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Therapy for *H. pylori*: Current concepts

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ABSTRACT

***Helicobacter pylori* plays an important role in the pathogenesis of chronic active gastritis, peptic ulcer and gastric mucosa-associated lymphoid tissue-lymphoma, and is also involved in carcinogenesis of the stomach. Since now no current first-line therapy is able to cure the infection in all treated patients. We evaluated data on the most successful therapy regimens—sequential, concomitant and quadruple therapies—and on the standard therapy available for *H. pylori* eradication. When therapy fails several factors may be involved: we reviewed both bacterial and host factors that can affect the eradication and that can be involved in therapeutic management of the *H. pylori* infection.**

Keywords: *Helicobacter pylori*; Sequential Therapy; Eradication

1. INTRODUCTION

Helicobacter pylori infection is a major cause of gastrointestinal-related morbidity and mortality worldwide. It is the principal cause of peptic ulcer disease (PUD) and low-grade, B-cell gastric lymphoma [1] and it has been associated to the pathogenesis of gastric adenocarcinoma [2-5]. Indeed, bacterial eradication prevents peptic ulcer disease recurrence and it is able to cure near 80% of localized low-grade gastric lymphomas. Among extra-digestive diseases, there is a significant association between *H. pylori* infection and both idiopathic thrombocytopenic purpura and idiopathic iron deficiency anemia [6,7]. Recent management guidelines from the Maastricht IV consensus conference still recommend a combination of PPI, clarithromycin, and amoxicillin for 7 - 14 days as first-line treatment of *H. pylori* infection in areas of low clarithromycin resistance or the combination of a proton pump inhibitor (PPI), bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10 - 14 days where there is a high clarithromycin resistance. However, due to an increased *H. pylori* resistance to different antibiotics, new strategies are required for the treatment of the infection [8]. Different antibiotics combinations, administered together with a proton pump inhibitor, have been proposed in the last decades. Unfortunately, there are still no available therapies able to eradicate *H. pylori* in all treated patients.

2. CURRENT THERAPIES

The most used first-line therapy regimen for *H. pylori* eradication is the triple therapy, which include the combination of two antibiotics (clarithromycin plus amoxicillin or metronidazole) with a proton pump inhibitors for at least seven days [9]. However, the eradication rates with the triple therapy has decreased from initial height of >90% to 80% or even 75% in some areas [10]. Current European guidelines confirmed the use of a standard 7-day triple therapy only in those areas where primary clarithromycin resistance is lower than 15% - 20%, whilst a prolonged 14-day regimen or quadruple bismuth therapy should be considered when bacterial resistance rate is higher [8]. Recent data found that following the prolonged 14-day triple therapy the eradication rate was still very poor (70%) in patients with non ulcer dyspepsia and in patients with peptic ulcer (81.7%) [11,12]. Indeed the eradication of the infection after a failed initial triple therapy is particularly difficult to achieve. In a recent study, the cumulative eradication rate was 89.6% by using three consecutive standard therapies in patients treated in clinical practice, being only 70.3%, 69.1% and 70% following first-, second-, and third-line regimens, respectively [13].

Quadruple therapy (PPI + Bismuth + Metronidazole + Tetracycline administered for 7 - 10 days) is a useful treatment in areas where metronidazole resistance is low and clarithromycin resistance is high. One large, ran-

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domized, controlled trial compared 7-day quadruple therapy with 7-day triple therapy [14] and a recent meta-analysis of nine studies that compares these two regimens [15] showed similar eradication rates (78% triple therapy vs 82% quadruple therapy). However, many of these comparative studies were performed before the emergence of high rates of clarithromycin resistance, so the results need to be interpreted with caution. A recent randomized controlled trial in Europe showed that quadruple therapy using a single capsule containing 3 antibiotics was superior to triple therapy, with an eradication rate of 93% compared to 68% with triple therapy [16], suggesting that this therapy could be a valid alternative to triple therapy. However, patients compliance to this therapy needs to be confirmed in further studies.

Non-bismuth quadruple therapy or "concomitant" therapy is the combination of proton pump inhibitor-clarithromycin-amoxicillin-nitroimidazole administered together. A recent meta-analysis of randomized trials showed that the eradication rate with non bismuth quadruple therapy was 90% compared to 78% with triple therapy [17]. Moreover, there was evidence of a better eradication rate with concomitant therapy lasting seven days (93%) [18]. Therefore concomitant therapy seems to be a valid alternative to triple therapy in those areas where bismuth is not available.

