Review article: non-bismuth quadruple (concomitant) therapy for eradication of *Helicobacter pylori*

J. P. Gisbert* & X. Calvet†

*Department of Gastroenterology, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IP), and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain.
†Department of Gastroenterology, Hospital de Sabadell, Departament de Medicina, Universitat Autònoma de Barcelona and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain.

Correspondence to:
E-mail: gisbert@meditex.es

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SUMMARY

Background
Traditional standard triple therapy for *Helicobacter pylori* infection (PPI-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 (PPI-clarithromycin-amoxicillin-nitroimidazole) in the treatment of *H. pylori* infection.

Methods
Bibliographical searches were performed in MEDLINE and relevant congresses.

Results
The first randomised comparison of the non-bismuth quadruple therapy and the sequential (PPI-amoxicillin 5 days plus PPI-clarithromycin-nitroimidazole 5 days) regimens recently concluded that both were similar in terms of efficacy and safety and that the sequential administration protocol may be unnecessarily complex. Several randomised controlled trials (and one meta-analysis) have demonstrated that non-bismuth quadruple therapy is more effective than and is equally well tolerated as standard triple therapy. A meta-analysis of 15 studies (1723 patients) revealed a mean *H. pylori* cure rate (intention-to-treat) of 90% for non-bismuth quadruple therapy. A tendency towards better results with longer treatments (7–10 days vs. 3–5 days) has been observed, so it seems reasonable to recommend the length of treatment by achieving maximal 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.

Conclusions
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.
INTRODUCTION

*Helicobacter 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–based (PPI), 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 rate has fallen considerably with this regimen.7

Two recent double-blind, US multicentre studies found disappointingly low eradication rates with standard therapy (77%)8,9, and two meta-analyses including more than 53 000 patients revealed the cure rate to be below 80%.10,11 Therefore, the ethics of continued use of standard triple therapy has recently been questioned, and alternative approaches have been recommended.12 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.13,14 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.15 Several randomised clinical trials (including pooled-data analyses and meta-analyses) have demonstrated that a sequential regimen is more effective than standard triple therapy.16–20 Therefore, some guidelines have proposed sequential therapy as an alternative to standard triple therapy for the eradication of *H. pylori*.21 However, a recent update of previous meta-analyses performed by a Cochrane Collaboration group22 found that the results obtained with the sequential regimen were clearly heterogeneous, and that eight recently published studies were unable to demonstrate differences between sequential and standard triple therapy. So, although the overall mean eradication rate with a sequential regimen was nearly 90%, a tendency towards lower efficacy with this regimen was observed in the more recent studies.23–26

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.27,28 In other words, does sequential administration represent an advantage or does it make therapy more complicated than necessary?12,29 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 efficacious. The concept of a “non-bismuth quadruple regimen” or “concomitant” regimen (the term used hereafter) has recently resurfaced. 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.30

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 May 2011 using the following keywords (all fields): (“*Helicobacter pylori*” OR “*H. pylori*”) AND [(concomitant OR concurrent OR quadruple OR clarithromycin AND (amoxicillin OR amoxicillin) 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 results 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.31,32 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. 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. In other words, concurrent administration of the three antibiotics as concomitant therapy proved more efficacious than when they were administered separately.

Proponents of sequential treatment (amoxicillin for 5 days, followed up 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, namely, prevention of the selection of secondary clarithromycin resistance. 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. 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. 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.

Efficacy of the Concomitant Regimen for Eradication of H. pylori

Studies evaluating the efficacy of the concomitant regimen are summarised in Table 1 and are represented graphically in Figure 1. These studies were performed in different countries in Europe, Asia, and Latin America and most were randomised 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 10 days (see below). Our analysis of the 15 studies (1723 patients) revealed a mean H. pylori cure rate (intention-to-treat) of 90% (95% confidence interval [95% CI] from 86% to 93%) (Figure 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; \( I^2 = 81\% \)), 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; the rates recorded in the remaining studies were >80% and even >90%. In fact, if this study is excluded, the mean eradication rate (intention-to-treat) of the remaining 14 studies increases to 92%, and the inter-study heterogeneity completely disappears (\( I^2 = 3\% \)). The explanation for this outlier is unclear, as the study has not yet been published as a peer-reviewed article, and information on the antibiotic susceptibility of H. pylori is not available in the abstract. Furthermore, even though the study 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.

