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Review Article

Helicobacter pylori Gastritis

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Abstract

Introduction: *Helicobacter pylori* (*H. pylori*) is the most prevalent bacterial infection affecting the humankind. Infection with *H. pylori* is incriminated with gastritis, peptic ulcer disease, gastric adenocarcinoma and gastric lymphoma.

Aim of Work: In this review, discussion of different aspects of *H. pylori* infection and associated gastritis will be presented; including epidemiology, pathophysiology, testing, and management approaches.

Methodology: A comprehensive and systematic search was conducted regarding *H. pylori* infection, *H. pylori* gastritis, diagnosis, and eradication. PubMed search engine and Google Scholar search engine were the mainly used database.

Conclusion: Socioeconomic status and living conditions play important role in acquisition of *H. pylori* infection early in life. Random testing for *H. pylori* infection is not indicated. Testing for *H. pylori* should be performed only when treatment of positive results is considered. The choice of initial test to diagnose *H. pylori* depends on whether upper endoscopy is planned or not, and recent use of some medication as PPIs. Endoscopy is not indicated to only diagnose *H. pylori* infection. Non-invasive tests of active *H. pylori* infection include stool antigen and urea breath test. Once the *H. pylori* infection is established, all patients should be treated. The initial antibiotic medication is guided by the presence of risk factors for macrolide resistance or history of penicillin allergy. Antibiotic regimens for *H. pylori* could be classified to 3 broad categories: bismuth, clarithromycin, and levofloxacin based regimens. Guideline and societies recommend extended duration of antibiotic therapy for 14 days.

Keywords: *Helicobacter pylori (H. pylori); Gastritis, Peptic Ulcer Disease, Gastric Adenocarcinoma; Gastric Lymphoma*

Introduction

Helicobacter pylori (*H. pylori*) is the most prevalent bacterial infection affecting the humankind [1,2]. In 1982, Marshall and Warren were able to identified and cultured gastric bacterium *H. pylori* for the first time [3]. This has led to better understanding of their role in gastritis and other conditions. Infection with *H. pylori* is incriminated with gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric lymphoma [4-7].

Gastritis implies inflammation of gastric mucosal while injury of mucosa without inflammation is regarded as gastropathy [8,9]. Multiple antibiotic regimens have been evaluated for infection with *Helicobacter pylori* [10-15]. However, fewer regimens have had consistent high eradication rates. In addition, data on *H. pylori* antibiotic resistance is scarce. The choice of optimal drug regimen depends on many factors as local antibiotic resistance, previous exposure and allergies to specific antibiotics, tolerability, and affordability.

In this review, discussion of different aspects of *H. pylori* infection and associated gastritis will be presented; including epidemiology, pathophysiology, testing, and management approaches.

Methodology

A comprehensive and systematic search was conducted regarding *H. pylori* infection, *H. pylori* gastritis, diagnosis, and eradication. PubMed search engine and Google Scholar search engine were the mainly used database. All relevant available and accessible articles of all types were reviewed and included. The terms used in search were: *Helicobacter pylori*, *H. pylori*, epidemiology, prevalence, diagnostic test, management, and eradication.

Epidemiology

H. pylori infection is the most common chronic bacterial infection worldwide [1,2]. Genetic sequencing studies estimated the presence of *H. pylori* infection since first migration from Africa around 58,000 years ago [16]. It is not exaggerative to say that about 50 percent of our planet population of all ages have *H. pylori* infection. Infection is more common in younger age in developing compared with industrialized countries [2]. Some studies suggest that most infections are acquired during childhood (some suggests before the age of 5) even in developed countries [2,17,18]. Once acquired, *H. pylori* infection persist with or without symptoms. Since the organism could be cultured from vomitus and stools, the transmission among family members during periods of illness is postulated [19,20]. African American and Hispanics are at higher risk compared with white population; these observation could be partially explained by socioeconomic differences [21,22]. Socioeconomic status and living conditions play important role in acquisition of *H. pylori* infection early in life. Overcrowding, number of siblings, sharing a bed, and lack of running water have all been linked to a higher rate of infection [23-25]. In Japan, economic improvement has been associated with decline in prevalence; the prevalence was 70 - 80, 45, and 25 percent of adults born before the fifties, in the fifties, and in the sixties respectively [26]. This rapid decline of infection has been attributed to economic development and sanitation improvement.

