

## CHOICE OF ANTIMICROBIAL DRUGS FOR THE ERADICATION OF *HELICOBACTER PYLORI* INFECTION

MURTAZA MUSTAFA

*School of Medicine Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia*

### ABSTRACT

*Helicobacter pylori* is the causative organism and has a possible role in the development of chronic peptic ulcer disease and gastric cancer. *H. pylori* is one of the most virulent pathogen to man. Despite the introduction of many new antimicrobial agents with enhanced activity against *H. pylori*, the high mortality rate associated with the organism in gastric cancer continues. *H. pylori* infection eradication is initiated for patients who are serological or UBT test positive and who have documented ulcer disease. Generally recommended regimens is the triple therapy with metronidazole and either bismuth sub-cylyclate or bismuth sub-citrate plus either amoxicillin or tetracycline for 14 days eradicates *H. pylori* infection in 70 – 95% of patients. Proton pump inhibitors directly inhibit *H. pylori* and appear to be potent urease inhibitors. Regimens to eradicate *H. pylori* are continually evolving; metronidazole and clarithromycin resistant strains are now common in many countries. In patients with gastric ulcer, a careful NSAID history is also important. The aim of this paper is to review some of the main regimens for the eradication of *H. pylori* infection.

*Key words: Helicobacter pylori, antimicrobials, regimen, triple therapy.*

### INTRODUCTION

*Helicobacter pylori* (formerly called *Campylobacter pylori*) were first discovered in 1982 as the causative organism and its possible role in the peptic ulcer disease.<sup>1</sup> *H. pylori* has been implicated in the development of chronic active gastric ulcer disease, gastric mucosa – associated lymphoid tissue (MALT) lymphoma, and gastric cancer. Isenberg in 1993 noted that in the preceding 3 years more than 120 papers were published due to the intense interest and possible role of *H. pylori* in peptic ulcer.<sup>2</sup> In virtually all cases, its presence is associated with type B inflammatory gastritis.<sup>3,4</sup> *H. pylori* associated gastritis is found in over 90% of patients with duodenal ulcers and is found in 50% to 70% of patients with benign gastric ulcers.<sup>5,6</sup> In addition, studies suggest that there may be an association between *Helicobacter pylori* colonisation and the development of gastric carcinoma.<sup>3,6</sup> Following infection with *H. pylori*, there is a local and systematic humoral response.<sup>7</sup>

*Helicobacter pylori* is a Gram – negative bacterium which chronically infects the gastric mucosa of humans, eventually leading to chronic gastritis, peptic ulcer and, in some individuals, gastric adenocarcinoma and low grade B-cell lymphoma. The actual mechanism by which *H. pylori* causes mucosal inflammation and damage are not well defined but probably involve both bacterial and host factors. The

bacteria invade the epithelial cell surface to a limited degree. Bacterial cytotoxins (proteases, lipase and phospholipase A and vaculating cytotoxin) and polysaccharide may damage the mucosal cells and the ammonia produced by the urease activity may directly damage the cells also.

Therapy to eradicate *H. pylori* is continuously evolving. Patients with duodenal ulcer are assumed to be infected with *H. pylori*, it is appropriate to try to eradicate the organism in these patients. All patients with proven *H. pylori* associated gastric ulcers or with mucosa associated lymphoid tissue (MALT) lymphoma should be treated. Whether *H. pylori* should be eradicated in patients with non-ulcer dyspepsia or in asymptomatic patients is still unclear. Whether eradication reduces the risk of gastric malignancy is still unknown in patients with gastric ulcer. It is important to rule out non-steroidal anti-inflammatory drugs (NSAID) ingestion as the cause of the ulcer rather than *H. pylori*. There are several therapeutic regimens used for the eradication of *H. pylori*. In the past therapy of peptic ulcer was divided into healing of ulcer and maintenance treatment to prevent recurrence. Therapy with less than 90% eradication rates is unacceptable. *Helicobacter pylori* eradication regimens greater than 90% in most patients are considered an appropriate therapy. This paper reviews the various therapeutic regimens for the eradication of *H. pylori* infection.

