Review of the evidence for *H. Pylori* treatment regimens

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OBJECTIVES

The 17th Expert Committee on the Selection and Use of Essential Medicines recommended the inclusion of omeprazole as a representative of proton pump inhibitors (PPIs) in the Core Model List. It recommended a review of antacids and histamine-2 receptor antagonists to assess their continued usefulness relative to PPIs in the Model List and a review of treatment regimens for *H. pylori* infections.

This review aims to recommend a protocol of *H. pylori* eradication for adults and children, facing the contemporary evidence of its clinical benefit for some upper gastrointestinal diseases, and the choices (agents, formulations, concentrations) which could be maintained or added to the current WHO Model List of Essential Medicines, in its 17.1 Section (Antacids and other antiulcer medicines, mainly comparing PPIs versus histamine-2 receptor antagonists). Also a review of the class of macrolides related to *H. pylori* eradication was performed in order to decide the inclusion of another agent in the 6.2.2 Section (Other antibacterials) of the same List, concerning its role in this context.

METHODS

Electronic searches of Medline, PubMed (using tools as Limits, such as publication date, any language, humans, meta-analysis, randomized controlled trial), The Cochrane Library, and BMJ Clinical Evidence, from 2005 to August 2010 were carried out, using search terms as *H. pylori* infection, *H. pylori* eradication therapy, proton pump inhibitors, histamine-2 receptor antagonists, macrolides, antibiotics, and probiotics. Additional references from identified articles were reviewed. Each article was screened for relevance and the full text acquired if determined to be relevant. Each full-text article was critically appraised regarding efficacy and safety in the treatment of *H. pylori* infection. This review excluded studies about efficacy and safety of theses medicines in other medical indications.

BACKGROUND

*Helicobacter pylori* is a gram-negative bacterium found on the luminal surface of the gastric epithelium. It induces chronic inflammation of the underlying mucosa and usually infects the stomach in the first few years of life. *H. pylori* can also colonize in human palatine tonsil tissues. The bacterium is not cleared by the body and the infection remains life-long unless treated with antibiotics. At least 50% of the world’s human population has *H. pylori* infection. The great majority of patients with *H. pylori* infection do not have any clinically significant complication. However, *H. pylori* infection is a cofactor in the development of three important upper gastrointestinal diseases: duodenal or gastric ulcers, gastric cancer and gastric mucosa-associated lymphoid-tissue (MALT) lymphoma. ¹
H. pylori is the main cause of peptic ulcer disease: 95% of duodenal and 70% of gastric ulcers are associated with Helicobacter pylori infection. A 1 to 2 weeks course of H. pylori eradication with antibiotics and antulcer medicines can accelerate the initial healing of duodenal peptic ulcers and has a significant benefit in preventing the recurrence of both gastric and duodenal ulcers once healing has been achieved. A Cochrane systematic review of 57 trials showed that eradication therapy was superior to ulcer healing drug (UDH) (34 trials, 3910 patients; RR of ulcer persisting = 0.66; 95% CI: 0.58-0.76) and no treatment (2 trials, 207 patients; RR = 0.37; 95% CI: 0.26-0.53) in duodenal ulcer healing. In gastric ulcer healing, no significant differences were detected between eradication therapy and UHD (15 trials, 1974 patients; RR = 1.23; 95% CI: 0.90-1.68). In preventing duodenal ulcer recurrence no significant differences were detected between eradication therapy and maintenance therapy with UHD (4 trials, 319 patients; RR of ulcer recurring = 0.73; 95% CI: 0.42-1.25), but eradication therapy was superior to no treatment (27 trials, 2509 patients; RR = 0.20; 95% CI: 0.15-0.26). In preventing gastric ulcer recurrence, eradication therapy was superior to no treatment (12 trials, 1476 patients; RR = 0.31; 95% CI: 0.22-0.45).²

In patients with bleeding peptic ulcers, antulcer maintenance treatment was not necessary to prevent ulcer recurrence after successful H. pylori eradication and ulcer healing, as demonstrated by a small (n=82 patients), 5-year, prospective, randomised, controlled study.³

Eradication of the infection provides a long-term cure of duodenal ulcers in more than 80% of patients whose ulcers are not associated with the use of non-steroidal anti-inflammatory medicines (NSAIDs). Nevertheless, a systematic review of seven randomized controlled trials and one meta-analysis showed that NSAID-naïve users benefit from testing for H. pylori infection and subsequent H. pylori eradication therapy prior to the initiation of NSAID. In contrast, H. pylori eradication is less effective than proton pump inhibitor (PPI) treatment in preventing ulcer recurrence in long-term NSAID users. The meta-analysis of five randomised trials (939 patients) that had compared H. pylori eradication vs. non-eradication or eradication vs. a proton pump inhibitor in patients receiving a non-steroidal anti-inflammatory agent confirmed the previous results. Peptic ulcer was developed in 7.4% vs. 13.3% (OR=0.43; 95% CI: 0.20-0.93) of patients in the eradicated and control groups, respectively. Sub-analyses showed a significant reduction of risk for non-steroidal anti-inflammatory drug-naïve users (OR = 0.26; 95% confidence interval: 0.14-0.49) but not for previously treated patients (OR = 0.95; 95% CI: 0.53-1.72).⁴

A meta-analysis of two studies (n= 385 NSAID users) compared eradication vs. a proton pump inhibitor in the prevention of peptic ulcer; 2.6% developed a peptic ulcer in the eradicated group vs. 0% in the proton pump inhibitor group (OR = 7.43; 95% CI: 1.27-43.6).⁵ Also a Dutch randomised trial concluded that H. pylori eradication therapy in patients on long-term NSAID treatment had no beneficial effect on the occurrence of ulcers, erosions, or dyspepsia.⁶

Peptic ulcer is the main cause for upper gastrointestinal haemorrhage, and H. pylori infection is the main etiologic factor for peptic ulcer disease. A Cochrane systematic review of 10 trials (n= 1048 H. pylori-positive patients) compared the efficacy of H. pylori eradication therapy versus antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer. Treatment of H. pylori infection was more effective than antisecretory non-eradication therapy (without or with long-term maintenance antisecretory therapy) in preventing recurrent bleeding from peptic ulcer. Mean percentage of rebleeding in H. pylori eradication therapy group was 2.9% versus 20% in the non-eradication therapy group without subsequent long-term maintenance antisecretory therapy (OR= 0.17; 95% CI: 0.10-0.32; NNT was 7; 95% CI: 5 to 11). The mean percentage of rebleeding in H. pylori eradication therapy group was 1.6% versus 5.6% in non-eradication therapy group with
long-term maintenance antisecretory therapy (OR= 0.24; 95% CI: 0.09-0.67; NNT was 20; 95% CI: 12 to 100).7

*Helicobacter pylori* infection role in non-ulcer dyspepsia is less clear. Most randomised trials of therapy for *H. pylori* eradication in patients with non-ulcer dyspepsia have shown no significant benefit regarding symptoms; a few have shown a marginal benefit, but this can be explained by the presence of unrecognized ulceration. There is thus little evidence that chronic *H. pylori* infection in the absence of gastric or duodenal ulceration causes upper gastrointestinal symptoms.1

To determine the effect of *H. pylori* eradication on dyspepsia symptoms in patients with non-ulcer dyspepsia, a Cochrane systematic review included 18 randomised controlled trials. There was a 10% relative risk reduction of dyspepsia symptoms at 3-12 months in the *H. pylori* eradication group (95% CI: 6%-14%; NNT was 14; 95% CI: 10-25) compared to placebo. Furthermore three trials compared bismuth based *H. pylori* eradication with an alternative pharmacological agent. These trials were smaller and had a shorter follow-up but suggested that *H. pylori* eradication was more effective than either H2 receptor antagonists or sucralfate in treating non-ulcer dyspepsia.8

Extensive epidemiologic data suggest strong associations between *H. pylori* infection and non-cardia gastric cancers. The risk of cancer is highest among patients in whom the infection induces inflammation of both the antral and fundic mucosa and causes mucosal atrophy and intestinal metaplasia. Eradication of *H. pylori* infection reduces the progression of atrophic gastritis, but there is little evidence of reversal of atrophy or intestinal metaplasia, and it remains unclear whether eradication reduces the risk of gastric cancer.9 In Japan, the relationship between *H. pylori* and gastric cancer has been demonstrated more clearly. Japanese guidelines consider *Helicobacter pylori* eradication therapy as a Grade A recommendation for the treatment and prevention of *H. pylori*-associated diseases such as gastric cancer.10 However, a multicenter prospective cohort study (n= 4133 peptic ulcer patients), over a mean follow-up of 5.6 years, did not identified that *H. pylori* eradication therapy significantly decreases the incidence of gastric cancer.11 In Taiwan, a large nationwide cohort study investigated whether early *H. pylori* eradication is associated with gastric cancer risk in patients with peptic ulcer diseases. There was no significant difference in gastric cancer risk between patients who received early *H. pylori* eradication and the general population, but late eradication was associated with an increased risk. Additionally early *H. pylori* eradication was associated with decreased risk of gastric cancer in patients with peptic ulcer diseases.12 The global burden of gastric cancer is considerable but varies geographically. According The Maastricht III Consensus Report eradication of *H. pylori* infection has the potential to reduce the risk of gastric cancer development.13

Epidemiologic studies have also shown strong associations between *H. pylori* infection and the presence of gastric MALT lymphomas. Furthermore, eradication of the infection produces histological and endoscopic improvement, as well as regression of most localized MALT lymphomas.14

In patients who underwent tonsillectomy for chronic recurrent tonsillitis, there is a significantly higher positive *H. pylori* rate (48%) in comparison with those having tonsillectomy for sleep-related breathing disorders (24%) with no recent history of tonsillitis. Based on this finding, future studies should be performed to elucidate whether eradication therapy for *H. pylori* is effective in decreasing recurrent inflammation of human palatine tonsils.15

The role of *H. pylori* infection was also demonstrated in unexplained iron deficiency anaemia (IDA), or chronic idiopathic thrombocytopenic purpura, although the data in support of these recommendations are scant.13 A meta-analysis16 of 15 observational studies and five
randomised trials was performed about the first issue. Pooled observational studies suggest an association between H. pylori and IDA (pooled OR: 2.22; 95% CI: 1.52-3.24). In the five RCTs, the eradication of H. pylori can improve hemoglobin and serum ferritin levels but not significantly. Another meta-analysis of eight studies found that H. pylori eradication therapy combined with iron administration is more effective than iron administration alone for the treatment of IDA. Eradication therapy has different effects on adults and children. Bismuth based triple therapy has a better response in terms of increased hemoglobin and serum ferritin concentrations than proton pump inhibitor (PPI) based triple therapy.17

A Mexican study19 evaluated the effect of Helicobacter pylori eradication and iron supplementation on the iron nutritional status in 38 infected children with iron deficiency or with anaemia. They received eradication treatment and were randomly assigned to daily supplementation for 3 months with ferrous sulphate or placebo. Non-infected children received ferrous sulphate. Children in whom H. pylori eradication was achieved showed an increase of 0.37g/dL (95% CI: 0.02-0.75) on the haemoglobin mean concentration compared to the non-infected children. Children who achieved H. pylori eradication and received ferrous sulphate supplementation showed an increase of 0.47g/dL (95% CI: 0.01-0.93) on the haemoglobin mean concentration compared to the non-infected children who received iron supplementation.