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. Antimicrobial resistance is largely responsible for the poor eradication rates with standard triple therapy. Culture and antimicrobial sensitivity testing of H. pylori are not widely available and, when they are available, they may not produce any clear clinical benefit. One meta-analysis reported an almost 60% decline in eradication rates with standard triple therapy if clarithromycin resistance was present. Therefore, the use of standard triple therapy has been recommended only in those areas where clarithromycin resistance is lower than 15–20%.2
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Publication year</th>
<th>Study design</th>
<th>Disease type</th>
<th>Therapy regimen</th>
<th>Days*</th>
<th>No. of patients</th>
<th>Eradication rate (%) (ITT)</th>
<th>Eradication rate (%) (PP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvet et al.</td>
<td>Spain</td>
<td>2000</td>
<td>NC</td>
<td>PUD</td>
<td>O 20 mg b.d. + A 1 g b.d. + C 500 mg b.d. + T 500 mg b.d.</td>
<td>4</td>
<td>56</td>
<td>49/56 (87.5)</td>
<td>49/54 (90.7)</td>
</tr>
<tr>
<td>Catalano et al.</td>
<td>Italy</td>
<td>2000</td>
<td>RCT</td>
<td>PUD</td>
<td>O 40 mg od + A 1 g b.d. + C 500 mg b.d. + M 500 mg b.d.</td>
<td>3</td>
<td>56</td>
<td>50/56 (89.3)</td>
<td>50/54 (92.6)</td>
</tr>
<tr>
<td>Chan et al.</td>
<td>China</td>
<td>2001</td>
<td>NC</td>
<td>PUD, NUD, others</td>
<td>O 20 mg b.d. + A 20 mg/kg t.d.s + C 7.5 mg/kg t.d.s + M 7.5 mg/kg 5 times a day</td>
<td>7</td>
<td>33</td>
<td>31/33 (94)</td>
<td>31/33 (94)</td>
</tr>
<tr>
<td>Molina-Infante et al.</td>
<td>Spain</td>
<td>2011</td>
<td>NC</td>
<td>PUD, NUD, others</td>
<td>PPI b.d. + A 1 g b.d. + C 500 mg b.d. + M 500 mg</td>
<td>10</td>
<td>81</td>
<td>70/81 (86)</td>
<td>70/80 (88)</td>
</tr>
<tr>
<td>Nagahara et al.</td>
<td>Japan</td>
<td>2000</td>
<td>RCT</td>
<td>PUD, NUD</td>
<td>R 10 mg b.d. + A 750 mg b.d. + C 200 mg b.d. + M 250 mg b.d.</td>
<td>5</td>
<td>55</td>
<td>52/55 (94.5)</td>
<td>52/53 (98.1)</td>
</tr>
<tr>
<td>Nagahara et al.</td>
<td>Japan</td>
<td>2001</td>
<td>RCT</td>
<td>PUD, NUD</td>
<td>R 20 mg b.d. + A 750 mg b.d. + C 200 mg b.d. + M 250 mg b.d.</td>
<td>5</td>
<td>80</td>
<td>74/80 (92.5)</td>
<td>74/79 (93.7)</td>
</tr>
<tr>
<td>Neville et al.</td>
<td>UK</td>
<td>1999</td>
<td>RCT</td>
<td>PUD, NUD, others</td>
<td>L 30 mg b.d. + A 1 g b.d. + C 250 mg b.d. + M 400 mg b.d.</td>
<td>5</td>
<td>56</td>
<td>49/56 (87.5)</td>
<td>49/54 (90.7)</td>
</tr>
<tr>
<td>Okada et al.</td>
<td>Japan</td>
<td>1998</td>
<td>RCT</td>
<td>PUD, NUD, others</td>
<td>O 20 mg b.d. + A 500 mg t.d.s + R 150 mg b.d. + M 250 mg t.d.s.</td>
<td>7</td>
<td>90</td>
<td>85/90 (94.4)</td>
<td>85/88 (96.6)</td>
</tr>
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<td>Okada et al.</td>
<td>Japan</td>
<td>1999</td>
<td>RCT</td>
<td>PUD, NUD, others</td>
<td>O 20 mg b.d. + A 500 mg t.d.s. + R 150 mg b.d. + M 250 mg t.d.s.</td>
<td>7</td>
<td>169</td>
<td>155/169 (92)</td>
<td>155/163 (95)</td>
</tr>
<tr>
<td>Treiber et al.</td>
<td>Germany</td>
<td>1998</td>
<td>RCT</td>
<td>PUD, others</td>
<td>O 20 mg b.d. + A 1 g b.d. + C 250 mg b.d. + M 400 mg b.d.</td>
<td>5</td>
<td>46</td>
<td>42/46 (91.3)</td>
<td>42/44 (95.5)</td>
</tr>
<tr>
<td>Treiber et al.(a)</td>
<td>Germany</td>
<td>2002</td>
<td>RCT</td>
<td>PUD, NUD, others</td>
<td>L 30 mg b.d. + A 1 g b.d. + C 250 mg b.d. + M 400 mg b.d.</td>
<td>3</td>
<td>80</td>
<td>65/80 (81.2)</td>
<td>65/76 (85.5)</td>
</tr>
<tr>
<td>Treiber et al.(b)</td>
<td>Germany</td>
<td>2002</td>
<td>RCT</td>
<td>PUD, NUD, others</td>
<td>L 30 mg b.d. + A 1 g b.d. + C 250 mg b.d. + M 400 mg b.d.</td>
<td>5</td>
<td>83</td>
<td>74/83 (89.2)</td>
<td>74/79 (93.7)</td>
</tr>
<tr>
<td>Wu et al.</td>
<td>Taiwan</td>
<td>2010</td>
<td>RCT</td>
<td>PUD, NUD, others</td>
<td>E 40 mg b.d. + A 1 g b.d. + C 500 mg b.d. + M 500 mg b.d.</td>
<td>10</td>
<td>115</td>
<td>107/115 (93)</td>
<td>107/115 (93)</td>
</tr>
<tr>
<td>Ferreccio et al.</td>
<td>Latin America</td>
<td>2011</td>
<td>RCT</td>
<td>PUD, NUD, others</td>
<td>L 30 mg b.d. + A 1 g b.d. + C 500 mg b.d. + M 500 mg b.d.</td>
<td>5</td>
<td>488</td>
<td>359/488 (73.6)</td>
<td>359/456 (78.7)</td>
</tr>
<tr>
<td>Kongchayanun et al.(a)</td>
<td>Thailand</td>
<td>2011</td>
<td>RCT</td>
<td>NUD</td>
<td>R 20 mg b.d. + A 1 g b.d. + C 1 g od + M 500 mg t.d.s.</td>
<td>5</td>
<td>50</td>
<td>45/50 (90)</td>
<td>45/50 (90)</td>
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<tr>
<td>Kongchayanun et al.(b)</td>
<td>Thailand</td>
<td>2011</td>
<td>RCT</td>
<td>NUD</td>
<td>R 20 mg b.d. + A 1 g b.d. + C 1 g od + M 500 mg t.d.s.</td>
<td>10</td>
<td>50</td>
<td>48/50 (96)</td>
<td>48/50 (96)</td>
</tr>
</tbody>
</table>
Clarithromycin resistance reduces the efficacy of sequential therapy, although the decrease in eradication rates was far lower than in triple therapy. Therefore, the sequential treatment regimen may be preferable when the prevalence of clarithromycin-resistant *H. pylori* infection is high, which is the case in many developed countries. Nevertheless, this suggestion must be interpreted with some caution, because the number of clarithromycin-resistant strains effectively exposed to sequential therapy is relatively low (55 in only 4 studies from which 41/55 [75%] were eradicated). This advantage of sequential therapy over standard triple therapy (i.e. 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 efficacious 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. The effect of clarithromycin resistance on the efficacy of concomitant regimens was negligible, with 95% efficacy in the one clarithromycin-sensitive arm, and 96% in the one clarithromycin-resistant arm. Nevertheless, this conclusion was based on only two studies. In the study by Okada *et al.*, *H. pylori* was eradicated in 15 out of 16 (94%) patients with roxithromycin-resistant strains and in 140 out of 147 (95%) patients with roxithromycin-sensitive strains. More recently, Wu *et al.* found no significant effect of antibiotic resistance on the efficacy of concomitant therapy: *H. pylori* was eradicated in three of four (75%) clarithromycin-resistant patients.