## THERAPIES

In *vitro* all *Helicobacter pylori* isolates are susceptible to a variety of antimicrobial agents including bismuth salts, amoxicillin, macrolides, nitro furans, tetracycline's, and aminoglycosides.<sup>8,9</sup> However, in *vitro* susceptibility is no guarantee of in *vivo* effectiveness. Primary resistance to imidazoles (such as metronidazole and tinidazole) occurs in 20 – 40 percent of isolates,<sup>10</sup> is most common in young women who may have received this agent for gynecological infections or persons from developing countries treated for parasitic infections. However primary resistance is present in isolates from both men and women in all age groups and is associated with prior exposure to a metronidazole, even decades earlier.<sup>11,12</sup>

There are numerous eradication regimens to cure *H. pylori* published. The optimal treatment regimens are still evolving.<sup>13</sup> Attempts to eradicate *H. pylori* with single agents have not been effective and may lead to antimicrobial resistance.<sup>14</sup> As a result most treatment trials are using combination therapy.<sup>15</sup> No optimal regimen has emerged.<sup>13</sup> Certain agents effective in *vitro* may be ineffective in *vivo* even in combination with other agents. Erythromycin is a good example of this phenomenon.<sup>16</sup> To date no acquired resistance to bismuth salts, amoxicillin, and tetracycline has been reported. In contrast, acquired resistance to quinolones is so frequent that it appears to preclude their use. Secondary resistance to imidazole occurs in 10 – 30 percent of cases, even in combination with other agents.<sup>17</sup> Triple therapy with bismuth salts, metronidazole and amoxicillin has resulted in eradication rates of 60 – 90 percent. Tetracycline appears to be at least as beneficial as amoxicillin, for two weeks.<sup>18-20</sup> A combination of clarithromycin, tripotassium dicitrato bismuthats, and omeprazole for 7 days cured *H. pylori* infection in 90 percent of patients and was well tolerated by most patients.<sup>21,22</sup> For patients hypersensitive to penicillin, substitute amoxicillin with metronidazole. Similar triple therapy was also used by other researchers.<sup>23,24</sup>

For treatment failure, a quadruple combination that include bismuth, a proton pump inhibitor metronidazole and tetracycline for 14 days, are less well tolerated than the first line combinations, but have a success rate of about 80 – 90 percent.<sup>25</sup> At present, there is insufficient evidence to make a strong recommendation about single most appropriate combination regimen for use after initial treatment failure.<sup>26</sup>

All over the World various trials using different drug regimens to cure *H. pylori* infection that includes: A study in US shows that extending sequential therapy to 14 days did not result in grade A result. However, 14 – days sequential concomitant hybrid

therapy achieved a Grade A success. Studies in different regions are needed to confirm these findings.<sup>27</sup> A high dose amoxicillin based eradication treatment is superior to standard triple therapy and equivalent to sequential therapy; compared to the later, the shorter duration may represent an advantage.<sup>28</sup> A sequential levofloxacin – based second line treatment is superior to quadruple therapy in *H. pylori* eradication, with a lower occurrence of side effects. However, the way of administration of levofloxacin does not influence its efficacy.<sup>29</sup>

Another group of researcher secured 80.7% eradication of *H. pylori* infection by using a triple therapy (rabeprazole, amoxicillin and clarithromycin) this is despite the high prevalence of clarithromycin resistant *H. pylori* in recent years in Japan. The advantage of rabeprazole is its ability to exhibit a rapid onset of increased pH from the first day of administration, providing a quick and favourable pH environment for antimicrobial activities.<sup>30</sup>

Investigators carried out eradication therapy in accordance to the scheme recommended at Maastricht conference (omeprazole, clarithromycin, amoxicillin within 7 days) achieved 97.4% cure of *H. pylori* infection. The remaining patients (2.6%) received therapy with four drugs: omeprazole, clarithromycin, amoxicillin and bismuth subcitron-D-nol.<sup>31</sup>

