

Original research

# European Registry on *Helicobacter pylori* management (Hp-EuReg): patterns and trends in first-line empirical eradication prescription and outcomes of 5 years and 21 533 patients

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## ABSTRACT

**Objective** The best approach for *Helicobacter pylori* management remains unclear. An audit process is essential to ensure clinical practice is aligned with best standards of care.

**Design** International multicentre prospective non-interventional registry starting in 2013 aimed to evaluate the decisions and outcomes in *H. pylori* management by European gastroenterologists. Patients were registered in an e-CRF by AEG-REDCap. Variables included demographics, previous eradication attempts, prescribed treatment, adverse events and outcomes. Data monitoring was performed to ensure data quality. Time-trend and geographical analyses were performed.

**Results** 30 394 patients from 27 European countries were evaluated and 21 533 (78%) first-line empirical *H. pylori* treatments were included for analysis. Pretreatment resistance rates were 23% to clarithromycin, 32% to metronidazole and 13% to both. Triple therapy with amoxicillin and clarithromycin was most commonly prescribed (39%), achieving 81.5% modified intention-to-treat eradication rate. Over 90% eradication was obtained only with 10-day bismuth quadruple or 14-day concomitant treatments. Longer treatment duration, higher acid inhibition and compliance were associated with higher eradication rates. Time-trend analysis showed a region-dependent shift in prescriptions including abandoning triple therapies, using higher acid-inhibition and longer treatments, which was associated with an overall effectiveness increase (84%–90%).

**Conclusion** Management of *H. pylori* infection by European gastroenterologists is heterogeneous,

## Significance of this study

### What is already known on this subject?

- *Helicobacter pylori* affects billions of people worldwide and is the main cause of chronic gastritis, peptic ulcer disease and gastric cancer.
- The ideal regimen to treat the infection remains unclear after more than 30 years of experience.

### What are the new findings?

- Triple therapy prescriptions (reporting cure rates of approximately 80%) have decreased, especially in those regions with high-clarithromycin resistance.
- Over 90% eradication was only obtained with 10-day bismuth quadruple therapies or 14-day concomitant treatment.
- From 2013 to 2018, the observed shift to longer treatment duration, higher acid inhibition and compliance provided an increase in the effectiveness.

### How might it impact on clinical practice in the foreseeable future?

- The results of this study indicate that the management of *H. pylori* infection by European gastroenterologists is heterogeneous, frequently suboptimal and discrepant with current recommendations. Consensus guideline improvements are being slowly incorporated into the daily clinical practice, which emphasises the importance of regular medical education and the need of surveillance.

suboptimal and discrepant with current recommendations. Only quadruple therapies lasting at least 10 days are able to achieve over 90% eradication rates. European recommendations are being slowly and heterogeneously incorporated into routine clinical practice, which was associated with a corresponding increase in effectiveness.

## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is a bacterial pathogen with a 50% worldwide prevalence, being the main cause of chronic gastritis, peptic ulcer disease and gastric cancer. However, the ideal strategy to manage *H. pylori* infection remains unclear. The diagnostic method, the use of culture and antibiotic susceptibility testing, the treatment to prescribe and the test to confirm eradication are debatable, and recommendations have changed over time.<sup>1–5</sup> Currently, most treatments are prescribed on an empiric basis, unaware of the bacterial antibiotic resistance profile. Noteworthy, recommendations have changed over time, with a shift from triple to quadruple therapies in the last consensus conferences.<sup>5–6</sup> Therefore, a continuous evaluation of practice outcomes using the different management options is required in order to achieve high-quality ‘evidence-based medicine’.

It is now accepted that chronic colonisation by *H. pylori* is an infectious disease and should be managed as such.<sup>7</sup> For this reason, an optimal anti-*H. pylori* regimen is currently defined as one that reliably offers a cure rate of at least 90%, accepted as an arbitrary threshold.<sup>8–9</sup> Triple therapies, using clarithromycin and amoxicillin, are still the most commonly used first-line therapies in spite of their failure in  $\geq 20\%$ – $30\%$  of patients. Resistance to clarithromycin has been identified as one of the major factors affecting *H. pylori* eradication success, and the rate of resistance to this antibiotic is steadily increasing in many geographical areas.<sup>10</sup> For this reason, non-bismuth quadruple regimen, comprising a proton pump inhibitor (PPI), amoxicillin, clarithromycin and a nitroimidazole, has more recently been used as first-line treatment,<sup>5–6–11–12</sup> and has improved the efficacy of triple therapy,<sup>13</sup> although its efficacy is impaired when dual metronidazole-clarithromycin resistance is present.

Bismuth has a strong bacteriostatic effect unaffected by resistance and displays a beneficial synergy when combined with several antibiotics, allowing to overcome bacterial resistance.<sup>14–15</sup> Thus, combinations containing bismuth may be promising options in settings where there are high, unknown or increasing *H. pylori* antibiotic resistance rates. Traditionally, bismuth has been prescribed in a quadruple regimen containing a PPI with tetracycline and metronidazole. However, the treatment schemes are complex, and bismuth salts and tetracycline are not available in many parts of the world; therefore, these drawbacks have caused a tendency to restrict its use to patients with penicillin allergy, or those who require rescue treatments after failure of a clarithromycin-containing first-line treatment.<sup>16–17</sup> The latest approach to *H. pylori* eradication has been the addition of bismuth to the standard triple therapy containing clarithromycin and amoxicillin, and this has also achieved encouraging results.<sup>18</sup>

Considering these treatment combinations, and all of the possible optimisations that can be added (length of treatment,<sup>19</sup> dose of PPI,<sup>20</sup> among others), it is hard to decide which treatment will provide good results ( $\geq 90\%$  cure rates) aligned with current recommendations and standards. Evidence from clinical trials will always be equivocal because it is impossible to perform a single randomised trial to evaluate all existing treatments. Network meta-analyses, however, may provide an acceptable pooled approach enabling analysis of combinations of data from

several treatment trials. However, evidence derived from clinical trials may not be extrapolated to clinical practice, in which there are no restrictive inclusion criteria, and where available care-time per patient and patient follow-up are more limited.<sup>21</sup>

Finally, there is a general delay from publication of recommendations to their implementation in routine clinical practice,<sup>22–23</sup> in which sometimes they reach full penetration after being outdated.<sup>24</sup> Therefore, scientists recommend long-term studies evaluating practice and outcome trends, and tools able to provide real-time data from real practice (local, regional and global).<sup>25</sup>

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 with different bacterial resistance patterns and treatment accessibility. For these reasons, our aim was to establish a large-scale long-term prospective clinical practice study providing an overview of the current situation regarding *H. pylori* management. The study would allow not only continuous assessment on the integration of clinical recommendations agreed on medical consensus but also monitoring of the temporal trends of management options and outcomes. These evaluations were aimed to decide on the best possible treatment strategies for improvement (globally and locally) ensuring that routine clinical practice is aligned with best standards of care.