Besides the cost of eradication therapy, there is concern about the potential adverse effects of this strategy, as increasing of the prevalence of reflux oesophagitis and gastroesophageal reflux disease (GERD).

A randomised, placebo-controlled, investigator-blinded trial evaluated the risk of reflux oesophagitis in 157 patients with functional dyspepsia after treatment for H. pylori infection. At 3 months and 12 months of follow-up, no difference was found in heartburn symptoms and in number of patients with reflux oesophagitis. A meta-analysis of 12 studies (7 RCTs and 5 cohorts) showed no significant association between H. pylori eradication and an increased risk of GERD in the population of dyspeptic patients.20

Facing the mentioned evidence, a one or two-week course of H. pylori eradication with antibiotics and antiulcer medicines can be used in the following gastrointestinal indications:

- for increasing the initial healing of duodenal peptic ulcers;
- for reducing the recurrence of both gastric and duodenal ulcers, either uncomplicated or bleeding ones, once healing has been achieved;
- for reducing recurrent bleeding due to gastric and duodenal ulcers, no needing antiulcer maintenance treatment;
- for preventing NSAID-related peptic ulcers in H. pylori infected people without previous ulcers who are naïve users of NSAIDs.

In contrast, H. pylori eradication shows only a marginal benefit in the treatment of non-ulcer dyspepsia. There are controversial results about its role for prevention of gastric cancer. Observational studies suggested that eradication of the infection causes regression of most localized gastric MALT lymphomas. At the moment there is insufficient evidence of its benefit in unexplained iron deficiency anaemia.
COMPARISON AMONG DIFFERENT AGENTS AND REGIMENS FOR _H. PYLORI_ ERADICATION THERAPY

FIRST-LINE THERAPY

INTERNATIONAL GUIDELINES

According to European\textsuperscript{13} and North American\textsuperscript{21} guidelines, there is a **first-line therapy** for treating _H. pylori_ infection. It consists of a **standard triple therapy** including a proton pump inhibitor (PPI) or ranitidine bismuth citrate, with any two antibiotics among amoxicillin, clarithromycin and metronidazole, given for 7-14 days to adults. The PPI-based triple therapy is also performed worldwide for _Helicobacter pylori_-associated diseases in childhood. A triple regimen with amoxicillin and metronidazole is acceptable where there is primary resistance to clarithromycin. In children with chronic _H. pylori_ gastritis, eradication should be considered if they have gastric atrophy or a family history of gastric cancer.\textsuperscript{22}

The duration of triple therapy vary in the American College of Gastroenterology guidelines (10-14 days)\textsuperscript{21} and in the Maastricht III Consensus Report guidelines (7 days).\textsuperscript{13}

SYSTEMATIC REVIEWS AND META-ANALYSES

**Effectiveness of different regimens**

The following table shows the common standard medicines for the **first-line therapy**.\textsuperscript{13, 21}

<table>
<thead>
<tr>
<th>Antiucler agents</th>
<th>Antibiotics</th>
<th>Condition</th>
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<tbody>
<tr>
<td>Triple therapy</td>
<td>Amoxicillin + clarithromycin or ranitidine bismuth citrate</td>
<td></td>
</tr>
<tr>
<td>proton pump inhibitor (PPI) or ranitidine bismuth citrate</td>
<td>Amoxicillin + metronidazole or Clarithromycin + metronidazole</td>
<td>Resistance to clarithromycin or Allergy to penicillins</td>
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<tr>
<td>Quadruple therapy</td>
<td>Bismuth salt + metronidazole + tetracycline</td>
<td></td>
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<tr>
<td>proton pump inhibitor (PPI) or H2 Receptor Antagonist</td>
<td>tetracycline</td>
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Even with the recommended triple regimens, _H. pylori_ eradication failure is still seen in more than 20\% of patients. The failure rate for first-line therapy may be higher in actual clinical practice, owing to the indiscriminate use of antibiotics. In part this is due to increasing clarithromycin resistance. In areas with a high prevalence of clarithromycin-resistant _H. pylori_ infection (>20\%) clarithromycin should be substituted by metronidazole. In patients allergic to penicillins, the standard first-line triple-therapy includes a PPI, clarithromycin and metronidazole.

A systematic review and meta-analysis of eight randomised trials (n=1,679) compared the efficacy and tolerability of clarithromycin triple and bismuth quadruple therapies as first-line treatment of _H. pylori_. Eradication was achieved in rates of 78.3\% *vs.* 77.0\% (RR=1.002; 95\% CI: 0.936-1.073) in patients allocated to quadruple and triple therapy, respectively. There was no statistically significant difference in side effects yielded by bismuth quadruple *vs.* clarithromycin triple therapy (RR=1.04; 95\% CI: 1.04-1.14). Patient compliance is similar for quadruple and triple therapies.\textsuperscript{23}
As an alternative initial treatment a **sequential regimen** was proposed – a proton-pump inhibitor plus amoxicillin for 5 days followed by a PPI plus clarithromycin and an imidazole agent for more 5 days. The rationale for this more complicated approach is that amoxicillin may weaken bacterial cell walls in the initial phase of treatment, preventing the development of drug efflux channels that inhibit such drugs as clarithromycin from binding to ribosomes. This may help to improve the efficacy of clarithromycin in the second phase of treatment. This regimen was reported to achieve an eradication rate of 93% versus a rate of 77% with standard triple therapy, in a meta-analysis of 10 randomised trials involving 2747 patients in Italy. However, only one study was double-blinded. Most patients were from Italy. There was clear evidence of publication bias. A systematic review and meta-analysis of ten randomised controlled trials in adults (n=3,006) compared sequential therapy (ST) with triple therapy (TT). The odds ratio (OR) for eradication of *H. pylori* with ST compared with TT favoured ST (OR= 2.99; 95% CI: 2.47-3.62; NNT of 6; 95% CI: 5-7). Three RCTs enrolled 260 children and adolescents, and the OR for eradication was 1.98 (95% CI: 0.96-4.07). There was no difference in the rate of side effects between the ST and the TT.  

**Duration of the therapy**

A meta-analysis included 11 studies that compared 7-day therapy with 10-day therapy, and 13 that compared 7-day therapy with 14-day therapy. The first comparison yielded relative risks for eradication of 1.05 (95% CI: 1.0 -1.10), and the second one yielded 1.07 (95% CI: 1.02-1.12). Meta-analysis of the 3 studies that compared 7-day with 14-day metronidazole-containing therapy yielded an RR of 1.08 (95% CI: 0.96-1.22). Available data suggest that extending triple therapy beyond 7 days is unlikely to be a clinically useful strategy.  

**Pharmacoeconomic Comparisons**

Current pharmacoeconomic comparisons among different regimens for *H. pylori* eradication are scarce. In an old study, using a meta-analysis of 119 trials (n= 6416 patients), 3 triple regimens (bismuth subsalicylate + metronidazole + tetracycline for 14 days; PPI + clarithromycin + metronidazole for 7 days; and PPI + clarithromycin + amoxicillin for 7 days) proved to achieve lower costs ($ 223 to $ 410) and recurrence rates (70% to 86%) in comparison with histamine2-receptor antagonist maintenance therapy (cost $425 and prevented recurrence in 72% of patients). Among the 3 regimens, the standard triple therapy for seven days presented discrete higher cost but lower recurrence rate in comparison with bismuth-based regimen for 14 days.  

**RANDOMISED CLINICAL TRIALS**

**Effectiveness of different regimens**

In a randomised trial, 232 *H. pylori*-infected patients received a 10 days sequential (n = 115) or concomitant (n = 117) quadruple therapy. Sequential or concomitant therapy with a PPI, amoxicillin, clarithromycin, and an imidazole agent are equally effective and safe for eradication of *H. pylori* infection. Resistance to clarithromycin, compliance, and adverse events reduced the level of eradication. Concomitant therapy may be more suitable for patients with dual resistance to antibiotics. However in a trial in Spain the eradication rate among patients randomly assigned to receive sequential therapy was only 84%, indicating a need to confirm its efficacy before it is used widely. Further robust assessments across a
much broader range of patients are required before sequential therapy could supplant existing treatment regimens and be generally recommended in clinical practice.\textsuperscript{30}

Another randomised trial evaluated four 10-day therapeutic schemes (115 patients per group): standard (omeprazole, clarithromycin and amoxicillin – OCA); triple (omeprazole, levofloxacin and amoxicillin – OLA); sequential (omeprazole plus amoxicillin for 5 days, followed by omeprazole plus clarithromycin plus metronidazole for 5 days – OACM); and modified sequential (using levofloxacin instead of clarithromycin – OALM). Eradication rates were lower with OCA than with all the other regimens \((P < 0.05)\) in a setting with high clarithromycin resistance. However, all of these therapies still have a 20\% failure rate.\textsuperscript{31}

\textbf{Pharmacoeconomic Comparisons}

A pharmacoeconomic comparison of seven different \textit{H. pylori} eradication regimens in 75 \textit{H. pylori} – positive patients with peptic ulcer disease or chronic gastritis, using real-world cost and effectiveness data ("successful eradication"), found that a triple regimen (omeprazole 40 mg b.i.d. + clarithromycin 500 mg b.i.d. + amoxicillin 1 g b.i.d.) and a quadruple one (ranitidine 300 mg + metronidazole 250 mg t.i.d. + amoxicillin 500 mg q.i.d. + bismuth 300 mg q.i.d.) were more cost-effective than the other treatment regimens. The eradication rates and cost-effectiveness ratios calculated for these protocols were 90\% (158.7 euros) for quadruple regimen and 90\% (195.8 euros) for triple regimen. Only direct costs were included in the analysis.\textsuperscript{32}

\textbf{Recommendation}

Based on these results, a triple first-line therapy for 7-14 days seems the preferable option for treating \textit{H. pylori} infection in patient naïve of treatment.

\textbf{SECOND LINE THERAPY}

Treatment failure is often related to \textit{H. pylori} resistance to clarithromycin or metronidazole (or both agents). Then, the choice of second-line treatment depends on which treatment is used initially.

The recommended standard second-line therapy is a quadruple regimen composed of tetracycline, metronidazole, a bismuth salt and a PPI.\textsuperscript{33} Quadruple regimens seem more effective as second-line treatment than triple regimens when a first-line triple regimen has failed to eradicate the infection. However, the evidence is limited in the comparison of second-line quadruple versus triple regimens, because most triple regimens did not contain a nitroimidazole.\textsuperscript{33}

Besides, bismuth salts are not available in some countries, including the United States, and tetracycline and metronidazole induce more frequently adverse effects and interactions in comparison with other antibiotics. In the case of failure of second-line therapy, the patients should be evaluated using a case-by-case approach.

\textbf{SYSTEMATIC REVIEWS AND META-ANALYSES}

\textit{Effectiveness of different regimens}

Meta-analysis of five RCTs (576 subjects) included in a systematic search of nine studies (10 treatment arms) that compared concomitant therapy of four medicines (a PPI,
clarithromycin, metronidazole, and amoxicillin) versus triple therapy (PPI, amoxicillin, clarithromycin or metronidazole) showed superiority of quadruple therapy over triple therapy (pooled OR = 2.86; 95% CI: 1.73-4.73). When examining the risk differences between triple and concomitant therapy the results were also in favour of the concomitant one with a pooled risk difference of 11.8% (95% CI: 3.8%–19.8%) for the intention-to-treat analysis. Considering the results presented in this meta-analysis, concomitant therapy appears to be an effective, safe and well tolerated treatment option for *H. pylori* infections, mainly for patients with dual resistance to antibiotics.  

