

WJGP 5<sup>th</sup> Anniversary Special Issues (1): *Helicobacter pylori***Treatment of *Helicobacter pylori* infection: Past, present and future**

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**Abstract**

*Helicobacter pylori* (*H. pylori*) is a major human pathogen associated with significant morbidity and mortality. However, after decades of efforts, treatment of *H. pylori* remains a challenge for physicians, as there is no universally effective regimen. Due to the rising prevalence of antimicrobial resistance, mainly to clarithromycin, efficacy of standard triple therapies has declined to unacceptably low levels in most parts of the world. Novel regimens, specifically experimented to improve the therapeutic outcome against antibiotic-resistant *H. pylori* strains, are now recommended as first-line empirical treatment options providing high efficacy (reportedly > 90% in intention to treat analysis) even in high clarithromycin resistance settings. These include the bismuth quadruple, concomitant, sequential and hybrid therapies. Due to the rapid development of quinolone resistance, levofloxacin-based regimens should be reserved as second-line/rescue options. Adjunct use of probiotics has been proposed in order to boost eradication rates and decrease occurrence of treatment-related side effects. Molecular testing meth-

ods are currently available for the characterization of *H. pylori* therapeutic susceptibility, including genotypic detection of macrolide resistance and evaluation of the cytochrome P450 2C19 status known to affect the metabolism of proton pump inhibitors. In the future, use of these techniques may allow for culture-free, non-invasive tailoring of therapy for *H. pylori* infection.

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**Key words:** *Helicobacter pylori*; Antibiotic resistance; Bismuth-quadruple; Concomitant; Sequential; Probiotics

**Core tip:** Worldwide increase in prevalence of macrolide resistance has accounted for the failure of standard therapies for the treatment of *Helicobacter pylori* (*H. pylori*) infection. Bismuth quadruple, concomitant, sequential and hybrid therapies are now recommended as first-line empirical treatments providing improved efficacy in high clarithromycin resistance settings. As quinolone resistance is rapidly increasing, levofloxacin should be preferentially used in second-line/rescue therapies. There is increasing evidence that adjunct probiotic supplementation improves the therapeutic outcome and tolerability. Genotypic characterization of *H. pylori* susceptibility to therapy may allow for a tailored therapeutic approach in the future.

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**INTRODUCTION**

Treatment of *Helicobacter pylori* (*H. pylori*) infection is paramount for the management of prevalent gastrointestinal

**Table 1** Factors reported to negatively affect the outcome of therapies for *Helicobacter pylori* infection

Pathogen-related	Host-related
Development of resistance to antibiotics	Non-compliance to treatment
High bacterial load in the stomach	Non-ulcer dyspepsia
Protective effect of the gastric mucus layer	Smoking
Intracellular location of many bacteria	CYP2C19 status (rapid metabolizer)
<i>CagA</i> negative	
Presence of dormant coccoid forms (not susceptible to antibiotics)	
Heteroresistant status (co-existence of strains susceptible and resistant to the same antibiotic)	

diseases, including peptic ulcer disease, gastric cancer and functional dyspepsia<sup>[1-3]</sup>. Moreover, extra-digestive disorders are now included as indications for eradication of *H. pylori*: idiopathic thrombocytopenic purpura, vitamin B12 deficiency and unexplained iron deficiency anemia<sup>[4]</sup>. Contrarily to other bacterial infections, for which susceptibility testing is commonly performed to guide treatment, culture of *H. pylori* is not widely available and requires performing endoscopy which is not well-tolerated by all patients and has a series of limitations, including the fact that *in vitro* susceptibility does not always guarantee *in vivo* eradication<sup>[5]</sup>. Hence, regimens for *H. pylori* have been routinely prescribed empirically, provided they have been previously tested and sufficiently tailored with regard to various parameters (*i.e.*; treatment dose, duration, dosing intervals *etc.*) to optimize cure rates and minimize side effects. However, the optimal treatment to eradicate *H. pylori* remains to be established, as no regimen is effective universally. Worldwide increase in resistance to key antibiotics, mainly clarithromycin (CAM), but also metronidazole (MNZ) and levofloxacin, is the main determinant of failure in the treatment of *H. pylori* infection<sup>[6,7]</sup>. In a recent systematic review, the global incidence of CAM resistance has been reported to be 17.2% ranging from 11.1% in Europe to 29.3% in America, whereas, in the same analysis, continental rates of resistance to MNZ were 17% and 44.1% respectively<sup>[8]</sup>. Antibiotic consumption for infections other than *H. pylori* is accounting for the wide increase in *H. pylori* antibiotic resistance rates<sup>[9,10]</sup>. Indeed, different national policies for antibiotic use are largely reflecting geographical distribution of *H. pylori* resistance: CAM resistance has been reported to be significantly higher in Southern European countries (reaching 49% in some areas of Spain) as compared to Northern Europe (*e.g.*, only 1% in the Netherlands) where policies for antibiotic use are more stringent<sup>[9]</sup>. Additionally to the development of antibiotic resistance, a series of both host and pathogen related factors may negatively impact on the performance of regimens to eradicate *H. pylori* (Table 1)<sup>[11,12]</sup>.

