Room for Improvement in the Treatment of *Helicobacter pylori* Infection

Lessons from the European Registry on H. pylori Management (Hp-EuReg)

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Background: Managing *Helicobacter pylori* infection requires constant decision making, and each decision is open to possible errors.

Aim: The aim was to evaluate common mistakes in the eradication of *H. pylori*, based on the "European Registry on *Helicobacter pylori* management".

Methods: European Registry on *Helicobacter pylori* management is an international multicentre prospective noninterventional registry evaluating the decisions and outcomes of *H. pylori* management by European gastroenterologists in routine clinical practice.

Results: Countries recruiting more than 1000 patients were included (26,340 patients). The most common mistakes (percentages) were: (1) To use the standard triple therapy where it is ineffective (46%). (2) To prescribe eradication therapy for only 7 to 10 days (69%). (3) To use a low dose of proton pump inhibitors (48%). (4) In patients allergic to penicillin, to prescribe always a triple therapy with clarithromycin and metronidazole (38%). (5) To repeat certain antibiotics after eradication failure (> 15%). (6) Failing to consider the importance of compliance with treatment (2%). (7) Not to check the eradication success (6%). Time-trend analyses showed progressive greater compliance with current clinical guidelines.

Conclusion: The management of *H. pylori* infection by some European gastroenterologists is heterogeneous, frequently suboptimal and discrepant with current recommendations. Clinical practice is constantly adapting to updated recommendations, although this shift is delayed and slow.

Key Words: *Helicobacter pylori*, *H. pylori*, amoxicillin, clarithromycin, metronidazole, levofloxacin, bismuth, non-bismuth, mistake, error

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Helicobacter pylori infection affects billions of people worldwide. This infection is the main cause of gastritis, peptic ulcer disease, and gastric cancer. However, even after

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> 30 years of experience in *H. pylori* treatment, the ideal regimen to treat this infection remains undefined.

Constant decision making is required in daily clinical practice, and each decision is open to possible errors. Misconceptions are very common in clinical practice, but they can be prevented. We have previously discussed the most common and relevant mistakes in clinical practice in the management of *H. pylori* infection.[1]

In contrast, the "European Registry on *Helicobacter pylori* management" (Hp-EuReg) brings together information on the real clinical practice in a majority of European countries, including thousands of patients.[2] 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.

Therefore, the aim of the present study was to evaluate the most common mistakes made by European Gastroenterologists in the eradication of *H. pylori*, based on the invaluable information included in the Hp-EuReg, a database registering systematically a large and representative sample of routine clinical practice in Europe. Our hope is that being aware of the mistakes will be followed by their correction and the consequent improvement in the quality of care of the patients with *H. pylori* infection.

METHODS

This analysis focused on the "Hp-EuReg", an international (27 countries), multicentre (300 investigators), prospective noninterventional registry that started in 2013 and was promoted by the European Helicobacter and Microbiota Study Group (http://www.helicobacter.org).

The Hp-EuReg protocol was approved by the Ethics Committee of La Princesa University Hospital (Madrid, Spain) on December 20, 2012 (document of the approval published),[2] and was prospectively registered at ClinicalTrials.gov under the code NCT02328131. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the Institution's Human Research Committee. Written, informed consent was obtained from each patient included in the study.

Monitoring (at least a 10% of the included records in each country and each hospital respectively), quality of the data, and a list of variables and outcomes are shown in the protocol publication.[2]

Data were recorded in an Electronic Case Report Form and collected and managed using REDCap hosted at "Asociación Española de Gastroenterología" (AEG; http://www.aegastro.es), a nonprofit Scientific and Medical Society focused on gastroenterology research.

The aim of the current study was to analyze common mistakes made by European Gastroenterologists in the eradication of *H. pylori*. The analysis was based both on the last guidelines and consensus conferences on *H. pylori*[3,4] (2016 to 2017) and on a recently published review evaluating the most common mistakes identified in the clinical practice in *H. pylori* infection.[1] From the 10 mistakes included in this review,[1] we decided to discard 3 because they might not be considered true mistakes, at least in some countries in Europe. Thus, we discarded the following mistakes: (1) "To consider sufficient an *H. pylori* cure rate of 80%, as this threshold may be considered to be arbitrary. (2) "To underestimate the benefit of adding bismuth to antibiotic treatment to eradicate *H. pylori* infection," as bismuth may not be available in some geographical regions. And (3) "To systematically supplement *H. pylori* eradication treatment with probiotics," as probiotics may not be available in some countries. Therefore, seven mistakes were evaluated in the present study, which are listed in Table 1.