## METHODS

### European Registry on *H. pylori* management

The ‘European Registry on *H. pylori* Management’ (Hp-EuReg) is an international multicentre prospective non-interventional registry recording information of *H. pylori* infection management since May 2013. Detailed information can be found in the published protocol,<sup>26</sup> and is summarised in online supplementary file 2.

### Statistical analyses

Continuous variables are presented as mean and SD. Qualitative variables are presented as absolute and relative frequencies with percentages (%). Graphical representations are used to show temporal trends in prescriptions. In the multivariate analysis, the effect was evaluated by calculating OR) and 95% CI. Statistical significance was considered at  $p < 0.05$ .

### Effectiveness analysis

The main outcome, which is treatment eradication rate, was studied in three sets of patients as follows: Intention-to-treat (ITT) analysis included all patients registered up to December 2017, 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) 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 (ie, a confirmatory test—success or failure—was available after eradication treatment). Overall (ITT, mITT and PP) analyses were performed jointly for patients treated empirically. Additional PP effectiveness analyses were performed separately in those patients with a result of in vitro susceptibility testing.

All 27 countries were clustered in five main regions based both on their geographical situation and the 2017 gross domestic product per capita (online supplementary file 3).

More than 100 different treatment schemes were used as first-line treatment. They were pooled in 13 categories (online supplementary file 4).

Similarly, PPI data were standardised using the PPI acid inhibition potency as defined by Kirchheiner<sup>27</sup> and Graham,<sup>28 29</sup> classified as low, standard and high dose PPI (online supplementary file 5).

The relation between eradication rate and age, gender, diagnosis, treatment length, PPI dose and compliance was studied in the mITT population considering six treatment categories (online supplementary file 6).

Mixed logistic regression models were used in a three-step strategy: the null model, the global mixed model with interaction between compliance and treatment and the mixed effects logistic regression for each treatment (online supplementary file 7).

## RESULTS

From May 2013 to June 2018, 30 394 cases were registered in the Hp-EuReg from 27 countries (distribution of patients per country is shown in online supplementary table 1). From those,

21 533 (91%) were first-line therapies included in the current analysis (figure 1). Most of them were empirically treated; however, in 11% of the cases, bacterial antibiotic resistance data were available and were evaluated separately.

## Geographical analysis

The 21 533 naïve patients were distributed in the following five geographical regions: east (3679), south-east (4299), south-west (10 118), centre (1985) and north (1452). The baseline characteristics are shown in table 1. A preliminary inspection showed high heterogeneity of practice and outcomes between European regions. For instance, 7-day treatment prescription was marginal in south-western Europe (1.7%), while it was mostly prescribed in south-eastern (60.0%) and northern (53.9%) regions. Most common treatments were also region specific: triple therapies were favoured in most of Europe (82%–88% in south-eastern and northern Europe, 67% in the east and 34% in south-west), whereas quadruple therapies were preferred in south-western and central Europe (63%–82%). Results of an additional cluster comparison performed between regions and the highest

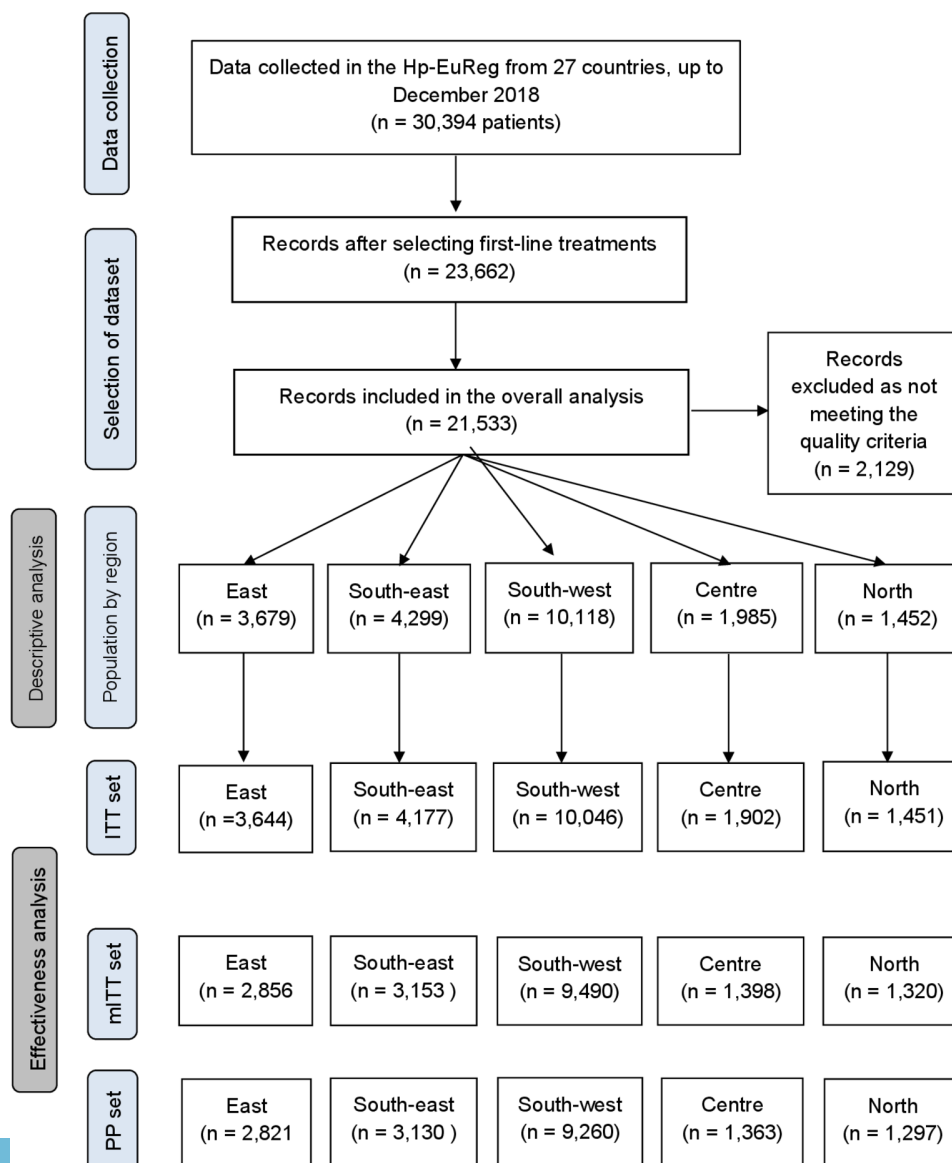


Figure 1 Study flow chart. ITT, intention-to-treat, mITT, modified ITT; PP, per-protocol.

