REVIEW

# Update on non-bismuth quadruple (concomitant) therapy for eradication of *Helicobacter pylori*

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**Background:** Traditional standard triple therapy for *Helicobacter pylori* (*H. pylori*) infection (proton pump inhibitor-clarithromycin-amoxicillin) can easily be converted to non-bismuth quadruple (concomitant) therapy by the addition of a nitroimidazole twice daily.

**Aim:** To critically review evidence on the role of non-bismuth quadruple therapy (proton pump inhibitor-clarithromycin-amoxicillin-nitroimidazole) in the treatment of *H. pylori* infection.

**Methods:** Bibliographical searches were performed in MEDLINE and relevant congresses up to December 2011. We performed a meta-analysis of the studies evaluating the concomitant therapy, and of the randomized controlled trials comparing the concomitant and the standard triple therapy.

**Results:** A meta-analysis of 19 studies (2070 patients) revealed a mean *H. pylori* cure rate (intention-to-treat) of 88% (95% confidence interval from 85% to 91%) for non-bismuth quadruple therapy. We performed a meta-analysis of the randomized controlled studies comparing the concomitant (481 patients) and the standard triple therapy (503 patients). The former was more effective than the latter: 90% versus 78% (intention-to-treat analysis). Results were homogeneous ($I^2 = 0\%$). The odds ratio for this comparison was 2.36 (95% confidence interval from 1.67 to 3.34). A tendency toward better results with longer treatments (7–10 days versus 3–5 days) has been observed, so it seems reasonable to recommend the length of treatment achieving the highest cure rates (10 days). Clarithromycin resistance may reduce the efficacy of non-bismuth quadruple therapy, although the decrease in eradication rates seems to be far lower than in standard triple therapy. Experience with the non-bismuth quadruple therapy in patients with metronidazole-resistant strains is still very limited.

**Conclusion:** Non-bismuth quadruple (concomitant) therapy appears to be an effective, safe, and well-tolerated alternative to triple therapy and is less complex than sequential therapy. Therefore, this regimen appears well suited for use in settings where the efficacy of triple therapy is unacceptably low.

**Keywords:** *Helicobacter pylori*, concomitant therapy, sequential therapy, clarithromycin, metronidazole, non-bismuth quadruple

## Introduction

*Helicobacter pylori* (*H. pylori*) infects approximately 50% of the adult population and is associated with a wide range of upper gastrointestinal diseases including gastritis, peptic ulcer disease, and gastric cancer.[1] The most widely recommended treatment in international guidelines for the eradication of *H. pylori* is the so called standard, or proton pump inhibitor (PPI)-based, triple therapy, which combines two antibiotics (clarithromycin plus amoxicillin or metronidazole) with a PPI for at least 7 days.[2–6] However, since the microorganism was discovered, the eradication rates

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have fallen considerably with this regimen.[7,8] Two recent double-blind, US multicenter studies both found disappointingly low eradication rates with standard therapy (77%),[9,10] and two meta-analyses including more than 53,000 patients revealed the cure rate to be below 80%.[11,12] Therefore, the ethics of continued use of standard triple therapy have recently been questioned, and alternative approaches have been recommended.[13] Attempts to increase the duration of triple therapy, thus prolonging exposure to antibiotics, have achieved controversial results, but have not generally resulted in remarkable benefits.[14,15] Consequently, new strategies to improve first-line treatment are still urgently needed.

One recent innovation, postulated as an alternative to standard triple therapy, is sequential treatment, which involves a simple dual regimen including a PPI plus amoxicillin for the first 5 days followed by a triple regimen including a PPI, clarithromycin, and tinidazole for the following 5 days.[16] Several randomized clinical trials (including pooled-data analyses and meta-analyses) have demonstrated that a sequential regimen is more effective than standard triple therapy.[17–21] Therefore, some guidelines have proposed sequential therapy as an alternative to standard triple therapy for the eradication of *H. pylori*.[22] However, a recent update of previous meta-analyses performed by a Cochrane Collaboration group[23] found that the results obtained with the sequential regimen were clearly heterogeneous, and that several recently published studies were unable to demonstrate differences between sequential and standard triple therapy. So, although the overall mean eradication rate with the sequential regimen was nearly 90%, a tendency towards lower efficacy with this regimen was observed in the more recent studies.[24–27]

Moreover, a relevant question is whether it is necessary to provide the drugs sequentially or if the four constituent components of sequential therapy can be given concurrently.[28,29] In other words, does sequential administration represent an advantage or does it make therapy more complicated than necessary?[13,30] In this regard, the triple combination of clarithromycin plus amoxicillin and a nitroimidazole with a PPI (but without bismuth) has previously been examined as a nonsequential regimen, which proved effective. The concept of a "non-bismuth quadruple regimen" or "concomitant" regimen (the term used hereafter) has recently resurfaced.[31] Traditional standard triple therapy (PPI-clarithromycin-amoxicillin) can easily be converted to concomitant therapy by the addition of 500 mg of metronidazole or tinidazole twice daily.[32]

The aim of the present article is to critically review evidence on the role of concomitant therapy in the treatment of *H. pylori* infection. We review the following aspects: rationale for use, efficacy of the regimen and the variables affecting it, comparison between the concomitant regimen and standard triple and sequential therapy, and finally, limitations of the concomitant regimen.