TABLE 1. Common Mistakes in the Treatment of *H. pylori* Infection

1. To use the standard triple therapy in areas where it is ineffective
2. To prescribe *H. pylori* eradication therapy for only 7-10 d
3. To use a low dose of proton pump inhibitors in *H. pylori* eradication regimens
4. In patients allergic to penicillin, to prescribe always a triple therapy with clarithromycin and metronidazole
5. To repeat certain antibiotics after *H. pylori* eradication failure
6. Failing to consider the importance of compliance with treatment
7. Not to check the success of *H. pylori* eradication after treatment

H. pylori indicates *Helicobacter pylori*.

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, 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, regardless of treatment result or whether they had a confirmatory test after the eradication treatment. In the current study, mITT and PP effectiveness results are provided.

Statistical Analyses

Continuous variables are presented as the arithmetic mean and respective standard deviation. Qualitative variables are presented as percentages and 95% confidence intervals. Differences between groups were analyzed with the χ^2 test. Significance was considered at $P < 0.05$. Time-trend analysis of prescription use and effectiveness was designed based on the year when treatment was prescribed to the patient. The variable treatment length was assessed using 3 categories, corresponding with the most frequent treatment durations: 7, 10, and 14 days. The variable dose of the proton pump inhibitor (PPI) was grouped in 3 categories as reported by Graham et al[5] and Kirchheiner et al:[6] low dose, when the potency of acid inhibition was between 4.5 and 27 mg omeprazole equivalents given twice a day; standard dose (for *H. pylori* eradication treatment), 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.

RESULTS

Overview

A final data set including those countries recruiting > 1000 patients was used. The highest recruiters by descending order were: Spain (14,751 cases), Russia (4462 cases), Italy (3289 cases), Slovenia (3193 cases), and Lithuania (1226 cases). In total 26,340 patients were analyzed for these 5 countries, representing 80% of the total cases registered in the Hp-EuReg

TABLE 2. Effectiveness of Triple Regimens in Europe

Country	Use, N (%)	mITT, N (%)	95% CI	PP, N (%)	95% CI
Overall use and effectiveness of triple regimens in naive patients					
Spain	3378 (31)	3162 (83)	81-84	3104 (83)	82-84
Russia	2120 (58)	1484 (79)	77-81	1457 (80)	78-82
Slovenia	2691 (99)	2061 (87)	85-88	2054 (87)	85-88
Italy	143 (7)	111 (86)	79-92	108 (87)	81-93
Lithuania	1048 (98)	175 (79)	73-85	173 (80)	7-86
Total	9380 (46)	6996 (83)	82-84	6896 (84)	83-85
Use and effectiveness (mITT) of standard triple therapy with a proton pump inhibitor clarithromycin and amoxicillin in naïve patients					
Spain	3156 (29)	2958 (84)	83-85	2843 (84)	83-85
Russia	2035 (56)	1415 (80)	78-82	1293 (81)	79-83
Slovenia	1848 (70)	1329 (88)	86-90	1309 (89)	87-91
Italy	133 (6)	102 (86)	80-94	93 (88)	81-95
Lithuania	1018 (95)	168 (79)	74-86	159 (81)	75-87
Total	8190 (40)	5972 (83)	83-85	5697 (84)	83-85
Use and effectiveness (mITT) of standard triple therapy with a proton pump inhibitor clarithromycin and metronidazole in naïve patients					
Spain	121 (1)	110 (65)	2-12	109 (65)	56-74
Russia	28 (1)	25 (64)	45-83	25 (64)	45-83
Slovenia	790 (29)	685 (85)	82-88	684 (85)	82-88
Italy	4 (0)	4 (75)	32-100	3 (100)	100-100
Lithuania	20 (2)	4 (100)	100-100	4 (100)	100-100
Total	963 (5)	828 (78)	79-85	825 (82)	79-85
Use and effectiveness (mITT) of triple therapy with a proton pump inhibitor, amoxicillin and metronidazole in naive patients					
Spain	101 (1)	94 (69)	63-89	40 (78)	65-91
Russia	57 (2)	44 (77)	60-88	39 (74)	60-88
Slovenia	53 (2)	47 (75)	71-100	10 (90)	71-100
Italy	6 (0)	5 (80)	45-100	3 (100)	100-100
Lithuania	10 (1)	3 (100)	100-100	2 (100)	100-100
Total	227 (1)	95 (80)	70-86	94 (79)	71-87