Pathophysiology of H. pylori gastritis

It is estimated that two-thirds of the world's population are affected by *H. pylori* gastritis; rendering it among top common chronic inflammatory and infectious disorders [27]. Most patients with *H. pylori* infection will show features of both acute and chronic gastritis. The organism resides primarily adjacent to epithelial cells at gastric mucosal surface and in gastric pits with affinity to mucous cells [28-30]. Gastric glands, other epithelial cells, and small intestine are usually not involved. The early stage of *H. pylori* gastritis start as antral predominant with minimal corpus involvement. In this early stage, excessive gastrin release and reduced somatostatin release occur. This leads to an increase in acid secretion, enough to cause duodenal ulcers in some patients [31]. Persistent inflammation causes loss of gastrin producing (G) cells and acid producing parietal cells with subsequent fall in acid secretion and the development of atrophy with

intestinal metaplasia [32]. These changes facilitate ascending migration of the bacteria, leading to corpus gastritis [33]. Chronic therapy with proton pump inhibitors (PPIs) accelerates the progression of *H. pylori* due to reducing hydrochloric acid secretion.

Indications for testing

Random testing for *H. pylori* infection is not indicated. Testing for *H. pylori* should be performed only when treatment of positive results is considered. Solid indications for testing include: suspicion of Low grade gastric mucosa associated lymphoid tissue (MALT) lymphoma; active peptic ulcer disease; early gastric cancer. Other indications for testing are controversial as limited data support the benefits [5,34-37]. Some studies have suggested testing < 60 years of age complaining of dyspepsia without any alarm features that indicate serious conditions [38,39]. As *H. pylori* is incriminated with the risk of gastric and duodenal ulcers and ulcer bleeding, it is proposed to test for it prior to aspirin and non-steroidal anti-inflammatory drugs as these drugs increase the risk of ulcers and complications. *H. pylori* can cause iron deficiency and iron deficiency anemia by interfering with absorption of oral iron. When patient is presented with unexplained iron deficiency, testing for *H. pylori* should be bore in mind. In addition, adults with immune thrombocytopenia may benefits from *H. pylori* eradication. However, the evidence for such benefits is limited.

The choice of initial test to diagnose *H. pylori* depends on whether upper endoscopy is planned or not. Endoscopy is not indicated to only diagnose *H. pylori* infection. When endoscopy is not indicated for other purposes, non-invasive tests of active *H. pylori* infection as stool antigen and urea breath test should be used. Additional factor that affect the choice of test is recent use of medications that may suppress the bacterial load of *H. pylori* (as PPIs and antibiotics), test availability, and cost. Optimally, patient should abstain from PPI for 1 - 2 weeks prior to test, and bismuth and/or antibiotic for 4 weeks of testing. These drugs decrease the sensitivity of all tests.

H. pylori hydrolysis urea to produce CO_2 and ammonia. The idea of Urea breath testing (UBT) is detecting the CO_2 in breath sample. To do that, urea is labeled with carbon isotope and given by mouth; labeled CO_2 is detected. The tests is easy, cheap, and fast (15 - 20 minutes). The sensitivity and specificity of UBT are approximately 88 to 95 percent and 95 to 100 percent, respectively [40]. Hence, a positive result is diagnostic. However, false-negative results may occur in patients on PPIs, bismuth, or antibiotics, or in the setting of active peptic ulcer bleeding [41,42].

Another non-invasive test is stool analysis for detection of *H. pylori* antigen. Positive results indicates an ongoing *H. pylori* infection. Hence, stool antigen testing can be used to establish the diagnosis and to confirm successful eradication [6]. The test is considered as the most cost-effective test of all tests in areas of low to intermediate prevalence of *H. pylori* [43]. The sensitivity and specificity of the laboratory-based monoclonal enzyme immunoassay are comparable to the UBT; the sensitivity is about 94 percent while the specificity is about 97 percent [44-48]. Similar to UBT, stool antigen testing is affected by bismuth, antibiotics, and PPIs. Therefore, patient should abstain from PPI for 1 - 2 weeks, bismuth and/or antibiotic for 4 weeks prior to test. In the setting of active bleeding from peptic ulcers, the specificity-but not the sensitivity- of the stool antigen testing may decrease [49,50].