**RANDOMISED CLINICAL TRIALS**

**Effectiveness of different regimens**

Triple therapies (PPI plus metronidazole and either amoxicillin or tetracycline) have also been tested as second-line therapies. Clarithromycin should be avoided as part of second-line therapy unless resistance testing confirms that the *H. pylori* strain is susceptible to the antibiotic. Eradication rates of approximately 75% can be achieved with second-line triple therapy based on antibiotic susceptibility testing. If susceptibility testing is not available, PPI plus amoxicillin and metronidazole for 14 days is an appropriate alternative.

Alternatively, recent data suggest that levofloxacin-based rescue therapy constitutes an encouraging triple second-line strategy. A PPI, levofloxacin, and amoxicillin for 10 days are more effective and better tolerated than bismuth quadruple therapy for persistent *H. pylori* infection.

A randomised trial compared a levofloxacin-based regimen (levofloxacin 750 mg, once a day + amoxicillin 1000 mg, twice a day + lansoprazole 30 mg, twice a day) versus a clarithromycin-based regimen (clarithromycin 500 mg, twice a day + amoxicillin 1000 mg, twice a day + lansoprazole 30 mg, twice a day), both for 10 days, as the second-line treatment for *Helicobacter pylori* infection, after 7 days of the same regimens, as a first-line therapy. When used as first-line treatment (n=432), the eradication rates of LAL (n=217) and CAL (n=215) were 74.2 and 83.7% (P=0.015) in the intent-to-treat (ITT) analysis, and 80.1 and 87.4% (P=0.046) in the per-protocol (PP) analysis, respectively. When used as second-line treatment, the eradication rates of LAL (n=26) and CAL (n=40) were 76.9 and 60% (P=0.154) in the ITT analysis, and 80 and 61.5% (P=0.120) in the PP analysis, respectively.

**Clinical trials in children concerning *H. pylori* eradication treatments are scarce.** A Iranian study randomised 100 children (mean age 12.36 ± 3.06 years) to receive triple therapy (PPI, amoxicillin and clarithromycin) or quadruple therapy. The eradication rates "per-protocol" and "intention-to-treat" approaches were 92% and 75.5% in the triple therapy group versus 84% and 68.8% in the quadruple regimen group, respectively.

**Duration of the therapy**

There is no consensus about duration of second-line therapy in children. A study randomised 275 consecutive *H. pylori*-infected children to receive triple therapy with 14 days of amoxicillin and clarithromycin and 21 days of proton pump inhibitor (group 1) and triple therapy including 7 days of amoxicillin and clarithromycin and 21 days of proton pump inhibitor (group 2). Subsequently, 89 patients not responding to the triple therapies received quadruple therapy comprising omeprazole (14 days), bismuth subcitrate (7 days), doxycycline (7 days), and metronidazole (7 days). There was no difference between both groups in triple therapy (P = 0.44). *Helicobacter pylori* was eradicated in 66.7% of patients at the end of the quadruple therapy. So, the different duration of the two treatment regimens
had no impact on eradication rates. Furthermore, quadruple therapy was necessary to achieve \( H. \text{pylori} \) eradication after triple therapy. 39

**THIRD AND FOURTH LINE THERAPIES**

Patients in whom \( H. \text{pylori} \) infection persists after a second course of treatment and for whom eradication is considered appropriate should be referred to a specialist with access to facilities for culturing \( H. \text{pylori} \) and performing sensitivity testing and experience with alternative treatments for the infection. Even after two consecutive failures, several studies have demonstrated that \( H. \text{pylori} \) eradication can finally be achieved in almost all patients if several rescue therapies are consecutively given. European guidelines recommend a **third-line treatment** based on the microbial antibiotic sensitivity.13 \( H. \text{pylori} \) isolates after two eradication failures are often resistant to both metronidazole and clarithromycin. Several regimens have been reported to be effective as salvage therapy in case series. The alternative candidates for third-line therapy are quinolones (levofloxacin, moxifloxacin), tetracycline, rifabutin and furazolidone. High-dose PPI plus amoxicillin and levofloxacin or rifabutin therapy has been associated with high rates of eradication. 40 However, caution is warranted in the use of rifabutin, which may lead to resistance of mycobacteria in patients with preexisting mycobacterial infection.1 Besides, rifabutin has been associated with rare but potentially serious myelotoxicity and ocular toxicity.21

Due to these disadvantages, rifabutin-based rescue therapy constitutes an empirical **fourth-line strategy** only after multiple previous eradication failures with key antibiotics such as amoxicillin, clarithromycin, metronidazole, tetracycline, and levofloxacin.36

The following tables show the different options of therapy and the most common regimens used.

**Options of \( H. \text{pylori} \) eradication therapy (eradication rates)** 13, 21, 24, 33, 37, 40, 41

| **Standard First-line therapy** |  
| Triple therapy \((70-86\%): \) PPI, amoxicillin, clarithromycin \((77\%) \) or |  
| PPI, amoxicillin, metronidazole \((\text{In infection resistant to clarithromycin}) \) or |  
| PPI, clarithromycin, metronidazole \((97\%) \) \((\text{In patients allergic to penicillin}) \) |  

| **Alternative First-line therapy** |  
| Sequential therapy: Days 1–5: PPI and amoxicillin |  
| Days 6–10: PPI, clarithromycin, metronidazole \((93\%) \) |  
| **Triple therapy:** PPI, levofloxacin, amoxicillin \((74.2\%) \) \((\text{In dual resistance to clarithromycin and metronidazole}) \) |  
| Quadruple therapy: PPI, bismuth, metronidazole, tetracycline \((78.3\%) \) \((\text{In areas where the resistance to clarithromycin or metronidazole is }\geq 20\% \text{ or in patients with recent or repeated exposure to clarithromycin or metronidazole}) \) |  

| **Standard Second-line therapy** |  
| Quadruple therapy: PPI, doxycycline, metronidazole, bismuth salt \((76\%) \) or |  
| PPI, doxycycline, metronidazole, amoxicillin \((\text{When bismuth salt is not available}) \) |  

| **Alternative Second-line therapy** |  
| Triple therapy: PPI, metronidazole, amoxicillin \((75\%) \) or |  
| PPI, metronidazole, doxycycline \((75\%) \) \((\text{In patients with penicillin allergy}) \) or |  
| PPI, levofloxacin, amoxicillin \((76.9\%) \) or |  
| PPI, furazolidone, amoxicillin \((76.1\%) \) |  

**Third-line treatment**
High-dose PPI, amoxicillin, tetracycline, levofloxacin, furazolidone-containing regimen (65.5%) or rifabutin

Regimens Used to Treat *Helicobacter pylori* Infection

**Standard initial treatment (use one of the following three options)**

*Triple therapy* (7–14 days)

PPI - healing dose, twice/day + Amoxicillin - 1 g, twice/day + Clarithromycin - 250-500 mg, twice/day

*Sequential therapy* (10 days)

Days 1-5: PPI - healing dose, twice/day + Amoxicillin - 1 g, twice/day

Days 6–10: PPI - healing dose, twice/day + Clarithromycin - 500 mg, twice/day + Tinidazole - 500 mg, twice/day

*Quadruple therapy* (10–14 days)

PPI - healing dose, twice/day + Bismuth salt - 120 mg, four times/day + Tetracycline - 500 mg, four times/day + Metronidazole - 500 mg, four times/day

**Second-line therapy (use one or the other)**

*Triple therapy* (7–14 days)

PPI - healing dose, once/day + Amoxicillin - 1 g, twice/day + Metronidazole – 400-500 mg, twice/day

*Quadruple therapy*, as recommended for initial therapy

a Omeprazole: 20 mg; esomeprazole: 20 mg; rabeprazole: 20 mg; pantoprazole: 40 mg; lansoprazole: 30 mg; tenatoprazole: 40 mg.

b If the patient has penicillin allergy, use metronidazole (400-500 mg, twice/day) and use clarithromycin at reduced dose of 250 mg twice per day.

**SELECTION OF DIFFERENT PHARMACOLOGIC CLASSES FOR H. PYLORI ERADICATION THERAPY**

**The role of Proton-Pump Inhibitors (PPI)**

Concerning these agents the following questions may be considered. Are they the best antisecretory agents to be added to antibiotics for *H. pylori* eradication? Which representative should be prescribed? What schedule is more efficacious? Is it necessary a long-term therapy after the eradication therapy course?

*Eight systematic reviews and meta-analyses, nine RCTs (approximately 3069 patients) and two economic evaluations were found which compare PPIs with other antisecretory agents, different PPIs, different schedules (relating to dosage and duration of use) and cost in H. pylori eradication therapy.*

**Comparison to other antisecretory agents**

Proton-Pump Inhibitors (PPI) are more commonly used in combination with antibiotics for *Helicobacter pylori* eradication. A meta-analysis of randomised clinical trials compared the efficacy of PPI vs. ranitidine bismuth citrate (RBC) and two antibiotics for 1 week. Mean *H. pylori* eradication with 7-day RBC-clarithromycin-amoxicillin, RBC-clarithromycin-metronidazole, and RBC-amoxicillin-metronidazole was 83%, 86%, and 71%, respectively. The meta-analysis showed comparable efficacy with RBC and PPI when they were combined with clarithromycin and amoxicillin (OR = 1.11; 95% CI: 0.88-1.40), or with amoxicillin and metronidazole (OR = 0.92; 95%CI: 0.60-1.41). However, when comparing PPI vs. RBC plus clarithromycin and an imidazole agent, higher cure rates with RBC than with PPI were demonstrated (OR = 1.65; 95% CI: 1.15-2.37). 42
Lanzoprazol-based regimen was compared with lafutidine-based regimen for *Helicobacter pylori* eradication. Both agents were combined with clarithromycin and amoxicillin, being used during 7 or 14 days. No significant difference was shown in eradication rates with both regimens, either in 7 days groups \(P = 0.94\) and \(0.95\), respectively, or in 14 days groups \(P = 0.70\) and \(0.49\), respectively. The treatment duration for 7 days or 14 days did not affect the eradication rates. In addition, the adverse effect rates and discontinuation rates were similar among the four groups. 43

**PPI representative to be chosen according efficacy**

Currently, omeprazole is the most widely used PPI for *Helicobacter pylori* eradication therapy. Few studies have compared double-dose new-generation PPI with omeprazole.