CI indicates confidence interval; mITT, modified intention-to-treat; N, total number of patients; PP, per protocol.

until June 2019. The results corresponding to each of the mistakes evaluated are reported below.

Mistake 1. To Use the Standard Triple Therapy in Areas Where it is Ineffective

The triple therapies prescribed as a PPI plus clarithromycin and either amoxicillin or metronidazole or combining a PPI with amoxicillin and metronidazole were the most frequently used first-line treatments (46%) in Europe. Overall effectiveness by mITT was 83%. Results are summarized in Table 2, where it is shown that standard triple therapy achieves always an eradication rate lower than 90%. The trends in use and effectiveness of these triple regimens are summarized in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/JCG/A643).

Mistake 2. To Prescribe H. pylori Eradication Therapy for Only 7 to 10 Days

The use and effectiveness of 7-, 10-, and 14-day treatments is summarized in Table 3, where it is shown that, for example, of those patients receiving a standard triple therapy, as many as 69% were treated for only 7 to 10 days, while only 31% received a 14-day regimen; and that the efficacy of the standard triple therapy administered for only 7 to 10 days was only 81%, while this figure increased up to 88% when it was prescribed for 14 d. On the basis of the frequency of therapies prescribed, we decided to evaluate the following ones: triple regimens (as PPI plus 2 antibiotics), non-bismuth quadruple therapy (ie, concomitant therapy as PPI-clarithromycin-amoxicillin-metronidazole) and bismuth-containing quadruple regimens (either in the standard form as PPI-metronidazole-tetracycline-bismuth salts, or as the 3-in-1single capsule Pylera) in any line of treatment. The trends in use and effectiveness of these treatments are summarized in Supplementary Table 2 (Supplemental Digital Content 1, http://links.lww.com/JCG/A643).

Mistake 3. To Use a Low Dose of Proton Pump Inhibitors in H. pylori Eradication Regimens

The use of acid inhibition for *H. pylori* treatment stratified by PPI dosage (low, standard, and high) is presented in Table 4, where it is shown that as many as 48% of the patients were treated with lower doses of PPI in the context of standard triple therapies. On the basis of the frequency of therapies prescribed, the analysis was restricted to triple regimens prescribed as a PPI plus clarithromycin and either amoxicillin or metronidazole or combining a PPI with amoxicillin and metronidazole. All cases reported as "low dose PPI" represent the proportion of mistake in the use of acid inhibition in triple therapies. The trends in PPI dosage prescriptions are summarized in Supplementary Table 3 (Supplemental Digital Content 1, http://links.lww.com/JCG/A643).

Mistake 4. In Patients Allergic to Penicillin, to Prescribe Always a Triple Therapy With Clarithromycin and Metronidazole

A total of 612 (2.3%) patients were reported to be allergic to penicillin. The use and effectiveness of triple therapy with clarithromycin and metronidazole and with quadruple therapy with metronidazole, tetracycline and bismuth salts (either in the standard form or as 3-in-1 single