Stool antigen testing using the polyclonal enzyme immunoassay is obsolete due to low sensitivity. The rapid in-office monoclonal immunochromatographic stool antigen tests has high specificity but low sensitivity renders its use less favorable [51].

Management: general consideration

Once the *H. pylori* infection is established, all patients should be treated. The initial antibiotic medication is guided by the presence of risk factors for macrolide resistance or history of penicillin allergy [52]. In patients with one or more risk factors for macrolide resistance, clarithromycin category should be avoided. Such risk factors include a prior exposure to macrolide therapy for any reason and high clarithromycin resistance rates ≥ 15 percent in the area or eradication rates with clarithromycin triple therapy ≤ 85 percent. The 15percent cut-off is commonly used [5,53]. Alternatively, bismuth quadruple therapy is recommended [5,6,52-55]. It is worth mentioning that the resistance rate may not be known in many areas and the percentage is some time guessed based on expert assumption [56]. Generally, data

frequently suggest that antibiotics for *H. pylori* infection have high resistance rates worldwide. In a systematic review and meta-analysis of 178 studies, from 65 countries, primary and secondary resistance to clarithromycin, metronidazole, and levofloxacin were high in the majority regions [57]. If risk factors for macrolide resistance are not present, clarithromycin-based triple therapy is the initial regimen to be used. The triple therapy include a proton pump inhibitor (PPI), amoxicillin, and clarithromycin. Other first-line antibiotic regimens for these patients include bismuth quadruple therapy and clarithromycin-based concomitant therapy.

In penicillin-allergic individuals, amoxicillin could be replaced by metronidazole. If the patients report metronidazole exposure within the past few years, bismuth quadruple therapy is the best option.

Guideline and societies recommend extended duration of antibiotic therapy for *H. pylori* associated infection. Clarithromycin-based triple therapy and bismuth quadruple treatment regimens should be taken for 14 days [5,6,53].

Management: antibiotic regimens

Antibiotic regimens for *H. pylori* could be classified to 3 broad categories: bismuth, clarithromycin, and levofloxacin based regimens.

The first category is bismuth-based quadruple therapy. It consists of bismuth subsalicylate, metronidazole, tetracycline, and a proton pump inhibitors (PPIs). The duration of treatment should be extended to 14 days [58]. This could be administered as separated formula or as a combination capsule. The FDA has approved a combination capsule that contains bismuth, metronidazole, and tetracycline. A regimen using the combination capsule is easier than standard quadruple therapy and could result in better adherence. Doxycycline could be used instead of tetracycline when it is not available [59,60]. Trials have found that 10 days of bismuth quadruple therapy lead to *H. pylori* eradication in was 91 percent of patient [6,61,62]. Recent meta-analysis on 12 randomized trials reported that bismuth quadruple therapy and clarithromycin triple therapy have comparable eradication rates [63]. Cases with metronidazole resistance will have similar eradication rates, this problem could be overcame by increasing the dose, duration, or frequency of therapy [64].

Clarithromycin-based category consists of different combination and approaches. The triple therapy comprises clarithromycin, amoxicillin, and a PPI. All these drugs are given twice daily. Similar to bismuth-based therapy, extended duration is recommended (14 days) as it is associated with higher eradication success [52,53,65]. Metronidazole could be used as an alternative to amoxicillin in penicillin-allergic individuals; however, metronidazole should be taken 3 times per day instead of two. Clarithromycin-metronidazole-PPI and clarithromycin-amoxicillin-PPIs are equivalent [5,66]. Successful eradication by clarithromycin triple therapy depends mainly on regional clarithromycin resistant [63,67]. In the United States, the eradication rates are below 80 percent [52]. In a meta-analysis of two trials, eradication rates for clarithromycin-sensitive *H. pylori* were 90% compared with only 22% in clarithromycin-resistant *H. pylori* [67].

