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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

Optimizing clarithromycin-containing therapy for *Helicobacter pylori* in the era of antibiotic resistance

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Abstract

The efficacy of triple therapy for *Helicobacter pylori* infection has dramatically declined over the last decade, largely related to increasing clarithromycin resistance rates. From a microbiological standpoint, bismuth quadruple therapy is the ideal replacement since it combines drugs for which resistance does not impair its efficacy. Nonetheless, several obstacles such as availability, complexity or tolerance prevent a general implementation of bismuth quadruple therapy, so non-bismuth quadruple regimens remain the best first-line treatment in clinical practice in many geographical areas. We review the rationale and efficacy of several optimization tools (increasing the length of duration, high-dose acid suppression, probiotics), which have been largely evaluated over the last 5 years to increase the effectiveness of standard triple therapy. Then, we update available evidence on the effectiveness of several non-bismuth quadruple therapies (sequential, concomitant, hybrid, miscellaneous therapy), which have gained interest lately. We also revise evidence on the efficacy of the aforementioned optimization tools for non-bismuth quadruples schemes and, finally we provide a novel regionalized therapeutic algorithm, based on novel formulas recently developed for predicting the outcome of non-bismuth quadruple regimens, upon local antibiotic resistance rates.

Key words: *Helicobacter pylori*; Eradication; Clarithromycin; Sequential; Concomitant; Hybrid; Antibiotic resistance; Bismuth

Core tip: Triple therapy is no longer effective to eradicate *Helicobacter pylori* infection in most settings across the world. Bismuth quadruple therapy has resurfaced as an ideal replacement, despite its implementation in clinical practice may be troublesome. As such, non-bismuth quadruple therapies remain in the therapeutic front line in clinical practice. This article updates available evidence over the last five years on the efficacy of several non-bismuth quadruple schemes and different tools used to optimize them, providing a novel regionalized therapeutic algorithm, according to novel predicting models based on local antibiotic resistance rates.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a worldwide infection that affects millions of people. This infection is currently the main cause of gastritis, gastroduodenal ulcer disease, and gastric cancer. It was thirty years ago that *H. pylori* was discovered[1] and twenty years ago that clarithromycin-

based triple therapy was established in clinical practice for the eradication of this infection[2]. Nowadays, the efficacy of triple therapy is seriously challenged in many parts of the world, where eradication rates have declined to unacceptably low levels, largely related to development of resistance to clarithromycin[3].

From a microbiological standpoint, the most rational way to overcome antibiotic resistance would be the use of a combination of drugs for which resistance does not appear to be a problem, so no clarithromycin-based regimens should be recommended in geographical areas with increasing clarithromycin resistance rates. In this context, bismuth-based quadruple therapy seems to be an attractive alternative treatment, especially in its most recent galenic formulation, bismuth subcitrate potassium, metronidazole, and tetracycline (BMT, sold under licence as Pylera®)[4]. However, this logical scenario is not a realistic approach in many settings for clinical practice owing to a number of obstacles. *H. pylori* infection is mostly diagnosed and treated by gastroenterologists, instead of microbiologists, so the bulk of treatment is prescribed on an empirical basis and articles seldom report data on antibiotic resistance. Furthermore, bismuth salts are not widely available, many countries are currently experiencing a general unavailability of tetracycline and the launch of Pylera®, the three-in-one capsule decreasing pill burden and improving compliance for bismuth quadruple therapy, onto the market is being troublesome as well.

As such, several non-bismuth quadruple therapies have made a leap towards the front line to tackle *H. pylori* infection. Indeed, a formula has been elegantly developed to predict the outcome of these therapies according to antibiotic resistance rates[5]. The aim of this review is to summarize optimization tools and therapeutic innovations published over the last 5 years (August 2008-August 2013) aimed at increasing the efficacy of *H. pylori* clarithromycin-based first-line therapies.

