + A + M	59 (13%)	7 (8%)	12 (13%)	40 (14.5%)	
Second line	PPI + A + L	273 (60%)	47 (55%)	71 (75.5%)	155 (56%)	$P < .05$
	PPI + A + L + B	37 (8%)	1 (1.2%)	6 (6.4%)	30 (11%)	
	PPI + C + L	13 (3%)	N.A	3 (3.1%)	10 (3.6%)	
Prior use (in either first line or second line)	C	414 (91%)	54 (63%)	90 (96%)	270 (98%)	$P < .001$
	L	391 (86%)	80 (94%)	87 (92.5%)	224 (81%)	$P < .01$
	M	145 (32%)	20 (23.5%)	23 (24.5%)	102 (37%)	$P < .05$
	B	58 (13%)	2 (2.3%)	8 (8.5%)	48 (17%)	$P < .001$

Note: ANOVA and chi-square tests were performed: *P*-values are reported in the table showing statistically significant differences between treatment groups for each demographic variable.

Abbreviation: A, amoxicillin; ASA, aminosalicylic acid; B, bismuth salts; BQT-Dox, doxycycline-containing bismuth quadruple therapy; BQT-Tet, tetracycline-containing bismuth quadruple therapy; BQT-three-in-one, three-in-one single-capsule bismuth quadruple therapy; C, clarithromycin; L, levofloxacin; M, metronidazole; N.A, not available; NS, non-statistically significant; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitor.

[a]Only the most frequently used first- and second-line treatment schemes are reported in the table, and therefore, total may not sum up a 100%.

In order to evaluate potential selection bias and propensity, the geographic distribution and demographics of the included cases were compared to the distribution and basal data of the rest of third-line Spanish cases registered in the Hp-EuReg, and no selection bias was identified (data not shown).

3.2 | Previous anti-*H pylori* treatments

The majority of patients had received previous triple therapy with clarithromycin in first line (86%) and with levofloxacin in second line (73%). The remaining patients had been prescribed quadruple

therapies. Regarding specific antibiotics, 41% and 39% of patients had received clarithromycin and levofloxacin, respectively, while 14% had been treated with metronidazole and 6% with bismuth salts (detailed data are shown in Table 1). Most patients received amoxicillin-containing regimens both in first line (80%) and in second line (71%), except in the case of penicillin allergy.

3.3 | Current treatment

Third-line treatments were prescribed in 10- and 14-day regimens, except BQT-three-in-one which was prescribed as 10-day regimen. The majority of treatments either used low PPI doses as in BQT-Dox (46%) or standard PPI doses as in BQT-Tet (50%), whereas low or high doses were mostly used in BQT-three-in-one (35% and 44%, respectively). Statistically significant differences were found for both the treatment length and PPI dose used between treatment groups. Further detail is shown in Table 2.

3.4 | Effectiveness

Of the 434 patients in the mITT population, 351 were cured (81%). Confirmation of *H pylori* eradication was performed by ^{13}C-urea breath test in 94% of the cases, with the monoclonal stool antigen test in 3%, whereas histology was used in an additional 3% of the remaining cases.

Compliance, ITT, mITT, and PP analyses per treatment group are shown in Table 3. Statistically significant differences ($P < .001$) were reported in the mITT effectiveness for treatment length between treatment groups (BQT-Tet, BQT-Dox, and BQT-three-in-one).

The mITT effectiveness of prior metronidazole use and different PPI doses are summarized in Table 4. Statistically significant differences ($P < .001$) were found in the mITT effectiveness for both the PPI dose and according to prior use of metronidazole (yes: 82% vs no: 91%) between treatment groups (BQT-Tet, BQT-Dox, and BQT-three-in-one).

TABLE 2 Characteristics of prescribed treatments

Treatment, N (%)		BQT-Tet	BQT-Dox	BQT-three-in-one
Length[a]	10 d	30 (35.3%)	41 (44%)	268 (97.5%)
	14 d	55 (65%)	50 (53%)	5 (1.8%)
PPI dose[a]	Low	22 (26%)	43 (46%)	96 (35%)
	Standard	42 (50%)	30 (32%)	58 (21%)
	High	20 (24%)	21 (22%)	120 (44%)

Abbreviations: BQT-Dox, doxycycline-containing bismuth quadruple therapy; BQT-Tet, tetracycline-containing bismuth quadruple therapy; BQT-three-in-one, three-in-one single-capsule bismuth quadruple therapy; PPI, proton-pump inhibitor, low-dose PPI—4.5-27 mg omeprazole equivalents, b.i.d, standard dose PPI—32-40 mg omeprazole equivalents, b.i.d, high-dose PPI—54-128 mg omeprazole equivalents, b.i.d.