## Search strategy

Bibliographical searches were performed in MEDLINE up to December 2011 using the following keywords (all fields): ("*Helicobacter pylori*" OR "*H. pylori*") AND concomitant OR concurrent OR quadruple OR (clarithromycin AND [amoxicillin OR amoxycillin]) AND (metronidazole OR tinidazole OR nitroimidazole). Articles published in any language were included. Reference lists from the trials selected in the electronic search were hand-searched to identify further relevant trials. We also conducted a manual search of abstracts from the scientific meetings of the International Workshop of the European *Helicobacter* Study Group, the United European Gastroenterology Week, and the American Digestive Disease Week. Abstracts of the articles selected in each of these multiple searches were reviewed, and those meeting the inclusion criteria were selected. References from reviews on *H. pylori* treatment with the concomitant regimen and from the works selected for the study were also examined to identify articles meeting the inclusion criteria. In the case of duplicate reports or studies obviously reporting results from the same study population, only the latest published data were used.

## Rationale/historical perspective of the concomitant regimen

In 1998, two groups of investigators, one in Germany and the other in Japan, proposed that a PPI, amoxicillin, clarithromycin, and nitroimidazole be given concurrently as a nonsequential four-drug, three-antibiotic, non-bismuth-containing quadruple regimen.[33,34] Despite the short duration of therapy (5 days on average), this approach provided high cure rates (>90% by intention-to-treat).

The efficacy of a triple regimen (PPI, clarithromycin, and a nitroimidazole) was known to be inversely related to bacterial load, and higher eradication rates were achieved in patients with a low bacterial density in the stomach.[35–37] Therefore, the addition of amoxicillin lowered bacterial load in the stomach, with the consequent improvement in the efficacy of the short course of triple therapy.[38] In other words, concurrent administration of the three antibiotics as

concomitant therapy proved more efficacious than when they were administered separately.[39]

Proponents of sequential treatment (amoxicillin for 5 days, followed by clarithromycin plus a nitroimidazole for a further 5 days) argue that initial use of amoxicillin could provide a key advantage in the eradication of *H. pylori*.[18] namely, prevention of the selection of secondary clarithromycin resistance.[40] Indeed, it is known that bacteria can develop efflux channels for clarithromycin, which rapidly transfer the drug out of the bacterial cell, preventing the binding of the antibiotic to the ribosome.[41–43] It has been speculated that the disruption of the cell wall caused by amoxicillin prevents the development of efflux channels by damaging the cell wall of the bacterium. In theory, this disruption could help to improve the efficacy of clarithromycin in the second phase of treatment.[40,44] However, the improved effect with sequential (and concomitant) therapy – as compared with standard triple therapy – may not be due to sequential administration itself, but to the larger number of antibiotics (three drugs) to which the organism is exposed or to the use of a nitroimidazole, which is not contained in the standard triple-drug regimen.[45,46]

## Efficacy of the concomitant regimen for eradication of *H. pylori*

Studies evaluating the efficacy of the concomitant regimen are summarized in Table 1.[33,34,47–63] These studies were performed in different countries in Europe, Asia, and America, and most were randomized controlled trials. Similar concomitant regimens were prescribed, with only minor modifications, namely, the PPI (omeprazole, lansoprazole, rabeprazole, or esomeprazole) and the nitroimidazole (metronidazole or tinidazole). However, duration of treatment varied markedly between 3 and 14 days (see below). Our analysis of the 19 studies (2070 patients) revealed a mean *H. pylori* cure rate (intention-to-treat) of 88% (95% confidence interval [95% CI] from 85% to 91%) (Table 2). The data were combined using the generic inverse variance method, which involves a weighted average of the effect estimates from the individual studies. The weight for each study is taken to be the inverse of the variance (one divided by the square of the standard error) of the effect estimate. As results were heterogeneous ($P < 0.001$; $I^2 = 80\%$), a random effect model (DerSimonian and Laird) was applied to perform the meta-analysis (using Review Manager 5.0.25, developed by the Cochrane Collaboration).

From those studies, the one performed in Latin America (including patients from Chile, Colombia, Costa

Rica, Honduras, Mexico, and Nicaragua) had markedly disappointing results, with a 74% eradication rate.[57] The explanation for this outlier is unclear, as information on the antibiotic susceptibility of *H. pylori* is not available in the article. Furthermore, even though the treatment lasted only 5 days, other studies with the same period of administration performed some years ago obtained excellent results (>90%) (see below for a more detailed discussion on the duration of treatment). We might speculate that 5-day concomitant regimens were effective enough a decade ago, but that increased antibiotic resistance rates have revealed the need for longer regimens.

