**ONLINE SUPPLEMENTARY MATERIAL**

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**Supplementary file 2.** Adverse events by treatment scheme

***Triple therapies***

In total, 8,014 patients treated with a triple regimen provided information on safety: PPI+C+A (6,741 cases), PPI+C+M (907 cases) and PPI+A+M (366 cases) reported an incidence of AEs of 15%, 20% and 22%, respectively.

The most frequent AEs with PPI+C+A were metallic taste and nausea (both in 4% of the cases) with a mean duration of 7.2 (±3.7) and 5.2 (±3.7) days, respectively. Metallic taste was severe in 12% of the patients.

All patients were given standard triple therapy as a PPI in combination with 1000 mg of amoxicillin and 500 mg of metronidazole, both twice daily, and therefore no sub-analysis could be performed by antibiotic dosage. However, the appearance of AEs with PPI+C+A occurred in approximately 14% of the cases when the treatment was administered for 7-10 days, and in 19% of the cases with 14-day treatment durations, with significant statistical differences (p<0.001) between treatment durations.

The most frequent AEs with PPI+C+M were metallic taste and dyspepsia, in 7% and 5% of the cases respectively, with a mean duration of 6.5 (±1.8) and 6.5 (±2.5) days, respectively. Metallic taste was severe in 11% of the patients.

The appearance of AEs with PPI+C+M occurred in 21% of the cases when given for 7 days, in 16% of the cases with 10 day-treatment and in 25% of the cases with 14-day regimens (Table 5), with no statistically significant differences between treatment durations. Also, patients were given different clarithromycin and metronidazole doses: when clarithromycin 250 or 500 mg b.i.d. was prescribed, AEs occurred in 19% and 23% of the cases respectively, but differences were not statistically significant. Likewise, when metronidazole 400 or 500 mg b.i.d. was administered, AEs occurred in 20% and 24% of the cases respectively, with no statistical differences between them.

The most frequent AEs with PPI+A+M were metallic taste, diarrhoea and nausea, all three occurring in 7% of the cases, with a mean duration of 7.6 (3.3) days for metallic taste and 7.4 (3.9) days both for diarrhoea and nausea. These two latter were severe in 11% of the cases each. No subgroup analysis detected statistically significant differences.

The remaining AEs occurred in less than 2% of the cases in all three triple regimens.

***Non-bismuth quadruple therapies***

In total, 4,185 patients treated with non-bismuth quadruple therapies provided information on safety: concomitant (PPI+C+A+nitroimidazole; 3,844 cases) and sequential (PPI+C+A+nitroimidazole; 341 cases) regimens reported an incidence of AEs of 17 and 25% and 7 and 19%, respectively when using tinidazole or metronidazole.

Metallic taste was the most frequent AE, being reported by 10% and 8% of the patients who were prescribed concomitant and sequential therapies, respectively; and was severe in 4% of the cases, with a mean duration of 8.4 (±3.2) days in both regimens.

All patients received the same antibiotic doses, but were treated with different treatment lengths (Table 5). Statistically significant differences were found in the incidence of AEs between treatment durations with PPI+C+A+M (p<0.05); AE incidences ranged from 19% with 7-day to 27% with 14-day regimens.

***Bismuth quadruple therapies***

In total, 2,720 patients treated with bismuth quadruple therapies reported information on safety: three-in-one single capsule Pylera® (2,304 cases), PPI+bismuth+tetracycline+M (230 cases) and PPI+bismuth+doxycycline+M (186 cases), reporting an AE incidence of 28%, 37% and 33% respectively.

Nausea was the most frequent AE reported with PPI+bismuth+tetracycline+M (20%) and its variant with doxycycline (17%), and was severe in 11% and 12% of the cases, respectively. Diarrhoea and nausea were the most frequent AEs with the three-in-one single capsule (both in 8% of cases), both mostly of mild to moderate intensity.

Classic bismuth quadruple therapy used metronidazole 500 mg/8h in all cases but was prescribed for 7, 10 or 14 days, with statistically significant differences (p<0.001) in the incidence of AEs between treatment durations: ranging from 21% with 7-day to 56% with 14-day regimens. Its variant with doxycycline was mainly administered for 10 and 14 days, reporting 17% and 45% of AEs, with statistically significant differences (p<0.001) between groups.

