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REVIEW

Approach to *Helicobacter pylori* infection in geriatric population

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Abstract

The prevalence of *Helicobacter pylori* (*H. pylori*) infection and its complications increase with age. The majority of infected individuals remain asymptomatic throughout the life but 10%-20% develops peptic ulcer disease and 1% gastric malignancies. The incidence of ulcers and their complications are more common in the older population resulting in higher hospitalization and mortality rates. The increased use of medications causing gastric mucosal damage and the decreased secretion of protective prostaglandins in elderly are major factors increasing gastric mucosal sensitivity to the destructive effects of *H. pylori*. Due to higher prevalence of gastrointestinal (GI) malignancies, upper GI endoscopy is mostly preferred in elderly for the diagnosis of infection. Therefore, "endoscopy and treat" strategy may be more appropriate instead of "test and treat" strategy for dyspeptic patients in older age. Urea breath test and stool antigen test can be used for control of eradication, except for special cases requiring follow-up with endoscopy. The indications for treatment and suggested eradication regimens are similar with other age groups; however, the eradication failure may be a more significant problem due to high antibiotic resistance and low compliance rate in elderly. Multidrug usage and drug interactions should always be considered before starting the treatment. This paper reviews briefly the epidemiology, diagnosis, disease manifestations, and treatment options of *H. pylori* in the geriatric population.

Key words: *Helicobacter pylori*; Epidemiology; Diagnosis; Treatment; Eradication; Elderly; Geriatrics; Geriatric population

Core tip: *Helicobacter pylori* (*H. pylori*) infection is more common in the older population and may cause significant complications with severe morbidity and mortality. There are similarities but also differences in the diagnosis and treatment of infection in elderly population than non-elderly. Health care providers to the geriatric population should take into consideration these nuances in the management of *H. pylori* infection in the older patients.

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INTRODUCTION

The discovery of *Helicobacter pylori (H. pylori)* by Marshall and Warren in 1983 resulted in a breakthrough in the understanding and management of gastric diseases. Currently, it is well known that *H. pylori* infection causes chronic gastritis that may progress into peptic ulcer

disease (PUD), gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma (MALToma)[1-3]. The ability of this bacterium to persist and establish a low-grade inflammatory state might induce an immunologic response that may influence the occurrence and progression of local and systemic diseases[4]. Indeed, *H. pylori,* now one of the best models for the investigation of infectious diseases, have been widely studied to the extent of finding its associations with extragastric disorders[5,6]. Despite the extensive knowledge on the virulence factors and immune manipulation mechanisms of *H. pylori*, there has been little success developing a vaccination for this organism[7]. Instead, eradication therapy is used for prevention and treatment. Recently, the eradication rates through the standard proton pump inhibitor (PPI)-based triple therapy has declined to unsatisfactory levels of 80% or less, possibly due to antibiotic resistance, poor compliance, and rapid metabolisms of PPI[8-10]. Therefore, several novel treatment regimens are emerging[11]. The frequency of *H. pylori* infection, its manifestations, and eradication options are variable and depend on many factors including age. In this review, we discuss the different aspects of *H. pylori* infection and its eradication in elderly.

H. PYLORI INFECTION IN GERIATRICS

Epidemiology

H. pylori infection becomes rarer in recent years especially in young and middle-aged populations due to improvements in the quality of healthcare and effective treatment options[12]. However, the rate of *H. pylori* infection and its complications are still increasing with age worldwide. Epidemiologic studies report higher prevalence of *H. pylori* infection in elderly with a ratio of over 70% in patients with gastrointestinal diseases and approximately 60% in asymptomatic patients[13,14]. Although the majority of the infected patients remain asymptomatic throughout the life, about 10%-20% of the patients will develop PUD, and 1% will develop gastric cancer and MALToma in addition to the possible extragastric complications[15,16]. Particularly elderly patients suffer from more serious complications resulting in higher hospitalization and mortality rates[17,18]. This difference in the geriatric population can be illustrated by several factors. Firstly, in an older patient, the presentation of *H. pylori* infection may be subtle or atypical, which may delay the diagnosis. With advanced age, the increased presence of concomitant diseases and multidrug therapy, especially medications causing gastric mucosal damage and bleeding (*e.g.,* nonsteroidal anti-inflammatory drugs (NSAID), bisphosphonates, antiplatelet drugs, warfarin), can lead to increased and severe complications of *H. pylori* infection[19]. In particular, NSAID and *H. pylori* are independently the two most important causes of peptic ulcer in adult population[20]. A meta-analysis showed that the peptic ulcer risk in *H. pylori* infected NSAID takers was 61 times more compared to *H. pylori* negative individuals not taking NSAID[21]. In parallel to this study, *H. pylori* infection in elderly NSAID users is also associated with a significantly increased ulcer risk, which should be a concern considering the common use of NSAID in elderly population[20]. Despite the unclear and rather complex synergy between *H. pylori* infection and NSAID, it is well known that both deteriorate mucosal defense mechanisms considerably. Besides, the decreased secretion of protective prostaglandins, as well as gastric acid (possibly due to fundal atrophic gastritis) with increased age can destruct the mucosal barrier[22,23]. Clinical studies performed in the United States have shown that the percentage of *H. pylori* screening in hospitalized elderly patients having PUD is only 40%-56%, with a 50%-73% treatment rate after a positive test result[24]. These results indicate that even if the clinical characteristics and epidemiologic distribution of *H. pylori* infection in the elderly have been extensively reported, the medical attention for the *H. pylori* infection in this population remains low.

