Journal of Tropical Diseases
ISSN: 2329-891X

Nicholas Martinez et al., J Trop Dis 2014, 2:1
DOI: 10.4172/2329-891X.1000129

Review Article Open Access

Management of *Helicobacter Pylori* Infection

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Abstract

Helicobacter pylori (H. pylori) is one of the most prevalent bacterial infections within the world and has been clearly associated with peptic ulcer disease, gastric adenocarcinoma, gastric Mucosa-associated Lymphoid Tissue (MALT) lymphomas, idiopathic thrombocytopenia purpura, sideropenic anemia and vitamin B12 deficiency. Multiple worldwide studies have been conducted to identify the optimal therapeutic regimen for *H pylori*. This article aims to review the evidence behind triple therapy, quadruple therapy, sequential therapy and other therapeutic regimens in the eradication of this problematic disease.

Keywords: Helicobacter pylori; *H. pylori*; Treatment

Introduction

Since the initial isolation of *Helicobacter pylori (H. pylori)* in 1982 by Warren and Marshall, the diagnosis and treatment of *H. pylori* has remained problematic [1]. Although the incidence varies by geographic location and socioeconomic conditions, *H. pylori* remains one of the most common bacterial infections in the world [2]. The estimated incidence of *H. pylori* within the United States is 30-40% [3]. The association between *H. pylori and* gastric ulcers, duodenal ulcers, gastric adenocarcinoma, gastric MALT lymphomas and specific anemias has been clearly established [4-8]. Testing for *H. pylori* in these conditions as well as patients experiencing dyspeptic symptoms is generally recommended [9]. A number of testing options are available including biopsy based (histology, rapid urease testing, culture, rapid polymerase testing), serology, 13C urea breath testing and stool antigen, however each test possess their individual advantage and disadvantage [10-12]. Once the diagnosis is established, multiple treatment regimens are available yet the optimal treatment regimen has not been established. We aim to review the treatment options in the management of *H. pylori* infection.

Initial Therapy

Triple therapy

Standard triple therapy within the United States includes: standard dose twice daily Proton Pump Inhibitor (PPI), Clarithromycin 500 mg twice daily and Amoxicillin 1,000 mg twice daily for a total of 7 to 14 days. PPI include: Lansoprazole 30 mg, Omeprazole 20 mg, Pantoprazole and Rabeprazole 20 mg. The initial eradication rates using the above treatment were reported to be between 71.9-83.8% [9,13,14]. However, more recent data has suggested that this combination has lost efficacy with a maximum eradication rate of 70% [15]. The decision to treat *H. pylori* with triple therapy should be based on the incidence of Clarithromycin resistance in the clinician's geographic location. Triple therapy should be considered a first line treatment if Clarithromycin resistance is less than 15% [16]. If the level of resistance is greater than 15%, alternative regimens should be considered. In patients with a Penicillin allergy, Metronidazole 500 mg twice daily can be used with comparable eradication rates (81%) [17]. In patients who are unable to tolerate PPI therapy, a randomized control study of 101 patients suggests similar eradication rates with H2-receptor antagonists (86% in PPI group versus 94% in Nizatidine group, P = 0.3) [18]. A meta-analysis of 21 studies evaluating the eradication efficacy of prolonged treatment duration of standard triple therapy demonstrated a relative risk for eradication of 1.05 in 7-day treatment when compared to 10-day treatment [19]. The same study demonstrated a relative risk for eradication of 1.07 for 7-day treatment compared to 14-day therapy; thereby suggesting that extending triple beyond seven days may not improve eradication response.

Quadruple

Bismuth quadruple therapy entails: bismuth 525 mg four times daily, metronidazole 250 mg four times daily, tetracycline 500 mg four times daily and a standard dose PPI for a total of 7-14 days. Given the reported eradication rate of 87%, some authors advocate bismuth based quadruple therapy as first line therapy for *H pylori* [20-22]. Clinicians may consider Bismuth based quadruple therapy as first line treatment in areas of high clarithromycin resistance (> 15 percent) or in patients with a documented penicillin allergy [16,23]. The regions within the United States that carry a high clarithromycin resistance include: the mid-Atlantic and Northeast, however the overall incidence of clarithromycin resistance appears to be rising. One limiting factor of quadruple therapy is the complexity of QID dosing and pill burden. A number of simplified bismuth regimens have been evaluated with similar eradication rates. Graham et al, reports a 92.3% eradication rate with twice daily quadruple therapy (Bismuth, Metronidazole, Rabeprazole and Tetracyline) [24]. The side effect profile of standard triple therapy versus quadruple therapy appears equivocal as the overall adverse event rate in the quadruple therapy treatment arm was 58.5% compared to 59.0% in the triple therapy arm [25,26]. Symptoms included: diarrhea, dyspepsia, nausea, abdominal pain, and taste perversion, changes in stool color or firmness and headache.