A second outlier study was performed by Toros et al[60] in Turkey, where only a 75% eradication rate was achieved despite the fact that high doses of metronidazole (500 mg three times daily) were used and a 14-day regimen was prescribed. It should be taken into consideration that, in Turkey, results with the standard triple therapy have also been far lower than expected. Thus, in a large randomized trial performed in Turkey, *H. pylori* eradication rates achieved with a PPI-clarithromycin-amoxicillin regimen for 7 and 14 days were only 24% and 43%, respectively.[64]

Finally, a third outlier study was performed by Choi et al[63] in Korea, where only a 63% cure rate was reported, although the study has not yet been published as a peer-reviewed article and only 38 patients were included.

The cure rates recorded in the remaining studies were >80% and even >90%. In fact, if these three outlier studies are excluded, the mean eradication rate (intention-to-treat) of the remaining 16 studies increased to 91%, and the interstudy heterogeneity almost completely disappeared ($I^2 = 10\%$).

## Effects of different variables on the efficacy of concomitant therapy

The efficacy of the concomitant regimen on *H. pylori* eradication depends on several factors.

### Clarithromycin resistance

Resistance rates for antimicrobial agents rise with indiscriminate use, and clarithromycin resistance may be due to the widespread use of this agent for upper respiratory tract infections.[65,66] Antimicrobial resistance is largely responsible for the poor eradication rates with standard triple therapy.[67–69] Culture and antimicrobial sensitivity testing of *H. pylori* are not widely available and, when they are, they may not produce any clear clinical benefit.[32,70–72] One meta-analysis reported an almost 60% decline in eradication rates with

**Table 1** Studies evaluating the efficacy of non-bismuth quadruple (concomitant) regimen for the treatment of *Helicobacter pylori* infection

| Author | Country | Publication year | Study design | Disease type | Therapy regimen | Days | No of patients | Eradication rate (%) (ITT) | Eradication rate (%) (PP) |
|---|---|---|---|---|---|---|---|---|---|
| Calvet et al[47] | Spain | 2000 | NC | PUD | O 20 mg bid + A 1 g bid + C 500 mg bid + T 500 mg bid | 4 | 56 | 49/56 (87.5) | 49/54 (90.7) |
| Catalano et al[48] | Italy | 2000 | RCT | PUD | O 40 mg od + A 1 g bid + C 500 mg bid + M 500 mg bid | 3 | 56 | 50/56 (89.3) | 50/54 (92.6) |
| Chan et al[49,†] | China | 2001 | NC | PUD, NUD, others | O 20 mg bid + A 20 mg/kg tid + C 7.5 mg/kg tid + M 7.5 mg/kg 5 times a day | 7 | 33 | 31/33 (94) | 31/33 (94) |
| Molina-Infante et al[50] | Spain | 2011 | NC | PUD, NUD, others | PPI bid + A 1 g bid + C 500 mg bid + M 500 mg | 10 | 155 | 132/55 (85) | 132/150 (88) |
| Nagahara et al[51] | Japan | 2000 | RCT | PUD, NUD | R 10 mg bid + A 750 mg bid + C 200 mg bid + M 250 mg bid | 5 | 55 | 52/55 (94.5) | 52/53 (98.1) |
| Nagahara et al[52] | Japan | 2001 | RCT | PUD, NUD | R 20 mg bid + A 750 mg bid + C 200 mg bid + M 250 mg bid | 5 | 80 | 74/80 (92.5) | 74/79 (93.7) |
| Neville et al[53] | UK | 1999 | RCT | PUD, NUD, others | L 30 mg bid + A 1 g bid + C 250 mg bid + M 400 mg bid | 5 | 56 | 49/56 (87.5) | 49/54 (90.7) |
| Okada et al[34] | Japan | 1998 | RCT | PUD, NUD, others | O 20 mg bid + A 500 mg tid + Ro 150 mg bid + M 250 mg tid | 7 | 90 | 85/90 (94.4) | 85/88 (96.6) |
| Okada et al[54] | Japan | 1999 | RCT | PUD, NUD, others | O 20 mg bid + A 500 mg tid + Ro 150 mg bid + M 250 mg tid | 7 | 169 | 155/169 (92) | 155/163 (95) |
| Treiber et al[33] | Germany | 1998 | RCT | PUD, others | O 20 mg bid + A 1 g bid + C 250 mg bid + M 400 mg bid | 5 | 46 | 42/46 (91.3) | 42/44 (95.5) |
| Treiber et al (a)[55] | Germany | 2002 | RCT | PUD, NUD, others | L 30 mg bid + A 1 g bid + C 250 mg bid + M 400 mg bid | 3 | 80 | 65/80 (81.2) | 65/76 (85.5) |
| Treiber et al (b)[55] | Germany | 2002 | RCT | PUD, NUD, others | L 30 mg bid + A 1 g bid + C 250 mg bid + M 400 mg bid | 5 | 83 | 74/83 (89.2) | 74/79 (93.7) |
| Wu et al[56] | Taiwan | 2010 | RCT | PUD, NUD, others | E 40 mg bid + A 1 g bid + C 500 mg bid + M 500 mg bid | 10 | 115 | 107/115 (93) | 107/115 (93) |
| Greenberg et al[57] | Latin America | 2011 | RCT | PUD, NUD, others | L 30 mg bid + A 1 g bid + C 500 mg bid + M 500 mg bid | 5 | 488 | 360/489 (73.6) | 348/442 (78.7) |
| Kongchayanun et al (a)[58] | Thailand | 2011 | RCT | NUD | R 20 mg bid + A 1 g bid + C 1 g od + M 500 mg tid | 5 | 50 | 45/50 (90) | 45/50 (90) |
| Kongchayanun et al (b)[58] | Thailand | 2011 | RCT | NUD | R 20 mg bid + A 1 g bid + C 1 g od + M 500 mg tid | 10 | 50 | 48/50 (96) | 48/50 (96) |
| Kim et al[59] | Korea | 2011 | RCT | – | L 30 mg bid + A 1 g bid + C 500 mg bid + M 500 mg bid | 5 | 135 | 123/135 (91.4) | 123/135 (91.4) |
| Toros et al[60] | Turkey | 2011 | NC | NUD | L 30 mg bid + A 1 g bid + C 500 mg bid + M 500 mg tid | 14 | 84 | 63/84 (75%) | 63/84 (75%) |
| Kwon et al (a)[61] | Korea | 2011 | RCT | – | L 30 mg bid + A 1 g bid + C 500 mg bid + M 500 mg bid | 5 | 48 | 42/48 (87.5%) | 42/48 (87.5%) |