***Levofloxacin-based triple and quadruple therapies***

In total, 2,162 patients treated with levofloxacin-based therapies reported information on safety: PPI+A+levofloxacin (1,603 cases) and PPI+A+levofloxacin+bismuth (559 cases), reporting an AE incidence of 21% and 32%, respectively.

Diarrhoea and nausea were the most frequent AEs, occurring in triple therapies in 8% and 6% of the cases respectively, and in quadruple therapies in 15% and 8.5% respectively; they were mostly mild.

Most of the patients were prescribed levofloxacin 500 mg/12h and therefore no sub-analysis could be performed by antibiotic dosage. Likewise, most of the patients were treated with 14-day PPI+A+levofloxacin+bismuth, and no statistical differences were observed with respect to 10-day regimens, showing approximately 31% of AEs in both schedules. The incidence of AEs ranged from 21% to 39% with 7-day and 14-day regimens, respectively, showing statistically significant differences (p<0.001) between groups.

**Supplementary table 1.** Case report form used for collection of information on adverse events****

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**Supplementary table 2.** Inclusion of patients reporting any adverse event per country

|  |  |  |
| --- | --- | --- |
| **COUNTRY** | **Frequency (N)** | **Percentage (%)** |
| Spain | 11,987 | 53.3 |
| Slovenia | 3,032 | 13.5 |
| Russia | 2,446 | 10.9 |
| Lithuania | 1,082 | 4.8 |
| Ukraine | 489 | 2.2 |
| Greece | 425 | 1.9 |
| Latvia | 418 | 1.9 |
| Portugal | 403 | 1.8 |
| Italy | 309 | 1.4 |
| UK | 261 | 1.2 |
| Norway | 260 | 1.2 |
| Hungary | 248 | 1.1 |
| Ireland | 240 | 1.1 |
| Israel | 227 | 1 |
| Turkey | 197 | 0.9 |
| Romania | 115 | 0.5 |
| Germany | 93 | 0.4 |
| France | 88 | 0.4 |
| Bulgaria | 63 | 0.3 |
| Croatia | 58 | 0.3 |
| Belgium | 25 | 0.1 |
| Switzerland | 20 | 0.1 |
| Denmark | 6 | 0 |
| Total | 22,492 | 100 |

**Supplementary table 3.** Intensity of each adverse event by treatment scheme

1. **Metallic taste**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mild, N** | **%** | **95% CI** | **Moderate, N** | **%** | **95% CI** | **Severe, N** | **%** | **95% CI** |
| **PPI+C+A** | 124 | 36 | (31-42) | 173 | 51 | (46-57) | 41 | 12 | (8.5-16) |
| **Concomitant (PPI+C+A+M)** | 250 | 66 | (61-71) | 114 | 30 | (25-35) | 16 | 4.2 | (2.1-6.4) |
| **PPI+three-in-one** | 90 | 72 | (64-80) | 34 | 27 | (19-35) | 1 | 0.8 | (0.02-4.4) |
| **PPI+C+A+B** | 264 | 86 | (82-90) | 40 | 13 | (9.1-17) | 4 | 1.3 | (0.36-3.3) |
| **PPI+A+L** | 12 | 44 | (24-65) | 14 | 52 | (31-73) | 1 | 3.7 | (0.09-19) |
| **PPI+C+M** | 34 | 45 | (33-57) | 33 | 44 | (32-56) | 8 | 11 | (3.0-18) |
| **PPI+A+L+B** | 34 | 79 | (66-92) | 9 | 21 | (7.6-34) | 0 | 0.00 | (0.00-8.2) |
| **Triple-A+M** | 19 | 68 | (49-87) | 7 | 25 | (7.2-43) | 2 | 7.1 | (0.88-24) |
| **Sequential (PPI+C+A+M)** | 13 | 57 | (34-79) | 9 | 39 | (17-61) | 1 | 4.3 | (0.11-22) |
| **PPI+B+Tc+M** | 24 | 63 | (47-80) | 12 | 32 | (15-48) | 2 | 5.3 | (0.64-18) |
| **PPI+B+A+J** | 5 | 39 | (14-68) | 6 | 46 | (19-75) | 2 | 15 | (1.9-45) |
| **PPI+B+D+M** | 17 | 90 | (67-99) | 2 | 11 | (1.3-33) | 0 | 0.00 | (0.00-18) |
| **Sequential (PPI+C+A+T)** | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **Concomitant (PPI+C+A+T)** | 1 | 50 | (1.3-99) | 1 | 50 | (1.3-99) | 0 | 0.00 | (0.00-84) |