Sequential therapy

Despite the eradication success of triple and quadruple therapy, alternative therapeutic regimens have been evaluated in the setting

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Received December 16, 2013; **Accepted** January 21, 2014; **Published** January 23, 2014

Citation: Nicholas Martinez MD, Karthik Garapati MD, Charles Randall MD (2014) Management of *Helicobacter Pylori* Infection. J Trop Dis 2: 129. doi: 10.4172/2329-891X.1000129

of increasing antibiotic resistance. Sequential therapy: twice daily PPI with Amoxicillin 1000 mg twice daily for five days, followed by PPI, Clarithromycin 500 mg twice daily and Tinidazole 500 mg twice daily for five days appears equally effective as quadruple therapy (93.3%) [27]. In patients with a penicillin or clarithromycin allergy, Levofloxacin 250 mg twice daily can be substituted. One study demonstrated 89% eradication rate in patients with Clarithromycin resistant strains [28]. Sequential therapy still represents a reasonable first line regimen despite Clarithromycin resistance however in the presence of dual Clarithromycin and Metronidazole resistance, the eradication rate is significantly reduced to 33.3% [27]. Other potential factors in the eradication rates of sequential therapy include the cost of treatment and adverse event rate. The estimated cost of a ten day course of sequential therapy is $164.20. The overall self reported adverse rates were 17.5 and 17.1% in the sequential therapy and standard triple therapy treatment arms, respectively.

Concomitant therapy

Concomitant therapy entails: Standard dose PPI, Amoxicillin 1000 mg twice daily, Clarithromycin 50m mg twice daily and Metronidazole 500 mg twice daily for 10-14 days. It is similar to sequential therapy in terms of eradication with an eradication rate of 94% and maybe a simpler regimen when compared to sequential therapy as all antibiotics are given at once [29]. A randomized trial comparing sequential and concomitant therapy, demonstrated comparable eradication rates (92.3% versus 93%, respectively) and similar adverse event rates (30.7% versus 26.9%) [27]. A regimen consisting of: esomeprazole and amoxicillin for seven days then esomeprazole, amoxicillin, clarithromycin, and metronidazole for 7 seven days (sequential-concomitant hybrid therapy) generated a 99.1% eradication rate in 117 patients [30].

Flouroquinolones based therapy

Levofloxacin based triple therapy has been previously evaluated as a potential treatment regimen for *H. pylori* eradication [31-34]. Therapy entails: Levofloxacin 500 mg daily, Amoxicillin 1000 mg BID and standard dose PPI for a total ten days. The reported eradication rate is 87% [34]. A previous randomized control study comparing Levofloxacin 250 mg daily, omeprazole 40 mg daily Nitazoxanide 500 mg twice daily and Doxycycline 100 mg daily for 7 and 10 days (LOAD 7, LOAD 10) demonstrated 89.4% and 90% eradication rates respectively [35,36]. Levofloxacin may thus represent a reasonable treatment regimen in the setting of Clarithromycin resistance however the 2007 American College of Gastroenterology guidelines suggest that although these results are encouraging, further validation within the United States is warranted.

Testing for Eradication

Non-endoscopic evaluation for the eradication of *H. pylori* is generally recommended 4 weeks after completion of therapy. A urea breath test or a fecal antigen test is the most common tested used to ensure eradication. We prefer the fecal antigen test as the post treatment sensitivity and specificity are 95 and 97%, respectively and is also endorsed by the USDA and Maastricht consensus [9,14,37]. The sensitivity of the urea breath test and fecal antigen are reduced with concurrent PPI, bismuth or antibiotics. It is generally recommended that PPI be held 7-14 days prior to urea breathe test.

Treatment Failure

Despite the above success in the eradication of *H pylori*, 20% of patients fail initial therapy. A previous meta-analysis of 16 articles with a pooled analysis of 75 treatment arms indicated that re-treatment with PPI based triple therapy or bismuth-based quadruple therapy carries a 69.8% and 75.8% re-eradication rate [38]. Re-treatment in a persistent *H. pylori* infection should avoid antibiotics that have been previously prescribed; i.e. if PPI based triple therapy was used as an initial therapy, bismuth based quadruple therapy or LOAD therapy should be considered. A previous study by Dore et al suggests that the optimal salvage therapy should include: Omeprazole 20 mg, Tetracycline 500 mg, Metronidazole and Bismuth subcitrate 240 mg twice daily with mid and evening meals for 14 days as 93% of patients achieved eradication [39].

Summary

H. pylorus remains a problematic and prevalent disease. A number of treatment regimens are in the clinician's arsenal however standard PPI based triple therapy and bismuth based quadruple therapy remain first line as the eradication rates remain relatively high (70-80%). The increase in clarithromycin resistance has led to the investigation of other therapeutic options including: Sequential therapy, Concomitant therapy and Levofloxacin based therapy as additional therapeutic regimens [40,41]. Confirming eradication is crucial and in the setting of persistent infection, bismuth based salvage therapy appears to represent a reasonable approach for salvage therapy.

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