Despite decades of efforts, treatment of *H. pylori* in-

fection remains a challenging issue for both researchers and practicing physicians. In the present article we aim to provide a comprehensive overview of perspectives on the past, present and future of *H. pylori* eradication.

## CLARITHROMYCIN-BASED TRIPLE THERAPIES: A DECLINING CLINICAL STANDARD

Historically, the first truly effective therapy for *H. pylori* infection, comprising of bismuth, tetracycline and MNZ, was proposed in 1990<sup>[13]</sup>. A few years later, use of CAM in a triple therapy, proposed by Bazzoli *et al.*<sup>[14]</sup>, was the start of CAM-based triple regimens, thereafter representing the gold standard in the treatment of *H. pylori*. In studies conducted during the 90's, standard triple therapies (STT) comprising of a proton pump inhibitor (PPI) *bid*, CAM 500 mg *bid* and amoxicillin 1000 mg *bid* or MNZ 500 mg (or 400 mg in England), all given for 7-14 d, provided consistently good results yielding > 80% eradication success and even > 90% was feasible<sup>[15,16]</sup>. Due to this high efficacy and relative simplicity, optimal safety profile, and large pharmaceutical company commitment, these regimens have been widely accepted in national expert panels and consensus recommendations worldwide as standard of care treatments for first-line eradication of *H. pylori*<sup>[17-20]</sup>. However, rising prevalence of CAM resistance has accounted for a significant decline in the efficacy of standard regimens. This decreasing efficacy was already evident in the meta-analyses published by the early 2000's, prompting significant changes in the paradigm of treating the infection. These included the introduction of the concept of cumulative treatment efficacy (requiring the patient to comply with more treatment courses; thus, more side effects and spreading of secondary antibiotic resistance), and later the introduction of a local threshold (15%-20%) of CAM resistance at which CAM should not be used empirically<sup>[17,18]</sup>. The decreased efficacy of standard treatments against CAM-resistant strains has been well-documented on a meta-analytic basis: In a meta-analysis by Fischbach and Evans, the success of triple therapy was decreased by 66.2% (95%CI: 58.2%-74.2%) when strains of *H. pylori* were resistant *vs* susceptible to CAM<sup>[7]</sup>. Congruently, a more recent analysis by Venerito *et al.*<sup>[21]</sup>, revealed similar results: including antimicrobial susceptibility data from 4 randomized clinical trials (RCTs), standard triple therapies successfully eradicated 88% of CAM-sensitive but only 14% of CAM-resistant *H. pylori* strains (risk difference = 0.75, 95%CI: 0.63-0.87). If MNZ is used, presence of MNZ resistance may also affect the therapeutic outcome<sup>[22]</sup>, although it is generally considered less important clinically. This is due to the fact that MNZ resistance may be largely overcome by increasing dose and prolonging treatment duration<sup>[23]</sup>. Lastly, *H. pylori* resistance to amoxicillin is exceptional and generally is not relevant clinically. In the light of increasing data confirming suboptimal performance (< 70%) in most