OPTIMIZING TRIPLE THERAPY

Increasing the length of duration

It has been postulated that extending the duration of triple therapy up to 14 d might result in higher and acceptable cure rates. In fact, recent European guidelines state that extending the duration of proton pump inhibitor (PPI)-clarithromycin-containing triple therapies from 7 to 10-14 d improves the eradication success by about 5% and may be considered[6]. Conclusions from reviews and meta-analysis are mostly consistent with showing a clinical benefit of extending the duration[7,8], but other have drawn the opposite conclusion[9]. Similarly, recent articles have disclosed a benefit of prolonging the length of triple therapy in Greece[10] and Croatia[11], whereas others from South Korea[12] and Turkey[13] could not demonstrate an advantage for this strategy. As such, prolonging *H. pylori* triple therapy seems to increase eradication rates, albeit whether it represents a clinically useful strategy should be locally evaluated.

Increasing acid-suppressive therapy

H. pylori typically resides within the mucus layer of the human stomach, being the bulk of organisms attached to surface cells. Most importantly, a proportion of the organisms may remain in a non-replicative but viable state, which notably reduces the effectiveness of antibiotics that require microbial replication to kill the organisms, such as clarithromycin and amoxicillin[3]. This non-replicative state, which turns *H. pylori* phenotypically resistant, is more likely when gastric pH ranges from 3 to 6. Increasing the pH in this layer to 6 or 7 allows the bacteria to enter the replicative state where they become susceptible to amoxicillin and clarithromycin[3]. Therefore, the stronger acid suppression is, the higher the likelihood of antibiotic therapy success.

PPI therapy (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomerpazole) are now widely used as the first-line acid inhibitors in eradication schemes. These drugs undergo hepatic metabolism *via* the CYP450 pathways and the isoforms CYP2C19 and, to a lesser extent, CYP3A4. There are interindividual differences in the activity of CYP2C19, which may impact PPIs pharmacokinetic behaviour and clinical efficacy[14,15]. Indeed, the phenotype of CYP2C19 is categorized into three groups: extensive or rapid metabolizer (EM), intermediate metabolizer (IM), and poor metabolizer (PM). The rate of CYP2C19 *rapid metabolizers* was proven to be higher in *Europe* and in North America (56%-81%), while the proportion was smaller (27%-38%) in the *Asian* population[16]. Significantly higher eradication rates of *H. pylori* have been observed in patients with poor and intermediate metabolizers phenotype when compared to extensive metabolizers[17]. As such, initial genotyping for this enzyme would be ideal before *H. pylori* therapy, since higher dosage in extensive metabolizers is likely to improve the clinical efficacy of PPIs for *H. pylori* therapy. Seeing as this approach is unrealistic in clinical practice, it is conceivable that all patients, especially in Europe and North America, should receive high-dose PPI therapy to circumvent the high rate of PPI rapid metabolizers.

As for the different PPI available molecules, a recent meta-analysis disclosed that he efficacy of omeprazole- and lansoprazole- based first-line triple therapies at the standard doses was dependent on CYP2C19 genotype status, which appeared not to affect the efficacy of the regimens including rabeprazole[18]. In line with this finding, two other recent meta-analyses have demonstrated that esomeprazole and rabeprazole provide better overall *H. pylori* eradication rates, especially in CYP2C19 extensive metabolizers[19,20].

Finally, updated European Guidelines for *H. pylori* management have also recommended high-dose PPI therapy using new generation-PPIs, pointing out that increasing the dose of PPI from, for example, 20 mg omeprazole twice daily to 40 mg of esomeprazole or rabeprazole

Table 1 Impact of adding probiotics to eradication therapy (mostly standard triple therapy) on eradication rates and side effects, evaluated in seven recent meta-analyses

Ref.	Probiotic strains	Eradication rates	Side effects
Tong *et al*[24], 2007	Lactobacillus and bifidobacterium	Significant increase	Significant Reduction
Wang *et al*[25], 2013			
Sachdeva *et al*[26], 2009	Lactoferrin	Significant Increase	Significant Reduction/ No impact
Zou *et al*[27], 2009			
Sachdeva *et al*[28], 2009	Fermented milk	Significant Increase	No impact
Zou *et al*[29], 2009	Lactobacillus	Significant Increase	Significant reduction
Szajewska *et al*[30], 2010	Saccharomyces boulardii	Significant increase	Significant reduction

twice daily may increase cure rates by 8%-12%[6].

