RECENT GUIDELINES FOR *H. PYLORI* ERADICATION THERAPY

Michael G. Lee* and Yvonne Dawkins

Department of Medicine, The University of the West Indies, Mona, Jamaica.

ABSTRACT

*Helicobacter pylori* infection is one of the commonest chronic infections worldwide with an estimated 50% of the world’s population being infected. Approximately, 15 to 20% of infected individuals will develop clinical disease. Up to 95% of patients with duodenal ulcer disease and about 70% with gastric ulcer disease will be infected. Infection is also associated with gastric carcinoma and gastric MALT lymphoma. *H. pylori* is associated with dyspepsia and may be associated with unexplained iron deficiency anaemia and idiopathic thrombocytopenic purpura. All patients with a positive test for *H. pylori* should be offered eradication therapy. Over the past decade, resistance to some of the antibiotics used have increased worldwide and is a growing problem which will lead to treatment failure in 38 to 55%, if these are used. First line regimes are most important for successful eradication and should have an eradication rate of at least 90% as eradication becomes difficult with subsequent therapy. There have been updated guidelines by three expert groups over the past year and one recommendation for first line therapy is bismuth quadruple therapy consisting of, Bismuth / Tetracycline / Metronidazole/ PPI. The alternative first line therapy is the concomitant or clarithromycin quadruple regime consisting of, PPI/ Clarithromycin/ Amoxicillin / Metronidazole. For rescue therapy four regimes were recommended a) bismuth quadruple b) concomitant regime, c) levofoxacin triple therapy and d) rifabutin triple therapy, PPI/ Rifabutin/ Amoxicillin. Knowledge of resistance patterns for antibiotics used or the success of a particular regime in the local area is important for successful eradication therapy.

KEYWORDS: *H pylori*, eradication, antibiotics, resistance.
INTRODUCTION

*Helicobacter pylori* infection is one of the commonest chronic infections worldwide with an estimated 50% of the world’s population being infected. *H. pylori* is acquired by faeco-oral or oro-oral means and infection usually occurs at a young age, especially in developing countries.\(^1,2\) There are no animal or environmental reservoir.\(^3\) Unless treated, colonization usually persists lifelong. *H. pylori* infection is a key factor in the etiology of various gastrointestinal and extra-intestinal diseases.\(^4\) Approximately, 15 to 20% of infected individuals will develop clinical disease as the majority remain asymptomatic.\(^5\)

Associated Disease

The majority of infected individuals will have chronic gastritis. Up to 95% of patients with duodenal ulcer disease and about 70% with gastric ulcer disease will be infected.\(^2\) However, these figures have decreased over the past decade, especially in developed countries, as *H. pylori* prevalence decrease and aspirin and NSAID induced ulcers increase in frequency. *H pylori* has been classified as a class 1 carcinogen as it is associated with a B-cell gastric lymphoma or MALT lymphoma.\(^6\) Infection is also associated with gastric carcinoma which is relatively common in countries with a high prevalence of infection. Individuals who tested positive for *H pylori* were between three and six times more likely to develop gastric cancer compared with uninfected controls.\(^7,8\) *H. pylori* is associated with dyspepsia and eradication will lead to long term symptomatic relief in a proportion of patients with uninvestigated and functional dyspepsia.\(^9,10\)