**SYSTEMATIC REVIEWS AND META-ANALYSES**

A systematic review and a meta-analysis of 4 studies compared the efficacy of esomeprazole versus omeprazole plus antibiotics, showing mean *H. pylori* eradication rates of 85% and 82% \((OR = 1.19; 95\%CI = 0.81-1.74)\), respectively. 44

A meta-analysis of 11 RCTs (2,159 subjects) found a mean *H. pylori* eradication rates of 86% (for esomeprazole) and 81% (for other PPI therapies) \((OR = 1.38; 95\% CI = 1.09-1.75)\). A focused meta-analysis of 6 selected high-quality studies produced an OR of this comparison that was closer to one \((1.17, 95\% CI = 0.89-1.54)\), with the results being statistically homogeneous. Sub-analysis that included only studies comparing different does of esomeprazole with omeprazole or pantoprazole did not reveal significant differences. No additional serious adverse events were reported. 45

Another meta-analysis (12 studies) evaluated the mean eradication rate of based triple regimens with pantoprazole (534 patients) versus other PPIs (603 patients). The mean eradication rate for *H. pylori* using pantoprazole plus antibiotics was 83%, and 81% when other PPIs were used \((OR = 1; 95\% confidence interval (CI) from 0.61 to 1.64)\). When sub-analysis was performed, including only studies comparing pantoprazole with omeprazole, or pantoprazole with lansoprazole, differences were also statistically non-significant. The meta-analysis of the six studies prescribing equivalent doses of all PPIs demonstrated similar results with pantoprazole and with other PPIs \((OR = 1.07; 95\% CI from 0.71 to 1.62)\), the results being statistically homogeneous. 46

**RANDOMISED CLINICAL TRIALS**

A randomised, prospective study allocated 576 consecutive patients with proven *H. pylori* infection to receive omeprazole (20 mg b.i.d.), or pantoprazole (40 mg b.i.d.), or rabeprazole (20 mg b.i.d.), or esomeprazole (40 mg b.i.d.), added to clarithromycin (500 mg b.i.d.) and amoxicillin (1 g b.i.d.) for one week. No difference was found between the eradication rates of these four PPIs. However, side-effects were more common in the esomeprazole-based triple therapy group than in the other groups \((P < 0.05)\). 47

Another study compared the efficacy and safety of 20 mg b.i.d. rabeprazole- and 40 mg daily esomeprazole-based triple therapy (with amoxicillin and clarithromycin) in primary treatment of *H. pylori* infection in 420 *H. pylori*-infected patients. Intention-to-treat analysis revealed that the eradication rate was 89.4% in the esomeprazole group and 90.5% in rabeprazole group \((P = 0.72)\). No differences were observed between groups in terms of compliance and adverse events. In conclusion, rabeprazole- and esomeprazole-based primary therapies for *H. pylori* infection are comparable in efficacy and safety. 48
The CYP2C19 polymorphism plays an important role in the metabolism of various proton-pump inhibitors. Several trials have produced conflicting data on eradication rates of *Helicobacter pylori* among CYP2C19 genotypes. However, a randomised trial (463 patients infected with *H. pylori*) concluded that efficacy of triple therapies that include lansoprazole or rabeprazole are not affected by CYP2C19 genetic polymorphisms. On the contrary, a meta-analysis found that the efficacy of omeprazole- and lansoprazole-based first-line triple therapies at the standard doses is dependent on CYP2C19 genotype status.

**Conclusion**

Facing the evidence, different PPIs have similar efficacy in the context of *H. pylori* eradication.

**PPI to be chosen according safety**

PPI safety is not a problem in a short-course eradication therapy at standard dosage. So, the attention should move towards the appropriate prescription of PPI, rather than the fear of PPI adverse effects. The debate has been focussed on the risk of adverse events related to long-term use of PPI. Potential risks associated with long-term PPI therapy include variations in bioavailability of common medications, vitamin B12 deficiency, *Clostridium difficile*-associated diarrhoea, community-acquired pneumonia, hip fracture, and development of corpus predominant atrophic gastritis, precursor of cancer. The long-term use of PPIs was not associated with hip fractures but was modestly associated with clinical spine, forearm or wrist, and total fractures in postmenopausal women.

Another concern is about interaction between long-term used PPIs and concomitantly administered medicines. Because PPIs give rise to profound and long-lasting elevation of intragastric pH, it is not surprising that they interfere with the absorption of concurrent medications. Drug solubility may be substantially reduced at neutral pH compared with acidic conditions. In this context, PPIs have been shown to reduce the bioavailability of many clinically relevant medicines (e.g. ketoconazole, atazanavir) by 50% or more compared with the control values. Soon after the introduction of omeprazole (a prototype PPI) into the market, it was reported that omeprazole was associated with 30% and 10% reductions in systemic clearance of diazepam and phenytoin, respectively. Numerous subsequent studies have been performed to investigate the interaction potential of PPIs associated with the metabolic inhibition of cytochrome P450 (CYP) enzyme activities; however, most such attempts have failed to find clinically relevant results. Nevertheless, recent large-scale clinical trials have raised concerns about possible interaction between omeprazole and clopidogrel plus aspirin that may attenuate the anti-aggregation effects of those medications and augment the risk of cardiovascular ischaemic events (CV). A randomised trial of omeprazole vs. placebo in clopidogrel users showed no difference in CV events (hazard ratio=1.02; 95%CI: 0.70-1.51). Thus, current evidence does not justify a conclusion that PPIs are associated with CV events among clopidogrel users, let alone a judgment of causality. As the presence of PPIs and clopidogrel in plasma is short lived, separation by 12-20 h should in theory prevent competitive inhibition of CYP metabolism and minimize any potential, though unproven, clinical interaction. PPI may be given before breakfast and clopidogrel at bedtime, or PPI may be taken before dinner and clopidogrel at lunchtime.

Nevertheless, this is not the common use of PPIs in *H. pylori* eradication. In a randomised trial (n=103 patients) omeprazole combined with amoxicillin/clarithromycin (OAC) or amoxicillin/metronidazole (OAM) induced mild side effects in 6 and 5 patients in OAC and OAM groups, respectively. The side effects were: skin rash, diarrhea, headache,
nausea, anorexia, and metallic taste. The symptoms of adverse events were mild and did not necessitate any additional treatment in both groups.\textsuperscript{55}

**Recommended dosage in the H. pylori eradication schedules**

The common oral doses of PPIs for adults\textsuperscript{1} correspond to those that are able to suppress gastric acid secretion.\textsuperscript{56} The common doses, all twice per day, are: 20 mg omeprazole, 20 mg esomeprazole, 20 mg rabeprazole, 40 mg pantoprazole, 40 mg tenatoprazole, and 30 mg lansoprazole. In some studies, esomeprazole has been given at a dose of 40 mg once per day. Low doses of rabeprazole (10 mg b.i.d.), when administered with two antibiotics, may be sufficient to eradicate *H. pylori* infection. \textsuperscript{57}

A systematic review investigated the use of PPIs in the paediatric population. All paediatric studies reviewed were limited to either omeprazole or lansoprazole. The dosage range for omeprazole used for *H. pylori* was 0.5-1.5 mg/kg/day, with a maximum dosage of 40 mg/day, and lansoprazole-containing regimens for *H. pylori* eradication used dosages ranging from 0.6-1.2 mg/kg/day, with a maximum dosage of 30 mg/day. \textsuperscript{58}

The next table shows the common PPI dosage employed in *H. pylori* eradication regimens and the omeprazole preparations currently included in the WHO Model Lists.

<table>
<thead>
<tr>
<th>PPI</th>
<th>Dosage Adult</th>
<th>Dosage Child≥ 2 years</th>
<th>16\textsuperscript{th} EML (updated 2010) and 2\textsuperscript{nd} EML 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>20 mg, twice/day</td>
<td>&lt; 20 kg: 10 mg once/day&lt;br/&gt;&gt; 20 kg: 20 mg once/day&lt;br/&gt;Maximum: 40 mg</td>
<td>Powder for oral liquid: 20 mg; 40 mg sachets.&lt;br/&gt;Solid oral form: 10 mg; 20 mg; 40 mg.</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>20 mg, twice/day or&lt;br/&gt;40 mg, once/day</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>10-20 mg, twice/day</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40 mg, twice/day</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30 mg, twice/day</td>
<td>&lt; 30 kg: 15 mg once/day&lt;br/&gt;&gt; 30 kg: 30 mg once/day</td>
<td>---</td>
</tr>
</tbody>
</table>

High-dose PPI has been used in standard triple therapy. A systematic search of six randomised trials comparing a standard dose of a PPI with high-dose PPI both twice a day in triple therapy (PPI, clarithromycin and either amoxicillin or metronidazole) for 7 days showed a mean intention-to-treat cure rate of 82% vs. 74% (RR: 1.09; 95% CI: 1.01-1.17) with high-dose PPI and standard dose, respectively. Subgroup analysis showed that the maximum increase was observed when the PPI compared were omeprazole 20 mg or pantoprazole 40 mg vs. esomeprazole 40 mg. \textsuperscript{59}

**Duration of treatment**

*Two RCTs (n= 1507) evaluated the duration of H. pylori eradication therapies. Both found similar eradication rates in 7- or 14-day regimens.*

A randomised study (598 patients) compared the efficacies of 7-day and 14-day omeprazole 20 mg-containing triple therapy. The eradication rates of the 7-day group were not inferior to those of the 14-day group in both intention-to-treat analysis (71.2% vs. 75.5%) and per-protocol analysis (83.6% vs. 86.6%). Incidences of adverse events were comparable. \textsuperscript{60}

The Hiper Study including 909 *H. pylori*-positive patients with duodenal ulcer compared the efficacy and safety of 1- and 2-week regimens of omeprazole, amoxicillin and
clarithromycin. The intention-to-treat (n = 907) and per protocol (n = 661) analyses showed no significant differences between the eradication rates of both regimens. Also there were no differences related to compliance and adverse effects.61

**Comparative cost**

PPIs are among the highest expenditure drugs covered by health care plans. During fiscal year 2001-2002, Medicaid programs nationwide spent nearly $2 billion on PPIs. Although the costs of individual PPIs vary widely, there is little variation in therapeutic effectiveness. 62 The generic omeprazole preparations would be expected to produce cost savings.

Economic evaluations are more frequent towards long-term therapies. *H. pylori* eradication can reduce long-term PPI-use in *H. pylori* positive-patients. A within-trial cost-effectiveness analysis was conducted from a British health service perspective. Significant reductions in resource use occurred comparing eradication with placebo. After 2 years, PPI prescriptions (full-dose equivalents) fell by 3.9 (P < 0.0001); clinician (GP) consultations by 2.4 (P = 0.0001); upper gastrointestinal (GI) endoscopies by 14.8% (P = 0.008); clinician GI-related home visits by 19.9% (P = 0.005) and abdominal ultrasound scans fell by 20.3% (P = 0.005). Average net savings/patient were pound 93 (95% CI: 33-153) after costs of detection and eradication had been deducted. In conclusion, *Helicobacter pylori* eradication in infected, long-term PPI users is an economically dominant strategy, significantly reducing overall healthcare costs and symptom severity.63

**Recommendation**

In conclusion, any PPI could be used in first-line triple *H. pylori* therapy, for 7 days, in standard doses, once or twice daily. For children only omeprazole and lansoprazole have been studied. High-dose induces a discrete increment on efficacy. For consolidated experience and lower cost, the preferable agent is omeprazole, already included in the WHO Model Lists.

**The Role of Antibiotics**

The choice of antibiotics for *H. pylori* eradication must consider three problems: penicillin allergy, treatment failure and microbial resistance to triple first line and quadruple second-line therapies. So, alternative rescue therapies have been proposed including new classes of antibiotics.

