antibiotics

Online Supplementary Material

File S1. Serious adverse events in first– and second–line therapies.

First line

PPI + C + A + M (Conc):

- Esophageal candidiasis and intense abdominal pain with disability (N = 1).
- Intestinal suboclution (N = 1).
- Intense diarrhea with disability (N = 1).

PPI + Single–capsule:

- Acute pancreatitis requiring hospitalization (N = 1).
- Clostridium difficile infection requiring hospitalization (N = 1).

Second line

PPI + L + A:

- Severe diarrhea (N = 1).

N: number of patients presenting the adverse event, PPI: proton pump inhibitor, C: clarithromycin, A: amoxicillin, M: metronidazole, Conc: concomitant administration of the drugs, Single–capsule: three–in–one single capsule, L: levofloxacin.

File S2.Proton pump inhibitor (PPI) 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.). This includes pantoprazole 10 mg, pantoprazole 20 mg, pantoprazole 40 mg, pantoprazole 80 mg, omeprazole 10 mg, omeprazole 20 mg, lansoprazole 15 mg, lansoprazole 30 mg, esomeprazole 10 mg, and rabeprazole 10 mg, all administered 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.). This includes omeprazole 40 mg, esomeprazole 20 mg, and rabeprazole 20 mg, all administered 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.). This includes omeprazole 80 mg, lansoprazole 60 mg, esomeprazole 40 mg, esomeprazole 80 mg, and rabeprazole 40 mg, all administered b.i.d.

File S3. Contribution log.

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Figure S1. Regional distribution of Spanish centres participating in the Hp–EuReg.



Table S1. Safety in first– and second–line treatment.

	Adverse events			
	1st line		***2nd line***	
Intensity	N (%)	95% CI	N (%)	95% CI
Mild	5,126 (62)	61–63	1,434 (47)	45–50
Moderate	5,126 (34)	33–36	1,434 (49)	46–52
Severe	5,126 (3.8)	3.2–4.3	1,434 (3.8)	2.9–5
Serious*	5,126 (0.1)	0.03–0.23	1,434 (0.07)	0.002–0.4

95% CI: 95%confidence interval, *Serious adverse event: event leading to hospitalization, disability, or death, or to birth defects on pregnant patients.

Table S2. Effectiveness in first– and second–line treatment according to duration.

Effectiveness	**ITT**						**mITT**						**PP**					
Days	**7**		**10**		14		7		10		14		7		10		14	
T	**N (%)**	**95% CI**	**N (%)**	**95% CI**	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
First line	159 (60)	52–68	6,237 (83)	83–84	3,668 (85)	84–86	159 (60)	52–68	6,011 (88)	87–89	3,522 (90)	89–91	158 (61)	53–68	5,858 (89)	88–90	3,449 (90)	89–91
PPI + C + A + M (Conc)	4 (100)	40–100	2,323 (85)	83–86	1,654 (88)	86–90	4 (100)	40–100	2,232 (88)	87–90	1,629 (92)	91–93	4 (100)	40–100	2,175 (89)	88–90	1,588 (92)	91–94
PPI + C + A	146 (59)	51–67	1,767 (80)	78–82	784 (77)	74–80	146 (59)	51–67	1,686 (84)	82–86	699 (86)	84–89	145 (59)	51–67	1,657 (84.5)	83–86	683 (87)	84–89
PPI + Single–capsule	2 (100)	16–100	1,566 (88)	86–89	3 (67)	9–99	2 (100)	16–100	1,533 (95)	94–96	2 (100)	16–100	2 (100)	16–100	1,507 (96)	95–97	2 (100)	16–100
PPI + Bi + C + A	0 (0)	NA	10 (80)	44–98	1,022 (88.5)	86–90	0 (0)	NA	9 (89)	52–100	1,004 (91)	89–93	0 (0)	NA	8 (100)	63–100	992 (91)	89–93
PPI + C + A + M (Seq)	0 (0)	NA	229 (79)	73–84	1 (100)	NA	0 (0)	NA	221 (81)	76–86	1 (100)	NA	0 (0)	NA	191 (84)	78–89	1 (100)	NA
PPI + C + M	2 (100)	16–100	89 (58)	48–69	33 (58)	39–75	2 (100)	16–100	82 (63)	52–74	29 (65.5)	46–82	2 (100)	16–100	81 (64)	53–75	29 (65.5)	46–82
Second line	17 (71)	44–90	1,345 (74)	72–76	1,051 (85)	83–87	17 (71)	44–90	1,265 (79)	77–81	1,007 (89)	87–91	17 (71)	44–90	1,241 (80)	77–82	986 (90)	88–92
PPI + L + A	4 (75)	19–99	680 (70)	66–73	259 (86)	81–90	4 (75)	19–99	647 (74)	70–77	241 (92)	88–95	4 (75)	19–99	636 (74)	70–77	240 (92.5)	88–96
PPI + Bi + L + A	0 (0)	NA	8 (50)	16–84	454 (87)	83–90	0 (0)	NA	6 (67)	22–96	444 (90)	86–92	0 (0)	NA	6 (67)	22–96	428 (90)	87–93
PPI + Single–capsule	0 (0)	NA	432 (80)	76–84	7 (86)	42–100	0 (0)	NA	399 (88.5)	85–91	7 (67)	22–96	0 (0)	NA	390 (89)	86–92	7 (67)	22–96
PPI + Mx + A	0 (0)	NA	21 (95)	76–100	114 (85)	77–91	0 (0)	NA	20 (100)	83–100	109 (89)	82–94	0 (0)	NA	20 (100)	83–100	109 (89)	82–94
PPI + C + A + M (Conc)	0 (0)	NA	51 (74.5)	60–86	68 (75)	63–85	1 (0)	NA	47 (81)	67–91	62 (84)	72–92	1 (0)	NA	46 (80)	66–91	62 (84)	72–92