TABLE 3. Use and Effectiveness of 7, 10 and 14-day Regimens in Europe

	7 d			10 d			7 or 10 d		14 d		
Country	**Use, N (%)**	**mITT, N (%)**	**95% CI**	**Use, N (%)**	**mITT, N (%)**	**95% CI**	**Mistake (%)**	**mITT (%)**	**Use, N (%)**	**mITT, N (%)**	**95% CI**
Use and effectiveness of 7, 10, and 14-day triple regimens in Europe											
Spain	169 (3)	169 (60)	53-68	3379 (68)	3210 (81)	80-82	71	71	1429 (29)	1297 (86)	83-87
Russia	260 (10)	216 (73)	66-79	14 (53)	1075 (81)	78-83	63	77	984 (37)	790 (90)	88-92
Slovenia	1584 (57)	1312 (86)	84-87	138 (5)	116 (85)	81-94	62	85	1070 (38)	722 (91)	89-93
Italy	79 (21)	68 (81)	71-91	274 (72)	232 (86)	81-91	93	84	28 (7)	21 (67)	43-85
Lithuania	553 (50)	143 (83)	77-90	376 (34)	51 (67)	53-80	84	75	182 (16)	1 (100)	13-99
Total	2645 (22)	1908 (81)	80-83	5567 (47)	4684 (81)	80-82	69	81	3693 (31)	2831 (88)	87-89
	7 d			10 d			10 or 14 d		14 d		
	Use, N (%)	mITT, N (%)	95% CI	Use, N (%)	mITT, N (%)	95% CI	Mistake (%)	mITT (%)	Use, N (%)	mITT, N (%)	95% CI
Use and effectiveness of 7, 10, and 14-day non-bismuth quadruple therapy in Europe											
Spain	6 (0)	6 (67)	22-95	2451 (57)	2346 (87)	86-89	57	77	1856 (43)	1780 (91)	89-92
Russia	20 (7)	9 (56)	21-86	120 (43)	54 (76)	64-88	50	66	141 (50)	42 (71)	56-86
Slovenia	20 (87)	19 (84)	60-96	1 (4)	0 (NA)	NA	91	NA	2 (9)	1 (100)	1.3-99
Italy	0	0	NA	164 (85)	151 (82)	76-88	85	41	29 (15)	14 (93)	66-99
Lithuania	0	0	NA	3 (100)	0 (NA)	NA	100	NA	0	0 (NA)	NA
Total	46 (1)	34 (74)	57-89	2739 (57)	2551 (87)	85-88	58	80	2028 (42)	1837 (90)	89-92
	7 d			10 d			14 d				
	Mistake, N (%)	mITT, N (%)	95% CI	Use, N (%)	mITT, N (%)	95% CI	Use, N (%)	mITT, N (%)	95% CI		
Use and effectiveness of 7, 10, and 14-day bismuth-containing quadruple therapy (standard form or Pylera) in Europe											
Spain	13 (0)	13 (77)	46-95	2654 (57)	2456 (90)	(89-91)	1969 (42)	1879 (89)	87-90		
Russia	42 (7)	32 (69)	51-86	587 (93)	521 (87)	(84-90)	0	267 (86)	82-90		
Slovenia	0 (NA)	0	NA	43 (96)	35 (94)	(81-99)	2 (4)	1 (100)	1.3-99		
Italy	4 (1)	4 (75)	19-99	412 (99)	288 (93)	(89-96)	1 (0)	1 (100)	1.3-99		
Lithuania	0 (NA)	0	NA	16 (100)	0 (NA)	NA	0	NA	NA		
Total	59 (1)	49 (71)	58-85	3712 (65)	3300 (90)	(89-91)	1972 (34)	2149 (88)	87-90		

CI indicates confidence interval; mITT, modified intention-to-treat; N, total number of patients; PP, per protocol.

TABLE 4. Acid inhibition Potency of Proton Pump Inhibitor use in Triple Regimens in Europe

Country	Low, N (% Mistake)	95% CI	Standard, N (%)	95% CI	High, N (%)	95% CI
Spain	1368 (41)	39-42	1223 (36)	35-38	782 (23)	22-25
Russia	1173 (56)	54-58	754 (36)	34-38	169 (8)	6.8-9.2
Slovenia	1385 (52)	50-54	50 (2)	1.3-2.4	1241 (46)	44-48
Italy	106 (85)	78-91	14 (11)	5.3-17	5 (4)	1.3-9.1
Lithuania	480 (46)	43-49	326 (31)	28-34	234 (23)	20-25
Total	4512 (48)	47-49	2367 (25)	24-26	2431 (26)	25-27

CI indicates confidence interval; high dose, 54 to 128 mg omeprazole equivalents; low dose, 4.5 to 27 mg omeprazole equivalents; standard dose, 32 to 40 mg omeprazole equivalents.

capsule Pylera) are reported in Table 5, where it is shown that 38% of patients allergic to penicillin received the triple therapy with clarithromycin and metronidazole, which achieved an eradication rate of 69%, while bismuth-based quadruple therapy, which was administered in 34% of the cases, achieved a higher efficacy (92%).