Although the reasons why the sequential regimen is more effective for resistant strains need to be clarified, some hypotheses may be put forward. These mechanisms may also explain why the concomitant regimen is effective for resistant strains. Indirect evidence supporting an advantage of a concomitant regimen over a sequential regimen comes from the recent study by Molina-Infante *et al.* The authors evaluated the efficacy of empiric concomitant therapy in a geographical area (in Spain) where sequential therapy had previously proved inefficient (76% cure rate in a prior study). Eradication rates for the concomitant regimen were 88% by per-protocol analysis and 86% by intention-to-treat analysis, and the authors concluded that in settings with high clarithromycin resistance (>15–20%) and documented failure of sequential therapy, concomitant therapy may achieve...
acceptable eradication rates. The reason for this theoretical advantage of concomitant therapy over sequential therapy (which should be confirmed in randomised 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...
the 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 sug-
gested that the sequential regimen may achieve a sig-
ificantly higher eradication rate than the tinidazole-free
standard triple therapies.19 On the other hand, experi-
ence with concomitant therapy in patients with metro-
idazole-resistant strains is still very limited. In the
study by Neville et al.51, similar eradication rates against
both metronidazole-sensitive (95%) and metronidazole-
resistant strains (85%) were achieved with the com-
comitant regimen. Okada et al.52 found that H. pylori was
eradicated in 25 of 27 (93%) patients with metronida-
zole-resistant strains compared with 130 of 136 (96%)
in patients with metronidazole-sensitive strains. How-
ever, Treiber et al.53 observed that 5-day concomitant
treatment eradicated H. pylori in 90% of metronidazole-
susceptible patients but in only 50% (8 of 16) of metro-
idazole-resistant patients. Finally, bismuth-based qua-
druple therapy has been proposed as a means of
overcoming imidazole resistance, and it remains to be
seen how concomitant therapy would perform in com-
parison.58