The prevalence of antimicrobial resistance is now such that all patients should be considered as having resistant infections. Clarithromycin-containing triple therapies now typically produce ≤ 80% cure and are no longer acceptable empiric therapy. Clarithromycin resistance of *H. pylori* is high, and triple regimen treatment containing clarithromycin should be decided based on susceptibility to the agent. Antimicrobial choices following treatment failure are best approached by susceptibility testing.64

In Japanese children, there was an increased fourfold of resistance from 1999 to 2007, with all clarithromycin-resistant strains showing low-level resistance. There was no difference in the eradication rate between 7 day and 10 or 14 day courses of therapy. The regimen with a PPI plus amoxicillin and metronidazole produced successful eradication in all patients with clarithromycin-resistant strains.65

A susceptibility-guided strategy, if available, is recommended in order to choose the best third-line treatment. Culture can reveal the presence of *H. pylori*-sensitive strains to
clarithromycin (the best effective) or other antimicrobials (such as amoxicillin, metronidazole and tetracycline). Conversely, in an empirical strategy, a not yet used therapy, can reach a high success rate. PPI, amoxicillin and a new antimicrobial (e.g. levofloxacin or furazolidone) could be used.⁶⁶

**Penicillins**

Amoxicillin, as part of a standard regimen for first-line therapy, has time-dependent bactericidal activity against *H. pylori*. A randomised trial (186 patients with *H. pylori* infection) compared amoxicillin 1000 mg + clarithromycin 500 mg + omeprazole 20 mg twice daily for 2 weeks *versus* amoxicillin 500 mg four times daily with clarithromycin 500 mg and omeprazole 20 mg twice daily for 2 weeks. There was no difference between both regimens relating to eradication rates, compliance and side effects. Therefore, considering patient’s comfort, a twice daily amoxicillin regimen was recommended.⁶⁷

In patients allergic to penicillin, *Helicobacter pylori* first-line treatment (omeprazole 20 mg b.i.d., clarithromycin 500 mg b.i.d. and metronidazole 500 mg b.i.d., for 7 days) and second-line rescue option (omeprazole 20 mg b.i.d., clarithromycin 500 mg b.i.d. and levofloxacin 500 mg b.i.d., for 10 days) could be used. In *H. pylori* infected patients allergic to penicillin, the generally recommended first-line treatment has lower efficacy for curing the infection. On the other hand, a levofloxacin-containing regimen represents a second-line alternative in the presence of penicillin allergy.⁶⁸

**Macrolides**

No information was found referring erythromycin use in *H. pylori* eradication therapy. Two antibiotics of this class have been studied for *H. pylori* eradication: clarithromycin and azithromycin.

**CLARITHROMYCIN**

**FIRST-LINE THERAPY**

*Two randomised clinical trials and five comparative studies evaluated the current role of clarithromycin in *H. pylori* eradication, regarding to microbial resistance, comparative effectiveness, preparation, dosage and economic evaluation.*

The notorious difficulty with clarithromycin is worldwide increasing *microbial resistance*. In areas with a high prevalence of clarithromycin-resistant *H. pylori* infection (>20%), this antibiotic cannot be included in an empirical strategy, and should be substituted by metronidazole or levofloxacin. A triple regimen treatment containing clarithromycin should be decided based on susceptibility to the agent. *When culture reveals the presence of *H. pylori*-sensitive strains, clarithromycin is the best effective macrolide*. Clarithromycin should be avoided as part of second-line therapy unless resistance testing confirms that the *H. pylori* strain is susceptible to the antibiotic. Even when resistant strains were detected in *H. pylori* infected children, clarithromycin-based 7-day triple therapy or sequential regimen achieved *H. pylori* eradication in 16 of 32 (50%) children with the A2143G mutation, in 8 of 10 patients with either A2142G or A2142C strains (80%) versus 112 of 116 children with susceptible strains (88.9%). A sequential regimen achieved higher cure rate than standard therapy in children with A2143G mutant strains (80% vs. nil; *P* < 0.001).⁶⁹

Local data regarding the primary resistance of *H. pylori* is necessary to decide the use of a clarithromycin-containing regimen. For instance, in Tunisia a study aimed to evaluate primary resistance of *H. pylori* to clarithromycin, metronidazole and amoxicillin through the
analysis of 273 strains isolated from adults and children. No resistance to amoxicillin was detected. For adults, resistance to clarithromycin and metronidazole was found respectively in 14.6% and 56.8%, and respectively in 18.8% and 25% in children. Overall, the rates of global primary resistance to clarithromycin and metronidazole in Tunisia were respectively determined in 15.4% and 51.3%.  

Concerning the preparation, a randomised trial (n=161 patients) compared the efficacy of modified-release clarithromycin (1000 mg once daily) or immediate-release clarithromycin (500 mg twice daily) in combination with amoxicillin 1000 mg twice daily and esomeprazole 40 mg once daily (one-week triple therapy) on the rates of ulcer healing and eradication of *H. pylori* in patients treated for *H. pylori*-associated peptic ulcer disease. In both the intent-to-treat and per-protocol analyses, the eradication rates and the ulcer healing rates were comparable in both formulation groups. So, modified-release clarithromycin 1000 mg once daily can be used as an alternative to immediate-release clarithromycin 500 mg twice daily for the treatment of *Helicobacter pylori*-associated peptic ulcer disease.  

Concerning dosage, the efficacy and safety of two doses of clarithromycin (400 mg/day and 800 mg/day) were investigated on a triple therapy regimen, including omeprazole in combination with amoxicillin. When patients with non-susceptibility to clarithromycin were excluded, eradication rates were > 80% for both gastric and duodenal ulcers in the two groups. Both regimens were well tolerated. For children, with the same schedule [omeprazole (1 mg/kg/day) + amoxicillin (50 mg/kg/day) + clarithromycin (15 mg/kg/day)] the eradication rate was 74%.  

A randomised study compared the efficacy of clarithromycin or metronidazole when they were combined with omeprazole and amoxicillin on eradication of *H. pylori* and ulcer healing in 100 subjects with *H. pylori*-positive peptic ulcer. All medicines were given twice daily for 7 days. There was no significant difference in eradication rates between the two groups on either analysis. The therapeutic regimen comprising metronidazole with low cost, good compliance and mild adverse events may offer a good choice for the *H. pylori* eradication therapy as an alternative to clarithromycin.  

Levofloxacin-containing triple therapy was proposed as another alternative for empirical first-line treatment for *H. pylori* infection. The efficacy and tolerability of the standard 7-day clarithromycin-containing triple therapy (esomeprazole 20 mg b.i.d., amoxicillin 1 g b.i.d., and clarithromycin 500 mg b.i.d.) was compared with the 7-day levofloxacin-containing triple therapy (esomeprazole 20 mg b.i.d., amoxicillin 1 g b.i.d., and levofloxacin 500 mg daily) in 300 consecutive *H. pylori*-positive patients. *H. pylori* eradication was similarly achieved in both groups, for both intention-to-treat and per-protocol analysis. More patients in the clarithromycin- than the levofloxacin-containing therapy group developed side effects from the medication (21.3% vs. 13.3%), respectively. The authors concluded that in places where the prevalence of primary resistance of *H. pylori* to amoxicillin and clarithromycin remains low, the standard 7-day clarithromycin-containing triple therapy is still valid as the most effective empirical first-line eradication therapy for *H. pylori* infection.  

Concerning economic evaluation of clarithromycin-based regimen, a pharmacoeconomic comparison of seven *H. pylori* eradication regimens showed that OCA regimen (omeprazole 40 mg bid + clarithromycin 500 mg bid + amoxicillin 1 g bid) was more cost-effective than the other four triple first-line treatments. 

In conclusion, for the first-line therapy, a standard triple clarithromycin-containing regimen is the best effective option in scenarios where resistance is lower than 20%. As part
of second-line therapy, clarithromycin has only place when resistance testing confirms that the *H. pylori* strain is susceptible to the antibiotic.

**Recommendation**

| Clarithromycin (500 mg coated-tablets and 125 mg/5 ml suspension) should be added to the WHO Model List to be used in standard triple first-line therapy for *H. pylori* eradication where the bacterial strains remain susceptible to the antibiotic. |

AZITROMYCIN

Among the new options against *H pylori* azithromycin has attracted substantial interest. Azithromycin is a macrolide antibiotic that has been shown to reach high concentrations in gastric tissue after oral administration; furthermore, these high concentrations are maintained for several days, which make it potentially useful in the eradication of *H pylori*. Clinical trials with triple therapy regimens that contain azithromycin have reported eradication rates of approximately 60%-80%, depending on the regimen and azithromycin dose used. However, results from some other available trials utilizing azithromycin have yielded conflicting results.

*One meta-analysis and four randomised clinical trials investigated the role of azithromycin in *H. pylori* eradication.*

A double-blind randomised trial (n=84 *H. pylori*-infected patients) compared 3 quadruple regimens containing azithromycin (6 g, 3 g, and 1.5 g) in combination with omeprazole 20 mg, amoxicillin 1 g, and bismuth 240 mg. There was no significant difference among eradication rates in the three groups (P=0.44). However, frequency of drug side effects between 6 g azithromycin group and 1.5 g azithromycin group was statistically significant (P=0.02).  

A randomised clinical trial (220 *H. pylori* positive patients) compared two regimens (azithromycin, ofloxacin, bismuth, and omeprazole versus clarithromycin, amoxicillin, bismuth, and omeprazole) for 2 weeks as second-line therapy for *H. pylori* eradication. The eradication rates were significantly higher in azithromycin-containing regimen in intention-to-treat analysis (P=0.027) and in per-protocol analysis (P = 0.026). No major adverse events occurred in both groups.

A meta-analysis of 14 randomised trials (n=1431 patients) that compared azithromycin-containing triple-therapy regimen with standard triple-therapy regimens for first-line treatment of *H. pylori* infection showed that azithromycin-containing triple-therapy regimens could be equally effective in eradication of *H. pylori* compared with standard first-line triple-therapy regimens (72.01% vs. 69.78% for patients with or without azithromycin; OR= 1.17; 95% CI: 0.64-2.14). The occurrence of side effects was 15.81% and 25.20% (OR = 0.58; 95% CI: 0.41-0.82) for treatment with or without azithromycin, respectively. Furthermore, the azithromycin-containing group had a lower occurrence of diarrhoea, nausea and taste disturbance.

One study evaluated the eradication rate, tolerability, and compliance of levofloxacin-azithromycin combined triple regimen in first- and second-line therapy for *H. pylori* eradication. 1) **First-line eradication:** an azithromycin-containing triple therapy (omeprazole 20 mg b.i.d., levofloxacin 500 mg o.d., and azithromycin 500 mg o.d.) was compared with standard triple therapy (omeprazole 20 mg b.i.d, amoxicillin 1.0 g b.i.d., and clarithromycin 500 mg b.i.d.) for 7 days. The eradication with azithromycin-containing triple therapy was lower than that of standard triple therapy, but there was no statistically significant difference (70.6% vs. 80.3%, P=0.390).
2) **Second-line eradication**: patients (n=59) who failed *H. pylori* eradication with standard triple therapy were randomised to receive a quadruple therapy (omeprazole 20 mg b.i.d., bismuth 120 mg q.i.d., metronidazole 500 mg t.i.d., and tetracycline 500 mg q.i.d.) or retreatment with azithromycin-containing triple therapy. Second-line eradication rate of levofloxacin-azithromycin combined triple therapy was significantly lower than that of bismuth-based quadruple therapy (*P*<0.0001). The compliances of all patients were more than 85%. Two of patients with levofloxacin-azithromycin combined triple therapy complained self-limiting side effects (mild dizziness; mild insomnia with general weakness). So, levofloxacin-azithromycin combined triple therapy did not evidence an advantage as the first-line or second-line *H. pylori* eradication. 79

Another double-blind randomised clinical trial compared the efficacy of two quadruple-therapy regimens – one with azithromycin (plus amoxicillin, omeprazole, and bismuth) and the other with metronidazole (plus amoxicillin, omeprazole, and bismuth) – for *H. pylori* eradication in 60 patients with dyspepsia, during 2 weeks. There was no significant difference in *H.pylori* eradication between the two groups (*P* = 0.939).