*H. pylori* may be associated with unexplained iron deficiency and iron deficiency anaemia (IDA) in some patients. IDA is more prevalent in *H. pylori* infected patients than uninfected controls by a factor of 2.8.\(^11\) Also, successful eradication in infected patients enchances the response to iron therapy compared to iron alone. In addition, eradication therapy in IDA results in improvement in haemoglobin level even without iron therapy.\(^12\) The exact pathogenesis is unknown, however several mechanisms may play a role. Anaemia may be arising from upper gastrointestinal blood loss which may be due to *H. pylori* associated lesions. Many patients with *H. pylori* infection have decreased gastric acid secretion due to atrophic gastritis of the body, as well as decreased gastric ascorbic acid concentration.\(^7,13\) This results in a decrease in the ferric form of iron found in food being reduced to the ferrous form which is necessary for iron absorption in the proximal small intestine. Iron is utilized by *H. pylori* for various metabolic processes and there may be competition for iron by the bacteria.\(^4\)
The other extra-intestinal disorder associated with *H. pylori* infection is idiopathic thrombocytopenic purpura (ITP). In patients with ITP and *H. pylori* infection, eradication of infection may lead to significant increase in platelet count.\[^{14}\] This response occurs in about 50% of patients, especially in areas where there is a high prevalence of *H. pylori* in the population. The pathogenesis is unknown but may involve the development of cross reactive antibodies to *H. pylori* and platelet antigens.\[^{15}\] *H. pylori* infection activates monocyte/macrophage function which increases platelet removal. Also, *H. pylori* infection causes a non-specific stimulation of the immune system which may lead to platelet removal.

**Who to Test**

All patients with peptic ulcer disease should be tested including patients with a past history of ulcer. Patients who have been treated for early gastric cancer should be tested.\[^{2}\] Patients with mucosal associated lymphoma (MALT) of the stomach should be tested as eradication of *H. pylori* will lead to remission in the majority with low grade or limited disease.\[^{16}\]

Patients with functional dyspepsia and young patients under age 50 years without alarm symptoms or signs with uninvestigated dyspepsia should be tested.

Patients on low dose aspirin and those starting chronic therapy with NSAIDs should be tested. Eradication of *H. pylori* in these patients will significantly decrease the incidence of ulcer disease and bleeding.\[^{17}\]

First degree family members of a patient with gastric cancer should be tested as there is a strong intra-family spread of infection.

Patients with unexplained iron deficiency and IDA and ITP should now be tested as *H. pylori* eradication will lead to improvement in many patients.

**Guidelines for Eradication Therapy**

All patients with a positive test for *H. pylori* should be offered eradication therapy. Therapy has become increasingly complex as over the past decade resistance to some of the antibiotics used have increased worldwide and is a growing problem which will lead to treatment failure in 38 to 55% if these are used for eradication therapy.\[^{18,19}\] Therefore, knowledge of sensitivity and resistance patterns for the common antibiotics used or the success of a particular regime in the local area is important for successful eradication therapy. Since antibiotic sensitivity is the most important determinant of successful eradication, it is
necessary to monitor antibiotic sensitivity and resistance to provide clinicians with data on the most appropriate and cost effective regimes for eradication.\cite{19} Patients should be asked about previous antibiotic use as this may predict possible resistance, especially to clarithromycin, levofloxacin and metronidazole. First line regimes are most important for successful eradication and should have an eradication rate of at least 90%. Successful eradication decreases and becomes difficult with second and third line therapy.

There have been updated guidelines by three expert groups over the past year and these are summarized.

The Canadian Association of Gastroenterology (CAG) published consensus guidelines for \textit{H. pylori} eradication therapy in 2016.\cite{20} An important recommendation was the duration of treatment for 14 days for all regimes including first line and treatment failures. This is due to the increasing failure of eradication therapy, and evidence that increase duration of therapy is associated with a greater proportion of successful eradication. The recommendation for first line therapy is bismuth quadruple therapy consisting of, Bismuth (qid)/ PPI (bid)/ Tetracycline (500 mg qid)/ Metronidazole (500 mg tid). The alternative first line therapy is the concomitant or clarithromycin quadruple regime consisting of, PPI bid/ Clarithromycin (500 mg bid)/ Amoxicillin (1gm bid)/ Metronidazole (500 mg tid). Triple therapy with PPI bid/ Clarithromycin (500 mg bid)/ Amoxicillin (1 gm bid) is recommended only in areas where this regime is known to have a good success rate of eradication or the resistance rate to clarithromycin is low (<15%). This is based on the significant impact of resistance to clarithromycin on successful eradication.