N: number of patients; PPI: proton-pomp-inhibitor; CI: confidence interval; NA: not available; A: amoxicillin C: clarithromycin; M: metronidazole; T: tinidazole; D: doxycycline; L: levofloxacin; B: bismuth; Tc: tetracycline; J: josamycin; three-in-one: three-in-one single capsule bismuth quadruple therapy.

1. **Diarrhoea**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mild, N** | **%** | **95% CI** | **Moderate, N** | **%** | **95% CI** | **Severe, N** | **%** | **95% CI** |
| **PPI+C+A** | 132 | 56 | (50-63) | 78 | 33 | (27-40) | 24 | 10 | (6.2-14) |
| **Concomitant (PPI+C+A+M)** | 291 | 73 | (68-77) | 94 | 24 | (19-28) | 15 | 3.8 | (1.8-5,7) |
| **PPI+three-in-one** | 85 | 42 | (35-49) | 114 | 56 | (49-63) | 5 | 2.5 | (0.80-5.6) |
| **PPI+C+A+B** | 145 | 69 | (63-76) | 60 | 29 | (22-35) | 5 | 2.4 | (0.78-5.5) |
| **PPI+A+L** | 54 | 38 | (29-46) | 88 | 61 | (53-69) | 2 | 1.4 | (0.17-4.9) |
| **PPI+C+M** | 15 | 54 | (33-74) | 16 | 46 | (37-77) | 0 | 0.00 | (0.00-12) |
| **PPI+A+L+B** | 60 | 66 | (56-76) | 27 | 30 | (20-40) | 4 | 4.4 | (1.2-11) |
| **Triple-A+M** | 12 | 43 | (23-63) | 13 | 46 | (26-67) | 3 | 11 | (2.3-28) |
| **Sequential (PPI+C+A+M)** | 2 | 50 | (6.8-93) | 2 | 50 | (6.8-93) | 0 | 0.00 | (0.00-60) |
| **PPI+B+Tc+M** | 10 | 35 | (15-54) | 17 | 59 | (39-78) | 2 | 6.9 | (0.85-23) |
| **PPI+B+A+J** | 12 | 50 | (28-72) | 11 | 46 | (24-68) | 1 | 4.2 | (0.11-21) |
| **PPI+B+D+M** | 4 | 40 | (12-74) | 5 | 50 | (19-81) | 1 | 10 | (0.25-45) |
| **Sequential (PPI+C+A+T)** | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **Concomitant (PPI+C+A+T)** | 1 | 17 | (0.42-64) | 4 | 67 | (22-96) | 1 | 17 | (0.42-64) |

N: number of patients; PPI: proton-pomp-inhibitor; CI: confidence interval; NA: not available; A: amoxicillin C: clarithromycin; M: metronidazole; T: tinidazole; D: doxycycline; L: levofloxacin; B: bismuth; Tc: tetracycline; J: josamycin; three-in-one: three-in-one single capsule bismuth quadruple therapy (Pylera®).