**Table 2** Current regimens to treat *Helicobacter pylori* infection

Treatment	Regimen
Bismuth-containing quadruple therapy	A PPI (standard dose, <i>bid</i> ), bismuth (standard dose, <i>qid</i> ) tetracycline (500 mg, <i>qid</i> ) and metronidazole (500 mg, <i>qid</i> ) for 10-14 d
Sequential therapy	A 5-d dual therapy with a PPI (standard dose, <i>bid</i> ) and amoxicillin (1 g, <i>bid</i> ) followed by a 5-d triple therapy with a PPI (standard dose, <i>bid</i> ), clarithromycin (500 mg, <i>bid</i> ) and metronidazole (500 mg, <i>bid</i> )
Concomitant therapy	A PPI (standard dose, <i>bid</i> ), clarithromycin (500 mg, <i>bid</i> ), amoxicillin (1 g, <i>bid</i> ) and metronidazole (500 mg, <i>bid</i> ) for 7-10 d
Hybrid therapy	A 7-d dual therapy with a PPI (standard dose, <i>bid</i> ) and amoxicillin (1 g, <i>bid</i> ) followed by a 7-d quadruple therapy with a PPI (standard dose, <i>bid</i> ), amoxicillin (1 g, <i>bid</i> ), clarithromycin (500 mg, <i>bid</i> ) and metronidazole (500 mg, <i>bid</i> )
Levofloxacin-based triple therapy	A PPI (standard dose, <i>bid</i> ), levofloxacin (500 mg, <i>bid</i> ) and amoxicillin (1 g, <i>bid</i> ) for 10 d

PPI: Proton pump inhibitor.

European countries, the recent Maastricht IV/ Florence consensus report has definitively displaced standard regimens as the empirical gold standard to eradicate *H. pylori*<sup>[41]</sup>. Instead, use of legacy triple regimens should take into account the local resistance pattern (thus, used only in areas in which CAM resistance is < 20%) or rely on susceptibility testing provided that pre-treatment culture is available (*i.e.*, used as tailored treatments).

## CURRENT THERAPIES FOR *H. PYLORI* INFECTION

Novel regimens, specifically experimented to improve the therapeutic outcome against antibiotic-resistant *H. pylori* strains, are now recommended as first-line empirical treatment options providing improved efficacy (reportedly > 90% in intention to treat analysis) in high CAM resistance settings. These regimens are summarized in Table 2.

### BISMUTH QUADRUPLE THERAPY

Bismuth quadruple therapy (BQT) currently represents a preferred first-line treatments option for areas with a high ( $\geq 20\%$ ) incidence of CAM resistance but also a valuable second-line treatment option when a CAM-based regimen has previously failed. It works independently to CAM achieving > 90% eradication in the presence of CAM resistance, whereas implementation of a high MNZ dose (1500-1600 mg/d) and prolonged (10-14 d) treatment duration allow for minimizing the impact on MNZ resistance, providing eradication rates > 85% even in regions with a high resistance to this drug<sup>[24]</sup>. A patient-friendly moncapsule (containing bismuth, MNZ and tetracycline) is available (Pylera®, Aptalis, Mont St Hilaire, QC, Canada) providing intention-to-treat eradication rates of 86% and 80% in two large RCTs conducted in North America and Europe respectively<sup>[25-27]</sup>. Contrarily, the ITT eradication rate with BQT was only 77.8% in a recent meta-analysis (*vs* 77% for STT), questioning both the efficacy as well as the superiority of the BQT over STT<sup>[28]</sup>. However, a substantial grade of study heterogeneity, especially with respect to MNZ dosing, should be acknowledged. The second-line efficacy of BQT has been also confirmed on a meta-analytic basis (30 studies) showing an average 77% second-

line efficacy (ITT) after failure of STT<sup>[29]</sup>. Third-line efficacy of BQT after two previous eradication failures with CAM- and levofloxacin-containing triple therapies was 65% (ITT) in a multi-center study from Spain<sup>[30]</sup>. Non-availability of bismuth salts or tetracycline in some countries as well as the potential toxicity of bismuth are the main limitations. However, including 4763 patients no differences with respect to tolerability were shown between non-bismuth and bismuth-containing groups except from dark stools being more common in the later<sup>[31]</sup>.