**Table 1** Baseline characteristics of *Helicobacter pylori* first-line empirical treatments by region

Variable	Overall	East	South-east	South-west	Centre	North
Number of patients	21 533	3679	4299	10 118	1985	1452
Female, N (%)	12 743 (59.2)	2180 (59.0)	2492 (58.0)	6147 (60.8)	1192 (60.0)	732 (50.0)
Age, mean (SD)	50.4 (18.0)	46.4 (15.0)	52.2 (15.0)	50.5 (15.0)	52.2 (15.0)	52.7 (18.0)
Penicillin allergy, N (%)	670 (3.1)	57 (1.5)	126 (2.9)	414 (4.1)	13 (0.7)	60 (4.1)
Indication						
Dyspepsia	17 800 (82.7)	2679 (7.8)	3507 (81.6)	8595 (84.9)	1896 (95.5)	1123 (77.3)
Ulcer disease	3733 (17.3)	1000 (27.2)	792 (18.4)	1523 (15.1)	89 (4.5)	329 (2.7)
Culture, N (%)	2396 (11.1)	67 (1.8)	219 (5.1)	365 (3.6)	1397 (70.4)	348 (24.0)
No resistance	1087 (45.4)	20 (29.7)	143 (65.3)	211 (57.8)	552 (39.5)	209 (60.1)
C	543 (22.7)	22 (32.4)	27 (12.1)	54 (14.9)	401 (28.7)	36 (10.2)
M	766 (32.0)	25 (37.8)	49 (22.2)	100 (27.5)	444 (31.8)	103 (29.7)
Dual C+M	321 (13.4)	2 (2.7)	15 (7.1)	18 (5.0)	233 (16.7)	19 (5.6)
Treatment length, N (%)						
7 days	4109 (19.6)	568 (16.2)	2548 (60.0)	165 (1.7)	68 (3.8)	760 (53.9)
10 days	11 461 (54.8)	2080 (59.2)	981 (23.1)	6220 (62.5)	1691 (94.0)	489 (34.7)
14 days	5361 (25.6)	867 (24.7)	719 (16.9)	3574 (35.9)	39 (2.2)	162 (11.5)
PPI dose, N (%)						
Low	10 090 (48.9)	1813 (56.6)	2556 (60.6)	3 920 (39.1)	718 (40.3)	1083 (76.9)
Standard	4211 (20.4)	1135 (35.6)	306 (7.3)	2572 (25.7)	75 (4.2)	123 (8.7)
High	6325 (30.7)	253 (7.9)	1357 (32.2)	3525 (35.2)	987 (55.4)	203 (14.4)
Compliance, N (%)						
No (<90% drug intake)	592 (3.0)	97 (2.7)	120 (3.0)	287 (3.0)	63 (4.3)	25 (1.8)
Yes (≥90% drug intake)	18 821 (97.0)	3447 (97.3)	3239 (96.4)	9370 (97.0)	1410 (95.7)	1355 (98.2)
Unknown	2119 (9.8)	134 (3.6)	940 (24.5)	461 (4.4)	512 (26)	72 (5.0)
Most frequent treatments, N (%)						
PPI-C+A	8478 (39.4)	1775 (48.2)	2571 (59.3)	3160 (31.2)	132 (6.6)	840 (57.9)
PPI-C+M	1046 (4.9)	28 (0.8)	816 (19.0)	127 (1.3)	4 (0.2)	71 (4.9)
PPI-A+M	561 (2.6)	56 (1.5)	92 (2.1)	51 (0.5)	3 (0.2)	359 (24.7)
PPI-A+L	405 (1.9)	227 (6.2)	28 (0.7)	132 (1.3)	6 (0.3)	12 (0.8)
PPI-C+A+T seq	1228 (5.7)	9 (0.2)	68 (1.6)	4 (0.0)	1128 (56.8)	19 (1.3)
PPI-C+A+M seq	620 (2.9)	25 (0.7)	175 (4.1)	281 (38.6)	92 (4.6)	47 (3.2)
PPI-C+A+T conc	190 (0.9)	1 (0.0)	51 (1.2)	0 (0.0)	121 (6.1)	17 (1.2)
PPI-C+A+M conc	4176 (19.4)	14 (0.4)	250 (5.8)	3910 (38.6)	1 (0.1)	1 (0.1)
PPI-C+A+B	1756 (8.2)	800 (21.7)	0 (0.0)	956 (9.4)	0 (0.0)	0 (0.0)
PPI-M+Tc+B	192 (0.9)	30 (0.8)	7 (0.2)	41 (0.4)	99 (5.0)	15 (1.0)
PPI-M+D+B	59 (0.3)	0 (0.0)	2 (0.0)	56 (0.6)	0 (0.0)	1 (0.1)
PPI+single capsule*	1351 (6.3)	0 (0.0)	1 (0.0)	1144 (11.3)	189 (9.5)	17 (1.2)
Other	1471 (6.8)	714 (19.4)	238 (5.5)	256 (2.5)	210 (10.6)	53 (3.7)

Low dose PPI: 4.5–27 mg omeprazole equivalents, two times per day (ie, 20 mg omeprazole equivalents, two times per day), standard dose PPI: 32–40 mg omeprazole equivalents, two times per day (ie, 40 mg omeprazole equivalents, two times per day), high dose PPI: 54–128 mg omeprazole equivalents, two times per day (ie, 60 mg omeprazole equivalents, two times per day).

\*Three-in-one single capsule containing bismuth, tetracycline and metronidazole.

A, amoxicillin; B, bismuth salts; C, clarithromycin; Conc, concomitant; D, doxycycline; L, levofloxacin; M, metronidazole; PPI, proton pump inhibitor; Seq, sequential; T, tinidazole; Tc, tetracycline.

recruiting countries are presented in online supplementary table 2.

### Baseline characteristics

Overall baseline characteristics, regional demographics and concomitant drug use are presented in table 1.

### Diagnosis

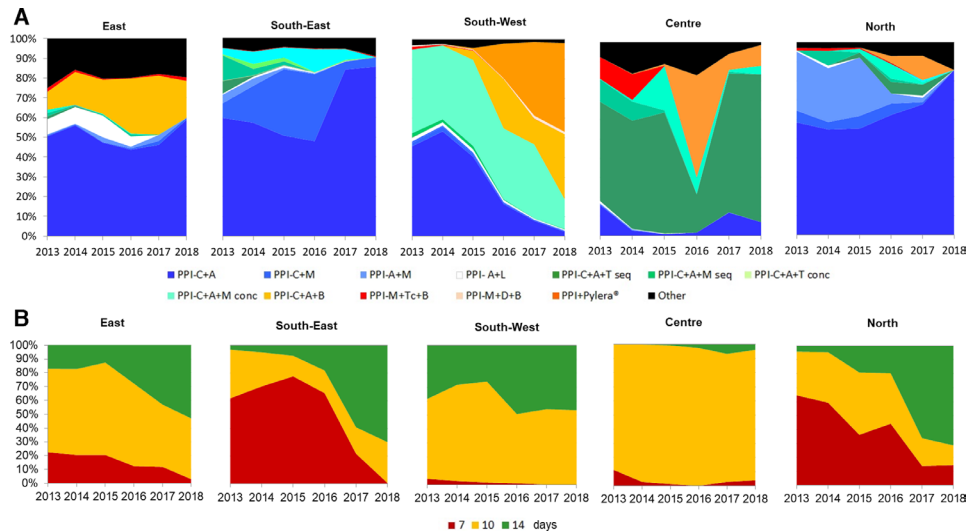
Methods used for diagnosis of the infection and confirmation of eradication are detailed in online supplementary file 8.