ITT: intention–to–treat, mITT: modified intention–to–treat, PP: per protocol, T: treatment prescribed, N: number of patients included in the analysis, %: proportion of patients presenting effectiveness, 95% CI: 95% confidence interval, PPI: proton pump inhibitor, C: clarithromycin, A: amoxicillin, M: metronidazole, Single–capsule: three–in–one single capsule, Bi: bismuth, L: levofloxacin, Tc: tetracycline, Conc: concomitant administration of the drugs, Seq: sequential administration of the drugs, NA: not applicable.

Table S3. Effectiveness in first– and second–line treatment according to the PPI dose.

Effectiveness	**ITT**						**mITT**						**PP**					
PPI doses	**Low**		**Standard**		High		Low		Standard		High		Low		Standard		High	
T	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
1st line	3708 (79.5)	78–81	2570 (84.5)	83–86	3696 (87)	86–88	3536 (84)	83–85	2464 (89)	88–90	3608 (92)	91–93	3421 (85)	84–86	2421 (89.5)	88–91	3537 (92)	91–93
PPI + C + A + M (Conc)	1705 (84)	82–86	760 (86)	84–89	1506 (89)	87–91	1623 (89)	87–90	744 (89)	86–91	1492 (92)	91–94	1574 (89)	87–91	731 (89)	87–91	1455 (93)	91–94
PPI + C + A	927 (70)	67–73	1114 (82)	80–84	639 (83)	80–86	880 (74)	71–77	1,049 (87)	85–89	584 (91)	89–93	866 (74)	71–77	1,032 (87)	85–89	569 (92)	89–94
PPI + Single–capsule	657 (87)	84–89	418 (86)	86–89	473 (91)	88–93	632 (93.5)	91–95	398 (95)	93–97	484 (97)	95–98	621 (94)	92–96	388 (96)	93–98	479 (97)	95–98
PPI + Bi + C + A	15 (87)	60–98	120 (97)	92–99	890 (88)	85–90	16 (82)	54–96	120 (97)	92–99	873 (91)	89–93	15 (87)	60–98	119 (97)	92–99	862 (91)	89–93
PPI + C + A + M (Seq)	187 (79)	72–84	12 (92)	62–100	31 (74)	55–88	179 (82)	76–87	12 (92)	62–100	31 (74)	55–88	149 (86)	79–91	12 (92)	62–100	31 (74)	55–88
PPI + C + M	59 (52.5)	39–66	43 (70)	54–83	22 (54.5)	32–76	58 (53)	40–67	39 (77)	61–89	16 (75)	48–93	57 (54)	41–68	39 (77)	61–89	16 (75)	48–93
2nd line	731 (71)	68–75	451 (74)	70–78	1,207 (85)	83–87	683 (77)	73–80	421 (79)	75–83	1,162 (89)	87–91	670 (77)	74–80	414 (80)	76–84	1,135 (90)	88–91
PPI + L + A	388 (68)	63–73	259 (71)	65–77	291 (85)	81–89	365 (72)	67–77	245 (75)	69–80	278 (89)	85–93	361 (72)	67–77	239 (76)	70–81	276 (89.5)	85–93
PPI + Bi + L + A	25 (60)	39–79	15 (87)	60–98	416 (88)	84–91	20 (75)	51–91	15 (87)	60–98	410 (90)	87–93	20 (75)	51–91	15 (87)	60–98	394 (90)	88–94
PPI + Single–capsule	198 (80)	74–85	72 (81)	70–89	165 (80)	73–86	184 (87)	81–92	65 (91)	81–97	152 (89)	83–93	180 (88)	83–93	65 (91)	81–97	146 (89)	83–94
PPI + Mx + A	3 (100)	29–100	18 (94)	73–100	114 (85)	77–91	3 (100)	29–100	17 (100)	81–100	109 (89)	82–94	3 (100)	29–100	17 (100)	81–100	109 (89)	82–94
PPI + C + A + M (Conc)	35 (80)	63–92	17 (59)	33–82	68 (75)	63–85	34 (82)	66–93	13 (77)	46–95	63 (82.5)	71–91	33 (82)	65–93	13 (77)	46–95	63 (82.5)	71–91