### SEQUENTIAL THERAPY

Sequential therapy uses the same antibiotics contained in STT but administered sequentially. It has been postulated that the initial course of amoxicillin disrupts the bacterial cell wall preventing the development of efflux channels transferring CAM out of the bacteria<sup>[32]</sup>. Although in the initial RCTs<sup>[33]</sup> (most of them conducted in Italy) and earlier meta-analyses sequential therapy was clearly superior to STT [ITT eradication 91.7% (95%CI: 90%-93%) *vs* 76.7% (95%CI: 75%-79%) for STT]<sup>[34]</sup>, more recent data from South America, Iran and South Korea revealed lower eradication rates (< 80%)<sup>[35-37]</sup>. Despite this sequential therapy seems to be fairly effective against CAM mono-resistant strains, being able to eradicate 72.8% of them, its efficacy against dual resistant (CAM and MNZ) strains was only 37% (range: 16.2% to 60.7%) when 8 studies with antibiotic susceptibility data were evaluated<sup>[38]</sup>. Critically, sequential therapy was not superior to either a 14-d triple therapy (RR = 1, 95%CI: 0.94-1.06) or a bismuth-based therapy (RR = 0.99, 95%CI: 0.94-1.05) in an extensive evaluation of 46 RCTs<sup>[38]</sup>.

### NON-BISMUTH QUADRUPLE (CONCOMITANT) THERAPY

A non-bismuth quadruple “concomitant” therapy is another valid first-line treatment option for areas with a high incidence of CAM resistance<sup>[39,40]</sup>. In 19 studies (2070 patients) the overall eradication rate with concomitant therapy was 88% (95%CI: 85%-91%) and 91% when 3 outlying studies with inherently short treatment duration (3-5 d) were excluded<sup>[41]</sup>. Indeed, treatment duration of

at least 7 d has been shown to be necessary for the success of concomitant therapy<sup>[42]</sup>, whereas extra-prolonging treatment to 14 d combined with a high PPI dose (omeprazole 40 mg × 2) may further boost cure rates to > 95%, as revealed by a non-inferiority multi-center trial<sup>[43]</sup>. An increased efficacy against dual resistant *H. pylori* strains has been proposed as the main strength of the concomitant over the sequential therapy<sup>[44]</sup>, though the two regimens have performed equally when compared using 338 patients in a high antibiotic resistance country (Spain)<sup>[45]</sup>. Indeed, by evaluating 106 patients with pre-treatment susceptibility testing, the concomitant therapy eradicated only 55% of dual-resistant strains *vs* 100% and 91% with CAM and MNZ resistance respectively<sup>[46]</sup>. Thus, both regimens seem to be prone to the deleterious impact of dual resistance, performing comparably (with about 81% of efficacy each) by pooling data of 6 comparative RCTs<sup>[38]</sup>.

## HYBRID THERAPY

A two-step dual-concomitant (hybrid) regimen, proposed by Hsu *et al*<sup>[47]</sup>, is another valuable treatment option competing with both the sequential and concomitant treatments. By evaluating data from 2 RCTs, hybrid therapy performed marginally, though not significantly, better as compared to sequential therapy (86.6% *vs* 81%)<sup>[38]</sup>, and comparably to concomitant therapy in a comparative study in which, interestingly, fewer adverse events occurred in the group treated with the hybrid regimen<sup>[43]</sup>. Further data is warranted to allow for definitive conclusions on the efficacy and tolerability of hybrid therapy.