Dual clarithromycin and metronidazole resistance
Sequential therapy has been reported to be absolutely inef-
fective in patients with dual resistance (clarithro-
mycin and imidazole).43 Primary dual resistance for clari-
thumbycin and imidazole has been shown to produce an
eradication rate of 50% (two of four) following 5 days of
concomitant therapy53 and 75% (3 of 4) after 7 days of
concomitant therapy.52

Comparative studies where both sequential and con-
comitant regimens are administered are clearly necessary.
In this respect, Wu et al.54 compared the efficacy of
sequential and concomitant therapy and analysed 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 se-
quential therapy group. In particular, patients with
dual resistance had a significantly lower eradication rate
after sequential therapy (present vs. absent: 33.3% vs.
95.1%; P < 0.0001), but not after concomitant therapy
(present vs. absent: 75.0% vs. 92.4%; P = 0.22; although
the low number of patients makes the possibility of a
type II error likely).

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

Patient demographics
The influence of age on the efficacy of concomitant
treatment is unclear. In the study by Neville et al.51, the
probability of eradication with concomitant treatment
decreased with age, whereas in that by Treiber et al.53,
younger age was associated with failure of eradication.
The only study that has evaluated concomitant therapy
in children showed encouraging results (94% eradica-
tion in 33 children).47

Gender was not found to be a significant predictive
factor for the success or failure of eradication when con-
comitant treatment was administered.51

Some data suggest that eradication following standard
triple therapies in patients with non-ulcer dyspepsia
tends to be lower than in patients with peptic ulcer.69–71

On the contrary, cure rates with a concomitant regimen
were surprisingly higher for non-ulcer dyspepsia than
that for ulcer patients in the study by Treiber et al.53

Concomitant treatment was not affected by smoking
in one study,46 which contrasts with reports for other
eradication regimens, where smoking increased the treat-
ment failure rate for H. pylori eradication.72

Finally, in the meta-analysis by Essa et al.73, meta-
regression analysis for treatment outcome regarding
randomised controlled trials showed that none of the
variables studied (age, gender, or endoscopy-based diag-
nosis) significantly explained the variation in treatment
efficacy between concomitant and triple therapy.