| Study | Country | Year | Design | Regimen | Days | N | N | | |
|---|---|---|---|---|---|---|---|---|---|
| Kwon et al (b)[61] | Korea | 2011 | RCT | L 30 mg bid + A 1 g bid + C 500 mg bid + M 500 mg bid | – | 7 | 49 | 44/49 (89.8%) | 44/49 (89.8%) |
| Moon et al[62] | Korea | 2011 | RCT | PPI bid + A 1 g bid + C 500 mg bid + M 500 mg bid | – | 7 | 53 | 43/53 (81.1%) | 43/53 (81.1%) |
| Choi et al[63] | Korea | 2011 | NC | R 20 mg bid + A 1 g bid + C 500 mg bid + M 500 mg tid | – | 14 | 38 | 24/38 (63.2%) | 24/38 (63.2%) |

**Notes:** Days of antibiotic treatment. †Pediatric patients.
**Abbreviations:** A, amoxicillin; bid, two times a day; C, clarithromycin; E, esomeprazole; ITT, intention-to-treat; L, lansoprazole; M, metronidazole; NC, non-controlled; NUD, non-ulcer disease; O, omeprazole; od, once daily; PP, perprotocol; PPI, proton pump inhibitor (at standard dose); PUD, peptic ulcer disease; R, rabeprazole; Ro, roxithromycin; RCT, randomized controlled trial; T, tinidazole; tid, three times a day.

standard triple therapy if clarithromycin resistance was present.[67,73] Therefore, the use of standard triple therapy has been recommended only in those areas where clarithromycin resistance is lower than 15%–20%.[2]

Clarithromycin resistance reduces the efficacy of sequential therapy, although the decrease in eradication rates was far lower than in triple therapy.[16,18–21,45,74] Therefore, the sequential treatment regimen may be preferable to triple therapy when the prevalence of clarithromycin-resistant *H. pylori* infection is high, which is the case in many developed countries.[45]

This advantage of sequential therapy over standard triple therapy (ie, higher eradication rates among patients with clarithromycin resistance) also seems to be applicable to concomitant therapy. An initial meta-analysis determined the effect of drug resistance on the efficacy of first-line treatment regimens for *H. pylori* and identified the most effective treatments in the presence of drug resistance; the results showed that resistance to clarithromycin or metronidazole may be overcome by using quadruple therapies, especially those containing both clarithromycin and metronidazole.[69] The effect of clarithromycin resistance on the efficacy of concomitant regimens was negligible, with 95% efficacy in the clarithromycin-sensitive arm, and 96% in the clarithromycin-resistant arm.[69] Nevertheless, this conclusion was based on only two studies.[53,54] More recently, Wu et al[56] found no significant effect of antibiotic resistance on the efficacy of concomitant therapy: *H. pylori* was eradicated in three out of four (75%) clarithromycin-resistant patients.

Finally, Molina-Infante et al[75] recently compared quadruple concomitant therapy and standard triple therapy for clarithromycin-susceptible *H. pylori* strains. A statistically nonsignificant tendency ($P = 0.2$) to better results was observed with concomitant therapy compared with standard triple therapy, both by per-protocol (88% versus 78%) and by intention-to-treat (88% versus 73%) analysis. Therefore, quadruple concomitant therapy may be more effective than standard triple therapy even for clarithromycin-susceptible *H. pylori*.

