

## Which Treatment in *Helicobacter pylori* Infection?

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### Abstract

For many years in *Helicobacter pylori*-positive patients, the most used eradication regimen has been the triple therapy, consisting by the association of two antibiotics usually chosen between amoxicillin, clarithromycin and metronidazole.

In recent years because of the increasingly resistance of this therapy, several options have been used. The most innovative regimen is sequential therapy, but maybe bismuth-containing quadruple therapy is the more frequently used worldwide. Other effective treatments are concomitant therapy or quinolone-containing triple therapy.

Moreover, further approaches have been developed such as the hybrid therapy or the quadruple in which three antibiotics are included in a single capsule.

The therapeutic approach for second-line therapy should be based on the regimen used in the first-line treatment trying to obtain the best eradication rate.

Instead, regarding the third-line therapy, the international guidelines recommend the culture-guided approach or in alternative a therapy based on local antimicrobial resistances.

This review attempts to summarize the many possibilities currently available in eradication of *Helicobacter pylori* infection.

**Keywords:** *Helicobacter pylori* infection; Eradication regimens; First-line therapy; Second-line therapy; Third-line therapy; Adjuvants

### Introduction

Since the original description of *Helicobacter pylori* (*H pylori*) by Marshall and Warren in 1982, gastroenterologists are constantly looking for new therapeutic combinations to get increasingly satisfactory eradication rates [1]. Because of his crucial role in the development of chronic gastritis, gastro duodenal ulcer and gastric cancer, the importance of its eradication is well known and it remains a global health issue also in western countries [2].

In fact, anti-*H pylori* treatment continues to be a challenge for physicians since bacterial resistance increased worldwide following large use of antibiotics, mainly for respiratory tract infections [1,3]. Moreover, *H pylori* is sensitive to few medications and their widespread use (and, sometimes, abuse) in fighting infections, particularly in the respiratory tract, has led to a reduction in their effectiveness against this bacterium [4]; furthermore, *H pylori* itself generates pharmacological resistances that differ with geographic area and they compromise successive second and third-line therapies [5-7].

The Maastricht conferences have suggested use of treatment packages consisting of two different regimens designed such that failure of initial therapy would prompt treatment with a second line therapy [8,9].

### First-line Therapy

The main international guidelines [4,10,11] recommend the standard *triple therapy* (PPI+amoxicillin+clarithromycin—all b.i.d.) as first-line regimen, although its effectiveness is clearly decreasing. Clarithromycin and metronidazole resistance is the most important cause involved in reducing the effectiveness of triple therapy which fluctuates from 72 to 78% [12-15], lower than the 80%, minimum eradication rate expected for an infectious disease [16].

In the area of clarithromycin-resistance <10% (i.e., the Netherland, Sweden, Ireland, Germany, and Malaysia) it's still possible to use standard triple therapy; however it should be abandoned in the areas

with clarithromycin resistance >20% (i.e., Spain, Turkey, Italy, Alaska, China, and Cameroon) [17,18].

Regarding duration of therapy there is no significant difference between a 7- and 14-day based triple therapy, but it must also be remembered that the longer the therapy is continued, the greater the side effects [1,4,13].

However, a recent study from Japan showed a very good eradication rate (>90%) using triple therapy with PPI, amoxicillin and metronidazole [19].

Alternative treatment options for *H pylori* infection are bismuth containing and non-bismuth containing quadruple therapy (sequential and concomitant) and triple therapy with new drugs such as levofloxacin, moxifloxacin, rifabutin and furazolidone [4].

The Maastricht IV/Florence consensus report recommends bismuth-containing and non-bismuth-containing quadruple therapy (sequential and concomitant) as first-line empirical treatment for *H pylori* infection in the area of high clarithromycin resistance [4].

*Sequential therapy* is the most innovative therapeutic change in *H pylori* infection and it should generally be greater over triple therapy. It consists of five days of PPI+amoxicillin followed by

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**Received** September 30, 2013; **Accepted** November 05, 2013; **Published** November 12, 2013

**Citation:** Manfredi M, Bizzarri B, Manzali E, Fugazza A, Gismondi P, et al. (2013) Which Treatment in *Helicobacter pylori* Infection?. Clin Exp Pharmacol 3: 139. doi:10.4172/2161-1459.1000139

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PPI+claritromycin+tinidazole for the next five days. Multicenter studies carried out in different countries (Taiwan, Italy, Morocco, China...) have confirmed the advantage for the sequential regimen over standard triple therapy [20]. According to some authors this treatment could be much more complex in terms of medication requirements, because of changing drugs during a treatment course might reduce patient compliance; however, it has been shown that in clinical practice, patients who are non-compliant with regard to taking drugs are no different than those who take triple therapy [21].

Non-bismuth quadruple therapy, also termed "concomitant" has been proposed and it consists in four drugs regimen containing PPI, clarithromycin, amoxicillin and metronidazole, which are all given for the entire duration of therapy (from 5 to 10 days). Recent studies showed advantages in terms of compliance and eradication rates which amount to 94.9% [20].

Recently, Hsu and colleagues, has reported an "hybrid therapy" (14-day therapy) consisting of a combination of sequential and concomitant therapy in particular PPI and amoxicillin for 7 days followed by a concomitant therapy for the next 7 days [3].