The comparison of two eradication regimens, omeprazole, clarithromycin and amoxicillin (OCA) and omeprazole, clarithromycin and metronidazole (OCM) for 7 days for *H. pylori* infection is effective enough and there is no predominance for their selection.<sup>32</sup> After eradication therapy recommended for *H. pylori* infection, the standardized incidence ratios (SIRs) of several cancers remained significantly elevated for several years. This indicates that patients treated for *H. pylori* infection still have a considerable risk for serious diseases, including gastric cancer.<sup>33</sup>

A fourth – line therapy with rifabutin in patients with three *H. pylori* eradication failures. Researchers noted an empirical fourth line rescue treatment with rifabutin may be effective in approximately 50% of cases. Therefore, rifabutin based rescue therapy constitutes a valid strategy after multiple previous eradication failures with antibiotics such as moxicillin, clarithromycin, metronidazole, tetracycline, and levofloxacin.<sup>34</sup>

Five day quadruple (amoxicillin, clarithromycin, metronidazole, and Inasorprazole) concomitant therapy is found to eradicate *H. pylori* in over 90% of patients. Therefore, concomitant therapy appears to be effective alternative to triple therapy as the first line treatment regimen of *H. pylori* eradication.<sup>35</sup>

Researchers in Korea noted that an annual *H. pylori* eradication rate was significantly decreased.

Eradication rates of 14 – day PPI – containing triple therapy were superior than that of 7 – day therapy. Repeated administration of the same first line treatment could be considered in progressive higher rate of eradication failure.<sup>36</sup>

A sequential therapy consisting of (rabeprazole, and amoxicillin for 7 days followed by rabeprazole, clarithromycin and metranidazole for next 7 days all given twice daily) achieved better eradication rate of *H. pylori* compared to standard second – line regimen ( $p < 0.01$ ). Sequential regimen may be an alternative to standard second line treatment of *H. pylori*.<sup>37</sup> Alevofloxacin – based regimen together with PPI and clarithromycin represents a second line alternative in patients allergic to penicillin and failing previous treatment with clarithromycin and metronidazole.<sup>38</sup>

In patients treated according to Maastricht 2 guidelines with esomeprazole, amoxicillin, and clarithromycin twice daily for 7 days is still highly effective in Sweden. This might be due to the low resistance to macrolides and the low consumption of macrolides in Sweden due to the Swedish strategic program against antibiotic resistance (STRAMA). The eradication rate is almost identical with results ten years ago.<sup>39</sup> Bismuthate tripossium dicitrate (BTD) dispose of antibacterial effect as well as anti-inflammatory action therefore it might improve the efficacy of eradication of *H. pylori* and reduce intensity of gastritis.<sup>40</sup>

Efficacy of minocycline (MNO) based metronidazole, bismuth and PPI quadruple second – line therapy for eradication of *H. pylori*. MNO based quadruple therapy regimen was effective for second – line therapy for *H. pylori*. It could be a kind of therapeutic option as second line treatment.<sup>41</sup>

*Helicobacter pylori* eradication of 94% was achieved by using a new variant of anti *H. pylori* sequential therapy a combination of, PPI, amoxicillin, clarithromycin and nifuratel (makmiror) for 10 days, 5 days, 5 days and 5 days respectively. In comparison with standard triple therapy. The new variant anti *H. pylori* sequential therapy can be recommended for eradication *H. pylori* as the regimen of first line therapy.<sup>42</sup>

### THERAPEUTIC ISSUES

There are many therapeutic issues that include:

1. The topical action of effective antibiotics is important.
2. At increased gastric pH levels, the efficacy of many antibiotics is enhanced, which may help explain the higher rates of eradication of *H. pylori* when antimicrobials are combined with H<sub>2</sub> blockers or omeprazole.
3. Compliance is important yet difficult because of high incidence of side effects with these regi-

mens.

