OPTIMUM TREATMENT REGIMENS FOR *HELICOBACTER PYLORI* INFECTION

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ABSTRACT

The treatment of Helicobacter pylori infection includes of current standard triple therapies consisting of a proton pump inhibitor, clarithromycin and amoxicillin or metronidazole on the basis of simplicity, safety, and efficacy. There are several factors determining the success of H. pylori eradication treatment. They include the components of a treatment regimen, the treatment duration, patient compliance, the presence of resistant or virulent strains of Helicobacter pylori and possibly the patient's gastric acid secretory status. PPI, clarithromycin 500 mg, amoxicillin 1 g or metronidazol 400 mg, all given bid for 7 days are the most commonly used combination regimens. RBC-based triple therapies, furazolidone or rifabutin containing regimens can be used as an alternative approach to PPI-based triple therapies in areas where bacterial resistant strains of H. pylory are concerned.

***Key words**: treatment, Helicobacter pylori, PPI, clarithromycin, amoxicillin, metronidazole, PAM, PMC, PAC, RBC*

Eradication of *H. pylori* infection heals type B chronic active gastritis, peptic ulcer disease, and virtually abolishes ulcer recurrence. Cure of the infection also results in a complete histological regression of gastric MALT lymphoma in 80% of the patients and prevents recurrence in almost all cases and may prevent metachronous occurrence of gastric adenocarcinoma following endoscopic resection of early gastric cancer. Recommendations for eradication treatment from major consensus conferences include all patients with *H. pylori* associated DU or GU and patients with a previously confirmed ulcer on continuous antisecretory maintenance therapy, patients who present with *H. pylori* associated ulcer bleeding, and patients with gastric MALT lymphoma. There is no evidence currently to support the routine treatment of *H. pylori* infection in all patients with non-ulcer dyspepsia and this is recommended only on a case by case basis. However, most consensus groups have acknowledged that patients with undiagnosed dyspepsia, in the primary care setting under the age of 45 years of age and without alarm symptoms, may benefit.

After more than a decade of trial and error, treatment to eradicate the infection has evolved from an initial approach, using complex bismuth based therapies, to current standard triple therapies consisting of a proton pump inhibitor, clarithromycin and amoxicillin or metronidazole on the basis of simplicity, safety and efficacy. This approach has been endorsed by consensus conferences in Europe, North America, and in the Asia Pacific region in 1996-1998. The recommendations have been based on numerous large randomized controlled clinical trials that consistently have achieved an eradication rate of > 80% by intent-to-treat analysis and > 90% by per-protocol analysis. In an extensive analysis of the literature, we have identified several factors determining the success of *H. pylori* eradication treatment. They include the components of a treatment regimen, the treatment duration, patient compliance, the presence of resistant or virulent strains of *H. pylori*, and possibly the patient's gastric acid secretory status. In a meta-analysis of 82 studies involving 110 treatment arms and 6123 patients, we have shown that clarithromycin at a dose of 500 mg bid was significantly more effective than 250 mg bid when given with a PPI and amoxicillin for 7 days by intent-to-treat analysis (86.6% vs 78.2%, $p<0.0001$). The eradication rates achieved with PPI twice daily were significantly higher than PPI once daily regimens. Bacterial resistance to clarithromycin and metronidazole plays an

important role in determining the success of *H. pylori* eradication treatments. There is a good correlation between bacterial resistance to clarithromycin and treatment failure; however, the clinical relevance of *H. pylori* resistance to nitroimidazoles detected in vitro has been controversial, especially in studies using the PMC combination. We have performed a meta-analysis of 44 treatment arms and 3084 patients treated with three different PPI-based triple therapies. The efficacy of PMC and PAM combinations was significantly reduced in the presence of metronidazole resistance, whereas, the efficacy of PAC regimen was not affected. When treatments were given to patients harboring metronidazole-sensitive strains of *H. pylori*, the eradication rates, by intent-to-treat analysis, were 93% for 7-day PMC, 92% for 7-day PAM, and 90% for 10-14-day PAM regimens, respectively. However, in the presence of metronidazole resistance, the efficacy was reduced by 14%, 41%, and 24%, respectively. Based on these results, we developed a model to predict the likelihood of treatment failure for the PMC and PAM regimens in the presence of metronidazole resistance with the PAC regimen as a reference. When metronidazole resistance exists, the relative risks of treatment failure increases by 2.2, 4, and 7.9-fold when patients are treated with the 7-day PMC, 10-14-day PAM, and 7-day PAM, respectively. The results indicate that metronidazole-containing regimens should be avoided when metronidazole resistance is suspected or proven. Indeed, it is recommended that PPI combinations with clarithromycin and metronidazole should not be used as first choice treatment since this utilizes the two most effective antibiotics for *H. pylori* infection together and failure with this regimen will make it much harder to eradicate the infection subsequently.

More recently, treatment combinations consisting of RSC, clarithromycin and amoxicillin or metronidazole given for 7 days have provided similar efficacy to PPI-based triple therapies for *H. pylori* eradication treatment. However, the lack of availability and relatively high cost of RBC limits its wide use.

To overcome the impact of bacterial resistance on the efficacy of eradication treatments, several newer agents such as furazolidone and rifabutin have been used as a substitute for metronidazole in bismuth-or PPI-based triple therapies in regions where the prevalence of metronidazole resistant strains is high. These combination treatments have shown promising results. However, compared to the currently recommended PPI-triple therapies, treatment-related adverse events are common, which can lead to high drop-out rates.

Esomeprazole (E), the new optical isomer of omeprazole, may provide more effective and predictable control of intragastric pH than existing PPIs. When given with amoxicillin and clarithromycin, EAC has been shown to be as effective as OAC for eradicating *H. pylori* infection in several comparative thals.

Bismuth based triple therapies are the oldest, least expensive, but highly effective treatment regimens for eradication of *H. pylori* infection. When used in PPI-quadruple therapies, high and consistent eradication rates can be achieved. However, the complexity of administration and poor patient compliance have limited its acceptance. Recently, a single capsule, containing colloidal bismuth subcitrate 40 or 60 mg (B), metronidazole 125 mg (M), and tetracycline 125 mg (T), has been developed and proven to be highly effective, when given with a PPI (or alone), for eradicating *H. pylori* infection in two studies, with eradication rates of greater than 85% by intent-to-treat analysis.

In conclusion, treatment to eradicate *H. pylori* infection has become the mainstay of care for treating patients with *H. pylori* associated peptic ulcer disease, chronic active gastritis, and gastric MALT lymphoma. Treatment regimens consisting of a PPI at the recommended dose, clarithromycin 500 mg, amoxicillin 1 g, or metronidazole 400 mg, all given bid for 7 days, are the most commonly used combination regimens. However, in the US, the recommended treatment duration is 10 to 14 days. RBC-based triple therapies, furazolidone or rifabutin containing regimens can be used as an alternative approach to PPI-based triple therapies in areas where bacterial resistant strains of *H. pylori* are concerned. Preliminary results with the newly developed BMT single capsule triple therapy are promising, however, large clinical trials are needed to compare its efficacy with the currently recommended PPI-based triple therapies. Since the management of treatment failures has become a challenging issue and secondary bacterial resistance mainly result from previous treatment failure, the most effective treatment regimen should always be used as the first line treatment choice to minimize the occurrence of treatment failure. This is a PPI with amoxicillin and clarithromycin.

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