Mistake 5. To Repeat Certain Antibiotics After H. pylori Eradication Failure

Repeating clarithromycin, levofloxacin or metronidazole in second-line treatment after a failed first-line use, occurred in 15%, 32%, and 10% of the cases, respectively. The effectiveness (mITT) of repeating antibiotics was below 90% in the overall analysis. The results by country are reported in Table 6, where it is shown that clarithromycin was repeated in second-line regimens in 15% of the cases, and the eradication rate achieved with this strategy was <80%; similarly, levofloxacin was repeated (in second-line) in 32% of the patients who were initially treated with quinolones. The trends of usage of repeating clarithromycin in second-line treatment are presented in Supplementary Table 4 (Supplemental Digital Content 1, http://links.lww.com/JCG/A643).

Mistake 6. Failing to Consider the Importance of Compliance With Treatment

Overall compliance with treatment and effectiveness in compliant and noncompliant patients, as well as the proportion of patients stopping treatment because of an adverse event are reported in Table 7, where it is shown that compliance with treatment was very high (97%, with similar figures in all countries). There were 2% of patients not complying with treatment because of other reasons (not specified) than occurrence of an adverse event (0.7% in Spain, 0.19% in Russia, 0.36% in Slovenia, 0.28% in Italy, and 0.02% in Lithuania). Trends in compliance are reported in Supplementary Table 5 (Supplemental Digital Content 1, http://links.lww.com/JCG/A643).

Mistake 7. Not to Check the Success of H. pylori Eradication After Treatment

The confirmation of the eradication was performed in 94% of the cases. Results by country are presented in Supplementary Table 6 (Supplemental Digital Content 1, http://links.lww.com/JCG/A643).

DISCUSSION

Each decision made in clinical practice is open to possible errors. In order to produce descriptive studies of the management of *H. pylori* infection, the "Hp-EuReg" aims to obtain a database registering systematically a large and representative sample of routine clinical practice of European gastroenterologists.[2] On the basis of this comprehensive database, we have reviewed some the most common mistakes in the treatment of *H. pylori* infection.

Mistake 1. To Use the Standard Triple Therapy in Areas Where it is Ineffective

The traditionally most commonly used first-line triple therapy—a PPI plus 2 antibiotics—fails in ~20% to 40% of patients.[7] Furthermore, the success rate of standard triple therapy is declining to unacceptable levels, mainly because of the increased resistance to antibiotics around the globe.[1,4,8–10]

Remarkably, the Hp-EuReg shows that standard triple therapy is the most commonly prescribed first-line regimen

TABLE 5. Use and Effectiveness of Triple (Proton Pump Inhibitor, Clarithromycin, Metronidazole) and Quadruple (Proton Pump Inhibitor, Bismuth, Tetracycline, Metronidazole) Therapies in Naive Patients Allergic to Penicillin

	Triple-C+M			Quadruple-M+Tc+B*		
Country	Mistake, N (%)†	mITT, N (%)	95% CI	Use, N (%)	mITT, N (%)	(95% CI)
Spain	115 (19)	107 (64.5)	55-74	192 (31)	177 (92)	88-96
Russia	9 (1.5)	9 (55.6)	21-86	8 (1.3)	7 (100)	59-100
Slovenia	93 (15)	65 (76.9)	66-88	NA	NA	NA
Italy	1 (0.2)	1 (100)	1.3-99	6 (0.9)	3 (100)	29-100
Lithuania	14 (2.3)	NA	NA	NA	NA	NA
Total	232 (38)	182 (68.7)‡	62-76	206 (33)	187 (92)‡	88-96

*Combines the classical bismuth quadruple (PPI, metronidazole, tetracycline and bismuth) and Pylera. Data for Pylera come mainly from Spain (142 cases).
†Mistake: proportion of PPI+C+M use in the total of treatments given in naïve patients allergic to penicillin.
‡Differences were statistically significant ($P < 0.05$) in the effectiveness (mITT) of Triple-C+M and Quadruple-M+Tc+B across countries.
B indicates bismuth; C, clarithromycin; CI, confidence interval; M, metronidazole; mITT, modified intention-to-treat; Tc, tetracycline.