For treatment failure, the CAG consensus recommended rescue therapy is, bismuth quadruple therapy, Bismuth/ PPI/ Tetracycline/ Metronidazole. The alternative rescue therapy recommended is levofloxacin triple therapy, PPI bid/ Levofloxacin (500 mg od)/ Amoxicillin (1 gm bid). After 3 treatment failures the recommendation is the rifabutin triple therapy, PPI/ Rifabutin (150 mg bid)/ Amoxicillin (1gm bid). Rifabutin is a rifamycin derivative which is used to treat \textit{Mycobacterium} infections and has fairly good activity against \textit{H. pylori}.\cite{21} Clarithromycin or Levofloxacin are not recommended for subsequent therapy if used in previous failed regimes.

The American College of Gastroenterology published their recommendations for eradication therapy in 2017.\cite{17} The recommendations cautioned against the use of triple therapy with
PPI/ Clarithromycin/ Amoxicillin and should be used only in areas where the resistance rate to clarithromycin is low (<15%) and given for 14 days, if this regime is used. The eradication rate for this regime is about 80%. The two main first line recommendations were, bismuth quadruple therapy consisting of Bismuth/ PPI/ Tetracycline/ Metronidazole (10-14 d). The alternative first line therapy is the concomitant regime or clarithromycin quadruple regime consisting, of PPI/ Clarithromycin/ Amoxicillin/ Metronidazole (10-14 d). Each of these regimes has an average 85-90% eradication rates. Three alternative first line regimes were suggested. Sequential therapy which has about an 84% eradication rate consist of, PPI (bid)/ Amoxicillin (1 gm bid) for 5–7 days then PPI (bid)/ Clarithromycin (500 mg bid) or Levofloxacin (500 mg od) / Metronidazole (500 mg tid) for a further 5-7 days. The second alternative regime is the hybrid regime which has about an 89% eradication rate and consist of PPI/ Amoxicillin for 7 days then PPI/ Amoxicillin/ Clarithromycin/ Metronidazole for 7 days. The third alternative first line regime is levofloxacin triple therapy which consists of PPI/ Levofloxacin/ Amoxicillin for 10 to 14 days.

For rescue therapy four regimes were recommended by the ACG, a) bismuth quadruple therapy, Bismuth/ PPI/ Tetracycline/ Metronidazole for 14 days, b) concomitant or clarithromycin quadruple regime, PPI/ Clarithromycin/ Amoxicillin/ Metronidazole for 14 days, c) levofloxacin triple therapy, PPI/ Levofloxacin/ Amoxicillin for 14 days and d) rifabutin triple therapy, PPI/ Rifabutin/ Amoxicillin for 10 days.

The Maastricht V/Florence Consensus Report was published in 2017.[22] The recommendations cautioned against the use of the PPI triple therapy, PPI/ Amoxicillin/ Clarithromycin as first line therapy and recommend its use only in areas where the resistance rate to clarithromycin is low (<15%) and should be given for 14 days, if used. The two first line recommendations were a) bismuth quadruple therapy, Bismuth/ PPI/ Tetracycline/ Metronidazole. The alternative first line therapy is the b) concomitant or clarithromycin quadruple regime, PPI/ Clarithromycin/ Amoxicillin/ Metronidazole.

For rescue therapy, the recommendation was the use of bismuth quadruple therapy in patients failing concomitant therapy or the use of concomitant therapy in patients failing bismuth therapy. The alternative rescue therapy recommended were levofloxacin triple therapy, PPI/ Levofloxacin/ Amoxicillin or rifabutin triple therapy, PPI/ Rifabutin/ Amoxicillin.
CONCLUSIONS
In conclusion, first line regimes are most important for successful eradication. Quadruple therapy, either bismuth (bismuth/ PPI/ tetracycline/ metronidazole) or concomitant (PPI/ clarithromycin/ amoxicillin/ metronidazole) is recommended for first line therapy. For treatment failure bismuth quadruple therapy, levofloxacin triple therapy and rifbutin triple therapy are recommended. Knowledge of sensitivity and resistance patterns for the common antibiotics used or the success of a particular regime in the local area is important for successful eradication therapy.

Conflict of Interest
The Authors declare no conflict of interest.

REFERENCES