### Temporal trend analysis

Figure 2A shows the prescription trends in Europe, where prescription shifts were region dependent: triple therapies did

nearly disappear in south-western and central Europe, while they remained in the east, south-east and north. Triple therapies decreased from over 50% of prescription in 2013/2015 to less than 32% in 2017/2018. Sequential therapies were prescribed in 8% in 2013 but yearly prescriptions were reduced up to 0.5% in 2018, and concomitant therapy from 21% in 2013/2014 to 11% in 2018. Use of bismuth quadruple therapies increased from 0%–2% in 2013/2014 to 20% in 2018.

Figure 2B depicts the trends on treatment duration, showing an increase in mean duration of treatments from 9.6 days in 2013, to 9.7 in 2014, 10.0 in 2015, 11.0 in 2016, 11.8 in 2017 and 11.8 days in 2018, with regional differences. A major change that appeared to consistently occur throughout Europe was the discontinuation of 7-day therapies, especially in south-eastern



**Figure 2** Treatment trends (2013–2018) in Europe per region. (A) Trends in the prescription of treatments. (B) Trends in the duration of treatments. A, amoxicillin; B, bismuth salts; C, clarithromycin; Conc, concomitant; D, doxycycline; L, levofloxacin; M, metronidazole; PPI, proton pump inhibitor; Seq, sequential; T, tinidazole; Tc, tetracycline.

and northern Europe, where it was still the most common therapy duration; however, 7-day therapies were scarcely used in other regions (online supplementary table 3).

Figure 3A shows the trends in daily PPI dose (milligrams of omeprazole equivalent) by region and year, whereas figure 3B shows the temporal trends in mean daily PPI dose. The potency of acid inhibition increased from a dose equivalent of 58 mg of omeprazole in 2013 to 75 mg in 2018, showing differences between regions. Mean daily dose of PPI increased in all regions except in central Europe where it decreased in 2017–2018. High doses of PPI were mainly used in south-eastern, south-western and northern Europe (online supplementary table 3).

**Treatment use and overall effectiveness**

Overall eradication rate increased from 2013 to 2018 independently of the population analysed:

- ▶ ITT: 70.1% (2013), 72.6% (2014), 74.5% (2015), 76.7% (2016), 75.2% (2017), 77.3% (2018).
- ▶ PP: 84.5% (2013), 85.1% (2014), 85.7% (2015), 87.4% (2016), 88.6% (2017), 88.1% (2018).
- ▶ mITT: 83.9% (2013), 84.5% (2014), 85.2% (2015), 86.8% (2016), 88.3% (2017), 87.8% (2018).

The effectiveness trends were region-specific (figure 4): Eastern Europe reported eradication rates lower than 70% in 2013 and 2014, but achieved 80% mITT in the following years. The remaining regions reported an overall treatment effectiveness higher than 80% in 2013. These rates increased

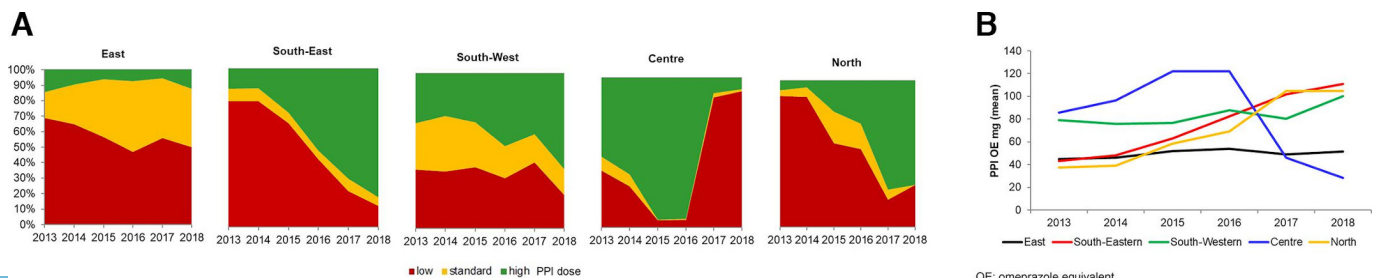
in south-eastern and south-western countries, but remained constant in the centre and north.

The effectiveness trends also appeared to be treatment dependent in each region (table 2).

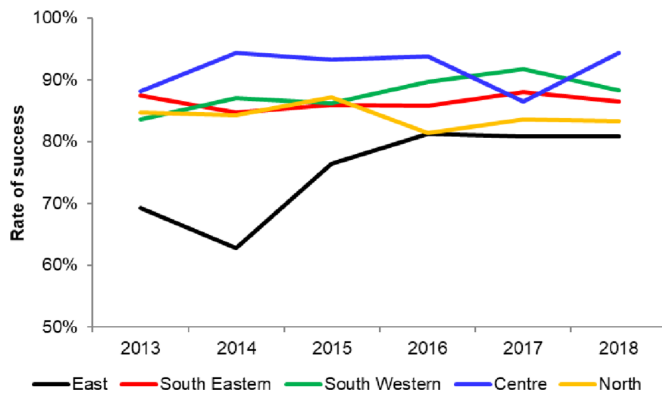
Triple therapy with clarithromycin and amoxicillin was the most frequent treatment in all regions but its eradication rate remained below 86.6% by mITT. None of the 12 treatments considered, except the concomitant therapy with clarithromycin, amoxicillin and tinidazole in the south-east, reached 90% effectiveness by mITT, whereas quadruple treatments achieved nearly 90% eradication rate. In general, single capsule bismuth quadruple treatment was the most successful, achieving approximately 90% mITT eradication in those regions where it was prescribed.

The effectiveness was likewise modified depending on the duration of treatment. Table 3 shows the impact of treatment duration (7, 10 or 14 days). Overall, effectiveness increased with longer treatment duration; and this was mostly marked with specific treatments, such as the triple therapy with clarithromycin and amoxicillin or when bismuth was added to this triple regimen.

An additional univariate subanalysis was performed to evaluate the effect of standard (recommended) or high dose PPI in those 14-day treatments not reaching 90% effectiveness (table 3).



**Figure 3** Trends (2013–2018) in the use of proton pump inhibitors (PPIs) in Europe per region. (A) Trends in the daily dose (low, standard and high) of PPI. (B) Trends in the mean daily dose of PPI.



**Figure 4** Trends in the eradication rate (modified intention-to-treat) by region.

### Resistance rates

Data on susceptibility tailored prescription of antibiotics are presented in Table 1 and supplementary file 9.

The effect of resistance on eradication rate in the most frequent first-line treatments is reported in online supplementary table 4.

### Mixed effects logistic regression

#### Null model

A null model without explanatory variables was developed to assess the proportion of variance of the outcome explained by grouping the cases in a second level 'centre'. There were 163 centres with an average of 89 cases per group. The variance of the intercept at centre level was 0.556 (SE 0.110) on the logit scale, and intraclass correlation coefficient (ICC) was 0.145; meaning the 14.5% of the variance of mITT effectiveness was explained by the differences between centres.