Probiotics

Probiotics are live organisms or produced substances that are orally administrated, usually in addition to conventional antibiotic therapy for *H. pylori* infection. They may modulate the human microbiota, stimulate the immune response and directly compete with pathogenic bacteria, besides preventing antibiotic side effects[21]. Indeed, probiotics have exhibited inhibitory activity against *H. pylori in vitro* and *in vivo*[22,23]. At the present time, 6 meta-analyses have been published addressing the benefit of *Lactobacillus and Bifidobacterium*[24,25], bovine lactoferrin[26,27], fermented milk-based[28], *Lactobacillus*[29] and *Saccharomyces boulardii*[30] probiotic formulations. The main results of these meta-analyses are summarized in Table 1. Available evidence collectively points towards a benefit of using probiotic for decreasing antibiotic-related side effects and, to a much lesser extent, increasing cure rates.

However, several considerations should be made before recommending probiotic in clinical practice. To begin with, they add complexity as they mean a fourth or fifth drug, depending on dealing with triple and quadruple therapies, and it may increase the risk of poor compliance with therapy. Furthermore, probiotics are "over-the-counter" medications and the cost of eradication therapy may notably rise. On the other hand, the role of probiotics in children is controversial, as they have shown to decrease antibiotic-related side effects but no impact on eradication rates[31]. In this line, several adult trials have disclosed as well negative results on cure rates for probiotic supplementation[32-34]. Most likely, the discordant results are probably related to the different products used, their different concentrations, probiotic strain, dose and the length of duration. Further studies refining the most effective probiotic and the patient profile which will most benefit from probiotic supplementation are needed before a general recommendation in clinical practice can be made.

Long-acting drugs

A recent study from Thailand reported 100% cure rates with 14-d high-dose PPI and long-acting clarithromycin[35]. However, there were no clarithromycin-resistant *H. pylori* strains in the study, so these drugs need further validation in other geographical areas with different patterns of antibiotic resistance. At the present time, no study has evaluated this attractive hypothesis. The use of long-acting macrolides (azithromycin) has been recently associated with increasing *H. pylori* resistante to clarithromycin[36]. Azithromycin is known to achieve high concentrations in the gastric mucus and gastric juice for several weeks after its administration, and this may lead to local subinhibitory concentrations and favour the selection of macrolide-resistant mutants, as above mentioned.

NON-BISMUTH QUADRUPLE TREATMENTS

Sequential therapy

Sequential therapy was developed in Italy in 2000 as a replacement for triple therapy[37,38]. It consists of 5 d of PPI therapy plus amoxicillin, followed by a further five days of PPI with two other antibiotics, usually clarithromycin and metronidazole. Up to 2008, the vast majority of studies on this therapeutic strategy had been conducted in Italy. In 2007, a randomized controlled trial from the same Italian authors showed a significant advantage of 10-day sequential over 10-d triple therapy (91% *vs* 78%, $P = 0.002$), being highly effective against clarihtromycin-resistant strains[39]. A pooled data analysis with Italian evidence showed promising eradication rates higher than 90%, even in patients with risk factors for triple therapy failure (clarithromycin or metronidazole resistance, non ulcer dyspepsia, smoking or the absence of the gene *CagA*)[40]. Indeed, several meta-analyses evidenced the advantage of sequential therapy over triple therapy[41-43]. Accordingly, it was suggested in 2007 by the American College of Gastroenterology Guidelines[44] and the European Maaastricht Consensus (Maastricht Ⅲ)[45], as well as in 2009 by the Second Asia-Pacific Consensus Guidelines[46], that sequential therapy was a promising therapy, but it required further evaluation outside Italy, before a generalized change in first-line *H. pylori* treatment was recommended.