## LEVOFLOXACIN-BASED THERAPIES

To overcome increasing CAM resistance, levofloxacin, a broad spectrum quinolone, has been used as a substitute of CAM in either triple or sequential regimens achieving > 90% cure rates, and even > 95% is feasible provided that the local resistance to levofloxacin is low (< 10%)<sup>[48,49]</sup>. However, levofloxacin also encounters clinically significant problems of antibiotic resistance, as resistance to quinolones currently exceeds 40% in America, 20% in Europe and 10% in Asia<sup>[8]</sup>. Due to the rapid development of secondary quinolone resistance, first-line use of levofloxacin is generally discouraged, and the drug is reserved for use in second-line/rescue regimens after failure of a CAM- and/or a MNZ-based regimen<sup>[50]</sup>. The good (cure rates 81%-87%) second-line efficacy of a levofloxacin triple therapy (LTT) has been confirmed in two meta-analyses published in 2006, both showing better results with LTT in comparison with second-line BQT<sup>[51,52]</sup>. Congruently, second-line efficacy of LTT was 88.7% in a more recent meta-analysis including RCTs up to October 2010<sup>[53]</sup>. Critically, use of LTT after failure of either a sequential or concomitant regimen has been reported to provide up to 97.8% of cumulative therapeutic efficacy<sup>[54]</sup>. Use of other quinolone agents, such

as Moxifloxacin and Sitafloxacin, has shown promising results<sup>[55,56]</sup>, though there is no evidence to support any therapeutic advantage over levofloxacin.

## FUTURE PERSPECTIVES

### Adjunct probiotics

Albeit different attempts have been made to restore the efficacy of standard treatments, such as increasing the PPI dose or prolonging treatment duration, none has been proved at a level to overcome today's antimicrobial resistance. An approach which has attracted growing interest is using probiotics in conjunction with regimens to eradicate *H. pylori*<sup>[57]</sup>. The expected benefit is twofold: boosting eradication and improving tolerability by preventing occurrence of treatment-related side effects. The pathogenic basis of a possible beneficial effect of probiotics on *H. pylori* eradication remains to be clarified, though some hypothesis have been put forward including strength of the mucosal barrier, competition for adhesion and immunomodulatory mechanisms<sup>[58]</sup>. Different trials used probiotics adjunctively to either standard or novel regimens in recent years providing contradictory results<sup>[59-62]</sup>. Although different single- or multi-strain compounds have been evaluated, there is currently evidence to support use of *Saccharomyces boulardii* (OR = 1.13; 95%CI: 1.05-1.21) or *Lactobacillus spp.* (OR = 1.78; 95%CI: 1.2-2.6) supplementation adjunctively to standard triple therapy<sup>[63,64]</sup>. In the most recent analysis assessing the effect of Lactobacillus-containing and Bifidobacterium-containing supplementation, the pooled odds ratio (ITT) with probiotic supplementation was 2.066 (95%CI: 1.398-3.055) for eradication and 0.305 (95%CI: 0.117-0.793) for the incidence of total side effects<sup>[65]</sup>. Interestingly, with respect to the prevention of side-effects, use of probiotics may be relevant only in a subset of patients, in particularly those with recurrent infection or history of gastrointestinal antibiotic-related side effects<sup>[57]</sup>. Further data is awaited to clarify the role, standardize regimens and assess the cost-effectiveness of probiotics in the treatment of *H. pylori* infection.

### Culture-free, non-invasive determination of *H. pylori* antibiotic susceptibility

Critically, even the novel treatments discussed above are to some (although to a lesser as compared to legacy therapies) degree prone to the impact of antibiotic resistance; eradication rates > 95% are infrequent, and even > 90% are disputed in some studies<sup>[35,66,67]</sup>. Furthermore, it is possible that the success of empirical treatments will further decline in the future as resistance to key antibiotics is constantly growing worldwide. In order to maintain high therapeutic efficacy, tailored treatment of *H. pylori* infection based on pre-treatment susceptibility testing appears as the ideal approach. This will prevent exposing the patient to repeated empirical treatments which increase the risk for side effects and promote development of secondary resistance. However, as