H. pylori CagA status
Some authors have demonstrated the importance of
H. pylori CagA status for the efficacy of antibiotic treat-
ment.74, 75 For example, Brouet et al.75 clearly stated
that the infection with cytotoxic strains is a good predic-
tive marker of successful therapy. These results have
been confirmed by Treiber et al. among ulcer patients
receiving concomitant treatment.53

Proton pump inhibitor type
Encouraging results have been obtained with the con-
comitant regimen including different PPIs (omeprazole,
lansoprazole, rabeprazole, or esomeprazole) (Table 1). These results are consistent with those obtained with the sequential regimen, with which pooled-data analyses and meta-analyses have demonstrated that the success rate among the different PPIs used was also similar.18, 19

Duration of treatment
Non-bismuth quadruple (concomitant) therapy was originally developed in an attempt to decrease the duration of treatment for \( \text{H. pylori} \) 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.59

In their meta-analysis (nine studies), Essa et al.73 showed that, despite the very short 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 Table 1 and Figure 1 show that, depending on the duration of treatment, mean \( \text{H. pylori} \) eradication rates for concomitant treatment were 3 days (85%), 4 days (88%), 5 days (89%), 7 days (93%) and 10 days (92%). Therefore, a trend towards better results with longer treatments was observed.

The only randomised trial to date that has compared a 5-day regimen of concomitant therapy with a 10-day regimen56 revealed a nonsignificant trend for higher cure rates with the longer regimen (96% with 10 days vs. 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 increase of eradication rates with longer regimens could be mainly dependent on the compensation (overcoming) of resistance of metronidazole.60–62 It may be suggested that, perhaps, using metronidazole at high dose (e.g. 500 mg t.d.s) might be another option of increasing the cure rate, instead of prolonging treatment duration. Nevertheless, even when clarithromycin-containing standard triple therapy is prescribed, prolonging exposure to antibiotics from 7 to 10–14 days may produce a slight increase in efficacy.13, 14

The real benefit of a highly effective first-line therapy is much greater than what the raw percentage data suggest.76 Furthermore, outcome was better in poor PPI metabolisers, a finding that is consistent with the concept that concomitant therapy could be further improved by modifying PPI dose and possibly duration of therapy.77 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 randomised studies have confirmed the superiority of concomitant therapy over standard triple therapy. A recent meta-analysis73 examined nine prospective trials treating \( \text{H. pylori} \) for up to 7 days with a concomitant regimen (PPI-macrolide-imidazole-amoxicillin). Treatment generally lasted 5 days (four in one study and seven 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 randomised controlled trials showed the superiority of concomitant therapy over triple therapy (odds ratio of 2.86; 95% CI, 1.73–4.73).

![Figure 3](image-url) | Meta-analysis comparing the efficacy of the concomitant regimen with that of standard triple therapy for the eradication of \( \text{H. pylori} \) infection (intention-to-treat).
We recently updated these analyses with a more recent study57 and have performed a meta-analysis including the randomised controlled studies that, to date (May 2011), have compared these two regimens. As summarised in Figure 3, 428 patients received the concomitant regimen and 418 the standard triple regimen. The former was more effective than the latter: 91.1% vs. 80.6% in the intention-to-treat analysis. As the results were very homogeneous (P = 0.45; I² = 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 2.4 (95% CI, 1.63–3.55) (Figure 3).

Tolerance
In the meta-analysis by Essa et al.73, no severe side effects were reported in any of the studies, apart from anaphylactic reactions to medication52, 52, 53. Mild-to-moderate side effects were reported in 27–51% of patients treated with the concomitant regimen (compared with 21–48% of patients treated with triple therapy).73 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 halfway through treatment. Therefore, trials comparing sequential with concomitant therapy using the same combination of drugs are necessary. Such comparisons would address whether or not the sequential element of sequential quadruple therapy is actually helpful.29 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.78

In this respect, Wu et al.54 recently performed a multicentre randomised 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% vs. 93%, respectively. Per-protocol cure rates were exactly the same: 93% with both regimens. The frequency of adverse events was also similar (31% vs. 27%), as was adherence to therapy (96% vs. 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.54 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 multi-resistant 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.79

A second randomised study has compared the concomitant regimen (5 days) and the sequential regimen (10 days) in seven Latin American populations55 and has reported disappointing results with both regimens (74% and 76% cure rates). 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.59 Considering changes in resistance rates, these data may not be valid today.65 As no recent data are available from Western populations with current rates of resistance, well-controlled studies are necessary.59 Nonetheless, the only study recently published in complete journal format reported excellent results: 93% eradication both by intention-to-treat and by per-protocol analysis with 10-day concomitant treatment54, suggesting that, at least with the 10-day regimen, favourable 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.15