In 2010, a critical review of the evidence highlighted several concerns in previous meta-analyses, such as lack of validation outside of Italy, low quality studies or insufficient information on the effect on antibiotic resistant strains[47]. In 2011, a large multicenter trial from Latin America showed no advantage of 10-d sequential therapy over 14-d triple therapy[48]. In 2012 and 2013, an updated meta-analysis in children and two systematic reviews in adults dealing with sequential therapy have been published[49-51]. The results are summarized in Table 2. From 2008 to 2012, cure rates of sequential therapy in studies conducted in Asia, Europe and Latin America remained significantly better than those of triple therapy, but mean eradication rates dramatically dropped by 15% (79%-81%) compared to Italian trials before 2008. A recent multi-

Table 2 Updated systematic reviews and meta-analyses (2008-2012) in children and adults comparing triple and sequential therapy for *Helicobacter pylori* infection

Ref.	Population and timeframe	*n*	Triple therapy (95%CI)	Sequential therapy (95%CI)	*P* value
Horvath *et al*[49], 2012	Children 2005-2012	857	71% (66-75)	78% (73-82)	
Zullo *et al*[50], 2013	Adults and children 2008-2012	2921	75.8% (73.5–78.1)	80.6% (78.5–82.7)	0.003
Kate *et al*[51], 2013	Adults and children 2008-2012	3247	71.4% (64-78)	81.7% (78-85)	0.02

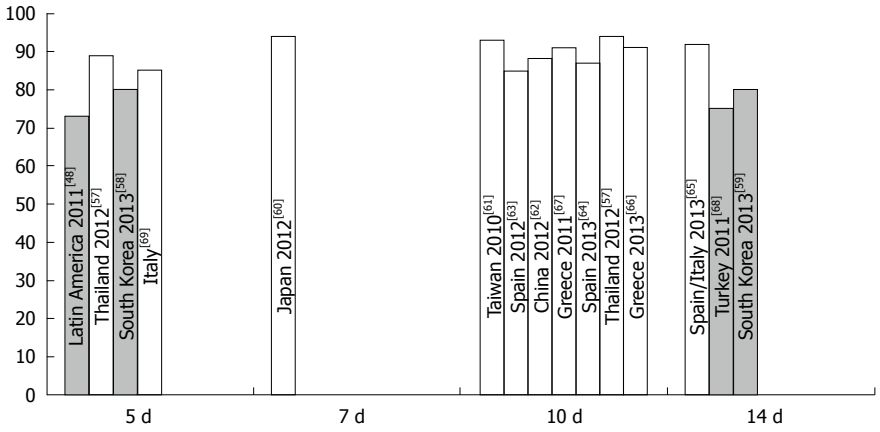

Figure 1 Intention-to-treat cure rates of concomitant therapy over the last three years in studies conducted in Latin America, Asia and Europe, broken down by the duration of therapy. Studies with Intention-to-treat (ITT) < 85% are grey marked.

center study performed in Taiwan comparing 14-d sequential and triple therapy has definitely shown the limitations of sequential therapy[52], since the efficacy of this regimen was impaired by either clarithromycin and metronidazole resistance. Finally, a recent meta-analysis performed by the Italian creators of the sequential therapy[53] showed a mean cure rate of 84% (95%CI: 82.1%-86.4%) for 10-d sequential therapy, being superior to seven day triple therapy, marginally superior to 10 d triple therapy but not superior to 14 d triple therapy. Right now, 10-d sequential therapy cannot be considered a good therapeutic option to overcome antibiotic resistance and its failure might be expected when dual resistant strains are > 5%[5].

The history of sequential therapy is a good one to learn. It was devised in 2000 in response to failure of triple therapy and was systematically compared to an "unfair comparator" (triple therapy), leading to a notable superiority of sequential therapy in meta-analyses. The treatment formula was not optimized and the detrimental effect of clarithromycin was noted, but not that of metronidazole[5]. It took as a decade to understand microbiological drawbacks of sequential therapy and we cannot afford to trip over the same stone when it comes to evaluating new *H. pylori* therapies.