**Despite the availability of oral liquid formulation, a search in PubMed of azithromycin use in children (176 citations between 2010 and 2008) found no article of its use for *H. pylori* eradication.**

**Recommendation**

At this moment, the conflicting results and marginal benefit provided by the literature do not recommend the inclusion of azithromycin as a component of first- and second-line therapies for *H. pylori* eradication for adults and children.

**Tetracyclines**

A microbiological study of a total of 110 *H. pylori* strains, isolated from dyspeptic patients during 2005 to 2008 in Iran, found that the rates of resistance to metronidazole and tetracycline were remarkably high and showed a considerable increase from 33-36.3% to 55.6% and 0-0.7% to 38.1%, respectively. However, the change in resistance rates of clarithromycin, amoxicillin and furazolidone was not statistically significant.

Tetracycline is commonly combined to other antibiotics in **second-line therapy** for *H. pylori* eradication. A randomised study (n = 415 consecutive *Helicobacter pylori*-positive patients) compared tetracycline-containing triple first-line treatment (lansoprazole + tetracycline + metronidazole – LTM) with standard triple first-line therapy (lansoprazole + amoxicillin + clarithromycin – LAC) for 14 days, as well as with bismuth-containing quadruple treatments:

- bismuth subcitrate + lansoprazole + tetracycline + metronidazole for 10 days – BLTM;
- ranitidine bismuth citrate + lansoprazole + tetracycline + metronidazole – RBLTM. The BLTM, RBLTM, and LTM treatment groups achieved a significantly better eradication rate than the LAC treatment group (*P* < 0.001). There was not any significant statistical difference between the groups of BLTM, RBLTM, and LTM. So, tetracycline triple treatment group achieved a significantly better eradication rate than the standard triple treatment group. The success ratio of LTM therapy was comparable with quadruple bismuth-based treatments.

Doxycycline has pharmacokinetic advantages, as a better oral absorption, not reduced by food or milk, and a longer half-life that allowed a longer interval between administrations (100 mg b.i.d.). A 14-day first-line triple therapy consisting of ranitidine bismuth citrate + amoxicillin + doxycycline was compared with ranitidine bismuth citrate + amoxicillin + tetracycline in 115 consecutive *H. pylori* – positive dyspeptic patients. There was no
statistical significant difference between the two regimens, neither of them being adequately effective for *H. pylori* eradication as a first line therapy. 83

As second-line options, a prospective study randomised 58 patients in whom a first eradication regimen containing clarithromycin had failed to receive rabeprazole + levofloxacin + furazolidone for 10 days (RLF) or rabeprazole + bismuth subcitrate + doxycycline + furazolidone (RBDF) for 10 days. Cure rates were similar in both regimens, as well as compliance. Side-effects (96% mild) were observed in 87% of the patients and were comparable between groups, except diarrhoea, which was more frequent in group RLF (*P*= 0.025). 84

**Recommendation**

| Doxycycline should substitute tetracycline in quadruple second-line therapy, and it is already included in the WHO Model List, as solid oral dosage form containing 50 mg and 100 mg (hydrochloride) and oral liquid containing 25 mg/5 ml; 50 mg/5 ml, with the restriction: use in children < 8 years only for life-threatening infections when no alternative exists. |

**Metronidazole**

Metronidazole is used in standard triple therapy, either in allergic or clarithromycin-resistant adults and children infected by *H. pylori*. This agent is included in WHO Model List as oral liquid (200 mg as benzoate/5 ml) and tablet (200 mg to 500 mg).

A randomised double-blind trial performed in 238 *H. pylori*-infected children, aged 3 to 15 years (mean 8.6), compared two 2-week triple therapy, with age adjusted doses of lansoprazole + amoxicillin + metronidazole or clarithromycin, all administered twice daily. The overall per-protocol eradication (n = 233) was similar in the two treatment regimens, 62.1% for the metronidazole and 54.7% for the clarithromycin-containing therapy. Eradication rate was higher in children >or= 23 kg (70.9%) than in children < 23 kg (45.7%). In children >or= 23 kg (n = 117) that received twice-daily administration of all medicines, efficacy of the metronidazole and clarithromycin-containing treatments were 69.5% and 72.4%, respectively. Significant differences for both treatments were found by weight, which could be the result of the once-daily proton pump inhibitor and clarithromycin or more antibiotic resistant strains in younger children. 85

It is important to recommend no ingestion of alcohol (as beverages or alcohol-containing formulation medicines) during the use of metronidazole, due to its interaction with metronidazole and disulfiram-like effect.

**Recommendation**

| Metronidazole for first- and second-line therapy is an effective agent and it is already included in the WHO Model Lists, as tablet containing 200 mg to 500 mg and oral liquid containing 200 mg (as benzoate)/5 ml. Ingestion of alcohol during the use of metronidazole must be avoided. |

**Bismuth salts**

Bismuth salts were investigated as an alternative in first-line treatment, due to increasing antibiotic-resistance. A randomised study compared the efficacy of a 14 day-bismuth-based quadruple regimen (bismuth subsalicylate + lansoprazole + tetracycline +
metronidazole – BLTM group) with a 14 day-proton pump inhibitor-based triple regimen (lansoprazole + amoxicillin + clarithromycin – LAC) for eradication of *H. pylori* in 212 consecutive *H. pylori*-positive patients with non-ulcer dyspepsia. The BLTM treatment achieved a significantly better eradication rate compared with LAC treatment in per protocol analysis (82.3% vs. 62.7%, *P* = 0.002). Mild to severe side-effects were more frequent in the BLTM group. 86

Diabetes mellitus (DM) patients (n=89) were randomised to receive either pantoprazole + clarithromycin + amoxicillin for 14 days, or pantoprazole + bismuth citrate + tetracycline + metronidazole for 14 days for *H. pylori* eradication. In both intention-to-treat (ITT) and per-protocol (PP) analyses, triple therapy demonstrated 51% eradication rates versus 81% and 85% in the quadruple therapy group (*P* < 0.05). Non-diabetic patients (as controls) had not different eradication rates with both strategies. So, the bismuth-based quadruple eradication regimen as first-line therapy achieved a high cure rate in patients with DM, and successful eradication may be beneficial on dyspeptic symptoms. 41

Another randomised study evaluated the efficacy of a bismuth-containing quadruple therapy (omeprazole + amoxicillin + clarithromycin + bismuth potassium citrate, twice a day) for *H. pylori* treatment in 160 patients with functional dyspepsia during 7 or 14 days. Fourteen-day therapy led to a significant increase of *H. pylori* eradication success when compared to 7-day therapy in the intention-to-treat analysis and the per-protocol analyses. The *H. pylori* resistance rates to metronidazole, clarithromycin and amoxicillin were 42.1, 18.0 and 0%. Fourteen-day therapy was significantly more effective in patients with clarithromycin-resistant strains. Incidences of adverse events were comparable. Adding bismuth and prolonging treatment duration can overcome *H. pylori* resistance to clarithromycin and decrease the bacterial load. Fourteen-day bismuth-containing quadruple therapy achieved ITT success rate 93% and could be recommended as the first-line eradication regimen.87

**Recommendation**

A 14-day bismuth-containing regimen is a complex scheme that demonstrates efficacy in *H. pylori* resistance, but is associated with a relatively high incidence of adverse effects, and bismuth salts are not available worldwide anymore. So its inclusion on the WHO Model List is not recommended.

**Nitrofurans**

The following information is provided by one systematic review (51 articles; *n* = 4946 patients) and meta-analysis (11 articles) and three small RCTs (total of 247 patients) that evaluated the effect of furazolidone- and nitrofurantoin-based regimens in the first-, second- and third-line therapies for *H. pylori* eradication. For the meta-analysis only RCTs were used which triple or quadruple regimens containing furazolidone were compared with the standard regimens.

A systematic review and meta-analysis88 evaluated the effect of furazolidone- and nitrofurantoin-based regimens in the eradication of *H. pylori* infection. In the first-line therapy, the pooled eradication rate of PPI-based regimens containing furazolidone was 76.3% (CI95%: 67.8-84.2); the odds ratio for furazolidone-based regimens versus standard triple therapies was 2.34 (CI 95%; 0.76-3.92); and quadruple regimens containing furazolidone were superior to triple therapies (83.4%; CI95%: 69.7-92.3; *P* = 0.01). Primary triple regimens containing furazolidone are slightly less efficient than the standard primary
combinations. In the second-line therapy, schedules containing furazolidone obtained eradication rates of 76.1% (CI 95%; 66.4-85.0; \( P = 0.28 \) versus primary regimens). In the third-line “rescue” therapies, furazolidone was efficient in 65.5% of the cases (CI95%; 56.3-75.5), which is significantly lower than the results obtained in the first- and second-line therapies (\( P = 0.0001 \) for both comparisons). Dizziness, nausea, vomiting, diarrhoea, abdominal pain, loss of appetite, taste disturbance, and rash were the dominant side-effects seen in patients receiving the regimens containing furazolidone, which were more frequent than in standard therapies (\( P = 0.02 \)). The combined odds ratio of side-effects for furazolidone-based versus standard therapies was 0.74 (CI95%; 0.32-1.98). The duration of treatment, but not the furazolidone dose, influenced the treatment outcome. Ceasing treatment due to side effects was more frequent in the case of regimens containing furazolidone.

An RCT (n= 60 patients receiving a quadruple regimen containing furazolidone as second-line therapy) found side effects in 11 patients, including mild dizziness, nausea, diarrhea and increased bowel movement. None of them needed treatment for their side effects.\(^9\)

Another study (n=157 patients) confirms that a one week regimen with furazolidone may help to decrease its side-effects. One week of furazolidone in combination with 2 weeks of amoxicillin, omeprazole, and bismuth subcitrate is a safe and cost-effective regimen for the eradication of \textit{H. pylori}. Adding metronidazole to the above regimen does not increase the eradication rate.\(^9\)

There is scarce information about the role of nitrofurantoin quadruple therapy for the treatment of \textit{H. pylori}. In a small pilot study (30 patients), \(^9\) nitrofurantoin quadruple therapy (omeprazole 20 mg + NF 100 mg + bismuth salicylate + tetracycline 500 mg, all t.i.d., for 2 weeks) eradicated the infection in 69.2% (50.6-85.0) of the cases.

**Recommendation**

| Facing the lower efficacy of nitrofurans, as well as the availability of safer agents in second-line or rescue quadruple therapies, furazolidone and nitrofurantoin should not be recommended in the WHO Model List for \textit{H. pylori} eradication at this time. |

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**Quinolones**

**LEVOFLOXACIN**

Two systematic reviews and meta-analyses, four RCTs (1531 patients) and five non-randomised studies (720 patients) provided information about the efficacy and safety of levofloxacin in comparison with other strategies for \textit{H. pylori} eradication.