1. **Nausea**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mild, N** | **%** | **95% CI** | **Moderate, N** | **%** | **95% CI** | **Severe, N** | **%** | **95% CI** |
| **PPI+C+A** | 192 | 58 | (53-64) | 114 | 35 | (29-40) | 27 | 7.3 | (5.1-11) |
| **Concomitant (PPI+C+A+M)** | 169 | 66 | (60-72) | 75 | 29 | (24-35) | 12 | 4.7 | (1.9-7.5) |
| **PPI+three-in-one** | 109 | 55 | (47-62) | 84 | 42 | (35-49) | 7 | 3.5 | (0.70-6.3) |
| **PPI+C+A+B** | 102 | 66 | (58-74) | 46 | 30 | (22-37) | 6 | 3.9 | (0.52-7.3) |
| **PPI+A+L** | 38 | 36 | (26-45) | 68 | 64 | (54-74) | 0 | 0.00 | (0.00-3.4) |
| **PPI+C+M** | 17 | 42 | (25-58) | 19 | 46 | (30-63) | 5 | 12 | (4.1-26) |
| **PPI+A+L+B** | 38 | 75 | (62-87) | 11 | 22 | (9.3-34) | 2 | 3.9 | (0.48-13) |
| **Triple-A+M** | 10 | 37 | (17-54) | 14 | 52 | (31-73) | 3 | 11 | (2.4-29) |
| **Sequential (PPI+C+A+M)** | 10 | 77 | (46-95) | 3 | 23 | (5.0-54) | 0 | 0.00 | (0.00-25) |
| **PPI+B+Tc+M** | 25 | 53 | (38-69) | 17 | 36 | (21-51) | 5 | 11 | (3.5-23) |
| **PPI+B+A+J** | 3 | 23 | (5.0-54) | 6 | 46 | (19-75) | 4 | 31 | (9.1-61) |
| **PPI+B+D+M** | 19 | 58 | (39-76) | 10 | 30 | (13-47) | 4 | 12 | (3.4-28) |
| **Sequential (PPI+C+A+T)** | 1 | 100 | NA | 0 | 0.00 | NA | 0 | 0.00 | NA |
| **Concomitant (PPI+C+A+T)** | 2 | 33 | (4.3-78) | 1 | 17 | (.42-64) | 3 | 50 | (12-88) |

N: number of patients; PPI: proton-pomp-inhibitor; CI: confidence interval; NA: not available; A: amoxicillin C: clarithromycin; M: metronidazole; T: tinidazole; D: doxycycline; L: levofloxacin; B: bismuth; Tc: tetracycline; J: josamycin; three-in-one: three-in-one single capsule bismuth quadruple therapy (Pylera®).

1. **Vomiting**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mild, N** | **%** | **95% CI** | **Moderate, N** | **%** | **95% CI** | **Severe, N** | **%** | **95% CI** |
| **PPI+C+A** | 49 | 54 | (44-65) | 35 | 39 | (28-50) | 6 | 6.7 | (0.96-12) |
| **Concomitant (PPI+C+A+M)** | 51 | 60 | (49-71) | 27 | 32 | (21-42) | 7 | 8.2 | (1.8-15) |
| **PPI+three-in-one** | 68 | 62 | (52-71) | 38 | 35 | (25-44) | 4 | 3.6 | (1.0-9.0) |
| **PPI+C+A+B** | 57 | 71 | (61-82) | 21 | 26 | (16-37) | 2 | 2.5 | (0.30-8.7) |
| **PPI+A+L** | 43 | 58 | (46-70) | 30 | 41 | (29-52) | 1 | 1.4 | (0.03-7.3) |
| **PPI+C+M** | 1 | 9.1 | (0.23-41) | 6 | 55 | (23-83) | 4 | 36 | (11-69) |
| **PPI+A+L+B** | 11 | 55 | (32-77) | 8 | 40 | (19-64) | 1 | 5.0 | (0.13-25) |
| **Triple-A+M** | 5 | 39 | (14-68) | 5 | 39 | (14-68) | 3 | 23 | (5.0-54) |
| **Sequential (PPI+C+A+M)** | 2 | 67 | (9.4-99) | 1 | 33 | (0.84-91) | 0 | 0.00 | (0.00-71) |
| **PPI+B+Tc+M** | 9 | 53 | (28-77) | 7 | 41 | (18-67) | 1 | 5.9 | (0.15-29) |
| **PPI+B+A+J** | 0 | NA | NA | 1 | 100 | NA | 0 | 0.00 | NA |
| **PPI+B+D+M** | 5 | 63 | (24-91) | 2 | 25 | (3.2-65) | 1 | 13 | (0.32-53) |
| **Sequential (PPI+C+A+T)** | 0 | 0.00 | NA | 1 | 100 | NA | 0 | 0.00 | NA |
| **Concomitant (PPI+C+A+T)** | 1 | 50 | (1.3-99) | 0 | 0.00 | (0.00-84) | 1 | 50 | (1.3-99) |

N: number of patients; PPI: proton-pomp-inhibitor; CI: confidence interval; NA: not available; A: amoxicillin C: clarithromycin; M: metronidazole; T: tinidazole; D: doxycycline; L: levofloxacin; B: bismuth; Tc: tetracycline; J: josamycin; three-in-one: three-in-one single capsule bismuth quadruple therapy (Pylera®).