Metronidazole and amoxicillin could be used together and the combination is called clarithromycin concomitant therapy. Hence, it comprises clarithromycin, amoxicillin, metronidazole (or tinidazole) and a PPI. In a meta-analysis of 19 randomized trials from Europe, Asia and Latin America, eradication rates were significantly higher with concomitant quadruple therapy as compared with clarithromycin triple therapy [68]. The efficacy of concomitant therapy was decreased in patients with clarithromycin-resistant *H. pylori* infection but to a smaller degree as compared with clarithromycin triple therapy. Clarithromycin-based hybrid therapy consists of amoxicillin and a PPI for seven days followed by concomitant therapy for seven days. Due to schedule complexity, the hybrid therapy is less commonly used as a first-line regimen. The eradication rate of hybrid therapy was estimated to be 89 percent in one meta-analysis of six randomized trials [69]. The regimen efficacy and tolerability is similar to that of concomitant and sequential regimens [70]. In the reverse hybrid therapy, the patient takes clarithromycin plus metronidazole in the first 7 days, amoxicillin and PPI for 12. This approach was associated with higher eradication rates compared with the conventional triple therapy [71]. Interestingly, the presence of clarithromycin resistance did not impact eradication rates in patients treated with reverse hybrid therapy.

Clarithromycin-based Sequential therapy is another approach of 10 days duration. Patients start with amoxicillin and a PPI for five days, followed by clarithromycin, metronidazole, and PPI for another five days [72]. Similar to hybrid therapy, the approach is considered complex with no superior benefits compared with the conventional triple therapy [53].

The third broad category of *H. pylori* antibiotic is Levofloxacin-based therapy. It is been suggested, though the evidence is limited, the presence of high resistance rates in North America [57]. The presence of resistance renders levofloxacin less effective in *H. pylori* eradication by 20 - 40 percent [52]. However, based on some trials, levofloxacin triple therapy may have a role as salvage regimen [52]. Levofloxacin triple therapy consists of levofloxacin, amoxicillin, and a PPIs. As all regimens, the duration of therapy should be extended for 10 - 14 days. In one meta-analysis, the eradication rates of 10 - 14 days levofloxacin triple were significantly higher than clarithromycin triple therapy for 7 days [70]. Pooling the eradication rates of levofloxacin triple therapy showed a higher success than clarithromycin triple therapy for 10 to 14 days. Similar to clarithromycin triple therapy, metronidazole could be used instead of amoxicillin in penicillin-allergic individuals. Levofloxacin quadruple therapy consist of the same three drugs of triple therapy plus doxycycline. Fewer data have examined the efficacy of this regimen. One open-label trial suggests a higher eradication rates with quadruple therapy for 7 - 10 days compared with clarithromycin triple therapy for 10 days [73]. More studies are needed to confirm the cost-effectiveness of such results. Another approach of levofloxacin-based therapy is sequential approach. Sequential therapy consists of amoxicillin and a PPI for 5 - 7 days followed by levofloxacin, amoxicillin, a metronidazole and a PPI for similar period. The eradication rates of 10 - 14 days sequential therapy was higher than clarithromycin triple therapy for 7-14 days or standard sequential therapy for 10 days, as shown in a meta-analysis of 6 randomized trials [74].

Summary and Conclusion

Helicobacter pylori was first identified and cultured in 1982. Genetic sequencing studies estimated the presence of *H. pylori* infection since first migration from Africa around 58,000 years ago. *H. pylori* is the most prevalent bacterial infection affecting the humankind. It is not exaggerative to say that about 50 percent of our planet population of all ages. The organism is incriminated with gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric lymphoma. Socioeconomic status and living conditions play important role in acquisition of *H. pylori* infection early in life. Overcrowding, number of siblings, sharing a bed, and lack of running water have all been linked to a higher rate of infection.

Random testing for *H. pylori* infection is not indicated. Testing for *H. pylori* should be performed only when treatment of positive results is considered. The choice of initial test to diagnose *H. pylori* depends on whether upper endoscopy is planned or not, and recent use of some medication as PPIs. Endoscopy is not indicated to only diagnose *H. pylori* infection. Non-invasive tests of active *H. pylori* infection include stool antigen and urea breath test.

Once the *H. pylori* infection is established, all patients should be treated. The initial antibiotic medication is guided by the presence of risk factors for macrolide resistance or history of penicillin allergy. Antibiotic regimens for *H. pylori* could be classified to 3 broad categories: bismuth, clarithromycin, and levofloxacin based regimens. Guideline and societies recommend extended duration of antibiotic therapy; Clarithromycin-based triple therapy and bismuth quadruple treatment regimens should be taken for 14 days.

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