4. Acquisition of resistance during antibiotic therapy is a concern, especially with metronidazole, and may explain why in some patients eradication of *H. pylori* fails with standard regimens.
5. Reinfection after eradication is uncommon and appears to occur at a rate of 1 – 3% annually.<sup>14,20</sup>

### ANTIBIOTIC SUSCEPTIBILITY TESTS AND THERAPY

Most laboratory susceptibility assays do not always predict clinical outcome except for metronidazole and clarithromycin. Routine testing of *H. pylori* isolates susceptibility to metronidazole is recommended by using agar dilution methods or by E. test.<sup>43</sup>

### PROBIOTIC AND HELICOBACTER INFECTION

Eli Metchnikoff was the pioneer in immunology for which he received the Noble prize. He also studied the beneficial effects of lactobacilli among Bulgarian farmers. Since last century lactobacilli and bifid bacteria have been promoted as being beneficial to health. Only since 1980s have been well – designed animal experiments and human clinical trials conducted on probiotics.<sup>44</sup>

Normal flora of healthy human colon contains large population of resident bacteria including lactobacilli. This normal flora is balance in complex ecosystem consisting in total of more than 400 species from 40 genera. When the normal flora is eliminated by changes in diet, stress or antibiotic treatment, a serious infection may follow due to drug resistant bacteria or *Candida albicans*.

Current evidence has presented in recent reviews, it is obvious from them that the four strains with most published clinical data are *Lactobacillus rhamnosus* GG, *Saccharomyces cereviceae* Boulardi, *Lactobacillus, paracasei* Shirota and *Biofidobacterium lactis* BB<sub>12</sub>.<sup>45,46</sup> Although there are 12 different strains of probiotic bacteria listed in the clinical evidence.

The mechanism of action of probiotics has been summarized by Filho – Lims et al.<sup>47</sup>

- Antagonism through production of inhibitory substances.
- Competition with the pathogen for adhesion sites for nutrition.
- Immunomodulation of the host.
- Inhibition of the toxin.

Probiotics, *Saccharomyces boulardii* have been suggested for the treatment of infectious gastroenteritis in general, and specifically for the treatment and prevention of *Clostridium difficile* associated diarrhoea (CDAD). In an early trail, diarrhoea was

resolved in 85% of treated patients, although the number of patients were low.<sup>48</sup>

Animal models provide evidence that development of bowel cancers may be prevented by probiotics, but the evidence is inconsistent and it is not yet possible to relate probiotic intake to prevention of the development of bowel cancer in humans. However stronger evidence has been obtained in studies on bladder cancer in the Japanese population using Shirota strain. Recent findings suggest that probiotics may help in atopic eczema, irritable bowel syndrome, and inflammatory bowel disease and *Helicobacter pylori* infections.<sup>44</sup>

Aso et al reported the protective effect of Lactobacillus casei strain Shirota on the recurrence of superficial bladder cancer.<sup>49</sup> Although associated immune responses were not assessed in these studies, enhanced natural killer cells (NK cells) activity in adults colon cancer patients given L. casei Shirota suggests that probiotic may suppress tumour development through activation of immune system.<sup>50</sup>

Several excellent reviews on the immunomodulatory effects of probiotics have been published. For example treatment with cocktail of lactobacilli strains significantly reduced the relapse rate and the severity of clinical symptoms in patients with pouchitis (inflammation of ileo – anal pouch formed after colectomy) compared with placebo.<sup>51</sup> There is also evidence that probiotic intake is effective in acute gastroenteritis and rotavirus diarrhea, antibiotic associated diarrhea, Crohn's disease and paediatric atopic disorders.

## CONCLUSION

The currently recommended *H.pylori* eradication regimens should have eradication rate of 90% or greater. Knowledge of regional drug resistant strains is extremely important. Quinolones in combination may be used if these agents maintain a low incidence of resistance development and adverse effects; they will contribute significantly to the eradication of *H. pylori* infection.

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