1. **Dyspepsia**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mild, N** | **%** | **95% CI** | **Moderate, N** | **%** | **95%CI** | **Severe, N** | **%** | **95%CI** |
| **PPI+C+A** | 67 | 48 | (39-56) | 67 | 48 | (39-56) | 7 | 5.0 | (1.0-8.9) |
| **Concomitant (PPI+C+A+M)** | 57 | 59 | (48-69) | 29 | 30 | (20-40) | 11 | 11 | (4.5-18) |
| **PPI+three-in-one** | 41 | 44 | (33-55) | 48 | 52 | (41-62) | 4 | 4.3 | (1.2-11) |
| **PPI+C+A+B** | 23 | 59 | (42-76) | 15 | 39 | (22-55) | 1 | 2.6 | (0.07-13) |
| **PPI+A+L** | 18 | 33 | (19-46) | 36 | 66 | (52-79) | 1 | 1.8 | (0.05-7.9) |
| **PPI+C+M** | 24 | 49 | (34-64) | 23 | 47 | (32-62) | 2 | 4.1 | (0.50-14) |
| **PPI+A+L+B** | 6 | 40 | (16-68) | 9 | 60 | (32-84) | 0 | 0.00 | (0.00-22) |
| **Triple-A+M** | 6 | 38 | (15-65) | 6 | 38 | (39-56) | 4 | 25 | (7.3-52) |
| **Sequential (PPI+C+A+M)** | 3 | 50 | (12-88) | 3 | 50 | (12-88) | 0 | 0.00 | (0.00-46) |
| **PPI+B+Tc+M** | 9 | 69 | (39-91) | 4 | 31 | (9.1-61) | 0 | 0.00 | (0.00-25) |
| **PPI+B+A+J** | 2 | 29 | (3.7-71) | 4 | 57 | (18-90) | 1 | 14 | (0.36-58) |
| **PPI+B+D+M** | 10 | 66 | (35-85) | 5 | 31 | (11-59) | 1 | 6.3 | (0.16-30) |
| **Sequential (PPI+C+A+T)** | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **Concomitant (PPI+C+A+T)** | NA | NA | NA | NA | NA | NA | NA | NA | NA |

N: number of patients; PPI: proton-pomp-inhibitor; CI: confidence interval; NA: not available; A: amoxicillin C: clarithromycin; M: metronidazole; T: tinidazole; D: doxycycline; L: levofloxacin; B: bismuth; Tc: tetracycline; J: josamycin; three-in-one: three-in-one single capsule bismuth quadruple therapy (Pylera®).

1. **Heartburn**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mild, N** | **%** | **95%CI** | **Moderate, N** | **%** | **95%CI** | **Severe, N** | **%** | **95%CI** |
| **PPI+C+A** | 48 | 61 | (49-72) | 24 | 30 | (20-41) | 7 | 8.9 | (2.0-16) |
| **Concomitant (PPI+C+A+M)** | 14 | 58 | (37-80) | 8 | 33 | (12-54) | 2 | 8.3 | (1.0-27) |
| **PPI+three-in-one** | 10 | 46 | (22-69) | 11 | 50 | (27-73) | 1 | 4.5 | (0.12-23) |
| **PPI+C+A+B** | 7 | 78 | (40-97) | 2 | 22 | (2.8-60) | 0 | 0.00 | (0.00-34) |
| **PPI+A+L** | 8 | 31 | (11-50) | 18 | 69 | (50-89) | 0 | 0.00 | (0.00-13) |
| **PPI+C+M** | 0 | 0.00 | (0.00-52) | 4 | 80 | (28-99) | 1 | 20 | (0.51-72) |
| **PPI+A+L+B** | 0 | 0.00 | (0.00-84) | 2 | 100 | (16-100) | 0 | 0.00 | (0.00-84) |
| **Triple-A+M** | 7 | 47 | (21-73) | 3 | 20 | (4.3-48) | 5 | 33 | (12-62) |
| **Sequential (PPI+C+A+M)** | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **PPI+B+Tc+M** | 2 | 67 | (9.4-99) | 1 | 33 | (0.84-91) | 0 | 0.00 | (0.00-71) |
| **PPI+B+A+J** | 2 | 100 | (16-100) | 0 | 0.00 | (0.00-84) | 0 | 0.00 | (0.00-84) |
| **PPI+B+D+M** | 0 | 0.00 | (0.00-84) | 1 | 50 | (1.3-99) | 1 | 50 | (1.3-99) |
| **Sequential (PPI+C+A+T)** | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **Concomitant (PPI+C+A+T)** | NA | NA | NA | NA | NA | NA | NA | NA | NA |