[a]The chi-square test showed statistically significant differences ($P < .001$) of treatment length and PPI dose between treatment groups (BQT-Tet, BQT-Dox, BQT-three-in-one) as reported in the table.

3.5 | Multivariate analysis

Logistic regression showed that compliance and no prior metronidazole use were significantly associated with higher eradication rates. Regarding the prescribed regimen, BQT-three-in-one was significantly superior to BQT-Dox. BQT-Tet superiority to BQT-Dox was borderline significant. No other included factor was associated with treatment effectiveness.

A sub-analysis performed to compare head-to-head BQT-three-in-one and BQT-Tet using the same logistic regression model (using the same variables as in the global model) showed no statistically significant difference (OR = 1.59; 95% CI = 0.75-3.22; $P = .23$). The results are shown in Table 5.

3.6 | Safety

Adverse reactions to treatment were suffered by 43% of cases; they were generally mild (44%) and of short duration (mean 7 days). The most common were nausea (20%), metallic taste (11%), diarrhea (15%), and vomiting (9.9%). The full list of adverse events is shown in Table 6.

4 | DISCUSSION

Some authors have reported encouraging experience with bismuth quadruple treatment in patients in whom one eradication treatment had previously failed to eradicate the infection, with a weighted mean eradication rate of 78%.[21] However, the sample size of the individual studies was, in general, remarkably low. To the best of our knowledge, our study with over 450 patients is the largest to evaluate a bismuth quadruple regimen as rescue therapy. Furthermore, the present study is the first one under the same protocol and in the same population comparing three different bismuth quadruple regimens: the standard with tetracycline, the substitution with doxycycline, and the single-capsule tetracycline-containing quadruple therapy.

The results of the present study, with an eradication rate of approximately 80%, although higher than those of a previous Spanish study,[22] may still be considered discouraging; however, we must take into consideration that this rescue regimen was prescribed empirically after two eradication failures with key antibiotics such as amoxicillin, clarithromycin, and levofloxacin. Susceptibility-guided therapies have been proposed as preferable to empirical rescue treatments after two treatment failures. However, the susceptibility-guided strategy has not been sufficiently supported in third-line rescue treatment.[23]

TABLE 3 Effectiveness and compliance according to treatment and length

Effectiveness, N (%)		Compliance	mITT, N	mITT	(95% CI)	PP, N	PP	(95% CI)
BQT-Tet	All	82 (97%)	64	76%	(66-86)	63	77%	(67-86)
	10 d*	29 (97%)	19	66%	(47-85)	19	66%	(47-85)
	14 d	45 (96%)	45	82%	(71-93)	44	83%	(72-94)
BQT-Dox	All	85 (93%)	58	65%	(55-76)	56	66%	(55-77)
	10 d*	37 (90%)	25	63%	(46-79)	23	63%	(45-79)
	14 d	53 (96%)	32	70%	(55-84)	32	71%	(57-85)
BQT-three-in-one	All	267 (95.5%)	261	88%	(83-92)	251	84%	(84-93)
	10 d*	249(96%)	222	88%	(83-92)	245	88%	(84-92)
	14 d	5 (80%)	5	100%	NA	4	100%	NA

Note: The chi-square test showed statistically significant differences in treatment length in the mITT set between treatment groups (BQT-Tet, BQT-Dox, BQT-three-in-one) as reported in the table.

Abbreviations: 95% CI, 95% confidence interval; BQT-Dox, doxycycline-containing bismuth quadruple therapy; BQT-Tet, tetracycline-containing bismuth quadruple therapy; BQT-three-in-one, three-in-one single-capsule bismuth quadruple therapy; ITT, intention-to-treat; mITT, modified intention-to-treat; NA, not applicable; PP, per-protocol.

*$P < .001$.