Concomitant therapy

The concept of a "non-bismuth quadruple regimen" or "concomitant" regimen (the term used hereafter) consists of converting standard triple therapy to a quadruple therapy by the addition of 500 mg of metronidazole or tinidazole twice daily. 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 four-drug, three-antibiotic, non-bismuth-containing quadruple regimen[54,55]. Despite the short duration of therapy (5 d on average), this approach provided, at that time, high cure rates (90% by intention-to-treat). After a few years of research, it fell into oblivion but resurfaced in 2010 as an alternative therapy to triple and sequential therapy[56]. Since then, eleven studies have evaluated its effectiveness in Latin America[48], Asia (Thailand[57], South Korea[58,59], Japan[60], Taiwan[61], China[62]) and Europe (Spain[63-65], Greece[66,67], Turkey[68] and Italy[65,69]). The results are disclosed in Figure 1, broken down by the lenght of therapy. Regardless of the duration of therapy, all studies showed intention-to-treat cure rates from 85% to 94%, with 4 exceptions (2 studies with a 5-d duration from Latin America (73.5%)[48] and South Korea (80.7%)[58], and 2 studies with a 14-d duration from Turkey (75%)[68] and South Korea (80.8%)[59].

In the aforementioned article by Graham *et al*[5], the efficacy of 14-d concomitant therapy was not impaired by neither clarithromycin nor metronidazole isolated resistance, but it is expected to fall below 90% when the prevalence of dual clarithromycin-metronidazole resistant strains is > 15%. Therefore, the authors state that it cannot be recommended in settings where metronidazole resistance is greater than 60% (*i.e.*, China, India, Iran or Central or South America) or in populations at high risk of dual resistance (*i.e.*, following clarithromycin or metronidazole treatment failures). These recommendations are in agreement with suboptimal results in Latin America[48], South Korea[58,59] and Turkey[68], where clarithromycin, but specially metronidazole, resistant *H. pylori* strains are

Table 3 Efficacy of sequential and concomitant therapy, with a duration of 10 to 14 d, on dual clarithromycin-metronidazole resistant *Helicobacter pylori* strains *n* (%)

Ref.	Treatment duration (d)	Patients	Eradication rates
Concomitant therapy			
Wu *et al*[61], Thailand, 2010	10	4	3 (75)
Huang *et al*[62], China, 2012	10	2	2 (100)
Molina-Infante *et al*[63], Spain, 2012	10	4	3 (75)
Molina-Infante *et al*[65], Spain-Italy, 2013	14	3	3 (100)
Georgopoulos *et al*[66], Greece, 2013	10	10	7 (70)
Total		23	18 (78)
Sequential therapy			
Vaira *et al*[39], Italy, 2007	10	4	0 (0)
Liou *et al*[52], Taiwan, 2013	14	8	3 (37)
Wu *et al*[61], Thailand, 2010	10	3	1 (33)
Huang *et al*[62], China, 2012	10	4	2 (50)
Molina-Infante *et al*[63], Spain, 2012	10	5	3 (60)
Romano *et al*[70], Italy, 2010	10	3	0 (0)
Total		27	9 (33)

Adapted from Georgopoulos *et al*[71], with permission.

very prevalent. Likewise, they match with good to excellent results in Southern Europe and some Asian countries, where claritrhromycin ranges from low (9%) to high (40%) figures, but metronidazole resistance remains in relatively low figures (< 30%-40%).

Sequential or concomitant therapy?

Several studies have lately evaluated the efficacy of sequential and concomitant non-bismuth quadruple therapies against clarithromycin and metronidazole resistant strains. Georgopoulos *et al*[71] nicely addressed this issue and we have adapted their results to exhibit the most recent evidence (Table 3). Concomitant and sequential therapies were successful against dual-resistant strains in 78% (18/23) and 33% (9/27) of the cases, respectively. Furthermore, a recent meta-analysis[72] comparing sequential and concomitant therapy has shown a significant adavantage (OR = 1.51; 95%CI: 1.06-2.17) of concomitant therapy (Figure 2). Overall, solid evidence point towards concomitant therapy being a more reasonable therapeutic option in areas with a high incidence of clarithromycin and/or metronidazole resistance[71], even though we cannot miss the fact that it is expected to fail when the prevalence of dual clarithromycin-metronidazole resistant strains is > 15%[7].