N: number of patients; PPI: proton-pomp-inhibitor; CI: confidence interval; NA: not available; A: amoxicillin C: clarithromycin; M: metronidazole; T: tinidazole; D: doxycycline; L: levofloxacin; B: bismuth; Tc: tetracycline; J: josamycin; three-in-one: three-in-one single capsule bismuth quadruple therapy (Pylera®).

1. **Abdominal pain**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mild, N** | **%** | **95%CI** | **Moderate, N** | **%** | **95%CI** | **Severe, N** | **%** | **95%CI** |
| **PPI+C+A** | 59 | 53 | (43-62) | 38 | 34 | (25-43) | 15 | 13 | (6.6-20) |
| **Concomitant (PPI+C+A+M)** | 109 | 67 | (60-75) | 42 | 26 | (19-33) | 11 | 6.8 | (2.6-11) |
| **PPI+three-in-one** | 70 | 56 | (47-65) | 47 | 38 | (29-46) | 8 | 6.4 | (1.7-11) |
| **PPI+C+A+B** | 107 | 82 | (70-85) | 18 | 14 | (7.5-20) | 6 | 4.6 | (0.62-8.5) |
| **PPI+A+L** | 14 | 54 | (33-75) | 11 | 42 | (21-63) | 1 | 3.8 | (0.10-20) |
| **PPI+C+M** | 4 | 33 | (9.9-65) | 3 | 25 | (5.5-57) | 5 | 42 | (15-72) |
| **PPI+A+L+B** | 16 | 64 | (43-85) | 8 | 32 | (12-52) | 1 | 4.0 | (0.10-20) |
| **Triple-A+M** | 9 | 43 | (19-66) | 7 | 33 | (15-57) | 5 | 24 | (8.2-47) |
| **Sequential (PPI+C+A+M)** | 3 | 75 | (19-99) | 1 | 25 | (0.63-81) | 0 | 0.00 | (0.00-60) |
| **PPI+B+Tc+M** | 5 | 36 | (13-65) | 5 | 36 | (13-65) | 4 | 28 | (8.4-58) |
| **PPI+B+A+J** | 1 | 17 | (0.42-64) | 4 | 67 | (22-96) | 1 | 17 | (23-68) |
| **PPI+B+D+M** | 9 | 45 | (23-68) | 9 | 45 | (23-68) | 2 | 10 | (1.2-32) |
| **Sequential (PPI+C+A+T)** | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **Concomitant (PPI+C+A+T)** | 3 | 75 | (19-99) | 0 | 0.00 | (0.00-60) | 1 | 25 | (0.63-81) |

N: number of patients; PPI: proton-pomp-inhibitor; CI: confidence interval; NA: not available; A: amoxicillin C: clarithromycin; M: metronidazole; T: tinidazole; D: doxycycline; L: levofloxacin; B: bismuth; Tc: tetracycline; J: josamycin; three-in-one: three-in-one single capsule bismuth quadruple therapy (Pylera®).