#### Global mixed effects model with interaction between compliance and treatment

The global mixed effects model showed a significant effect of compliance, with an OR of 6.8 (4.1 to 11.3), as well as an effect of treatment on mITT effectiveness. Using quadruple therapies with a PPI-clarithromycin-amoxicillin-bismuth as the reference category, ORs (95% CI) were as follows: triple with clarithromycin-amoxicillin 0.494 (0.39 to 0.622), triple with clarithromycin-metronidazole 0.220 (0.156 to 0.311), sequential with clarithromycin-amoxicillin-metronidazole/tinidazole 0.452 (0.305 to 0.669), concomitant with clarithromycin-amoxicillin-metronidazole/tinidazole 1.130 (0.879 to 1.453), and the single capsule bismuth quadruple 1.766 (1.240 to 2.516), showing significantly higher mITT eradication rates in quadruple therapies compared with triple or sequential therapies. The interaction between compliance and treatment was significant ( $p=0.02$ ), showing that the difference in eradication rate between compliant and non-compliant patients changed from treatment to treatment. The interaction between compliance and treatments in terms of effectiveness is plotted in figure 5, which shows that independently of the treatment considered, in compliant patients, the rate of eradication (ranging between 80% and 95%) was always higher compared with non-compliant patients. The effect of non-compliance on the mITT eradication rate was lower in concomitant therapy with clarithromycin-amoxicillin-metronidazole/tinidazole and quadruple therapy with a PPI-clarithromycin-amoxicillin-bismuth than in the remaining treatments.

### Mixed effects logistic regression by treatment

The final mixed effects logistic regression models were different for each treatment considered. To compare treatments easily, a tabular summary was built detailing the first level independent variables, the random variance component and ICCs for each model (table 4), whereas the final models are described in online supplementary file 10.

### DISCUSSION

In the present manuscript, we analysed the changes in *H. pylori* treatment outcomes throughout a period of 5 years (2013–2018) across Europe. We found gastroenterologists' management of *H. pylori* in Europe is extremely heterogeneous (over 100 different first-line schemes), but a set of standard treatment schemes are most widely used: two-thirds as triple therapies and a quarter as quadruple therapies, and both generally prescribed as 10-day regimens. Moreover, our data show that there are strong regional differences in practice among European gastroenterologists. In this sense, our study shows that the generally unrecommended triple therapies have been abandoned in southern Europe, and are disappearing in eastern regions; however, their use is still widespread in central and northern Europe. This finding evidences an incomplete penetration or implementation of the last consensus conferences, which recommended switching from triple to quadruple therapies.<sup>4–6</sup> This lack of update in clinical practice causes a high rate of failures (>20% in those patients), far from the current arbitrary threshold for acceptance of a proposed treatment ( $\geq 90\%$  eradication rate).<sup>6,8,9</sup>

However, our trend analyses of first-line prescriptions showed that European gastroenterologists are at last adapting their practice to recommendations: some regions have dropped or are abandoning triple therapies, causing an overall drop of prescriptions from 50% to less than 20%. Furthermore, central, northern and south-western Europe are increasing PPI dose and lengthening treatment duration (7-day therapies have decreased from one-third of prescriptions to less than 1%, being currently marginal in all regions). As expected, this improvement in adherence to guidelines and recommendations has correlated with an improvement in efficacy rates, reaching in 2018 almost the proposed minimum 90% cure rate by ITT.

This manuscript focused on the most relevant first-line treatments used according to either their popularity or their success rate. The most commonly prescribed treatment was standard triple therapy with a PPI, clarithromycin and amoxicillin, achieving lower than 90% eradication rate even when given for 14 days, as previously described in the literature.<sup>30,31</sup> Moreover, in our study this treatment was greatly affected by clarithromycin resistance, reducing the effectiveness to below 50% in patients harbouring resistant strains. In this respect, pretreatment clarithromycin resistance in our study was 23%, quite higher than the 15% resistance threshold generally considered (although the number of patients with susceptibility testing in the Hp-EuReg was very limited). However, triple therapy could still be used in those areas with low clarithromycin resistance and proven high effectiveness.

One of the proposed options chosen to improve triple therapy has been to combine PPI, amoxicillin, clarithromycin and metronidazole in one single scheme, the so-called 'non-bismuth quadruple treatment', given as either a sequential or concomitant regimen. Non-bismuth quadruple sequential treatment comprises PPI with amoxicillin combined during a first phase, and a second phase with a PPI, clarithromycin and metronidazole, respectively, each phase lasting for at least 5 days. Although

**Table 2** Effectiveness of most common first-line empirical treatments per region

	N	Non-evaluable		Failure	Success	Eradication rate		
		n	%	n	n	ITT	PP	mITT
<b>East</b>								
PPI-C+A	1775	26	1.5%	739	1010	57.7%	82.3%	81.5%
PPI-C+M	28	0	0.0%	11	17	60.7%	68.0%	68.0%
PPI-A+M	56	0	0.0%	22	34	60.7%	75.6%	75.6%
PPI-A+L	227	0	0.0%	191	36	15.9%	17.1%	16.7%
PPI-C+A+T seq	9	0	0.0%	9	0	0.0%		
PPI-C+A+M seq	25	0	0.0%	10	15	60.0%	68.2%	68.2%
PPI-C+A+T conc	1	0	0.0%	1	0	0.0%		
PPI-C+A+M conc	14	0	0.0%	5	9	64.3%	90.0%	90.0%
PPI-C+A+B	800	3	0.4%	191	606	76.0%	89.6%	89.2%
PPI-M+Tc+B	30	0	0.0%	6	24	80.0%	92.3%	92.3%
PPI-M+D+B	0	0						
PPI+single capsule*	0	0						
Other	714	6	0.8%	281	427	60.3%	72.6%	71.9%
Total in the region	3679			1466	2178	59.8%	77.0%	76.3%
<b>South-east</b>								
PPI-C+A	2571	113	4.4%	1013	1445	58.8%	86.7%	86.6%
PPI-C+M	816	7	0.9%	217	592	73.2%	85.4%	85.3%
PPI-A+M	92	0	0.0%	64	28	30.4%	80.0%	80.0%
PPI-A+L	28	0	0.0%	6	22	78.6%	84.0%	84.6%
PPI-C+A+T seq	68	0	0.0%	9	59	86.8%	86.8%	86.8%
PPI-C+A+M seq	175	0	0.0%	37	138	78.9%	84.7%	81.2%
PPI-C+A+T conc	51	0	0.0%	4	47	92.2%	94.0%	92.2%
PPI-C+A+M conc	250	0	0.0%	28	222	88.8%	91.7%	91.4%
PPI-C+A+B	0	0						
PPI-M+Tc+B	7	0	0.0%	1	6	85.7%	100.0%	100.0%
PPI-M+D+B	2	0	0.0%	1	1	50.0%	50.0%	50.0%
PPI+single capsule*	1	0	0.0%	0	1	100.0%	100.0%	100.0%
Other	238	9	3.8%	73	156	68.1%	83.3%	83.0%
Total in the region	4299			1453	2717	65.2%	86.5%	86.2%
<b>South-west</b>								
PPI-C+A	3160	1	0.0%	682	2477	78.4%	84.3%	83.7%
PPI-C+M	127	0	0.0%	55	72	56.7%	63.7%	63.2%
PPI-A+M	51	0	0.0%	13	38	74.5%	79.2%	77.6%
PPI-A+L	132	1	0.8%	24	107	81.7%	85.2%	84.9%
PPI-C+A+T seq	4	0	0.0%	1	3	75.0%	100.0%	100.0%
PPI-C+A+M seq	281	0	0.0%	65	216	76.9%	84.2%	81.8%
PPI-C+A+T conc	0	0						
PPI-C+A+M conc	3910	12	0.3%	540	3358	86.1%	90.3%	89.8%
PPI-C+A+B	956	10	1.0%	108	838	88.6%	91.7%	91.6%
PPI-M+Tc+B	41	0	0.0%	8	33	80.5%	84.6%	82.5%
PPI-M+D+B	56	0	0.0%	11	45	80.4%	82.4%	81.8%
PPI+single capsule*	1144	43	3.8%	151	950	86.3%	95.2%	94.6%
Other	256	5	2.0%	82	169	67.3%	78.3%	76.8%
Total in the region	10 118			1740	8306	82.7%	88.1%	87.5%
<b>Centre</b>								
PPI-C+A	132	0	0.0%	56	76	57.6%	85.7%	85.4%
PPI-C+M	4	0	0.0%	1	3	75.0%	100.0%	75.0%
PPI-A+M	3	0	0.0%	0	3	100.0%	100.0%	100.0%
PPI-A+L	6	0	0.0%	3	3	50.0%	75.0%	60.0%
PPI-C+A+T seq	1128	70	6.2%	243	815	77.0%	92.4%	91.7%
PPI-C+A+M seq	92	0	0.0%	35	57	62.0%	87.5%	86.4%
PPI-C+A+T conc	121	3	2.5%	14	104	88.1%	96.3%	93.7%
PPI-C+A+M conc	1	0	0.0%	1	0	0.0%		
PPI-C+A+B	0	0						