Hybrid therapy: A new kid on the block

Hybrid sequential-concomitant regimen is a therapeutic innovation which includes a proton pump inhibitor (PPI) plus amoxicillin for 14 d, adding clarithromycin and a nitroimidazole for the final 7 d. In other words, it is a 7-d first dual phase (PPI + amoxicillin) followed by a 7-d quadruple phase (PPI + amoxicillin + clarithromcyin + nitroimidazole). In 2011, a pilot study revealed outstanding cure rates [97% intention-to-treat (ITT) analysis] in three Taiwanese centers[73]. However, the rate of clarithromycin resistance in this region is low (7%) and required further validation in setting with different patterns of resistance. In 2012, hybrid therapy demonstrated to achieve significantly higher ITT cure rates over sequential therapy (89.5% *vs* 76.7%, $P = 0.001$) in Iran[74], a setting with high rates of antibiotic resistance. More recently, a noninferiority trial conducted in Spain and Italy[65] showed that both optimized concomitant and hybrid therapy achieved ITT eradication rates > 90% in settings with high rates of clarithromycin and metronidazole resistance. In this trial, hybrid therapy led to successful eradication in 1 out of 3 (33%) dual resistant strains. These are preliminary small numbers and definitely further research is warranted on this matter. Finally, a pilot study conducted in Italy[69] compared 5-d concomitant therapy, 10-d sequential therapy and 14-d hybrid therapy. Surprisingly, 5-d concomitant and 10-d sequential therapy achieved acceptable cure rates (> 90% on PP analysis), but not hybrid therapy (80%).

CAN WE OPTIMIZE NON BISMUTH QUADRUPLE REGIMENS?

Duration of therapy

As for sequential therapy, 10-d sequential therapy was not superior to 14 d triple therapy, but 14-d sequential therapy proved to be superior to 14-d triple therapy[5,52,53]. Furthermore, metronidazole resistance undermines 10-d sequential therapy at 20% and 14-d sequential therapy at 30%[5].

Regarding concomitant therapy, meta-analyses have shown that the outcome is duration dependent[75,76]. In a recent head-to-head comparison in Thailand[57], 5-d proved unsatisfactory compared to 10-d concomitant therapy, besides 5-d concomitant therapy has also shown its failure in Latin America[48] and South Korea[58]. In the authors' experience, 14-d concomitant[65] achieved the best ITT results (92%) compared to studies evaluating 10-d concomitant therapy (86%-87%)[63,64].

Acid suppression

Both triple therapy and non-bismuth quadruple therapy contain amoxicillin and clarithromycin. As such, it is conceivable to speculate that the above mentioned data are valid for both therapies. Further studies are warranted to elucidate whether high-dose PPI therapy and either esomeprazole or rabeprazole show superiority for non-bismuth quadruple regimens (as it has been the case with triple therapy).

Probiotics

At the present time, data on the usefulness of probiotics for *H. pylori* eradication with quadruple therapies is anecdotical. Two recent trials[77,78] showed a reduction of side effects of probiotics combined with bismuth quadruple therapy and sequential therapy, but no increase in cure rates. No study has evaluated the addition of probiotics to concomitant or hybrid therapy.