Indirect evidence supporting an advantage of a concomitant regimen over a sequential regimen comes from a recent study.[50] The authors evaluated the efficacy of empiric concomitant therapy in a geographical area (Spain) where sequential therapy had previously proved inefficient (76% cure rate in a prior study[24]). Eradication rates for the concomitant regimen were 88% by per-protocol analysis and 85% by intention-to-treat analysis, and the authors concluded that in settings with high clarithromycin resistance (>5%–20%) and

**Table 2** Meta-analysis of efficacy (intention-to-treat) of studies evaluating the concomitant regimen for the treatment of *Helicobacter pylori* infection

| Study or subgroup | Eradication rate | SE | Weight | Eradication rate IV, random, 95% CI |
|---|---|---|---|---|
| Calvet et al[47] | 0.875 | 0.044 | 4.2% | 0.88 [0.79, 0.96] |
| Catalano et al[48] | 0.893 | 0.041 | 4.4% | 0.89 [0.81, 0.97] |
| Chan et al[49] | 0.939 | 0.042 | 4.3% | 0.94 [0.86, 1.02] |
| Choi et al[63] | 0.632 | 0.078 | 2.6% | 0.63 [0.48, 0.78] |
| Greenberg et al[57] | 0.736 | 0.02 | 5.5% | 0.74 [0.70, 0.78] |
| Kim et al[59] | 0.91 | 0.024 | 5.3% | 0.91 [0.86, 0.96] |
| Kongchayanun et al[58] | 0.9 | 0.042 | 4.3% | 0.90 [0.82, 0.98] |
| Kongchayanun et al[58] | 0.96 | 0.028 | 5.1% | 0.96 [0.91, 1.01] |
| Kwon[61] | 0.875 | 0.048 | 4.0% | 0.88 [0.78, 0.97] |
| Kwon[61] | 0.9 | 0.043 | 4.3% | 0.90 [0.82, 0.98] |
| Molina-Infante et al[50] | 0.864 | 0.038 | 4.6% | 0.86 [0.79, 0.94] |
| Moon et al[62] | 0.81 | 0.054 | 3.6% | 0.81 [0.71, 0.92] |
| Nagahara et al[51] | 0.945 | 0.031 | 5.0% | 0.94 [0.88, 1.01] |
| Nagahara et al[52] | 0.925 | 0.029 | 5.1% | 0.93 [0.87, 0.98] |
| Neville et al[53] | 0.875 | 0.044 | 4.2% | 0.88 [0.79, 0.96] |
| Okada et al[34] | 0.944 | 0.024 | 5.3% | 0.94 [0.90, 0.99] |
| Okada et al[54] | 0.917 | 0.021 | 5.5% | 0.92 [0.88, 0.96] |
| Toros et al[60] | 0.75 | 0.047 | 4.0% | 0.75 [0.66, 0.84] |
| Treiber et al[33] | 0.913 | 0.042 | 4.3% | 0.91 [0.83, 1.00] |
| Treiber et al[55] | 0.813 | 0.044 | 4.2% | 0.81 [0.73, 0.90] |
| Treiber et al[55] | 0.892 | 0.034 | 4.8% | 0.89 [0.83, 0.96] |
| Wu et al[56] | 0.93 | 0.024 | 5.3% | 0.93 [0.88, 0.98] |
| Total (95%CI) | | | 100.0% | 0.88 [0.85, 0.91] |

Heterogeneity: Tau² = 0.00; Chi² = 107.58, df = 21 (*P* < 0.00001); I² = 80%
Test for overall effect: Z = 53.68 (*P* < 0.00001)

**Abbreviations:** CI, confidence interval; IV, inverse variance; SE, standard error.

documented failure of sequential therapy, concomitant therapy may achieve acceptable eradication rates.[50] The reason for this theoretical advantage of concomitant therapy over sequential therapy (which should be confirmed in randomized controlled trials including both regimens in the same study) may be a lower effect of antibiotic resistance on the eradication rate with concomitant therapy (when all three antibiotics are administered concurrently) or the longer period of time each antibiotic is prescribed (5 days in the sequential regimen and 7–10 days in the 7 to 10-day concomitant regimen).

## Nitroimidazole resistance

Despite the inclusion of tinidazole, it has been suggested that the sequential regimen may achieve a significantly higher eradication rate than the tinidazole-free standard triple therapies.[20] On the other hand, experience with concomitant therapy in patients with metronidazole-resistant strains is still very limited. In the study by Neville et al,[53] similar eradication rates against both metronidazole-sensitive (95%) and metronidazole-resistant (85%) strains were achieved with the concomitant regimen.

Okada et al[54] found that *H. pylori* was eradicated in 25 out of 27 (93%) patients with metronidazole-resistant strains compared with 130 out of 136 (96%) patients with metronidazole-sensitive strains. However, Treiber et al[55] observed that 5-day concomitant treatment eradicated *H. pylori* in 90% of metronidazole-susceptible patients but in only 50% (8/16) of metronidazole-resistant patients. Finally, bismuth-based quadruple therapy has been proposed as a means of overcoming imidazole resistance, and it remains to be seen how concomitant therapy would perform in comparison.[76]

## Dual clarithromycin and metronidazole resistance

Sequential therapy has been reported to be absolutely ineffective in patients with dual resistance (clarithromycin and imidazole).[45] Primary dual resistance for clarithromycin and imidazole has been shown to produce an eradication rate of 50% (2/4) following 5 days of concomitant therapy[55] and 75% (3/4) after 7 days of concomitant therapy.[54]

Comparative studies where both sequential and concomitant regimens are administered are clearly necessary.