**SYSTEMATIC REVIEWS AND META-ANALYSES**

A systematic review and meta-analysis evaluated the efficacy and tolerance of levofloxacin-based rescue regimens in comparison with quadruple therapy for \textit{H. pylori} eradication failures. Mean eradication rate with levofloxacin-based regimens was 80%. Ten-day regimens were more effective than 7-day combinations (81% vs. 73%; \( P < 0.01 \)). The meta-analysis showed better results with levofloxacin than with the quadruple combination (81% vs. 70%; OR = 1.80; 95% CI = 0.94-3.46). This difference reached statistical significance and heterogeneity markedly decreased when only high-quality studies were considered. Meta-analysis showed less adverse effects with levofloxacin than with quadruple regimen, both overall (19% vs. 44%; OR = 0.27; 95% CI = 0.16-0.46) and regarding severe adverse effects (0.8% vs. 8.4%; OR = 0.20; 95% CI =0.06-0.67).\(^9\)
Another meta-analysis of 13 RCTs that compared levofloxacin-based triple therapy vs. bismuth-based quadruple therapy found similar eradication rates of both regimens (OR = 1.43; 95% CI: 0.82-2.51; P = 0.21). But the eradication rates demonstrated superiority of the 10-day levofloxacin-based triple therapy over 7-day bismuth-based quadruple therapy (OR = 4.79; 95% CI: 2.95-7.79; P < 0.00001). Levofloxacin-based triple therapy was better tolerated than bismuth-based quadruple therapy (OR = 0.41; 95% CI: 0.27-0.61; P < 0.0001), with lower rates of discontinuation of therapy due to adverse events (OR = 0.13; 95% CI: 0.06-0.33; P < 0.0001).93

**RANDOMISED CLINICAL TRIALS AND OTHER COMPARATIVE STUDIES**

**FIRST-LINE THERAPY**

Four hundred-fifty patients *H. pylori* infected were randomly assigned to receive 3 regimens: group 1 (CAE): Clarithromycin 500 mg twice daily, Amoxicillin 1000 mg twice daily, Esomeprazole 20 mg twice daily; group 2 (LAE): Levofloxacin 500 mg once daily, Amoxicillin 1000 mg twice daily, Esomeprazole 20 mg twice daily; group 3 (CLE): Clarithromycin 500 mg twice daily, Levofloxacin 500 mg once daily, Esomeprazole 20 mg twice daily. All the regimens were administered for 7 days. *H. pylori* eradication (intention to treat) was successful in 90.6%, 84.7% and 78.6% with CLE, LAE, and CAE, respectively. There was a significant difference (P<0.001) regarding treatment success in CLE and LAE regimens when compared with CAE. There was no difference among the treatment groups with regard to the incidence and severity of adverse events reported.94

An open-label trial randomly assigned 189 consecutive patients to receive levofloxacin 500 mg + esomeprazole 40 mg + clarithromycin 500 mg once daily for 7 days (LEC group) or amoxicillin 1 g + esomeprazole 40 mg + clarithromycin 500 mg twice daily for 7 days (AEC group). By intention-to-treat and per-protocol analysis, the *H. pylori* eradication rate was 78.9% (71/90; 95% CI: 70.3-87.5%) and 83.5% (71/85; 95% CI: 75.5-91.6%) respectively, in the LEC group; and 74.8% (74/99; 95% CI: 66.0-83.5%) and 86.0% (74/86; 95% CI: 78.6-93.5%) respectively, in the AEC group. The incidence and tolerability of side effects were similar between the two groups.95

In a previously mentioned study,37 432 patients randomly received one of two regimens: levofloxacin (750 mg once a day), amoxicillin (1000 mg twice a day) and lansoprazole (30 mg twice a day) for 7 days (LAL Group) or clarithromycin (500 mg twice a day), amoxicillin (1000 mg twice a day) and lansoprazole (30 mg twice a day) for 7 days (CAL group). The eradication rates of LAL and CAL were 74.2 and 83.7% (P=0.015) in the intent-to-treat analysis, and 80.1 and 87.4% (P=0.046) in the per-protocol analysis, respectively. So the standard regimen achieved a higher eradication rate than LAL as the first-line treatment.

A non-randomised study (n=123 consecutive patients) compared levofloxacin, esomeprazole and amoxicillin (group I; first 59 patients) with levofloxacin, esomeprazole and clarithromycin (group II; next 64 patients) for one week. Both regimens demonstrated similar efficacy (cure rates: 96% vs. 93%, in groups I and II, respectively). Minor side effects occurred in 29% of patients in group I and in 41% of patients in group II. Major side effects that warranted discontinuation of therapy occurred in two patients in group II. So, the combination with amoxicillin seems to be better tolerated than the combination with clarithromycin.96

A randomised trial (n= 460 patients) compared clarithromycin and levofloxacin in triple and sequential first-line regimens for 10 days. The schemes were the following: standard OCA: omeprazole, clarithromycin and amoxicillin; triple OLA: omeprazole,
levofloxacin and amoxicillin; sequential standard OACM: omeprazole plus amoxicillin for 5 days, followed by omeprazole plus clarithromycin plus metronidazole for 5 days; modified sequential OALM: omeprazole plus amoxicillin for 5 days, followed by omeprazole plus levofloxacin plus metronidazole for 5 days. Eradication rates were lower with OCA than with all the other regimens ($P < 0.05$). Levofloxacin-based triple and sequential therapies were superior to standard triple scheme as first-line regimens in a setting with high clarithromycin resistance. However, all of these therapies still have a 20% failure rate. No differences in compliance or adverse effects were demonstrated among treatments.31

### Conclusion

The studies comparing levofloxacin versus clarithromycin in triple, quadruple or sequential regimens for first-line therapy showed variable efficacy, better or similar levofloxacin tolerability, and more effectiveness with 10-day versus 7-days regimens of levofloxacin. Even when the superiority was evidenced, all alternative therapies still have a 20% failure rate.

### SECOND-LINE THERAPY

One study (n=160) investigated different dosage (500 mg once or twice daily) and length (7, 10 or 14 days) of triple levofloxacin-based regimens used as an alternative second-line treatment. Eradication of *H. pylori* infection was successful in all four schemes. Based upon duration of treatment, eradication rates were: 67.5% in 7 days groups and 87.5% in 10 days groups ($P=0.004$). Dosage of levofloxacin did not affect the eradication rates (77.5% both in the once daily and twice daily groups). Mild adverse events were reported overall in 16% of patients (22.5% in 7 days groups; 27.5% in 10 days groups; $P=0.58$; 12% in the once daily group; 32.5% in the twice daily group; $P=0.04$).97

Another study assessed the efficacy and tolerability of omeprazole 20 mg b.i.d., clarithromycin 500 mg b.i.d. and levofloxacin 500 mg b.i.d. for 10 days as a second-line rescue option in 35 patients allergic to penicillin who have failed *H. pylori* first-line treatment (omeprazole-clarithromycin-metronidazole for 7 days). Per-protocol and intention-to-treat eradication rates were both 73% (11/15; 95%CI=45-92%). Compliance with treatment and follow-up was complete in all the cases. Adverse events were reported in 4 patients (20%), which did not prevent the completion of treatment: mild nausea (2 patients), and vomiting and myalgias/arthralgias (1 patient).98

The efficacy and tolerability of a triple second-line levofloxacin-based regimen (levofloxacin 500 mg b.i.d., amoxicillin 1 g b.i.d., and omeprazole 20 mg b.i.d. for 10 days) was investigated in 300 consecutive patients with *H. pylori* eradication failure. Per-protocol and intention-to-treat eradication rates were 81% (95% CI 77-86%) and 77% (73-82%). Adverse effects were reported in 22% of the patients, mainly including nausea (8%), metallic taste (5%), abdominal pain (3%), and myalgias (3%); none of them were severe.98

A levofloxacin-based quadruple therapy (esomeprazole 40 mg b.i.d., bismuth subcitrate 240 mg b.i.d., amoxicillin 1 g b.i.d., levofloxacin 500 mg b.i.d. for 7 days) was compared with a traditional quadruple therapy (esomeprazole 40 mg b.i.d., bismuth subcitrate 240 mg b.i.d., metronidazole 400 mg t.d.s. and tetracycline 500 mg q.d.s.) in 102 patients with resistant *H. pylori* infection. In intention-to-treat analysis *H. pylori* eradication was achieved in 73% vs. 88% ($P = 0.046$) subjects in levofloxacin and metronidazole/tetracycline groups, respectively. Per-protocol eradication rates were 78% and 94% ($P = 0.030$), respectively in the same groups. So, levofloxacin-based quadruple therapy was inferior to traditional quadruple therapy for resistant *H. pylori* infection.99
Conclusion

Based upon two meta-analyses and four small non-randomised studies, levofloxacin-containing triple or quadruple regimens are safer, but no more effective alternatives as a second-line rescue therapy for \textit{H. pylori} resistant infection in comparison to standard regimens.

THIRD-LINE THERAPY

A prospective multicenter study evaluated the efficacy and tolerability of a third-line levofloxacin-based regimen (levofloxacin 500 mg b.i.d., amoxicillin 1 g b.i.d., and omeprazole 20 mg b.i.d. for 10 days) in 76 patients with two consecutive \textit{H. pylori} eradication failures. Per-protocol and intention-to-treat eradication rates were 66\% (95\% CI: 56-75\%) and 60\% (50-70\%). Adverse effects were reported in 25\% of the patients, mainly including metallic taste (8\%), nausea (8\%), myalgia/arthralgia (5\%), and diarrhea (4\%); none of them were severe. 100

Economic data about the use of levofloxacin for \textit{H. pylori} eradication were not found.

MOXIFLOXACIN

\textbf{Two systematic reviews and meta-analyses and three RCTs (691 total patients) provided information about efficacy and safety of moxifloxacin in comparison with other strategies for \textit{H. pylori} eradication in first- and second-line therapies. One non-randomised study (361 patients) analysed the \textit{H. pylori} resistance degree to moxifloxacin in different periods.}

\textbf{SYSTEMATIC REVIEWS AND META-ANALYSES}

A meta-analysis of four randomized RCTs (n= 772 patients) compared moxifloxacin-based triple therapy versus clarithromycin-based triple therapy for \textbf{first-line treatment} of \textit{H. pylori} infection. The mean eradication rate was 84.1\% vs. 73.6\% in the moxifloxacin and clarithromycin groups, respectively. There was a slightly statistical significance between the two groups (RR= 1.13; 95\% CI: 1.01-1.27; \textit{P}=0.04). There was no statistically significant difference in the overall side effects (RR=0.61; 95\% CI: 0.25-1.48; \textit{P}<0.28).101

Another meta-analysis compared a moxifloxacin-based triple therapy with a bismuth-based quadruple therapy as \textbf{second-line therapy} for persistent \textit{H. pylori} infection. The results suggested that the eradication rates of the moxifloxacin-based triple therapy had a slight superiority to bismuth-based quadruple therapy, but there was no significant difference between them.93