Continued

Table 2 Continued

	N	Non-evaluable		Failure	Success	Eradication rate		
		n	%	n	n	ITT	PP	mITT
PPI-M+Tc+B	99	0	0.0%	28	71	71.7%	95.9%	95.9%
PPI-M+D+B	0	0						
PPI+single capsule*	189	8	4.2%	82	99	54.7%	98.0%	95.2%
Other	210	2	1.0%	164	44	21.2%	84.6%	83.0%
Total in the region	1985			627	1275	67.0%	92.3%	91.2%
North								
PPI-C+A	840	1	0.1%	178	661	78.8%	84.8%	84.3%
PPI-C+M	71	0	0.0%	21	50	70.4%	76.6%	75.8%
PPI-A+M	359	0	0.0%	72	287	79.9%	86.5%	86.7%
PPI-A+L	12	0	0.0%	3	9	75.0%	90.0%	90.0%
PPI-C+A+T seq	19	0	0.0%	10	9	47.4%	100.0%	100.0%
PPI-C+A+M seq	47	0	0.0%	13	34	72.3%	71.1%	72.3%
PPI-C+A+T conc	17	0	0.0%	12	5	29.4%	100.0%	100.0%
PPI-C+A+M conc	1	0	0.0%	1	0	0.0%		
PPI-C+A+B	0	0						
PPI-M+Tc+B	15	0	0.0%	3	12	80.0%	91.7%	92.3%
PPI-M+D+B	1	0	0.0%	0	1	100.0%	100.0%	100.0%
PPI+single capsule*	17	0	0.0%	4	13	76.5%	92.9%	86.7%
Other	53	0	0.0%	20	33	62.3%	84.2%	84.6%
Total in the region	1452			337	1114	76.8%	84.7%	84.4%
All regions								
PPI-C+A	8478	141	1.7%	2668	5669	68.0%	84.6%	84.1%
PPI-C+M	1046	7	0.7%	305	734	70.6%	81.6%	81.3%
PPI-A+M	561	0	0.0%	171	390	69.5%	84.3%	84.2%
PPI-A+L	405	1	0.2%	227	177	43.8%	46.6%	46.3%
PPI-C+A+T seq	1228	70	5.7%	272	886	76.5%	92.1%	91.4%
PPI-C+A+M seq	620	0	0.0%	160	460	74.2%	83.0%	80.8%
PPI-C+A+T conc	190	3	1.6%	31	156	83.4%	95.7%	93.4%
PPI-C+A+M conc	4176	12	0.3%	575	3589	86.2%	90.4%	89.9%
PPI-C+A+B	1756	13	0.7%	299	1444	82.8%	90.8%	90.6%
PPI-M+Tc+B	192	0	0.0%	46	146	76.0%	92.4%	91.8%
PPI-M+D+B	59	0	0.0%	12	47	79.7%	81.5%	81.0%
PPI+single capsule*	1351	51	3.8%	237	1063	81.8%	95.5%	94.6%
Other	1471	22	1.5%	620	829	57.2%	76.6%	75.8%
Total in all regions	21 533	320	1.5%	5623	15 590	73.5%	86.2%	85.6%

\*Three-in-one single capsule containing bismuth, tetracycline and metronidazole.

A, amoxicillin; B, bismuth salts; C, clarithromycin; Conc, concomitant; D, doxycycline; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; PP, per protocol; PPI, proton pump inhibitor; Seq, sequential; Tc, tetracycline.

it was successfully proposed and implemented in the early 2000s,<sup>32</sup> it has been falling into disuse and it accounted for less than 10% of first-line treatments in our study. The eradication rate of the sequential therapy in our study (86%) was superior to that of triple therapies but still below 90%. Furthermore, sequential therapy is affected by single and, especially, by dual resistance to clarithromycin and metronidazole,<sup>13</sup> scoring below 80% and 75% in single and dual resistances, respectively.

Non-bismuth quadruple concomitant therapy includes the same drugs as sequential therapy but they are all taken together, with benefits in terms of simplicity, for both patients and physicians. The literature is clear regarding its superiority to triple therapies and, although more debatable, it is better than the quadruple sequential therapy as well.<sup>12 33-35</sup> Our study showed that concomitant regimen during 10 days with standard acid inhibition was still unable to reach the 90% cure rate arbitrary threshold, but optimised regimens lasting 14 days and/or

using high dose PPIs did achieve over 90% eradication even in clarithromycin-resistant strains.

Another treatment that has resurfaced recently in light of increased resistance rates is bismuth quadruple therapy, which contains a PPI, bismuth salts, tetracycline and metronidazole.<sup>34 36</sup> This combination has been available as a rather complicated multiprescription regimen scheme for many years, but recently, a three-in-one single, combination treatment has emerged.<sup>37</sup> In the literature, both the traditional and the single capsule bismuth quadruple regimens achieve eradication rates near or superior to 90% irrespective of clarithromycin resistance, and even overcoming metronidazole resistance.<sup>37-39</sup> In our study, they both achieved this threshold in 10-day treatments, even though the treated population was biased towards a higher prevalence of penicillin allergy, which has been proposed to be a risk factor for treatment failure.<sup>40</sup> As in previous literature,<sup>37</sup> metronidazole resistance did not significantly affect these bismuth quadruple regimens in our study.



**Table 3** Effectiveness of first-line empirical treatments according to duration

	ITT eradication rate				PP eradication rate				mITT eradication rate			
	N	Treatment duration			N	Treatment duration			N	Treatment duration		
		7 days	10 days	14 days		7 days	10 days	14 days		7 days	10 days	14 days
PPI-C+A*	8337	60.4%	71.5%	73.2%	6647	83.0%	84.8%	86.7%	6743	82.7%	84.2%	86.2%
PPI-C+M*	1039	74.0%	57.4%	54.3%	898	84.8%	67.3%	67.9%	903	84.4%	66.7%	67.9%
PPI-A+M	561	69.3%	77.4%	25.0%	458	80.7%	85.9%	80.0%	463	80.8%	85.7%	80.0%
PPI-A+L	404	8.6%	78.0%	74.2%	371	8.9%	86.8%	85.2%	382	8.8%	85.4%	85.2%
PPI-C+A+T seq	1158	NA	77.5%	NA	957	NA	92.1%	NA	969	NA	91.5%	NA
PPI-C+A+M seq*	620	NA	74.4%	NA	528	NA	82.9%	NA	569	NA	80.8%	NA
PPI-C+A+T conc	187	NA	85.4%	89.5%	162	NA	95.5%	100.0%	167	NA	92.8%	100.0%
PPI-C+A+M conc	4164	NA	84.8%	88.2%	3891	95.0%	88.9%	92.2%	3992	90.9%	88.3%	92.1%
PPI-C+A+B	1743	50.0%	74.6%	86.6%	1577	76.9%	86.6%	92.6%	1594	76.9%	86.2%	92.4%
PPI-M+Tc+B	192	NA	75.3%	83.3%	157	NA	93.8%	88.2%	159	NA	93.1%	88.2%
PPI-M+D+B	59	NA	93.8%	78.0%	54	NA	93.3%	81.1%	58	NA	93.8%	80.0%
PPI+single capsule†	1300	NA	82.1%	NA	1102	NA	95.4%	NA	1124	NA	94.5%	NA
Other	1449	62.1%	73.4%	54.5%	1073	73.7%	85.0%	60.4%	1094	73.7%	84.4%	59.7%
Total	21 213	61.1%	76.9%	79.6%	17 875	78.5%	87.8%	88.3%	18 217	78.2%	87.0%	88.0%

\*An effectiveness univariate analysis was performed accounting 10-day or 14-day treatments prescribed together with high doses PPI only, and following therapies reached over 90% mITT eradication rate: 14-day PPI-C+A (89.6%), 10-day PPI-C+A+M seq (91.6%), 10-day or 14-day PPI-C+A+M conc (both 92.7% and 92.8%), 10-day PPI-C+A+B (95.5%), 10-day PPI-M+Tc+B (95.2%). A  $\chi^2$  test was also performed and significant comparisons (10 days vs 14 days with high-dose PPIs) were reported in the table (\*). Additional pair-wise comparison (by means of  $\chi^2$  test and Fisher exact test) were performed between following treatments: 10-day sequential, 14-day concomitant and 10-day bismuth quadruple: statistically significant differences ( $p < 0.001$ ) were found in all comparisons in favour of the 14-day concomitant and 10-day bismuth quadruple therapies.

†Three-in-one single capsule containing bismuth, tetracycline and metronidazole.

A, amoxicillin; B, bismuth salts; C, clarithromycin; Conc, concomitant; ITT, intention-to-treat; L, levofloxacin; M, metronidazole; mITT, modified-intention-to-treat; NA, Not applicable; PP, per protocol; PPI, proton pump inhibitor; Seq, sequential; Tc, tetracycline.

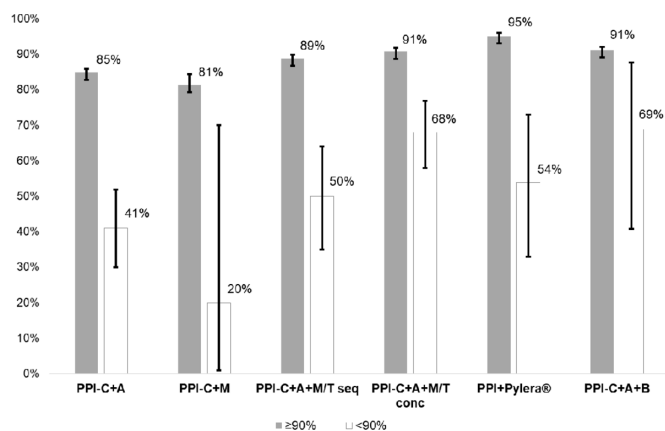
Finally, bismuth may also be combined with clarithromycin and amoxicillin to improve the efficacy of standard triple therapy. This approach has not been widely used in the literature, but a few studies have been published recently with encouraging results and have promoted a change in practice.<sup>41 42</sup> Our results with this treatment were also promising when prescribed for 14 days, scoring over 90% eradication by mITT.

In our mixed multilevel analysis, several factors were found to be independently associated with treatment effectiveness, especially adherence to treatment, with a global OR of approximately 7. Remarkably, compliance was excellent (97%) and was indeed the factor which was mostly associated with higher eradication rate in all treatment categories evaluated, with an OR ranging from 4 (concomitant treatment) to 50 (quadruple therapy with

clarithromycin, amoxicillin and bismuth). Additionally, use of the recommended dose of PPI improved cure rates in all treatment categories, although when high instead of standard doses were used, no additional benefit was found as shown in table 4.

Findings from the present study should be interpreted with caution on account of a number of limitations. First of all, this study is not a randomised controlled clinical trial; therefore, comparisons of treatments must be taken with care, due to unidentified allocation biases that may affect effectiveness. These include different local resistance rates, the age of treatment groups, treatment and care costs for patients and providers, and the use of the mITT analysis versus the traditional ITT (which could overestimate eradication) among others. However, these limitations are inherent to studies focused on clinical practice, which are necessary to elucidate the outcomes in routine practice.

Another drawback is that inclusion rates and numbers varied between centres, regions and countries according to the number of *H. pylori* infections managed in each outpatient clinic. For example, standard clinics in regions with low infection prevalence may obviously attend a lower number of *H. pylori*-infected patients, thus affecting their inclusion rates. Although results may not be fully representative of the general population, it is important to mention that in those highest recruiting countries such as Spain, there was a wide variety of centre types (large hospitals vs small outpatients clinics) and therefore this could balance the distribution and the representativeness of the population. In any case, in our sensitivity analysis, we did not identify any significant bias derived from high versus low inclusion countries. In addition, even if we may think heterogeneity was inevitably present, it is important to highlight that the standard triple therapy did not reach an optimal effectiveness in any of the regions; and, by contrast, in all the regions, all quadruple regimens (concomitant, single capsule bismuth quadruple



**Figure 5** Eradication rate (and 95% CI) by treatment according to compliance. A, amoxicillin; B, bismuth salts; C, clarithromycin; Conc, concomitant; M, metronidazole; PPI, proton pump inhibitor; Seq, sequential; T, tinidazole.

**Table 4** Mixed effects logistic models for each first-line empirical treatment category

Fixed effects	Triple-C+A				Triple-C+M				Sequential-C+A+T/M			
	OR		95% CI		OR		95% CI		OR		95% CI	
	Lower	Upper	P value	OR	Lower	Upper	P value	OR	Lower	Upper	P value	
Age-centred	1.005	1.001	1.010	0.045	0.992	1.005	0.245	1.013	1.001	1.026	0.049	
Sex	1.156	0.993	1.351	0.061	1.187	1.789	0.413	1.977	1.292	3.026	0.002	
Diagnosis	1.354	1.093	1.677	0.006	1.730	3.199	0.081	1.389	0.557	3.466	0.481	
Length												
7 days	1				1							
10 days	1.452	1.125	1.875	0.002	0.564	1.281	0.172	1				
14 days	1.547	1.109	2.159	0.010	0.665	1.737	0.406					
PPI dose OEt												
Low	1				1							
Standard	1.449	1.168	1.788	0.001	3.680	10.020	0.011	3.193	0.831	12.729	0.091	
High	1.634	1.251	2.135	<0.001	1.806	3.019	0.024	1.832	1.113	3.014	0.017	
Compliance	7.576	4.497	12.765	<0.001	41.479	850.79	0.016	22.241	7.310	67.670	<0.001	
Constant	0.546	0.306	0.976	0.041	0.066	1.240	0.077	0.186	0.056	0.612	0.006	
Random effects	Estim.	SE			Estim.	SE		Estim.	SE			
Variance	0.788	0.189		<0.001	1.541	0.852	<0.001	0.633	0.362		<0.001	
ICC	0.193				0.312			0.161				
	Concomitant-C+A+T/M				Single capsule bismuth quadruple*				Quadruple-C+A+B			
	OR		95% CI		OR		95% CI		OR		95% CI	
	Lower	Upper	P value	OR	Lower	Upper	P value	OR	Lower	Upper	P value	
Age-centred	0.994	0.988	0.999	0.039	1.001	1.017	0.825	0.996	0.984	1.008	0.502	
Sex	1.365	1.075	1.735	0.011	0.609	1.036	0.055	1.005	0.694	1.457	0.977	
Diagnosis	1.500	1.037	2.161	0.031	1.706	4.294	0.212	1.546	0.893	2.676	0.120	
Length												
7 days	1				1							
10 days	0.460	0.055	3.831	0.473	1			1				
14 days	0.536	0.064	4.499	0.566				1.913	0.999	3.661	0.051	
PPI dose OEt												
Low	1				1			1				
Standard	1.662	1.127	2.452	0.010	1.191	2.517	0.648	2.151	1.077	4.294	0.027	
High	1.699	1.192	2.421	0.003	1.132	2.268	0.726	1.377	0.677	2.803	0.296	
Compliance	4.586	2.640	7.964	<0.001	24.919	63.744	<0.001	48.873	1.514	15.505	0.007	
Constant	3.549	0.406	31.003	0.252	1.016	2.709	0.975	1.058	0.304	3.675	0.929	
Random effects	Estim.	SE			Estim.	SE		Estim.	SE			
Variance	0.312	0.138		<0.001	0.370	0.298	0.015	0.328	0.219		<0.002	
ICC	0.087				0.101			0.091				

\*Three-in-one single capsule containing bismuth, tetracycline and metronidazole.

†Comparison between standard dose PPI (reference) and high dose PPI were performed and no statistically significant differences were found in any of the treatment categories.

A, amoxicillin; B, bismuth salts; C, clarithromycin; Estim, Estimate; ICC, intraclass correlation coefficient; ITT, intention-to-treat; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; NA, Not applicable; OE, omeprazole equivalent; PP, per protocol; PPI, proton pump inhibitor; Tc, tetracycline.

and bismuth-amoxicillin-clarithromycin quadruple therapies) achieved  $\approx 90\%$  eradication rates, which confers consistency to the cluster-by-cluster analysis of the data.

Finally, our intention to study clinical practice forced us to register as many open management options as possible; this increases heterogeneity and sometimes limits the amount of data obtainable from each case. For example, individual antibacterial resistance was available in a relatively low proportion of cases, translating what happens in day-to-day clinical practice in Europe. In the future, PCR testing could ease bacterial antibiotic susceptibility evaluation if such method is shown to be reliable in faecal samples, which would avoid invasive testing such as endoscopy.

In contrast to these limitations, we believe that this type of study has a number of strengths that compensate the weaker areas. The open inclusion criteria ensure that our data represent the real clinical practice of the participant centres, and it allow the evaluation of the widest range of therapeutic options and patient contexts. Although data are heterogeneous, the analyses showed that the measure of the effect is consistent throughout Europe. Moreover, the large number of recruiters and countries has provided, to our knowledge, the largest international prospective series on *H. pylori* treatment under a common research protocol. This has enabled us to perform multivariate analyses to control for confounding variables, data bias and heterogeneity, to develop regional and time-trend approaches. The inclusion of centres with different levels of experience in *H. pylori* gave us a wide view of real practice. Finally, a high-quality method has been used to register, store, manage and monitor the data by the use of Online Platform for Collaborative Research AEG-REDCap, which provides stability and coherence to the data with programmed and real-time quality controls, queries, reports and statistics.

In light of these results, we may conclude that in order to obtain over 90% eradication rates consistently, to avoid retreatment and to prevent patient dropout, physicians should be encouraged to use quadruple therapies, because these are the only regimens that consistently achieve eradication rates  $\geq 90\%$ . Those treatments were as follows: 14-day non-bismuth quadruple concomitant therapy (PPI, amoxicillin, clarithromycin and metronidazole), 14-day standard triple plus bismuth (PPI, bismuth, amoxicillin and clarithromycin) and 10-day bismuth quadruple therapy (PPI, bismuth, tetracycline and metronidazole). If antibiotic resistance rates are high in the local geographical area, and especially if dual resistance to clarithromycin and metronidazole is greater than 15%, bismuth quadruple therapy may be the most reliable choice.

Prescribing physicians must also take into consideration that regardless of the treatment chosen or the clinical context, compliance with treatment was the most relevant factor for achieving successful eradication, so treatment, procedures and expectations must be carefully explained to the patient.

Although overall *H. pylori* cure rates in the European Registry are relatively disappointing, different regions of Europe are slowly and heterogeneously incorporating recommended practices such as prescribing quadruple therapies for 2 weeks with an increased dose of acid inhibition. The observed ongoing adaptation of real clinical practice to recommendations gives room for hope, especially considering the parallel improvement (up to 10% in some regions) in overall efficacy in Europe in only 5 years.

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