ITT: intention–to–treat, mITT: modified intention–to–treat, PP: per protocol, T: treatment prescribed, N: number of patients included in the analysis, %: proportion of patients presenting effectiveness, PPI: proton pump inhibitor, Low: ≈ 20 mg omeprazole equivalents b.i.d., Standard: ≈ 40 mg omeprazole equivalents b.i.d., High: ≈ 60 mg omeprazole equivalents b.i.d., 95% CI: 95% confidence interval, C: clarithromycin, A: amoxicillin, M: metronidazole, Single–capsule: three–in–one single capsule, Bi: bismuth salts, L: levofloxacin, Tc: tetracycline., Conc: concomitant administration of the drugs, Seq: sequential administration of the drugs.

Table S4. Effectiveness, safety and compliance of the most frequent first– and second–line therapies prescribed to penicillin–allergic patients.

	Effectiveness						Adverse events		Compliance	
	ITT		mITT		PP					
T	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
1st line	408 (76)	71–80	384 (81)	77–85	376 (82)	78–86	393 (24)	20–28	394 (97)	94–98
PPI + Single–capsule	151 (85)	79–91	141 (94)	88–97	136 (95)	90–98	143 (27)	20–35	144 (94)	89–98
PPI + C + M	117 (60)	50–69	109 (64)	55–73	109 (64)	55–73	114 (15)	9–23)	113 (99)	95–100
PPI + C + L	38 (79)	63–91	37 (81)	65–92	36 (83)	67–94	37 (24)	12–41)	37 (97)	86–100
PPI + Tc + Bi + M	34 (85)	69–95	33 (88)	72–97	33 (88)	72–97	34 (38)	22–56	34 (100)	90–100
2nd line	136 (73.5)	65–81	131 (77)	69–84	125 (79)	71–86	134 (36)	28–45	134 (94)	89–97
PPI + Single–capsule	34 (71)	53–85	33 (73)	55–87	30 (80)	61–92	32 (28)	14–47	32 (94)	79–99
PPI + C + L	29 (69)	49–85	26 (77)	56–91	25 (76)	55–91	29 (24)	10–44)	29 (86)	68–96
PPI + Tc + Bi + M	21 (90.5)	70–99	20 (95)	75–100	20 (95)	75–100	21 (90.5)	70–99	21 (100)	84–100

ITT: intention–to–treat, mITT: modified intention–to–treat, PP: per protocol, T: treatment prescribed, N: number of patients analized for each variable, %: proportion of patients presenting the variable (success, adverse events o good compliance), 95% CI: 95% confidence interval, PPI: proton pump inhibitor, Single–capsule: three–in–one single capsule, C: clarithromycin, M: metronidazole, L: levofloxacin, Tc: tetracycline, Bi: bismuth.

Table S5. Effectiveness in first– and second–line treatment according to duration in penicillin–allergic patients.

Effectiveness	**ITT**						**mITT**						**PP**					
Days	7		10		14		7		10		14		7		10		14	
T	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
1st line	5 (60)	15–95	335 (78)	73–82	67 (69)	56–79	5 (60)	60(15–95)	315 (83.5)	79–87	63 (73)	60–83	5 (60)	15–95	308 (84)	80–88	63 (73)	60–83
PPI + Single–capsule	NA	NA	150 (85)	79–91	1 (100)	NA	NA	NA	140 (94)	88–97	1 (100)	NA	NA	NA	135 (95)	90–98	1 (100)	NA
PPI + C + M	2 (100)	16–100	84 (58)	47–69	31 (61)	42–78	2 (100)	16–100	78 (63)	51–74	29 (65.5)	46–82	2 (100)	16–100	78 (63)	51–74	29 (65.5)	46–82
PPI + C + L	NA	NA	33 (79)	61–91	4 (100)	40–100	NA	NA	32 (81)	64–93	4 (100)	40–100	NA	NA	32 (81)	64–93	4 (100)	40–100
PPI + Tc + Bi + M	NA	NA	29 (83)	64–94	5 (100)	48–100	NA	NA	28 (86)	67–96	5 (100)	48–100	NA	NA	28 (86)	67–96	5 (100)	48–100
2nd line	1 (100)	NA	94 (67)	57–76	40 (87.5)	73–96	1 (100)	NA	88 (72)	61–81	41 (88)	74–96	1 (100)	NA	84 (74)	63–83	40 (90)	76–97
PPI + Single–capsule	NA	NA	33 (70)	51–84	1 (100)	NA	NA	NA	32 (72)	53–86	1 (100)	NA	NA	NA	29 (79)	60–92	1 (100)	NA
PPI + C + L	1 (100)	NA	24 (67)	45–84	4 (75)	19–99	1 (100)	NA	21 (76)	53–92	4 (75)	19–99	1 (100)	NA	20 (75)	51–91	4 (75)	19–99
PPI + Tc + Bi + M	NA	NA	13 (85)	55–98	8 (100)	63–100	NA	NA	12 (92)	62–100	8 (100)	63–100	NA	NA	12 (92)	62–100	8 (100)	63–100