TABLE 4 Effectiveness by modified intention-to-treat according to predictive factors

Factors	N, %	BQT-Tet	95% CI	BQT-Dox	95% CI	BQT-three-in-one	95% CI
Prior metronidazole use	Yes*	20 (75%)	(51-91)	22 (55%)	(31-78)	99 (82%)	(74-89)
	No*	64 (77%)	(66-86)	67 (69%)	(57-80)	162 (91%)	(87-96)
PPI dose	Low*	22 (73%)	(50-89)	39 (69%)	(53-85)	92 (83%)	(74-91)
	Standard*	41 (68%)	(53-84)	30 (60%)	(41-79)	55 (95%)	(85-99)
	High*	20 (95%)	(75-100)	20 (65%)	(41-85)	113 (89%)	(83-96)

Note: The chi-square test showed statistically significant differences in the modified intention-to-treat effectiveness between treatment groups (BQT-Tet, BQT-Dox, and BQT-three-in-one) according to prior use of metronidazole (yes vs no) or PPI dose, as reported in the table.

Abbreviations: BQT-Dox, doxycycline-containing bismuth quadruple therapy; BQT-Tet, tetracycline-containing bismuth quadruple therapy; BQT-three-in-one, three-in-one single-capsule bismuth quadruple therapy; PPI, proton-pump inhibitor.

*$P < .001$.

At present, it acknowledges only therapies that have been optimized should be recommended. The traditional bismuth quadruple therapies used in the literature varied greatly in terms of drug composition, including PPI, metronidazole, and bismuth dosage and frequency of administration. Prior studies have shown that in the presence of metronidazole-susceptible infections, short-duration treatments are effective, whereas in areas with proven resistance to metronidazole, duration of therapy and dosage of metronidazole appear to be critical variables.[24] In the current study, the comparisons were unable to take these variables into account as susceptibility was not assessed; thus, the results were averages of within populations that may differ in the presence of critical variables.

In our study, *H pylori* culture and antibiogram were not systematically performed; therefore, we were not aware of the metronidazole resistance in our study, which is the main limitation of our data. However, a recent multicenter study investigated the rate of primary antibiotic resistance of *H pylori* in 18 European countries and found the rate for metronidazole to be 35%.[25] The rate of metronidazole resistance in Spain was investigated as part of the aforementioned European multicenter study and was shown to be slightly lower, 28%.[25] However, the rate after one or two failed attempts, especially if metronidazole was previously used, rose up to 70%.[26]

Metronidazole resistance is high in almost all parts of the world, but it has been suggested that it does not interfere with the therapeutic effect of bismuth-containing quadruple therapies probably due to a synergism between metronidazole and bismuth to overcome this antibiotic resistance.[27,28] However, several studies have demonstrated that resistance to metronidazole has a slight negative effect on the efficacy of bismuth quadruple therapy[29,30] or even a clear negative effect.[31-34] Accordingly, in our study, eradication rates were 5%-10% less effective in those patients that had previously received (and failed) a treatment with metronidazole; this was true for any bismuth-containing quadruple regimen with tetracycline (either in the standard form or with the three-in-one single-capsule presentation) or doxycycline. However, optimized 14-day BQT-three-in-one treatment was reported to achieve over 95% effectiveness, and 100% of metronidazole-resistant strains were eradicated.[35] Nevertheless, randomized controlled trials comparing the different bismuth quadruple presentations would be desirable.[36]

In our study, 26% of patients received a doxycycline-containing regimen. In a recent meta-analysis of 6 case-control studies, Niv et al found no difference in eradication with regimens containing doxycycline compared with those containing tetracycline.[37] Unfortunately, none of these studies were randomized, and none compared head-to-head tetracycline- and doxycycline-containing bismuth quadruple therapies. Only two studies directly compared doxycycline- vs tetracycline-containing bismuth regimens, with one favoring tetracycline and the other showing no difference, but in any case the effectiveness of bismuth quadruple therapy with doxycycline was insufficient.[38]

TABLE 5 Multivariate analysis

Logistic regression	OR	95% CI	*P*-value
Compliance vs no compliance	2.96	(1.01-8.84)	<.05
No prior metronidazole use vs prior use	1.96	(1.15-3.33)	<.05
BQT-Tet vs BQT-Dox	1.67	(0.85-3.29)	.14
BQT-three-in-one vs BQT-Dox	4.46	(2.51-8.27)	<.001
BQT-three-in-one vs BQT-Tet	1.59	(0.75-3.22)	.23

Note: Dependent variable: mITT. Included variables: prescribed treatment, age, sex, treatment length, PPI dose, compliance, and prior use of metronidazole.

Abbreviation: 95% CI, 95% confidence interval; BQT-Dox, doxycycline-containing bismuth quadruple therapy; BQT-Tet, tetracycline-containing bismuth quadruple therapy; BQT-three-in-one, three-in-one single-capsule bismuth quadruple therapy; OR, odds ratio.