TABLE 6. Use and Effectiveness of Repeating the Same Antibiotic in First- and Second-line Treatment

	First-line Antibiotic = Clarithromycin			First-line Antibiotic = Levofloxacin			First-line Antibiotic = Metronidazole		
	Repeating Clarithromycin in Second Line			Repeating Levofloxacin in Second Line			Repeating Metronidazole in Second Line		
Country	N (%)	mITT, N (%)	95% CI	N (%)	mITT, N (%)	95% CI	N (%)	mITT (N)	95% CI
Spain	167 (8)	157 (80)	73-86	9 (16)	9 (78)	40-97	70 (10)	64 (78)	67-89
Russia	264 (61)	140 (80)	73-87	18 (82)	10 (90)	55-100	16 (40)	10 (80)	44-97
Slovenia	19 (6)	16 (63)	35-84	0	0	NA	11 (8)	11 (73)	39-94
Italy	48 (11)	41 (73)	58-88	3 (19)	3 (100)	29-100	2 (1)	1 (100)	1.3-99
Lithuania	9 (11)	3 (100)	29-100	0	0	NA	0	0	NA
Total, N	507 (15)	357 (78)	74-83	30 (32)	22 (86)	65-97	99 (10)	86 (78)	68-87

CI indicates confidence interval; mITT, modified intention-to-treat; N, total of patients.

(46%) in Europe. Furthermore, this regimen achieves a mean eradication rate (mITT) in Europe of only 83% (being always <90%, ranging from 79% in Russia and Lithuania, to 87% in Slovenia), emphasizing that in many geographical areas (at least in Europe) the efficacy of the standard triple therapy is clearly suboptimal and therefore should be abandoned in these areas. Quadruple regimens—including bismuth and non-bismuth therapies—should be prescribed instead.[8]

However, more important than the rate of error at a certain moment, is the evolution over time of the management of *H. pylori* infection by European gastroenterologists. Thus, in the Hp-EuReg, a shift in trends of first-line treatment use was identified: triple therapy prescription decreased from >50% in 2013 to ~40% in 2019. A paradigmatic example of improvement with time is that of Spain, where the use of triple therapies decreased from 24% in 2014 to 0% in 2019.

Mistake 2. To Prescribe H. pylori Eradication Therapy for Only 7 to 10 Days

Overwhelming evidence is available supporting the use of longer—14 days—treatments for most of the eradication regimens.[8,11–13] A meta-analysis from the Cochrane Collaboration concluded that the optimal duration of triple therapy is at least 14 days.[10] Accordingly, the Maastricht and the Toronto Consensus Reports stated that the treatment duration of PPI-clarithromycin based triple therapy should be extended to 14 days.[3,4] With 14-day therapy the PPI-clarithromycin-amoxicillin combination remains effective until clarithromycin resistance exceeds ~15%. In contrast, for triple therapy with a PPI, amoxicillin and metronidazole, it has been shown that prolonging the treatment duration can overcome the negative effect of metronidazole resistance.[14]

In the Hp-EuReg, of those patients receiving a standard triple therapy, as many as 69% were treated for only 7 to 10 days (in some countries, such as Italy, this figure was 93%), while only 31% received a 14-day regimen. The efficacy (mITT) of the standard triple therapy administered for only 7 to 10 days was only 81%, while this figure increased up to 88% when it was prescribed for 14 days. Fortunately, this mistake was progressively found less frequently and, at present, the prescription of 7-day standard triple therapy regimens has almost disappeared: in the Hp-EuReg it decreased from 29% in 2013 to only 3% in 2019; accordingly, the mean duration of these triple treatments was 9.9 days in 2013 and 13.1 days in 2019.