ITT: intention–to–treat, mITT: modified intention–to–treat, PP: per protocol, T: treatment prescribed, N: number of patients analized for each variable, %: proportion of patients presenting efficacy, 95% CI: 95% confidence interval, PPI: proton pump inhibitor, Single–capsule: three–in–one single capsule, C: clarithromycin, M: metronidazole, L: levofloxacin, Tc: tetracycline, Bi: bismuth, NA: not applicable.

Table S6. Effectiveness in first and second–line treatment according to PPI dose in penicillin–allergic patients.

E	**ITT**						**mITT**						**PP**					
PPI doses	Low		Standard		High		Low		Standard		High		Low		Standard		High	
T	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
1st line	160 (69)	61–76	128 (83)	75–89	112 (78)	69–85	152 (73)	65–80	122 (87)	80–92	103 (86)	78–92	148 (74)	66–81	120 (87.5)	80–93	101 (87)	79–93
PPI + Single–capsule	62 (84)	72–92	31 (90)	74–98	55 (84)	71–92	57 (93)	83–98	28 (100)	88–100	53 (91)	79–97	54 (94)	85–99	27 (100)	87–100	52 (92)	82–98
PPI + C + M	55 (53)	39–66	41 (71)	55–84	21 (57)	34–78	55 (53)	39–66	38 (76)	69–89	16 (75)	48–93	55 (53)	39–66	38 (76)	60–89	16 (75)	48–93
PPI + C + L	11 (54.5)	23–83	19 (84)	60–97	7 (100)	59–100	10 (60)	26–88	19 (84)	60–97	7 (100)	59–100	9 (67)	30–93	19 (84)	60–97	7 (100)	59–100
PPI + Tc + Bi + M	12 (67)	35–90	19 (95)	74–100	3 (100)	29–100	11 (73)	39–94	19 (95)	74–100	3 (100)	29–100	11 (73)	39–94	19 (95)	74–100	3 (100)	29–100
2nd line	49 (61)	46–75	24 (79)	58–93	61 (80)	68–89	44 (68)	52–81	24 (79)	58–93	61 (82)	70–91	41 (73)	57–86	23 (78)	56–93	59 (83)	71–92
PPI + Single–capsule	20 (75)	51–91	2 (100)	16–100	12 (58)	28–85	20 (75)	51–91	2 (100)	16–100	11 (64)	31–89	18 (83)	59–96	2 (100)	16–100	10 (70)	35–93
PPI + C + L	11 (54.5)	23–83	6 (83)	36–100	11 (73)	39–94	8 (75)	35–97	6 (83)	36–100	11 (73)	39–94	8 (75)	35–97	5 (80)	28–100	11 (73)	39–94
PPI + Tc + Bi + M	2 (0)	NA	5 (100)	48–100	14 (100)	77–100	1 (0)	NA	5 (100)	48–100	14 (100)	77–100	1 (0)	NA	5 (100)	48–100	14 (100)	77–100

E: effectiveness, ITT: intention–to–treat, mITT: modified intention–to–treat, PP: per protocol, PPI: proton pump inhibitor, Low: ≈ 20 mg omeprazole equivalents b.i.d., Standard: ≈ 40 mg omeprazole equivalents b.i.d., High: ≈ 60 mg omeprazole equivalents b.i.d., T: treatment prescribed, N: number of patients analized for each variable, %: proportion of patients presenting efficacy, 95% CI: 95% confidence Interval, Single–capsule: three–in–one single capsule, C: clarithromycin, M: metronidazole, L: levofloxacin, Tc: tetracycline, Bi: bismuth, NA: not applicable.