Sequential therapy is a novel treatment method that was firstly introduced in Italy in 2000 [19]. It is a 10-day treatment consisting of a PPI and amoxicillin 1 gr (both twice daily) administered for the first 5 days followed by triple therapy consisting of a PPI, clarithromycin 500 mg, and tinidazole 500 mg (all twice daily) for the remaining 5 days. A recent systematic review and meta-analysis showed a high eradication rate (>90%) of standard sequential therapy [20].

The efficacy of sequential therapy towards standard triple therapy has been proved in several randomized trials and the success rate of the sequential regimen was distinctly higher, in all studies were a "head-to-head" comparison was performed the sequential regimen was significantly superior to either 7-day or 10-day standard triple therapies [21].

3. FACTORS THAT AFFECT TREATMENT RESPONSE

1) Resistance

One of the main reasons for the poor performance of treatments is the increasing number of *H. pylori* strains resistant to antibiotics especially clarithromycin and metronidazole. Indeed antimicrobial resistance is responsible for the declining rates of *H. pylori* eradication seen in many countries. Clarithromycin acts interrupting bacterial protein synthesis and the resistance is caused by a mutation in the organism that prevents binding of the antibiotic to the ribosome of *H. pylori*. A rapid efflux pathway may also develop in *H. pylori* when exposed to anti-microbial agents. The drug is rapidly pumped out of the organism preventing the anti-microbial effect. It has been suggested that sequential therapy may be more effective than triple therapy because the initial treatment with a proton pump inhibitor and amoxicillin poisons the cell wall of the organism preventing the development of efflux channels [22]. A systematic review of *H. pylori* therapy found that when clarithromycin was the key drug in a regimen, eradication rates fell by 56% if clarithromycin resistant strains were present. Furthermore nitroimidazole resistance causes a reduction in efficacy of 50% with triple and quadruple therapies [23].

2) Patient's adherence to treatment

Patients taking less than 80% of their treatment regimen have a high rate of treatment failure, and failed treatment is associated with the emergence of anti-microbial resistance [24]. It should always be emphasized to the patient that successful eradication depends on full compliance with the treatment. A least a short time should be taken to counsel the patient, explaining the procedures involved in taking complicated drug therapies and describing the side-effects to improve the outcome.

3) Side-effects and smoking habit

Up to 50% of patients have mild side-effects while taking *H. pylori* treatment and less than 10% of patients stop treatment because of side-effects. Some of the most common side-effects are metallic taste, especially by using metronidazole or clarithromycin, constipation while taking bismuth based treatments, and diarrhea or stomach cramps. However there is no significant difference in side effects among the different treatments available.

Smoking reduces the success rate of standard triple therapy mainly altering antibiotics delivering into the gastric mucosa. Indeed, reduction in gastric blood flow and mucus secretion or an increased acid hypersecretion can reduce the antibiotic activity [25].

4. FUTURE THERAPIES

According to current European Guidelines, if first line therapy fails with triple therapy either a bismuth-based quadruple therapy or a levofloxacin-based triple regimen should be used, while treatment should be guided by antimicrobial susceptibility testing after failure of second-line therapy [8]. Therapy failure mainly depends on primary resistance to different antibiotics, especially clarithromycin, which is increasing worldwide [26]. Many studies have addressed the identification of novel therapeutic target either genes (*i.e*. genes required for *H. pylori in vitro* survival or for mucosal colonization, genes involved in cellular motility, etc.) [27,28] or cellular

functions (*i.e*. chemotaxis, protein folding) [29]. Indeed, some molecules have shown a very high bactericidal level of activity against *H. pylori in vitro* and some molecules preserve antibacterial activity even at low pH values as needed in the presence of gastric acid.

5. CONCLUSION

The best treatment for the eradication of *H. pylori* is still lacking. It is well known that standard triple therapy has a poor efficacy to cure the infection because of the increased resistance to clarithromycin which is the key antibiotic. Nevertheless current guidelines still recommend this treatment in areas with low clarithromycin resistance (less than 15% - 20%). In those areas where the resistance is higher sequential, quadruple or concomitant therapies are recommended for first-line empirical treatment. New therapeutic targets are now under consideration but currently there is still no answer to the question about what is the best replacement for *Helicobacter pylori* eradication therapy.

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