There were no differences in eradication rates between 14-day hybrid and 14-day concomitant therapies, but the compliance is better with the hybrid than the concomitant regimen. Furthermore, this novel therapy also achieved an excellent eradication rate, almost 100% [3].

In recent years *bismuth-containing quadruple therapy* which were commonly used in 80-90's, has been rediscovered. Because of their abandonment for several years, now bismuth salts are achieving excellent results in eradication of *H pylori* infection. In fact, this therapy as first-line regimen demonstrated an eradication rate of >90%; however the optimal treatment duration remains unclear but a 10-14 day course is most commonly employed in clinical practice [3].

Triple therapy with new drugs such as levofloxacin, gemifloxacin, moxifloxacin is also studied for the first or second line treatment. Quinolone-containing triple therapy might be considered in populations with claritromycin resistance greater than 15-20% and quinolone resistance lower than 10%. This therapy showed an eradication rate ranged between 72-96% across studies [22].

A novel therapeutic approach consisting of quadruple therapy with PPI plus a single capsule containing three antibiotics (bismuth subcitrate, metronidazole and tetracycline) has recently been developed. This regimen achieved a good eradication rate (92-93%) in the 10-day course of therapy [23] which became excellent (97.1%) when therapy was prolonged for two weeks [24]. This format offers the advantages of taking three antibiotics in a single capsule and overcoming resistance to metronidazole. The side effects seem to be similar to those of the standard triple therapy.

## Second-line Therapy

Choice of second-line therapy depends on what has been used as first-line; therefore it should use different constituent antibiotics. Quinolone-based, bismuth-based and non-bismuth-based treatments are all acceptable options for second-line therapy [4,10,11,25].

The best second-line therapy remains unclear, however the current Maastricht-IV guidelines suggest that after failure of a PPI-clarithromycin-containing treatment, either a bismuth-containing quadruple therapy or levofloxacin-containing triple therapy is recommended [4].

Manfredi et al. had chosen a 10-day levofloxacin-containing triple

therapy as second-line after a course of sequential therapy, providing a good cumulative eradication rate of the *H pylori* infection, at least in northern Italy, in only two rounds [26].

However, a recent study suggested to use the best locally available therapy for both first- and second-line regimen for a period of 14 days, avoiding levofloxacin in areas where *H pylori* fluoroquinolone resistance is high. Anyway, the final goal should be to achieve an eradication rate of at least 90% with second-line therapy [25].

Currently a standard empirical third-line therapy is lacking. The Maastricht IV/Florence Consensus Report recommends using bacterial culture with antimicrobial sensitivity test to select antibiotics in the third-line regimen.

In this regards, three interesting studies from China [27], Taiwan [28] and Italy [29] have shown promising results through this strategy. Overall, *H pylori* eradication was obtained in 90% of subjects treated by culture-guided therapy.

Several years ago our groups achieved a better eradication rate treating a group of children with culture-based tailored therapy than those treated to empirical triple therapy [30].

In alternative, international guidelines recommend an empirical therapy based on local antibiotic resistances. A 10 days quadruple therapy (PPI+bismuth subcitrate+amoxicillin+levofloxacin) achieved a good eradication rate of 84% [31].

Also, quadruple furazolidone-containing therapy is another effective approach to treat refractory *H pylori* infection. This treatment (PPI+bismuth salts+furazolidone+tetracycline for 7 days) achieved a very good eradication rate of 90% [32].

Eradicating *H pylori* infection, we cannot forget the high incidence of treatment-related side effects (such as dysgeusia with a metallic taste, diarrhea, nausea, epigastric discomfort), due to modification of the intestinal microbiota as a result of antibiotic use [2,33].

Several meta-analyses have demonstrated that the addition of *adjuvants*, mainly *Lactobacillus* spp, *Bifidobacterium* spp, *Saccharomyces* spp and *Bacillus* spp, reduce eradication-related side effects and then improve patient's compliance [33,34].

However, data on improvement of *H pylori* eradication rate by probiotics are still conflicting. Several studies demonstrated an increase in eradication rates but others showed similar eradication rates using probiotics than placebo. Perhaps, these differences are due to different strains used and various treatment durations of probiotics among studies [3].

## Conclusion

*Helicobacter pylori* are one of the most common infections in humans causing several gastrointestinal diseases such as gastritis, peptic ulcer, and gastric cancer. For this reasons, gastroenterologists have been trying to knock it down since its discovery.

Over all these years, we have realized that the eradication of this infection is not so easy to get.

The goal of *H pylori* therapy should be to cure all patients with therapies achieving at least 90%, and preferably 95% or more, cure rates. The therapy of choice should be the one that offers the highest eradication rate and thus produces the smallest proportion of patients requiring repetition of treatment [35].

During the last years, the triple therapy is evidently decreased of

effectiveness with very low eradication rates. For these reasons many alternative treatment approaches have been developed.

Treatment failure increases the percentage of second-line and third-line therapies, raising the expense of treatment and the number of patients who have to undergo many antibiotic treatments. So, if you must choose between two therapies, it is illogical and unethical to advise using the one with the lower eradication rate as the initial therapy [25].

Therefore in conclusion, the best eradication therapy of *H pylori* infection should be based on antimicrobial susceptibility. In this regards, nowadays, molecular methods from biopsies (real-time PCR and FISH) have become one of the most promising techniques than culture [36].

Alternatively, if antimicrobial susceptibility tests are not available, empirical therapy based on local antibiotic resistance still remains the best therapeutic option.

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