The original experience with doxycycline concluded that it could not successfully substitute tetracycline in bismuth triple therapy.[39] In that study, patients were randomized to receive either doxycycline or tetracycline triple therapy in conjunction with bismuth and metronidazole (but without a PPI). Of the patients taking doxycycline, only 65% achieved *H pylori* eradication, compared with 75%-85% of those taking tetracycline ($P < .05$). Most available doxycycline data relate to substitution of both tetracycline and metronidazole for doxycycline and amoxicillin.[40-42] Doxycycline quadruple regimens with PPI, amoxicillin, and bismuth salts as second- and third-line therapies have been used for the treatment of *H pylori* infection, with eradication rates ranging between 66% and 90%,[41] comparable to those obtained in the present study (63%-70%). In summary, the results of our study and previous studies suggest that, at present, doxycycline should be probably avoided in the context of a bismuth quadruple regimen.

The complexity of bismuth quadruple therapy hampers its acceptability for general use.[43] It requires the administration of 4 drugs with a complex scheme. Furthermore, bismuth salts and tetracycline are not available in some countries. However, these drawbacks may be overcome thanks to a novel single capsule containing bismuth, metronidazole, and tetracycline, which has recently become available.[27] Its recent availability in Spain has allowed including in our study patients taking the BQT-three-in-one after two failed attempts, achieving nearly 90% eradication rates.

Previous studies demonstrated that a first-line 10-day quadruple therapy consisting of omeprazole plus the BQT-three-in-one achieved approximately 90% *H pylori* eradication rates.[17,29,34,44] More recently, the BQT-three-in-one has been demonstrated to be also an effective option as rescue therapy.[17] Delchier et al administered

TABLE 6 Adverse events

Adverse event, N (%)	Incidence	Mild	Moderate	Severe	Length (mean days)	BQT-Tet	BQT-Dox	BQT-three-in-one	*P*-value
Nausea	92 (20%)	53 (58%)	35 (38%)	4 (4.3%)	7.2	35 (41%)	12 (13%)	45 (16%)	<.001
Metallic taste	48 (11%)	37 (79%)	10 (21%)	0 (0%)	8.8	30 (35%)	5 (5.3%)	13 (4.7%)	<.001 T vs D* and T vs P*
Diarrhea	69 (15%)	28 (41%)	39 (57%)	2 (2.9%)	5.7	22 (26%)	3 (3.2%)	44 (16%)	<.001
Vomiting	45 (9.9%)	26 (58%)	17 (38%)	2 (4.4%)	4.9	15 (18%)	3 (3.2%)	27 (9.8%)	<.05
Fatigue	47(10%)	12 (26%)	27 (57%)	8 (17%)	8.7	10 (12%)	4 (4.3%)	33 (12%)	NS
Abdominal pain	31 (6.8%)	16 (52%)	15 (48%)	0 (0%)	6.9	5 (5.9%)	4 (4.3%)	22 (8%)	NS
Anorexia	38 (8.4%)	5 (13%)	29 (76%)	4 (11%)	8.7	6 (7.1%)	0 (0%)	32 (12%)	<.05
At least one:									
Adverse event	190 (43%)					52 (61%)	27 (30%)	111 (42%)	<.001
Severe adverse event	23 (12%)					1 (2%)	5 (19%)	17 (15%)	<.05

Note: Chi-square test was performed among the different treatment groups (BQT-Dox, BQT-Tet, and BQT-three-in-one): *P*-values for each adverse event are reported in the table.

Abbreviation: N.S, non-statistically significant.

*Significant comparisons showing differences between groups.

BQT-three-in-one to 49 patients who failed ≥1 previous course of standard triple therapy with or without up to three supplemental treatments, and the eradication rates ranged from 93% to 94%.[45] Muller et al prescribed BQT-three-in-one to 103 patients who were infected with a *H pylori* strain resistant to metronidazole, clarithromycin, and fluoroquinolone or who failed multiple lines of treatment using these three antibiotics, achieving eradication in 83% of the cases,[30] similar to our results. Likewise, Rodriguez de Santiago et al prescribed BQT-three-in-one to 103 patients who had previously failed two treatments (with clarithromycin and levofloxacin), achieving eradication in 82% of the cases,[46] also in line with previous results.

Compliance with treatment was excellent in our study, with over 90% of patients taking at least 90% of the prescribed drugs, either with tetracycline (in the standard form with the four components provided separately or with the BQT-three-in-one presentation) or with doxycycline. In particular, compliance with BQT-three-in-one and with the standard triple therapy has been reported to be similar.[27] Nevertheless, although the new single-capsule formulation can simplify the administration of this therapy, its principle disadvantage is that three capsules still need to be taken four times daily, and a PPI needs to be taken separately twice daily.