1. **Fatigue**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mild, N** | **%** | **95%CI** | **Moderate, N** | **%** | **95%CI** | **Severe, N** | **%** | **95%CI** |
| **PPI+C+A** | 51 | 40 | (31-49) | 62 | 49 | (30-47) | 14 | 11 | (5.2-17) |
| **Concomitant (PPI+C+A+M)** | 69 | 63 | (53-72) | 33 | 30 | (21-39) | 8 | 7.0 | (2.0-13) |
| **PPI+three-in-one** | 58 | 40 | (32-48) | 71 | 49 | (40-57) | 16 | 11 | (5.6-16) |
| **PPI+C+A+B** | 25 | 76 | (60-92) | 7 | 21 | (5.7-37) | 1 | 3.0 | (0.08-16) |
| **PPI+A+L** | 8 | 23 | (7.5-38) | 24 | 69 | (52-85) | 3 | 8.6 | (1.8-23) |
| **PPI+C+M** | 5 | 42 | (15-72) | 5 | 42 | (15-72) | 2 | 17 | (2.1-48) |
| **PPI+A+L+B** | 1 | 9.1 | (0.23-41) | 10 | 91 | (59-100) | 0 | 0.00 | (0.00-28) |
| **Triple-A+M** | 2 | 50 | (6.8-93) | 1 | 25 | (0.63-81) | 1 | 25 | (0.63-81) |
| **Sequential (PPI+C+A+M)** | 0 | 0.00 | (0.00-52) | 5 | 100 | (48-100) | 0 | 0.00 | (0.63-81) |
| **PPI+B+Tc+M** | 3 | 27 | (6.0-61) | 6 | 55 | (23-83) | 2 | 18 | (2.3-52) |
| **PPI+B+A+J** | 2 | 40 | (5.3-85) | 2 | 40 | (5.3-85) | 1 | 20 | (0.51-72) |
| **PPI+B+D+M** | 5 | 56 | (21-86) | 4 | 44 | (14-79) | 0 | 0.00 | (0.00-34) |
| **Sequential (PPI+C+A+T)** | 1 | 50 | (1.3-99) | 1 | 50 | (0.63-81) | 0 | 0.00 | (0.00-84) |
| **Concomitant (PPI+C+A+T)** | NA | NA | NA | NA | NA | NA | NA | NA | NA |

N: number of patients; PPI: proton-pomp-inhibitor; CI: confidence interval; NA: not available; A: amoxicillin C: clarithromycin; M: metronidazole; T: tinidazole; D: doxycycline; L: levofloxacin; B: bismuth; Tc: tetracycline; J: josamycin; three-in-one: three-in-one single capsule bismuth quadruple therapy (Pylera®).

1. **Anorexia**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mild, N** | **%** | **95%CI** | **Moderate, N** | **%** | **95%CI** | **Severe, N** | **%** | **95%CI** |
| **PPI+C+A** | 26 | 36 | (24-47) | 39 | 53 | (41-66) | 8 | 11 | (3.1-19) |
| **Concomitant (PPI+C+A+M)** | 18 | 47 | (33-65) | 18 | 47 | (33-65) | 2 | 5.3 | (0.64-18) |
| **PPI+three-in-one** | 14 | 24 | (12-35) | 42 | 71 | (59-84) | 3 | 5.1 | (1.1-14) |
| **PPI+C+A+B** | 5 | 50 | (19-81) | 5 | 50 | (33-65) | 0 | 0.00 | (0.00-31) |
| **PPI+A+L** | 8 | 14 | (4.2-24) | 44 | 79 | (67-90) | 4 | 7.1 | (2.0-17) |
| **PPI+C+M** | 2 | 25 | (3.2-65) | 3 | 38 | (8.5-76) | 3 | 38 | (8.5-76) |
| **PPI+A+L+B** | 1 | 25 | (0.63-81) | 3 | 75 | (19-99) | 0 | 0.00 | (0.00-60) |
| **Triple-A+M** | 7 | 44 | (20-70) | 7 | 44 | (8.5-76) | 2 | 13 | (1.6-38) |
| **Sequential (PPI+C+A+M)** | 2 | 67 | (9.4-99) | 1 | 33 | (0.84-91) | 0 | 0.00 | (0.00-71) |
| **PPI+B+Tc+M** | 3 | 30 | (6.7-65) | 6 | 60 | (26-88) | 1 | 10 | (0.25-45) |
| **PPI+B+A+J** | 1 | 50 | (1.3-99) | 1 | 50 | (1.3-99) | NA | NA | NA |
| **PPI+B+D+M** | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **Sequential (PPI+C+A+T)** | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **Concomitant (PPI+C+A+T)** | NA | NA | NA | NA | NA | NA | NA | NA | NA |

N: number of patients; PPI: proton-pomp-inhibitor; CI: confidence interval; NA: not available; A: amoxicillin C: clarithromycin; M: metronidazole; T: tinidazole; D: doxycycline; L: levofloxacin; B: bismuth; Tc: tetracycline; J: josamycin; three-in-one: three-in-one single capsule bismuth quadruple therapy (Pylera®).