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.73 Furthermore, the quality of the studies is low in most cases. Thus, there are no double-blind randomised 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.73
Complexity of therapy
Poor adherence is the second most important reason for failure of H. pylori eradication after antibiotic resistance. One in 10 patients on triple therapy are estimated to fail to take even 60% of their medication,80 a threshold at which significantly lower rates of eradication have been proven.88, 81 The concomitant regimen is slightly more complex than standard triple therapy, because it involves the intake of an additional drug (twice a day). Nevertheless, the concomitant regimen and standard triple regimen seem to be characterised by similar adherence, at least in clinical trials.73

Lack of validation in clinical practice
The lower H. pylori eradication rates achieved in some studies probably reflect the fact that they were performed under conditions of clinical practice in a relatively unselected population. In this setting, higher rates of non-adherence and dropout during follow-up are to be expected. In contrast, patients treated within the framework of a clinical trial may have a better clinical outcome.82 The low rate of withdrawal may not be reproducible outside the trial setting, especially if the prescribing physician does not explain the temporary nature of most side effects and the importance of completing the regimen as prescribed (four drugs each time).

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 and/or low antimicrobial resistance.

Unsuitability for penicillin-allergic patients
H. pylori eradication is a challenge in penicillin-allergic patients.83, 84 The concomitant regimen includes amoxicillin and, therefore, is not suitable for patients with penicillin allergy.85 However, such a limitation also applies for one of the standard triple therapies suggested in the European guidelines (PPI-amoxicillin-clarithromycin).17

Limitation of future treatment options after failure of eradication
All regimens require an adequate backup or rescue therapy.63, 64, 78 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.16 In this respect, the first choice for eradication treatment should probably not be a regimen combining clarithromycin and metronidazole.63, 78 Although this regimen is very effective, patients who are not cured will have at least single, and usually double, resistance66, and few logical empirical treatment options are subsequently available.78 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 multiply resistant strains, as evidenced by culture testing after the second failed course.87

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.88–90 Zullo et al.91 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.92 prescribed a 10-day triple regimen with a PPI, levofloxacin and amoxicillin, H. pylori infection was successfully cured in 68% of cases. In another study, Perna et al.92 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. 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.17, 93, 94 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 (i.e. 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 (i.e. a regimen including the same antibiotics as the concomitant therapy) were able to eradicate the bacterium with bismuth-based quadruple therapy.95
Lack of comparison with bismuth-based quadruple therapy

Concomitant therapy has not been compared with bismuth-based quadruple therapy (a PPI, bismuth salt, tetracycline and a nitroimidazole). Bismuth-based quadruple therapy seems to overcome metronidazole resistance and is not influenced by macrolide resistance.\(^96, 97\) Thus, this regimen has been recommended as the treatment of choice when clarithromycin resistance rates are \(\geq 15\%\) in the community.\(^28\) Nevertheless, two meta-analyses failed to find a significant difference in success rates between bismuth-based quadruple therapy and standard triple therapy, both of which were suboptimal.\(^97, 98\) The main disadvantage of a bismuth-based quadruple regimen is its complexity, as it has the highest daily pill burden.\(^78\) However, this drawback may be overcome, thanks to a novel single capsule containing bismuth, metronidazole and tetracycline that has recently become available.\(^78, 99–102\) This new formulation can simplify the regimen to make it more acceptable for general use.\(^78, 99–101\) However, its principal disadvantage is that three capsules still need to be taken four times daily, and a PPI needs to be taken separately twice daily.\(^28\) A final and relevant limitation is that bismuth salts are not available in many countries.

CONCLUSIONS

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.\(^59\) It is clear that alternative treatment regimens are urgently needed, particularly for patients with clarithromycin-resistant strains of \(H.\) \(pylori.\)\(^103\)

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 randomised 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 randomised controlled trials (and one meta-analysis) have demonstrated that concomitant therapy is more effective than and equally well tolerated as standard triple therapy. A meta-analysis of 15 studies revealed a mean \(H.\) \(pylori\) cure rate of 90\% for concomitant therapy. A tendency towards better results with longer treatments (7–10 days vs. 3–5 days) with the concomitant regimen has been observed, so it seems reasonable to recommend the length of treatment by achieving maximal 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 that 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: (i) much of the data previously mentioned are relatively old; (ii) the number of patients included in most studies evaluating the concomitant regimen is low; (iii) the concomitant regimen has not been sufficiently validated in clinical practice; (iv) there is still insufficient information on the effect of antibiotic resistance on efficacy; and (v), no comparisons with bismuth-based quadruple therapy are available.

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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