\textbf{RANDOMISED CONTROLLED TRIALS}

For a \textbf{second-line} eradication treatment in \textit{H. pylori} infection, a study randomised 160 patients to receive one of the following 7-day treatment regimens: (1) OMM: omeprazole 20 mg twice a day, moxifloxacin 400 mg/day, metronidazole 500 mg three times a day; and (2) OBMT: omeprazole 20 mg twice a day, colloidal bismuth subcitrate 120 mg four times a day, metronidazole 500 mg three times a day, tetracycline 500 mg four times a day. The eradication rates were 73.2\% and 78.9\% with moxifloxacin-based triple therapy, and 53.8\% and 64.6\% with bismuth-based quadruple therapy, by intention-to-treat (\textit{P} = 0.018) and per-protocol (\textit{P}= 0.088) analyses, respectively. Adverse events and compliance were similar in both regimens.102
Another study evaluated the effectiveness of moxifloxacin, amoxicillin and esomeprazole (moxifloxacin in **four regimens**) in 393 previously untreated patients infected by *H. pylori*. The patients were randomly assigned to different dosage (800 mg b.i.d. for 10 days and 400 mg o.i.d. for 10 days) and duration (moxifloxacin 800 mg b.i.d. for 5, 7 and 10 days) of the **triple first-line therapy**. A statistically significant difference was reached between moxifloxacin 800 mg b.i.d. for 10 days and the same dosage for 5 (*P*<0.01) or 7 (*P*<0.05) days, and versus moxifloxacin 400 mg/day for 10 days (ITT: *P*<0.05; PP: *P*<0.04). The high cost of moxifloxacin-based treatment, however, may limit its wide use as first-line treatment of *H. pylori* infection.\(^{103}\)

Moxifloxacin resistance was investigated in 138 patients randomly assigned into two groups: group 1 received moxifloxacin 400 mg/d during 7 days and the other received moxifloxacin 400 mg/d during 10 days, both combined with amoxicillin 1 g twice daily and lansoprazole 30 mg twice daily. Eradication rates were 84% and 76% in the first group and 90% and 84% in the second group, according to the PP and ITT analysis (*P* = NS). Among 129 patients (86% of study group), 6% of strains were primary resistant to moxifloxacin. Eradication of moxifloxacin sensitive/resistant strains was 98%*/66%* (*P* < 0.05).\(^{104}\)

**NON-RANDOMISED STUDY**

A prospective study investigated efficacy and safety of a moxifloxacin-containing **triple therapy** (moxifloxacin 400 mg q.i.d., amoxicillin 1000 mg b.i.d., esomeprazole 20 mg b.i.d.) as **second-line treatment** for *Helicobacter pylori* infection, given for 7, 10 and 14 days. A week treatment achieved eradication rates of 75.6/83.8% (ITT/PP). Moxifloxacin resistance was 5.6% (2004). When therapy was extended to 10 days, eradication rates were 71.9/82.6% (ITT/PP); moxifloxacin resistance had increased to 12% (2005-2006). The final group of patients who were treated for 14 days also had low eradication rates (68/79.9%), but there was no statistical significance in the efficacy among the treatment periods. Moxifloxacin resistance was 28.2% (2007-2008). Side-effect increased with treatment duration (*P* = 0.001). The 7-day moxifloxacin-containing triple therapy produced an unacceptably low eradication rate. Increasing the duration of therapy the expected increased did not materialize, most likely because of coincident marked increase in the prevalence of resistance to moxifloxacin. Tailored treatment based on antibiotic susceptibility testing might be more effective in the achievement of high eradication rate when rapid antibiotic resistance such as moxifloxacin is occurring.\(^{105}\)

Economic data about the use of moxifloxacin for *H. pylori* eradication were not found.

**CIPROFLOXACIN**

Ciprofloxacin is the unique quinolone already included in the current WHO Model Lists. A Medline search for its role in *H. pylori* eradication found only an old randomised, double-blind, placebo controlled trial (n=36 patients).\(^{106}\) The *H. pylori* infection cleared in 13 of 17 patients (76%) in the ciprofloxacin group versus 5 of 19 (26%) in the placebo group. Studies that investigate resistance to quinolones includes ciprofloxacin and evidenced an increased resistance rate for these antibiotics in last years.
Recommendation

Levofloxacin and moxifloxacin should not be included in the Model List as alternative regimens for first-line therapy or second- and third-line rescue therapies for *H. pylori* resistant infection, due to insufficient evidence of a superior efficacy, a still 20% failure rate, the availability of other alternative therapies for this context, and the easily acquired resistance to quinolones in countries with a high consumption rate of these antibiotics.

**Rifabutin**

Despite rifabutin be already listed as an antituberculosis medicine, it is only used as a rescue therapy in empirical fourth-line therapy *H. pylori* infection. The publicized experience is scarce. Besides, usually there is an adequate rate of cure with third-line regimens, without need of rifabutin-based schemes. Additionally, caution is warranted in the use of rifabutin, which may lead to resistance of mycobacteria in patients with preexisting mycobacterial infection.

Recommendation

The inclusion of rifabutin for *H. pylori* fourth-line therapy should not be recommended under the context of essential medicines in the WHO Model List.

**Probiotics**

Three systematic reviews and meta-analyses (3678 patients) and four RCTs (1627 total patients) provided information about efficacy and safety of the use of non-antimicrobial add-on medications (such as lactoferrin, probiotics and others) in patients with more than one *H. pylori* treatment failure, with the aims either to improve the eradication rate or to minimize side effects.

**SYSTEMATIC REVIEWS AND META-ANALYSES**

A meta-analysis of ten randomised trials (n= 963 patients) evaluated the effect of fermented milk-based probiotic preparations on *Helicobacter pylori* eradication and demonstrated a significant but discrete improvement in *H. pylori* eradication rates by approximately 5-15%, whereas the effect on adverse effects was heterogeneous. 107

Another meta-analysis of nine randomised trials (n = 1343) that compared bovine lactoferrin supplementation to placebo or no treatment added to anti- *H. pylori* regimens demonstrated that bovine lactoferrin potentially improves *H. pylori* eradication rates (86.57% vs. 74.44% for controls; OR=2.26; 95%CI: 1.70-3.00), and could be considered helpful for patients with eradication failure. Furthermore, lactoferrin shows a positive impact on *H. pylori* therapy-related side-effects, especially for nausea (OR=0.15; 95%CI: 0.04-0.54).108

The same authors performed another meta-analysis (8 RCTs; 1372 patients) to evaluate whether adding Lactobacilli to *H. pylori* eradication regimens could improve eradication rates and reduce side effects during anti-*H. pylori* treatment. Pooled *H. pylori* eradication rates were 82.26% vs. 76.97% (OR= 1.78; 95%CI = 1.21-2.62) for patients with or without Lactobacilli by intention-to-treat analysis, respectively. The occurrence of total side effects had no significant difference. However, Lactobacilli supplementation group had lower occurrence of diarrhoea, bloating and taste disturbance.109
RANDOMISED CONTROLLED TRIALS

An Italian randomised study compared standard triple therapy (esomeprazole, clarithromycin, amoxicillin) with bovine lactoferrin (bLf) and probiotics (Pbs) plus standard triple therapy for *H. pylori* eradication in 206 patients. The results suggested that the addition of bLf and Pbs could improve the standard eradication therapy for *H. pylori* infection and reduce the side effects of antibiotic therapy.\textsuperscript{110}

In another randomised trial, 991 HP infected patients were allocated into one of three groups: (A) PPI-based 7-day triple therapy, (B) the same triple therapy plus *Saccharomyces boulardii* for 4 weeks, and (C) the same 7-day triple therapy plus *S. boulardii* and a mucoprotective agent for 4 weeks. According to the results of an intention-to-treat analysis, HP eradication rates for the groups A, B, and C were 71.6\% (237/331), 80.0\% (264/330), and 82.1\% (271/330), respectively (*P* = 0.003). According to the results of a per-protocol analysis, the eradication rates were 80.0\% (237/296), 85.4\% (264/309) and, 84.9\% (271/319), respectively (*P* = 0.144). The frequency of side effects in group B (48/330) and C (30/330) was lower than that in group A (63/331) (*P* < 0.05). This study suggests that supplementation with *S. boulardii* could be effective for improving HP eradication rates by reducing side effects thus helping completion of eradication therapy. However, there were no significant effects on HP eradication rates associated with the addition of mucoprotective agents to probiotics and triple therapy.\textsuperscript{111}

The same group of investigators compared the efficacy, safety and compliance of a type of yogurt (containing *Lactobacillus acidophilus* HY2177, *Lactobacillus casei* HY2743, *Bifidobacterium longum* HY8001, and *Streptococcus thermophilus* B-1) added to PPI-based triple therapy (yogurt group, n = 168; 1 bottle per day, for 3 weeks) with those of triple-only standard therapy (control group, n = 179; PPI b.i.d., clarithromycin 500 mg b.i.d., and amoxicillin 1 g b.i.d., for 7 days). By intention-to-treat analysis the eradication rates were similar in both groups. However, by per-protocol (PP) analysis, the eradication rate in the yogurt group was higher than that in the control group (87.5\% vs. 78.7\%; *P* = 0.037). The frequency of adverse effects in the yogurt group were higher than in the control group (41.1\% vs. 26.3\%; *P* = 0.003).\textsuperscript{112}

A double-blind, placebo-controlled, randomised trial compared a 7-day, triple eradication regimen (omeprazole 0.5 mg/kg b.i.d., amoxicillin 25 mg/kg b.i.d., clarithromycin 10 mg/kg b.i.d.) supplemented with *Lactobacillus* GG (LGG) or with placebo in 83 children with *H. pylori* infection. The groups did not differ with respect to *H. pylori* eradication rates (69\% vs. 68\%; RR = 0.98; 95\% CI: 0.7-1.4), and with respect to adverse effects, as well.\textsuperscript{113}

**Recommendation**

The available evidence of benefit of these non-antimicrobial add-on medications on *H. pylori* eradication is limited and further research is necessary to confirm the findings. So they are not recommended for inclusion on the WHO Model List.
SUMMARIZED RECOMMENDATION

<table>
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<tr>
<th>Recommendation</th>
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<th>To be added on the WHO Model List</th>
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<tbody>
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<td><strong>First-line therapy (triple regimen)</strong></td>
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<tr>
<td>Proton pump inhibitor (PPI)</td>
<td>Omeprazole *&lt;br&gt; Powder for oral liquid: 20 mg; 40 mg sachets.&lt;br&gt; Solid oral dosage form: 10 mg; 20 mg; 40 mg.</td>
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<tr>
<td>Amoxicillin</td>
<td>Amoxicillin*&lt;br&gt; Powder for oral liquid: 125 mg (anhydrous)/5 ml; 250 mg (anhydrous)/5 ml&lt;br&gt; Solid oral dosage form: 250 mg; 500 mg (anhydrous).</td>
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<tr>
<td>Clarithromycin</td>
<td>Clarithromycin #&lt;br&gt; Powder for oral liquid: 125 mg/5 ml.&lt;br&gt; Solid oral dosage form: 250 mg, 500 mg.</td>
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<tr>
<td>Metronidazole</td>
<td>Metronidazole *&lt;br&gt; Oral liquid: 200 mg (as benzoate)/5 ml.&lt;br&gt; Tablet: 200 mg to 500 mg.</td>
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<td><strong>Second-line therapy (triple or quadruple regimens)</strong></td>
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<td></td>
</tr>
<tr>
<td>Proton pump inhibitor (PPI)</td>
<td>Omeprazole (see above)</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Doxycycline *†&lt;br&gt; Oral liquid: 25 mg/5 ml; 50 mg/5 ml&lt;br&gt; Solid oral dosage form: 50 mg; 100 mg (hydrochloride).</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Metronidazole (see above)</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Amoxicillin (see above)</td>
<td></td>
</tr>
</tbody>
</table>

* Also listed on the 2nd. WHO Model List of Essential Medicines for Children (updated March 2010)
# To be added on the WHO Model List of Essential Medicines for Children, as well.
† Doxycycline: Use in children <8 years only for life-threatening infections when no alternative exists.

References:


