

ONLINE SUPPLEMENTARY MATERIAL

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Supplementary file 2. Hp-EuReg description and protocol

The study was approved by the Ethics Committee of La Princesa University Hospital (Madrid, Spain) and was prospectively registered in ClinicalTrials.gov (NCT02328131). The Hp-EuReg Scientific Committee currently 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 protocol²⁷ reported criteria for country selection, national coordinators, gastroenterologist recruiting investigators and a list of variables and outcomes. Initially, 27 European countries with over 300 recruiters were selected.

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, hosted at “Asociación Española de Gastroenterología” (AEG; www.aegastro.es), a non-profit Scientific and Medical Society focused on Gastroenterology research.

Data extraction was performed in June 2018 and was subject to monitoring (at least a 10% of the included records per country and centre) and quality check.

Supplementary file 3. Regional clusters of the participating Hp-EuReg countries

1. East. Low gross domestic product per capita (GDP) (€ 2.5K to 11K):
Ukraine, Serbia, Bulgaria, Turkey, Russia, Romania.
2. South-east. Low-medium GDP (€ 13K to 24K): Croatia, Poland,
Hungary, Latvia, Lithuania, Greece, Slovenia.
3. South-western. Medium GDP (€ 21K to 30K): Portugal, Spain.
4. Centre. Medium-high GDP (€ 30K to 40K): Italy, France.
5. North. High GDP (€ 40K to 80K): The United Kingdom, Belgium,
Germany, Finland, The Netherlands, Ireland, Israel, Norway,
Switzerland.

Supplementary file 4. First-line empirical treatment category pools for the univariate analysis

1. Triple –C+A (a PPI together with clarithromycin and amoxicillin)
2. Triple –C+M (a PPI together with clarithromycin and metronidazole)
3. Triple –A+L (a PPI together with clarithromycin and levofloxacin)
4. Triple –A+M (a PPI together with amoxicillin and metronidazole)
5. Sequential –C+A+M (a PPI together with clarithromycin, amoxicillin and metronidazole given in a sequential way)
6. Sequential –C+A+T (a PPI together with clarithromycin, amoxicillin and tinidazole given in a sequential way)
7. Concomitant –C+A+M (a PPI together with clarithromycin, amoxicillin and metronidazole)
8. Concomitant –C+A+T (a PPI together with clarithromycin, amoxicillin and tinidazole given in a concomitant way)
9. Quadruple –C+A+B (a PPI together with clarithromycin, amoxicillin and bismuth salts)
10. Bismuth quadruple –M+Tc+B (a PPI together with metronidazole, tetracycline and bismuth salts given in the standard way)
11. Quadruple –M+D+B (a PPI together with metronidazole, doxycycline and bismuth salts given in the standard way)
12. Pylera[®] single capsule (a proton pump inhibitor together with the three- in one single capsule given as stated in the technical sheet)
13. Others (including more than 80 different 1st-line treatments with frequencies lower than 0.5%)

C – clarithromycin, M – metronidazole, T – tinidazole, A – amoxicillin, B – bismuth salts, Tc – tetracycline

Supplementary file 5. Proton pump inhibitor categories: low, standard and high acid inhibition

1. Low dose PPI: ranging from 4.5 to 27 mg omeprazole equivalents, b.i.d. (i.e. 20 mg omeprazole equivalents, b.i.d.).
2. Standard dose PPI: ranging from 32 to 40 mg omeprazole equivalents, b.i.d. (i.e. 40 mg omeprazole equivalents, b.i.d.).
3. High dose PPI: ranging from 54 to 128 mg omeprazole equivalents, b.i.d. (i.e. 60 mg omeprazole equivalents, b.i.d.).

Supplementary file 6. First-line empirical treatment category pools for the multivariate analysis

1. Triple –C+A
2. Triple –C+M
3. Sequential –C+A+T/M (including Sequential –C+A+T and Sequential –C+A+M)
4. Concomitant –C+A+T/M (including Concomitant –C+A+T and Concomitant –C+A+M)
5. Bismuth quadruple (including Quadruple –M+Tc+B, and Pylera[®])
6. Quadruple –C+A+B

C – clarithromycin, M – metronidazole, T – tinidazole, A – amoxicillin, B – bismuth salts, Tc – tetracycline

The following treatment categories were not considered due to their low relative frequencies and the unsuitability to aggregate them with the other treatments: triple with amoxicillin-metronidazole, triple with amoxicillin-levofloxacin, quadruple with metronidazole-doxycycline-bismuth and ‘Others’.

Supplementary file 7. Mixed logistic regression models

Mixed logistic regression models were used to study the relation between eradication and other variables. Also, in order to evaluate the potential impact of underlying differences of patient outcomes between different hospitals, a second level variable “centre”, including a random hospital-specific intercept, was included. The strategy consisted in the following:

Null model

A null model was run including the outcome variable and the second-level aggregation identifier ‘centre’. The intra-class correlation coefficient (ICC), which estimates the proportion of outcome variance explained by the existing differences between centres, was derived from the variance decomposition of the intercept coefficient variance on the logit scale.

Global mixed model with interaction between compliance and treatment

This model was created including all six treatment categories in order to evaluate the effectiveness of treatments controlled by the hospital-specific intercept. It also focused on the interaction between compliance and treatment since it was suspected that the influence of compliance on eradication would be different depending on the treatment considered.

Mixed effects logistic regression for each treatment

Mixed effects logistic regression was developed in successive blocks for each treatment. The first block included the independent variables at the patient level: sex (female [reference], male), age-centred, indication (dyspepsia

[reference], ulcer), treatment length (7 [reference], 10 and 14 days), PPI dose (low [reference], standard and high dose) compliance (<90% [reference] and $\geq 90\%$); along with the second-level variable 'centre'. Afterwards, those predictor variables not reaching statistical significance (i.e. $p > 0.05$ level) were removed stepwise, allowing the addition of those that reached significance during the process or removing those that had lost it. In the second block, the interaction between compliance and any other variable that had reached statistical significance in the first block was studied, as well as the interaction between treatment length and PPI dose. Non-statistically significant interactions were removed in order to obtain the final models for each treatment. Also, during data recording or data quality controls some information (inadequate or confusing data) was lost. Missing-data imputation procedures were not used. Statistical analyses were carried out with IBM SPSS 23.0. and STATA 12.0.

Supplementary file 8. *H. pylori* diagnostic methods

Most patients (66%) underwent invasive endoscopic procedures for diagnosis of the infection. Confirmation of eradication was performed in 71.4% of the cases; by excluding on-going cases (i.e. less than 6 months of follow-up and without confirmation of eradication), this figure increased to 95%. The most common reasons for lack of confirmation were patient refusal and/or patient not attending the examination. The most common non-invasive method for confirmation of eradication was the ¹³C-urea breath test (73%). Centres from regions with higher GDP per capita (centre and north) performed more invasive diagnoses and more cultures and antibiograms (from 1.8-5.1% cultures in low to medium GDP countries to 24.0-70.4% in richest areas), providing susceptibility tailored prescription of antibiotics in routine clinical practice.

Supplementary file 9. Bacterial antibiotic resistances

Bacterial antibiotic resistance data were available in 2,396 patients (11.1%) of the sample. Single resistance (i.e. at least to one antibiotic) was reported for 54.0% of the strains. Resistance in naïve patients varied per region: clarithromycin bacterial resistance was reported in 10.6% and 11.9% of the cases in the north and centre, respectively; in 14.2% in the south-west; and in 24.5% and 27.5% in eastern and south-eastern Europe, respectively.

Resistance to the most common antibiotics was: 766 patients (32.0% of cultures) to nitroimidazoles, 543 patients (22.7%) to clarithromycin, and 321 patients (13.4%) reported dual resistance to both clarithromycin and nitroimidazole.

In the overall analysis, a successful eradication was achieved in 88.7% of patients without resistance, in 81.6% of patients with resistance to clarithromycin, in 83.8% of patients with resistance to nitroimidazoles, and in 83.5% of patients with dual resistance. The effect of the bacterial resistance in naïve patients is reported by treatment in Supplementary table 4.

Supplementary file 10. Mixed effects logistic regression: final models by first-line empirical treatment

Triple with clarithromycin-amoxicillin

The final model included the first level variables: indication, treatment length, PPI dose and compliance, whereas the variable 'age centred' was discarded during the stepwise selection process. ORs (95% CI) were as follows: indication 1.422 (1.152 – 1.756); 10 days treatment length 1.443 (1.118 – 1.864), 14 days treatment length 1.552 (1.112 – 2.166); standard dose PPI 1.447 (1.169 – 1.790), high dose PPI 1.639 (1.255 – 2.140) and compliance 7.638 (4.536 – 12.862). None of the interactions studied reached statistical significance. Variance of the random component was 0.791 (SE 0.190).

Triple with clarithromycin-metronidazole

The final model included the first level variables PPI dose and compliance. ORs (95% CI) were as follows: standard dose PPI 3.320 (1.229 – 8.971), high dose PPI 1.698 (1.032 – 2.793); compliance 32.149 (1.674 – 617.13). None of the interactions studied reached statistical significance. Variance of the random component was 1.541 (SE 0.852).

Sequential with clarithromycin-amoxicillin-metronidazole/tinidazole

The final model included the first level variables: age centred, sex, PPI dose and compliance. ORs (95% CI) were as follows: age 1.013 (1.001 – 1.027) for each year above the mean; sex male 1.988 (1.300 – 3.042); standard dose PPI 3.301 (0.862 – 12.641), high dose PPI 1.834 (1.117 – 3.021); compliance 22.212 (7.301 – 67.574). None of the interactions studied reached statistical

significance. Variance of the random component was 0.619 (SE 0.357).

Concomitant with clarithromycin-amoxicillin-metronidazole/tinidazole

The final model included the first level variables: age centred, sex, diagnosis, PPI dose and compliance. ORs (95% CI) were as follows: age 0.994 (0.989 – 0.999) for each year above the mean; sex male 1.366 (1.075 – 1.735); diagnosis 1.498 (1.038 – 2.162); standard dose PPI 1.702 (1.158 – 2.504), high dose PPI 1.802 (1.296 – 2.507) and compliance 4.512 (2.600 – 7.829). None of the interactions studied reached statistical significance. Variance of the random component was 0.321 (SE 0.140).

Bismuth Quadruple (including single capsule bismuth quadruple)

The final model included the first level variable compliance and its OR (95% CI) was 23.582 (9.401 – 59.155). No interaction was studied. Variance of the random component was 0.374 (SE 0.306).

Single capsule Bismuth Quadruple

An additional model was run exclusively including those cases treated with Pylera®. After forced introduction of the variables, the single first level variable reaching statistical significance was compliance (data not shown in table 4). Therefore, the final model included the first level variable compliance and its OR (95% CI) was 23.131 (9.038 – 59.197). No interaction was studied. Variance of the random component was 0.321 (SE 0.256).

Quadruple with clarithromycin-amoxicillin-bismuth

The final model included the first level variables: age centred, treatment length, PPI dose and compliance. The variable treatment length, evaluated two levels, 10 and 14 days and reached statistical significance ($p = 0.011$) during the variable stepwise selection process. Moreover, a significant interaction between treatment length and PPI dose was found ($p = 0.014$). ORs (95% CI) were as follows: 14 days treatment length with respect to 10 days 4.479 (1.418 – 14.148); standard dose PPI 2.795 (1.190 – 6.566), high dose PPI 4.620 (1.165 – 18.319) and compliance 5.235 (1.670 – 16.416). The interaction between treatment length and PPI dose, nuanced the effects of these two variables on mITT effectiveness; that is, when the PPI dose was low, the effect of the 14-day treatment on eradication was higher than 10-day treatment, OR 4.479 (1.418 – 14.148). However, this effect was not significant with standard PPI doses, OR 0.394 (0.091 – 1.704); and was reversed when the PPI dose was high, OR 0.123 (0.022 – 0.723). Variance of the random component was 0.228 (SE 0.180).

Supplementary Table 1. Inclusion of patients per country

COUNTRY	FREQUENCY (N)	PERCENTAGE (%)
SPAIN	9,864	45.8
RUSSIA	2,763	12.8
SLOVENIA	2,272	10.6
ITALY	1,749	8.1
NORWAY	661	3.1
LITHUANIA	615	2.9
LATVIA	572	2.7
GREECE	464	2.2
UKRAINE	410	1.9
TURKEY	268	1.2
PORTUGAL	254	1.2
IRELAND	251	1.2
FRANCE	236	1.1
HUNGARY	215	1.0
U.K.	169	.8
ROMANIA	129	.6
ISRAEL	103	.5
BULGARIA	98	.5
CROATIA	92	.4
BELGIUM	73	.3
POLAND	69	.3
GERMANY	65	.3
SWITZERLAND	56	.3
THE NETHERLANDS	37	.2
DENMARK	29	.1
SERBIA	11	.1
FINLAND	8	.0
TOTAL	21,533	100

Supplementary Table 2. Baseline characteristics of regional cluster comparison with highest recruiting countries

Percentages (%)	Spain	Russia	Slovenia	Italy	Norway	Latvia	Pool	Else ¹
Participation (inclusion rate)	46	13	10	6.7	4.4	3.3	83	17
Female	62	60	62	64	51	65	60.5	59
Penicillin allergy	4.6	1.9	2.5	0.4	4.2	1.5	2.5	3.1
Compliance	97	96	95	94.5	97	98.5	96	95
No confirmation of eradication	3.0	16	9.0	6.4	0.4	0.2	5.9	5
Invasive diagnosis	55	64	88.5	88	75	77	75	66
10-day treatments	62.5	67	11	95.2	52	32	53	58.5
mITT in 10-day treatments	82.5	70	78	83.0	86	83	80	80.5
PPI+C+A	82	64	57	NA	92	90	77	77
PPI+C+A+M/T seq	81	70	81	86	NA	NA	79.5	84
PPI+M+Tc/D+B	73	79	NA	97.5	90	NA	85	83
PPI+Pylera [®]	91	NA	88	92	NA	NA	90	92
PPI+C+A+M/T	86	NA	88	79	NA	NA	84	86

mITT – modified intention-to-treat, NA – not applicable/unknown, PPI – proton pump inhibitor, Seq – sequential, C – clarithromycin, M – metronidazole, T – tinidazole, A – amoxicillin, D – doxycycline, B – bismuth salts, Tc – tetracycline, Pool – pooled data from high recruiting countries, ¹pooled data from the remaining countries (Greece, Ukraine, Turkey, Ireland, The United Kingdom, Hungary, Portugal, Romania, France, Lithuania, Croatia, Belgium, Israel, Switzerland, Bulgaria, Germany, The Netherlands, Denmark, Poland, Serbia, Finland).

Supplementary Table 3. Prescription trends (2013 to 2018)

	2013	2014	2015	2016	2017	2018
N	3,942	5,004	4,156	4,204	3,391	778
PPI-C+A+B	0.5%	0.9%	5.2%	17.2%	10.2%	15.3%
Pylera [®]	0.0%	0.0%	0.5%	12.0%	24.5%	22.3%
PPI-M+Tc+B	2.3%	1.9%	0.4%	0.2%	0.3%	0.4%
PPI-C+A+M/T ¹	20.0%	21.4%	26.9%	22.3%	21.2%	10.6%
PPI-C+A+M/T ²	8.1%	3.4%	1.8%	0.9%	0.3%	0.5%
PPI-A+L	2.1%	2.2%	3.2%	1.9%	0.3%	0.3%
PPI-A+M	4.1%	3.0%	1.7%	0.9%	0.9%	0.6%
PPI-C+M	3.9%	6.4%	9.0%	6.6%	1.4%	1.0%
PPI-C+A	53.6%	54.3%	42.7%	28.2%	30.5%	34.0%
Other	4%	4%	7%	8%	7%	9%
7 days	31.3%	28.1%	24.7%	16.7%	7.8%	1.8%
10 days	48.3%	52.7%	55.9%	46.4%	46.9%	43.9%
14 days	20.5%	19.2%	19.4%	36.8%	45.3%	54.2%
Low dose PPI ³	62%	57%	47%	36%	39%	28.5%
Standard dose PPI	19%	25.5%	26.5%	24.5%	24%	29%
High dose PPI	19%	18%	26%	39%	37%	43%
Mean omeprazole equivalent dose of PPI (mg)						
All regions	58	63	72	79	73	75
Centre	86	97	122	122	46	28
East	45	46	52	54	49	51
North	37	39	58	69	105	105
South-east	43	48	63	82	102	111
South-west	79	76	77	88	80	100

C – clarithromycin, M – metronidazole, T – tinidazole, A – amoxicillin, D – doxycycline, B – bismuth salts, Tc – tetracycline, PPI: proton-pump-inhibitor, ¹quadruple therapy given in a concomitant way, ²quadruple therapy given in a sequential way, ³Low dose PPI – 4.5 to 27 mg omeprazole equivalents, b.i.d., Standard dose PPI – 32 to 40 mg omeprazole equivalents, b.i.d, High dose PPI – 54 to 128 mg omeprazole equivalents, b.i.d.

Supplementary Table 4. Effectiveness of eradication treatments (per-protocol analysis) according to antibiotic resistance pattern in naïve patients.

	No resistance			Clarithromycin			Metronidazole			Levofloxacin			Dual (C + M)		
	E	N	%E	E	N	%E	E	N	%E	E	N	%E	E	N	%E
PPI+C+A	306	345	89	10	23	43.5	11	137	83	29	41	71	4	7	57
PPI+C+A+M	32	34	94	10	11	91	9	11	82	5	6	83	4	5	80
PPI+C+M	16	20	80			NA			NA			NA			NA
PPI+C+A+T	193	218	88.5	25	29	86	18	218	85	156	172	91	104	123	85
PPI+C+A+B	3	3	100			NA			NA			NA			NA
PPI+C+A+M	31	36	86	5	7	71	16	27	59	5	6	83	5	8	62.5
PPI+A+M	43	49	88	21	25	84	4	5	80	5	5	100	1	1	100
PPI+A+L	5	5	100	5	5	100	12	14	86			NA	11	13	85
PPI+Pylera®	23	26	88.5	6	7	86	19	22	86	18	19	95	9	12	75
PPI+C+A+T	22	24	92	24	24	100	24	24	100	21	22	95.5	14	14	100
PPI+M+Tc+B	3	3	100	9	10	90	6	6	100	2	3	67	5	5	100

E – eradication (number of cured patients), N – total resistant patients, NA – not applicable/unknown, PPI – proton pump inhibitor, Conc – concomitant, Seq – sequential, C – clarithromycin, M – metronidazole, A – amoxicillin, L – levofloxacin, B – bismuth salts, Tc – tetracycline.