mentioned, current means of performing endoscopy and *H. pylori* culture are invasive, do not 100% reflect in vivo susceptibility, and are time-consuming as culture requires 3-10 d and susceptibility testing (*e.g.*, by Etest, AB bioMérieux, Solna, Sweden) will require additional 3-4 d. These limitations preclude systematical performance of *H. pylori* culture, which is currently recommended only for cases with at least two empirical treatment failures. A class-wide resistance to macrolides is the result of point mutations in three adjacent nucleotide positions (*A2143G*, *A2142G* and *A2142C*) in the peptidyl transferase loop of the *23S rRNA* gene<sup>[68,69]</sup>. These three point mutations account for 90% of cases of primary CAM resistance in Western countries. In recent years, molecular testing methods have been developed for these mutations including a standard polymerase chain reaction (PCR) and other PCR-based methods including PCR-restriction fragment length polymorphism, PCR-DNA enzyme immunoassay, PCR oligonucleotide ligation assay and PCR-line probe assay, as well as Real-time PCR assay which represents a powerful advancement of the basic PCR<sup>[70-72]</sup>. These methods may offer rapid and highly accurate results in the genotypic detection of CAM resistance, including detection of the hetero-resistant status (*i.e.*, co-existence of strains susceptible and resistant to the same antibiotic) known to account for a significant number of treatment failures<sup>[73,74]</sup>. These techniques can be directly applied on gastric biopsy specimens or used in association with minimally-invasive techniques (*e.g.*, oro-gastric brushing or gastric wash) or non-invasively using stool specimens<sup>[75-77]</sup>. Importantly, genotypic detection of CAM resistance is also possible with Fluorescence In-Situ Hybridization, which can be also applied on paraffin-embedded specimens<sup>[78,79]</sup>. Detection of levofloxacin resistance based on the detection of *gyrA* mutations is also available<sup>[80]</sup>. Two Asian studies have provided data on the potential utility of a tailored therapeutic approach based on the molecular detection of *H. pylori* resistance to CAM. Tailored treatment using a simple PPI/MNZ regimen successfully eradicated the pathogen in 94.3% *vs* 71.4% using empirical standard treatment<sup>[77]</sup>. In a larger study (218 patients), CAM was replaced by MNZ in the triple regimen if a CAM-resistant strain was detected. Eradication rates were 91.2% in the tailored group *vs* 79.1% and 75.9% by using empirical MNZ- and CAM-based triple therapies ( $n = 308$  in each control group) respectively ( $P < 0.001$ )<sup>[81]</sup>.

### Pharmacogenomics

Genetic variability in the activity of the cytochrome P450 (CYP) 2C19 (CYP2C19) is known to influence the plasma levels of PPIs, and thus treatment of *H. pylori* infection<sup>[82,83]</sup>. Three distinct genotypes are recognized: rapid, intermediate and poor metabolizers. Preliminary data on the potential use of pharmacogenomics has been provided by a RCT with 300 *H. pylori*-positive patients randomized to either a 1 wk standard regimen or to personalized therapy based on both CYP2C19 and CAM susceptibility status assessed by genetic testing<sup>[84]</sup>. The ITT eradication

rates were significantly higher in the tailored group (96% *vs* 70%) without an increase of the final per-patient cost for successful eradication. In the future, both practical and logistic issues should be addressed before a molecular-based approach can be widely adopted as a genuine basis for the individualization of *H. pylori* eradication therapies.

## CONCLUSION

For more than a decade, triple regimens have been the standard of care therapies for *H. pylori* infection. However, in more recent years, rising prevalence of macrolide resistance has accounted for a significant decline in the performance of these regimens, resulting in the necessity of more treatment courses in order to eradicate the pathogen. In order to maintain high therapeutic efficacy, regimens with an improved performance against antibiotic-resistant *H. pylori* strains are now recommended as preferred first-line treatments. The concomitant and sequential regimens are currently the best validated first-line therapeutic options. Hybrid therapy is another effective CAM-based alternative and a relevant competitor to both these treatments. BQT is also a valid treatment for high CAM resistance settings, but also an effective second-line regimen when a CAM-based regimen fails. Due to the rapid development of quinolone resistance, levofloxacin-based regimens should be currently reserved as second-or-more-line treatment options. While efforts to improve empirical treatments continue, the fields of genotypic detection of *H. pylori* antimicrobial susceptibility and pharmacogenomics offer a fascinating new perspective. This is to guarantee 100% therapeutic efficacy: fast, culture-free and non-invasive.

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