The non-bismuth quadruple therapy (mainly the so called concomitant regimen) has been recommended as one of the first-line treatments, especially in areas with high clarithromycin resistance.[3,4,15] A trend toward better results with this regimen has also been observed with longer treatments.[1,8,15] Accordingly, the Maastricht and the Toronto Consensus Reports also stated that the recommended treatment duration of non-bismuth quadruple therapy (concomitant) is 14 days.[3,4] However, in the Hp-EuReg, most (58%) of the non-bismuth quadruple regimens were prescribed for only 7 to 10 days and, as expected, the cure rate with this duration was suboptimal (80%), while the 14-day regimen achieved higher (90%) cure rates.

TABLE 7. Use and Effectiveness in Compliant (>90% Drug Intake) and Noncompliant (<90% Drug Intake) Patients

	Overall Compliants			Compliants Experiencing AEs			Overall Noncompliants			Noncompliants Because of AEs		
Country	N (%)	mITT, N (%)	95% CI	N (%)	mITT, N (%)	95% CI	N (%)	mITT, N (%)	95% CI	N (%)	mITT, N (%)	95% CI
Spain	13438 (97)	13296 (97)	86-87)	1278 (35)	1214 (85)	83-87	431 (3)	309 (61)	55-66	268 (7)	214 (61)	54-68
Russia	3994 (97)	3273 (84)	82-85	309 (23)	248 (81)	75-86	115 (3)	54 (44)		72 (5)	45 (64)	49-79
Slovenia	2482 (96)	2394 (87)	86-88)	107 (35)	12 (67)	35-90	91 (4)	12 (58)	28-85	7 (2)	7 (86)	42-99
Italy	2312 (96)	2271 (89)	88-90	607 (95)	537 (87)	84-90	100 (4)	44 (34)	19-49	34 (5)	26 (46)	25-67
Lithuania	210 (97)	200 (80)	74-86	46 (87)	39 (77)	62-91	7 (3)	2 (0)	NA	2 (4)	NA	NA
Total N	22436 (97)	21434 (87)	86-87	2347 (86)	2050 (85)	83-86	744 (3)	421 (56)	51-60	383 (14)	292 (61)	55-67

AEs indicates adverse events; CI, confidence interval; mITT, modified intention-to-treat; N, total number of patients.

Mistake 3. To Use a Low Dose of Proton Pump Inhibitors in H. pylori Eradication Regimens

Acid inhibition is a key component of *H. pylori* treatment.[8] There is clear evidence that high-dose PPI can improve the cure rates of *H. pylori* eradication treatment, including a meta-analysis showing that in triple therapy, twice a day PPI is better than a single daily dose;[16] and another meta-analysis showing that high-dose PPI increases cure rates by around 6 to 10% in comparison with standard doses.[17] Accordingly, the Maastricht V consensus report stated that the use of high-dose PPI twice a day (eg, omeprazole 40 mg bid) increases the efficacy of triple therapy.[4] However, in the Hp-EuReg, as many as 48% of the patients were treated with lower doses of PPI in the context of standard triple therapies. Fortunately, this percentage has decreased over time, from 67% in 2013 to 20% in 2019. From another perspective, the daily PPI dose has increased from a dose equivalent to 54 mg of omeprazole in 2013 to 104 mg in 2019.

Mistake 4. In Patients Allergic to Penicillin, to Prescribe Always a Triple Therapy With Clarithromycin and Metronidazole

When penicillin allergy is present, replacing amoxicillin with metronidazole has been generally recommended in PPI-based triple combinations. However, a relatively low efficacy has been reported with the combination of a PPI-clarithromycin-metronidazole in these patients,[18–20] which might be related, at least in part, to increasing resistance rates to both clarithromycin and metronidazole.[21] In contrast, recent studies have achieved encouraging results in patients allergic to penicillin, when prescribing a bismuth-based quadruple regimen (PPI-bismuth-tetracycline-metronidazole),[20,22] given the co-administration of bismuth overcomes the negative effect of metronidazole resistance and efficacy is not influenced by clarithromycin resistance.[23] In accordance with Maastricht consensus recommendations,[4] in patients with penicillin allergy, the bismuth quadruple therapy should be preferred to the PPI-clarithromycin-metronidazole combination in areas of high clarithromycin resistance. In the Hp-EuReg, 38% of patients allergic to penicillin received the triple therapy with clarithromycin and metronidazole, which achieved a disappointing eradication rate of 69%. On the contrary, bismuth-based quadruple therapy, which unfortunately was administered in only 34% of the cases, achieved a much higher efficacy (92%).