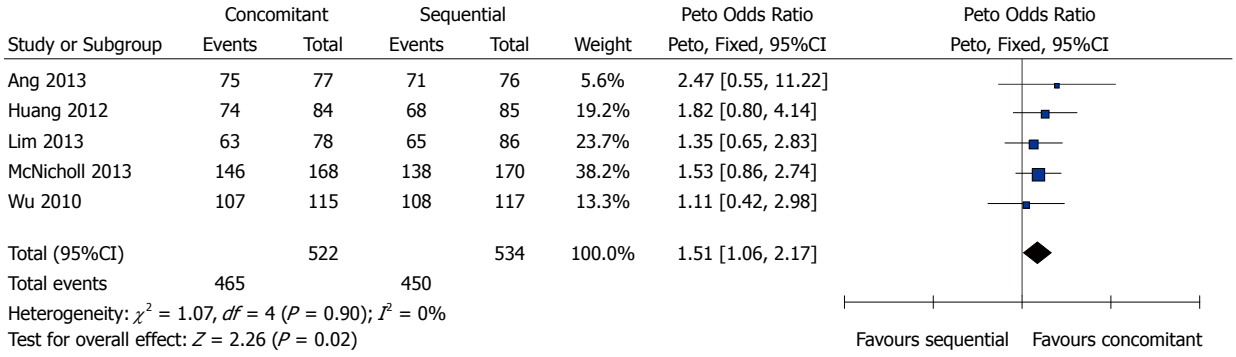

Figure 2 Forest plot comparing sequential and concomitant therapy with a similar duration[72].

Optimization of non-bismuth quadruple therapies (increasing antibiotic burden or increasing length of duration) adds complexity and might impact negatively on compliance with therapy. Regardless of the effect on cure rates, probiotics might be important to improve tolerance and compliance. On the contrary, they are "over-the-counter" drugs, therefore increasing costs, and add a fifth drug and may as well add complexity. More studies are required to refine the role of probiotics for these therapies and depict the patient characteristic that would benefit from coadyuvant probiotic supplementation.

MISCELLANEOUS THERAPY: THE SUPER-OPTIMIZATION

Recently, an interesting pilot study from Colombia evaluating a "super-optimized" therapy, so called "miscellaneous", has been published[79]. It consists of high-dose metronidazole (500 t.d.s) all along the therapy (15 d), dividing the remaining drugs in three 5-d phases: (1) First 5 d (lansoprazole 30 mg *bid* and amoxicillin 1 g *bid*); (2) Days 6 to 10: lansoprazole 30 mg *qds*; and (3) Days 11 to 15: lansoprazole 30 mg *bid* and clarithromycin 500 mg *bid*.

Therefore, this quadruple therapy has an optimized duration (15 d), high-dose PPI, high-dose metronidazole during 15 d trying to overcome the high rate of resistance (> 70%-80%) in Latin America and, of note, has a halfway period in which acid suppression is optimized (lansoprazole 120 mg/d) in order to avoid selection of non-replicative *H. pylori* strains. In this pilot study, miscellaneous therapy led to successful eradication rates [94% and 91% by per protocol (PP) and ITT, respectively], with a high rate of full compliants (96%) and acceptable side effects rate (55%), all of them mild.

Miscellaneous therapy is obviously burdened by its complexity and maybe its cost, depending on the geographical location, but provides an interesting and effective therapeutic tool in settings with metronidazole resistance > 40%, in which theoretically Maastricht IV precludes using metronidazole[6]. Definitely, more studies are awaited in this line of work to overcome antibiotic resistance.

THERAPEUTIC ALGORITHM

Following this review, we propose a modified therapeutic algorithm for first-line *H. pylori* therapy (Figure 3). The success of treatments for infectious diseases is predictable if one knows the pattern of resistance and the effect of resistance on the regimens tested[5]. Clarithromycin resistance was the Achiles heel for triple therapy and now dual clarithromycin resistance rates is the Achiles heel for non-bismuth quadruple therapies. Non-bismuth sequential, hybrid and concomitant therapies are expected to fail if the rate of dual-resistant strains are > 5%, > 9% and > 15%, respectively. As such, eradication therapy should be "regionalized" depending on the prevalence of clarithomycin and metronidazole resistant strains. Currently, triple therapy should only be acceptable if eradication rates > 90% have been documented.

TAKE-HOME MESSAGES

Optimization tools for triple therapy

(1) Prolonging *H. pylori* triple therapy up to 14 d increases eradication rates by approximately 5%, albeit the clinical benefit of this strategy should be evaluated locally; (2) High-dose PPI therapy is recommended for triple therapy, especially in Europe and North America, where the prevalence of PPI extensive metabolizers is higher; (3) A discrete advantage of esomeprazole and rabeprazole over omeprazole, pantoprazole and lansoprazole has been shown in recent meta-analyses; and (4) Overall, probiotics seem to increase eradication rates and reduce antibiotic side-effects in adults, but they cannot be recommended for clinical practice yet.