In this respect, Wu et al[56] compared the efficacy of sequential and concomitant therapy and analyzed the effects of antibiotic resistance. Dual resistance did not influence the level of eradication in the concomitant therapy group, but significantly affected that of the sequential therapy group. In particular, patients with dual resistance had a significantly lower eradication rate after sequential therapy (present versus absent: 33.3% versus 95.1%; $P < 0.0001$), but not after concomitant therapy (75.0% versus 92.4%, respectively; $P = 0.22$; although the low number of patients makes the possibility of a type II error likely).

Finally, Molina-Infante et al[75] recently compared quadruple concomitant and sequential therapies for clarithromycin-resistant and dual clarithromycin and metronidazole resistant strains. Per-protocol and intention-to-treat eradication rates for clarithromycin-resistant strains with concomitant and sequential treatments were 100% (4/4) and 80% (4/5), and for dual clarithromycin- and metronidazole-resistant strains they were 66% (2/3) and 75% (3/4). Therefore, the authors concluded that both quadruple concomitant and sequential regimens may maintain acceptable eradication rates for clarithromycin-resistant and for dual clarithromycin- and metronidazole-resistant strains.

In summary, concomitant therapy may be more suitable than sequential therapy for patients with dual resistance to antibiotics. Nevertheless, one would suspect that neither concomitant nor sequential therapy would be a good choice in the face of known dual resistance.[13] In any case, these considerations are based on results from small samples; therefore, more data are needed before a reliable conclusion can be drawn.

## Duration of treatment

Non-bismuth quadruple (concomitant) therapy was originally developed in an attempt to decrease the duration of treatment for *H. pylori* infection. In studies performed in the late 1990s, data from Europe and Japan suggested that a short course of 3–5 days with three antibiotics and a PPI could achieve reasonable eradication rates.[66]

In their meta-analysis (nine studies), Essa et al[77] showed that, despite the very short treatment durations of some of the trials, concomitant therapy yielded excellent results but duration of therapy became a significant variable, with longer duration tending to produce higher eradication rates.

The results of the studies included in Tables 1 and 2 show that, depending on the duration of treatment, mean *H. pylori* eradication rates for concomitant treatment were: 3 days (85%), 4 days (88%), 5 days (83%), 7 days (91%),

and 10 days (90%). Therefore, a trend toward better results with longer treatments was observed.

The only randomized trial to date that has compared a 5-day regimen of concomitant therapy with a 10-day regimen[58] revealed a nonsignificant trend for higher cure rates with the longer regimen (96% with 10 days versus 90% with 5 days). Although the authors conclude that both durations were "similar", a type II error may not be ruled out, and this 6% difference may be clinically relevant.

The real benefit of a highly effective first-line therapy is much greater than the raw percentage data suggest.[78] As safety is similar and the increase in costs relatively low, it seems reasonable to recommend the length of treatment achieving maximal cure rates (10 days), even though the expected improvements will be moderate.

## Comparison between the concomitant regimen and the standard triple regimen
### Efficacy

Several randomized studies have confirmed the superiority of concomitant therapy over standard triple therapy. A recent meta-analysis[77] examined nine prospective trials treating *H. pylori* for up to 7 days with a concomitant regimen (PPI-macrolide-imidazole-amoxicillin). Treatment generally lasted 5 days (4 days in one study and 7 days in another). Overall, concomitant therapy was effective in 90% of patients in the intention-to-treat analysis and 93% in the per-protocol analysis. Pooled estimates of the five randomized controlled trials showed the superiority of concomitant therapy over triple therapy (odds ratio of 2.86; 95% CI, 1.73–4.73).

We recently updated these analyses with a more recent study[59] and have performed a meta-analysis including the randomized controlled studies that, to date (December 2011), have compared these two regimens. As summarized in Table 3, 481 patients received the concomitant regimen and 503 the standard triple regimen. The former was more effective than the latter: 90% versus 78% in the intention-to-treat analysis. As the results were very homogeneous ($I^2 = 0\%$), a fixed effect model (Peto method) was used to perform the meta-analysis (Review Manager 5.0.25). The odds ratio for this comparison was 2.36 (95% CI, 1.67–3.34) (Table 3).