Mistake 5. To Repeat Certain Antibiotics After H. pylori Eradication Failure

After a failed first treatment, the remaining *H. pylori* will show very high resistance to some of the antibiotics administered, except to amoxicillin, tetracycline and rifabutine which is unusual, even after failure of treatment including those antibiotics.[24] By contrast, after treatment failure, resistances to clarithromycin, quinolones and metronidazole approach virtually 100%. As the efficacy of quinolone and clarithromycin-containing regimens is strongly affected by quinolone and clarithromycin resistance, repeating these drugs in rescue treatments is discouraged.

Of note, some studies have demonstrated that after *H. pylori* eradication failure, the repetition (even of exactly the same antibiotic regimen) is not exceptional in clinical practice.[25,26] In the Hp-EuReg, clarithromycin was repeated in second-line regimens in 15% of the cases and, as expected, the eradication rate achieved with this strategy was very low (< 80%). Similarly, levofloxacin was repeated (in second-line) in 32% of the patients who were initially treated with quinolones.

Mistake 6. Failing to Consider the Importance of Compliance With Treatment

Together with antibiotic resistance, compliance with therapy is the most important factor predicting *H. pylori* eradication. Unfortunately, the problem of compliance is quite frequent. Thus, it has been proven that 10% of patients prescribed *H. pylori* eradication therapy fail to take even 60% of medications.[27] In another study, only 88% of the patients consumed > 85% of doses.[28] However, in the Hp-EuReg, compliance with treatment (defined as having taken at least 90% of the prescribed drugs) was very high (97%, with similar figures in all countries). Furthermore, if non-compliant patients because of adverse effects were excluded, the rate of compliance with treatment increased up to 98%. Poorer levels of compliance with therapy are associated with significantly lower levels of *H. pylori* eradication.[29,30] Accordingly, in the Hp-EuReg, compliance with treatment was the most relevant factor for achieving successful eradication, regardless of the treatment chosen.[31] Thus, mean eradication rate in patients compliant with treatment in the Hp-EuReg was 87%, while this figure decreased to 56% in noncompliant ones.

Mistake 7. Not to Check the Success of H. pylori Eradication After Treatment

According with the Maastricht Consensus and the American College of Gastroenterology, several arguments could be raised in favor of systematically checking *H. pylori* eradication in all patients.[32,33] In the Hp-EuReg, confirmation of eradication by the participant gastroenterologists was not performed in <10% of the cases (furthermore, in only 1% of cases this lack of confirmation was because the physician did not ask for the confirmation test). The surveys evaluating in different countries and settings the percentage of patients in whom *H. pylori* eradication was confirmed showed figures ranging widely from 8% to 92%, with a mean value of only 50%.[1] The high confirmation rate found in the Hp-EuReg may be because of the highly specialised and motivated physicians participating in this registry (in contrast perhaps to Primary Care practitioners)[34] and to the wide availability of diagnostic tests (in fact *H. pylori* eradication confirmation tests was a requirement to participate in the Hp-EuReg).

CONCLUSIONS

In the present study we have assessed some of the most common mistakes made by some European gastroenterologists in the eradication of *H. pylori*, based on the invaluable information of the Hp-EuReg. This has allowed us to confirm that the management of *H. pylori* infection by European gastroenterologists is heterogeneous, and frequently discrepant with current recommendations. The level of penetration of recommendations in the participating European countries is still poor and delayed, even though some improvements from guidelines have been partially incorporated. The barriers for implementation, access to diagnostic tests and treatments and to continuous medical education, should be removed in order to provide optimal care. One of the main reasons for poor adherence is lack of or limited dissemination, and this is a shared responsibility between medical societies, health systems/providers, and individual professionals.

APPENDIX

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