Sequential therapy

Updated data in both children and adults point towards lower eradication rates than previously reported. Despite sequential therapy keeps on showing an advantage over triple therapy, unacceptable cure rates have been recently reported, without a therapeutic advantage over 14-d triple therapy. Its efficacy dramatically decreases upon the existence of metronidazole and dual clarithromycin and metronidazole resistant strains.

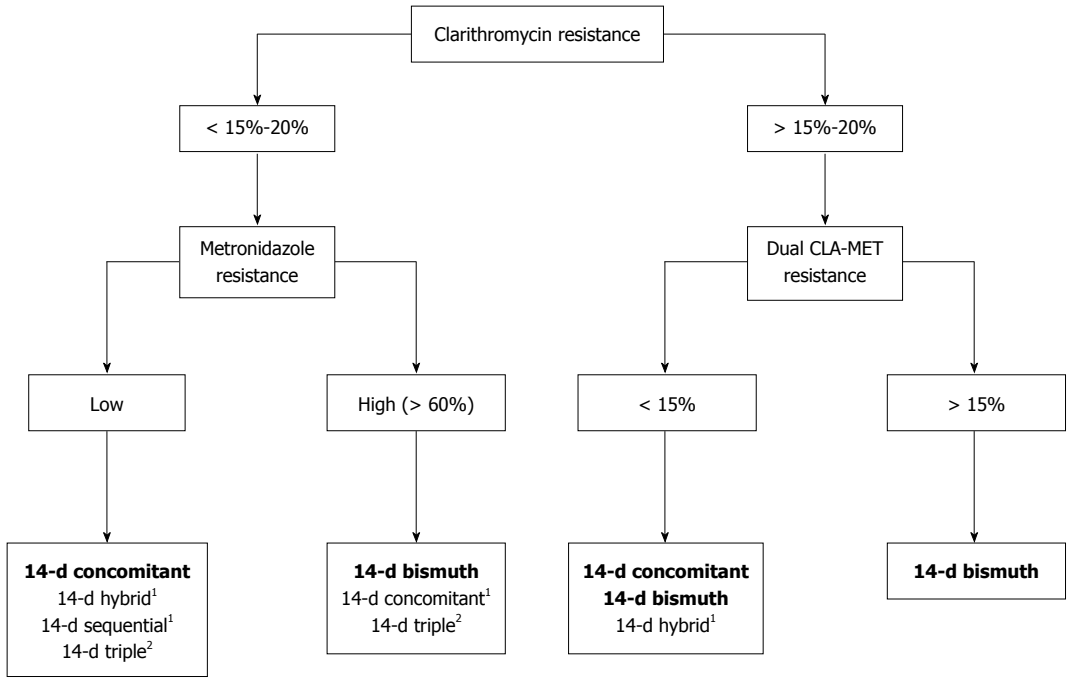

Figure 3 Regionalized therapeutic algorithm for *Helicobacter pylori* infection, based on clarithromycin and metronidazole resistance patterns. [1]Use conditioned to the rate of dual-resistant strains. Sequential, hybrid and concomitant therapies are expected to fail if the rate of dual clarithromycin- and metronidazole-resistant strains in > 5%, > 9% and > 15%, respectively; [2]Use if eradication rates > 90% have been documented.

Concomitant therapy

Emerging evidence has shown concomitant therapy to be an effective therapy (> 90% cure rates) in Southern Europe and some Asian countries (Thailand, Taiwan, Japan, China). Compared to sequential therapy, its efficacy is less impaired by clarithromycin and metronidazole resistant strains and therefore seems to be the best replacement for triple therapy. However, it has been proven unsuccessful in Turkey and South Korea, where both clarithromycin and specially metronidazole, resistance rates are notably high.

Hybrid therapy

It is a therapeutic innovation combining sequential and concomitant therapy, with a 7-d first dual phase (PPI + amoxicillin) followed by a 7-d quadruple phase (PPI + amoxicillin + clarithromcyin + nitroimidazole). It has currently demonstrated an advantage over sequential therapy and not to be inferior to concomitant therapy, although further research is warranted.

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