### Tolerance

In the meta-analysis by Essa et al,[77] no severe side effects were reported in any of the studies, apart from anaphylactic reactions to medication.[34,54,55] Mild to moderate side effects were reported in 27%–51% of patients treated with the

**Table 3** Meta-analysis comparing the efficacy (intention-to-treat) of the concomitant regimen with that of standard triple therapy for the eradication of *Helicobacter pylori* infection

| Study or subgroup | Concomitant events | Total | Standard events | Total | Weight | Peto odds ratio peto, fixed, 95% CI | Year | Peto odds ratio peto, fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Treiber et al[33] | 42 | 46 | 38 | 42 | 5.7% | 1.10 [0.26, 4.69] | 1998 | |
| Neville et al[53] | 49 | 56 | 33 | 56 | 17.3% | 4.24 [1.84, 9.74] | 1999 | |
| Nagahara et al[51] | 52 | 55 | 40 | 50 | 9.0% | 3.77 [1.19, 12.00] | 2000 | |
| Catalano et al[48] | 50 | 56 | 45 | 55 | 10.8% | 1.82 [0.63, 5.23] | 2000 | |
| Nagahara et al[52] | 74 | 80 | 65 | 80 | 14.4% | 2.67 [1.07, 6.65] | 2001 | |
| Moon et al[62] | 43 | 53 | 55 | 85 | 21.2% | 2.21 [1.04, 4.69] | 2011 | |
| Kim et al[59] | 123 | 135 | 116 | 135 | 21.6% | 1.66 [0.79, 3.51] | 2011 | |
| **Total (95% CI)** | | **481** | | **503** | **100.0%** | **2.36 [1.67, 3.34]** | | |

Total events 433 392

Heterogeneity: Chi$^2$ = 4.76, df = 6 ($P$ = 0.57); $I^2$ = 0%
Test for overall effect: Z = 4.85 ($P$ < 0.00001)

(Forest plot: scale from 0.005 to 200; Standard therapy — Concomitant therapy)

**Abbreviation:** CI, confidence interval.

concomitant regimen (compared with 21%–48% of patients treated with triple therapy).[77] These observations suggest that concomitant and standard triple therapies have a similar safety profile.

## Comparison between concomitant and sequential regimens

One potential problem with sequential therapy is its complexity, as it requires switching from a dual to a triple therapy half way through treatment. Therefore, trials comparing sequential with concomitant therapy using the same combination of drugs are necessary. Such comparisons would address whether the sequential element of sequential quadruple therapy is actually helpful.[30] A direct head-to-head comparison between sequential and concomitant therapy would also tell us which of these two competitors can eventually replace the current first-line triple therapies.[79]

In this respect, Wu et al[56] recently performed a multicenter randomized comparison of 10-day sequential therapy with 10-day concomitant therapy, including 232 *H. pylori*-infected patients from three hospitals in Taiwan. Intention-to-treat eradication rates were similar for both regimens: 92% versus 93%, respectively. Per-protocol cure rates were exactly the same: 93% with both regimens. The frequency of adverse events was also similar (31% versus 27%), as was adherence to therapy (96% versus 98%). Therefore, the authors concluded that sequential and concomitant administration of the same drugs provides similar results in terms of efficacy and safety and that the sequential administration protocol may produce unnecessary complexity for both patients and physicians compared with concurrent prescription of all the medications from the outset.[56] The study, however, was

performed in a population with a very low rate of clarithromycin and dual clarithromycin-metronidazole resistance; therefore, the potential advantage of concomitant therapy in multiresistant strains may not been adequately appreciated. In fact, the rate of antibiotic resistance in Taiwan is very low, and excellent cure rates (almost 90%) have also been recently reported with standard triple therapy.[80]

A second randomized study has compared the concomitant regimen (5 days) and the sequential regimen (10 days) in seven Latin American populations[57] and has reported disappointing results with both regimens (74% and 76% cure rates, respectively). By contrast, the eradication rate achieved with the standard triple therapy administered for 14 days was statistically higher (82%).

## Limitations of concomitant therapy

The results of the aforementioned studies are encouraging, although a number of limitations may affect the strength of their conclusions (see below).

## Old data

Many of the previously mentioned data (see Table 1) are from a decade ago, when the rates of clarithromycin and metronidazole resistance were quite low.[66] Considering changes in resistance rates, these data may not be valid today.[72] As few recent data are available from Western populations with current rates of resistance, well-controlled studies are necessary.[66] Nonetheless, a recently study published in complete journal format reported excellent results: 93% eradication both by intention-to-treat and by per-protocol analysis with 10-day concomitant treatment,[56] suggesting that, at least with the 10-day regimen, favorable results

may still be obtained. Obviously, further robust assessment across a much broader range of patients is required before concomitant therapy can be generally recommended in clinical practice.[16]

## Small sample size and low quality of studies

The sample in most studies evaluating the concomitant regimen comprises fewer than 100 patients (Table 1). In particular, all the individual studies included in the only meta-analysis published to date had a small sample size.[77] Furthermore, the quality of the studies is low in most cases. Thus, there are no double-blind randomized controlled trials with this regimen, and only two of the trials included in the meta-analysis by Essa et al were single-blinded, thus limiting the quality of the available evidence.[77]

## Insufficient information on the effects of antibiotic resistance

As most of the published studies failed to evaluate clarithromycin and nitroimidazole resistance, available information is insufficient to truly judge this antimicrobial regimen according to its applicability in populations with high or low antimicrobial resistance.