Current recommendations state that the treatment duration of bismuth quadruple therapy should be extended to 14 days, unless 10-day therapies are proven effective locally.[1] Metronidazole resistance significantly impairs the effectiveness of either 7- or 10-day regimens.[47] Thus, several studies have suggested that prolonging treatment duration of the bismuth quadruple therapy may overcome the negative influence of metronidazole resistance and may be associated with a significantly higher eradication rate.[35,48-53] In the present study, bismuth quadruple therapy was, not surprisingly, less effective in patients with prior metronidazole use, but this negative effect was observed more markedly with 10-day than with 14-day regimens.

It has been suggested that bismuth-containing quadruple therapy is associated with a relatively high incidence of adverse effects. In fact, side effects were reported in 45% of our patients, the most common being gastrointestinal, but none of them was classified as serious. Therefore, it may be concluded, in agreement with previous studies, that the bismuth quadruple regimen is generally well-tolerated, although frequent, most adverse events are mild-to-moderate in severity and only exceptionally force to treatment discontinuation. It has also been suggested that doxycycline may be better tolerated than tetracycline, which has been the case in our study (30% vs 61% adverse events) although other authors have reported opposite results.[39] Finally, the use of tetracycline has also been associated with frequent but generally mild adverse effects.[27,29,30,34,44,45]

In summary, the conclusion of the present study is that a tetracycline-containing bismuth quadruple treatment (either with the traditional or with the three-in-one formulation) is an acceptable and safe third-line alternative after two previous *H pylori* eradication failures with key antibiotics such as amoxicillin, clarithromycin, and levofloxacin. The use of doxycycline instead of tetracycline in the context of a bismuth quadruple therapy should not be recommended, as it seems to be less effective. Direct head-to-head comparisons of 14- and 10-day bismuth quadruple therapies are needed to identify the optimal duration of therapy and to test whether antisecretory dosage is another critical variable, especially in areas with high resistance to metronidazole.

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CONFLICT OF INTEREST

Dr Gisbert has served as speaker, consultant, and advisory member for or has received research funding from Mayoly, Allergan, and DiaSorin. Dr P Nyssen has received funding from Allergan. Dr Pérez Aisa has received payment from Allergan and Mylan for formative actions. Dr Castro has received payment from Allergan for formative actions. Dr Huguet has served as speaker and has received research funding from Casen Recordati. The rest of the authors have declared no conflict of interest.

AUTHORS CONTRIBUTION

Olga P Nyssen, Scientific Director, member of the project's Scientific Committee, planned and coordinated the study, designed and programmed the electronic case report form, analyzed the data, wrote the manuscript draft, and approved the submitted manuscript. Angeles Perez-Aisa, Luis Rodrigo, Manuel Castro, Pilar Mata Romero, Juan Ortuño, Jesus Barrio, Jose Maria Huguet, Ines Modollel, Noelia Alcaide, Cristobal de la Coba, Manuel Dominguez-Cajal, Alfredo Lucendo, Xavier Calvet, Monica Perona, Barbara Gomez, Blas Jose Gomez Rodriguez, Pilar Varela, Manuel Jimenez Moreno, Manuel Dominguez-Cajal, Liliana Pozzati, Diego Burgos, and Luis Bujanda collected and helped interpreting data, critically reviewed the manuscript draft, and approved the submitted manuscript. Ana Garre coordinated and monitored data collection, interpreted data, critically reviewed the manuscript draft, and approved the submitted manuscript. Maria Caldas and Elena Resina supervised and interpreted data, critically reviewed the manuscript draft, and approved the submitted manuscript. Ignasi Puig, Scientific Director, member of the project's Scientific Committee, critically reviewed the manuscript draft and approved the submitted manuscript. Colm O'Morain, member of the project's Scientific Committee, designed the protocol, planned the

study, collected and analyzed the data, critically reviewed the manuscript draft, and approved the submitted manuscript. Francis Megraud, member of the project's Scientific Committee, designed the protocol, planned the study, analyzed the data, critically reviewed the manuscript draft, and approved the submitted manuscript. Javier P. Gisbert directed the project and the project's Scientific Committee, obtained funding, designed the protocol and planned the study, analyzed and interpreted the data, collected patients, critically reviewed the manuscript draft, and approved the final submitted manuscript.

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