## Limitation of future treatment options after failure of eradication

All regimens require an adequate back-up or rescue therapy.[70,71,79] However, it remains unclear how failure of concomitant therapy should be managed. One potential disadvantage of concomitant therapy is that patients with failed eradication would have limited options for further treatment, because they would already have received three different antibiotics: amoxicillin, clarithromycin, and nitroimidazole.[17] In this respect, it has been suggested that the first choice for eradication treatment should probably not be a regimen combining clarithromycin and metronidazole.[70,79] Although this regimen is very effective, patients who are not cured will have at least single, and usually double, resistance,[81] and few logical empirical treatment options are subsequently available.[79] Some authors have demonstrated that initial regimens containing both clarithromycin and nitroimidazole are associated with significantly worse results overall, with lower eradication rates after logically chosen second-line therapy and sensitivity-directed third-line therapy; the poor results were due to the emergence of multiple resistant strains, as evidenced by culture testing after the second failed course.[82]

However, the recent appearance of levofloxacin may overcome this problem, as levofloxacin-containing rescue therapy constitutes an encouraging empirical second-line or even third-line strategy after multiple previous *H. pylori* eradication failures with key antibiotics such as amoxicillin, clarithromycin, metronidazole, and tetracycline.[83–85] Zullo et al[86] recently performed a pilot study on patients who failed sequential therapy (a regimen including the same antibiotics as concomitant therapy). Following 10-day triple therapy with a PPI, levofloxacin, and amoxicillin, *H. pylori* infection was successfully cured in 86% of cases. In another study, Perna et al[87] prescribed a 10-day triple regimen with a PPI, levofloxacin, and amoxicillin in patients in whom first treatment with either standard 10-day triple or sequential therapy (only 10 patients) had failed. *H. pylori* was eradicated in 73% of cases, although the authors do not provide separate efficacy rates depending on the first (failure) treatment. Finally, Gisbert et al[88] evaluated the efficacy of a second-line levofloxacin-containing triple regimen (PPI-amoxicillin-levofloxacin) in 35 patients after "sequential" or "concomitant" treatment failure; *H. pylori* eradication rate was 80%. Respective cure rates for "sequential" and "concomitant" failure regimens were 67% and 90%.

These data seem to indicate that a triple regimen (PPI-levofloxacin-amoxicillin) is a suitable approach for second-line treatment in patients whose sequential – and probably also concomitant – therapy fails.[18,89,90] Therefore, the concomitant regimen plus levofloxacin-containing triple therapy may be an adequate therapeutic strategy for the management of *H. pylori* in clinical practice. However, given the rise in resistance to this antibiotic, the prevalence in each country must be taken into account.

Finally, bismuth-based quadruple therapy (ie, PPI, bismuth, tetracycline, and nitroimidazole) could be an alternative in patients whose concomitant therapy fails. Thus, the results of a recent study showed that all patients who had failed sequential therapy (ie, a regimen including the same antibiotics as the concomitant therapy) were able to eradicate the bacterium with bismuth-based quadruple therapy.[91]

## Conclusion

Standard triple therapy is still the most widely used treatment in clinical practice. However, the prevalence of clarithromycin and metronidazole resistance has increased substantially in recent years, and there has been a corresponding decrease in the eradication rate for *H. pylori* infection. Eradication rates are at their lowest levels since a decade ago and are likely to fall further as antimicrobial resistance becomes more

prevalent worldwide.[66] It is clear that alternative treatment regimens are urgently needed, particularly for patients with clarithromycin-resistant strains of *H. pylori*.[92]

Sequential therapy has been proposed as an alternative to standard triple therapy for eradication of *H. pylori*. However, the sequential approach, which may be more complicated than necessary, does not appear to offer specific advantages. In fact, the first randomized comparison of the sequential and the non-bismuth quadruple concomitant regimens recently concluded that sequential and concomitant administration of the same drugs provide similar results in terms of efficacy and safety.

Several randomized controlled trials (and one meta-analysis) have demonstrated that concomitant therapy is more effective than, and equally well tolerated as, standard triple therapy. Our meta-analysis of 19 studies revealed a mean *H. pylori* cure rate of roughly 90% for concomitant therapy. A tendency toward better results with longer treatments (7–10 days versus 3–5 days) with the concomitant regimen has been observed, so it seems reasonable to recommend the length of treatment achieving the highest cure rates (10 days).

Clarithromycin resistance may reduce the efficacy of concomitant therapy, although the decrease in eradication rates seems to be far lower than in standard triple therapy. Therefore, it has been suggested that the concomitant regimen may be preferable when the prevalence of clarithromycin-resistant *H. pylori* infection is high, which is the case in many developed countries. Experience with the concomitant therapy in patients with metronidazole-resistant strains is still very limited.

Although the aforementioned results are encouraging, a number of limitations should be taken into account: (1) much of the data previously mentioned are relatively old; (2) the number of patients included in most studies evaluating the concomitant regimen is low; (3) the concomitant regimen has not been sufficiently validated in clinical practice; and (4) there is still insufficient information on the effect of antibiotic resistance on efficacy.

In summary, non-bismuth quadruple concomitant therapy appears to be an effective, safe, and well-tolerated alternative to standard triple therapy and is less complex than sequential therapy. Therefore, this regimen appears well suited for use in settings where the efficacy of triple therapy is unacceptably low.

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## Disclosure

The authors report no conflicts of interest in this work.

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