Diagnosis

H. pylori infection can be diagnosed by noninvasive or invasive methods. The selection of the appropriate test may vary with the clinical setting[2,25,26]. Noninvasive tests include ^{13}C-urea breath test (UBT), stool antigen test (SAT), and serology. The UBT is a readily available test with an accuracy rate of > 97.9% in elderly patients regardless of the cognitive function, comorbidity, and co-treatment status[27-29]. The SAT is reported to have a sensitivity of 76%-81% and specificity of 80%-93% in hospitalized elderly patients[30,31], although these numbers may have been presumably improved with the recent advances in the SAT method. Currently, the laboratory SAT format (ELISA) with monoclonal antibodies is recommended rather than the rapid in-office test due to the significant difference in the accuracy[26]. Both UBT and SAT can be used for infection follow-up after eradication therapy because of their ability to detect active infection[26]. The serology test is a widely used and inexpensive test, but its diagnostic accuracy is variable[32] and only validated IgG tests should be used[26]. Positive serology may indicate a past infection, and thus it cannot be used for infection follow-up after eradication[33,34]. In elderly patients with immunodeficiency or protein malnutrition, false negative serology results may occur due to lack of antibody response[29,35]. However, serology is helpful in patients with low bacterial load (*e.g.*, use of antimicrobial and antisecretorial agents, bleeding, presence of malignant lesions, *etc.*) and therefore remains the only test that is not affected by local changes in the stomach. Also, for all invasive and noninvasive tests except for serology, discontinuation of PPI use for two weeks prior to testing is necessary[26].

Invasive techniques requiring an endoscopy are usually preferred in elderly patients due to the higher prevalence of gastrointestinal malignancies, as well as for their superiority in analyzing the severity of gastritis and detecting premalignant lesions[36,37]. *H. pylori* can be detected through histological examination or by indirect assess-

ment of the biopsy specimen with urease test, culture, or polymerase chain reaction (PCR) analysis[38,39]. The urease test provides inexpensive and rapid detection, however it has lower sensitivity in patients aged 60 years and older[38]. Cultures can assess the susceptibility of the strain to antimicrobial agents, which is important for the management of the infection[40]. Nonetheless, false negative results might be obtained with cultures due to frequent antibiotic use in elderly. PCR detection of *H. pylori* infection offers sensitive and accurate results rapidly and it is increasingly becoming popular. PCR assays allow simultaneous detection, quantification, genotyping, and virulence factor identification, as well as determination of antibiotic resistant and cancer susceptible strains of *H. pylori*[39,41]. Despite the common statement of histopathology being the "gold standard" for diagnosis of *H. Pylori* infection, its accuracy depends on sampling locations and presence of atrophic gastritis[42]. In addition, the frequent antibiotic and PPI use, as well as active and recent bleeding may alter the sensitivity. Therefore, discontinuation of PPIs two weeks prior to endoscopy, and specimen collection from both the body and antrum are recommended[42]. In particular, it has been recently reported that in patients with extensive gastric atrophy, the corpus greater curvature is the optimum biopsy site for histopathologic evaluation[43].

Although current guidelines recommend a general "test and treat" strategy for the uninvestigated dyspepsia[26], in populations with higher gastric cancer risk like elderly patients, "endoscope and treat" strategy is preferred especially considering the lower acurracy of the noninvasive tests in the elderly[44,45]. In addition, *H. pylori* infection in elderly might be asymptomatic or present with other symptoms than dyspepsia. For example, the inflammation caused by chronic *H. pylori* infection may result in atrophic gastritis and subsequently vitamin B12 deficiency[46]. Therefore, a complete work-up for *H. pylori* is not only limited to diagnostic tests for detecting the infection, but also includes the complications and comorbidities of the disease.

EFFECTS OF ERADICATION THERAPY ON *H. PYLORI* ASSOCIATED DISEASE MANIFESTATIONS

Peptic ulcer disease and associated bleeding

H. pylori infection and NSAID/aspirin use have independent and additive effects on the higher prevalence of PUD and ulcer bleeding in the elderly[47,48]. *H. pylori* positive NSAID users have an almost two fold increased risk of peptic ulcer bleeding compared to NSAID users without *H. pylori*[49]. Taken together with the increased likelihood of bleeding associated with NSAID use in elderly (approximately 7 times more frequent than young adults)[20], the concomitant presence of NSAID use and *H. pylori* infection in elderly should raise a potential concern for PUD and associated bleeding.

The eradication of *H. pylori* in elderly patients with PUD heals ulcers in over 95% of patients[50], improves symptoms in over 85% of patients[51], and dramatically lowers the recurrence rate from 41.6% to 2.2%[52]. For prevention of both duodenal ulcer recurrence (RR = 0.19) and gastric ulcer recurrence (RR = 0.31) *H. pylori* eradication is superior to no treatment[53].

It is well established that the eradication of *H. pylori* prior to use of NSAID/aspirin is beneficial in prevention of PUD and associated bleeding[54]. However, the influence of *H. pylori* eradication in NSAID/aspirin users is controversial. Based on multiple studies in this regard, the most recent Maastricht IV/ Florence Consensus Report[26] have slightly different recommendations for long term NSAID and low dose aspirin users. For NSAID users it is recommended to have continued PPI treatment in addition to *H. pylori* eradication. For low dose aspirin users, *H. pylori* test should be performed if there is a history of PUD. After eradication in these patients, the incidence of gastric bleeding remains low even without gastroprotective agents[26].

Functional dyspepsia and gastritis

Patients with dyspepsia and *H. pylori* infection are reported to have functional dyspepsia (FD) rather than PUD, although the eradication benefit is less evident in FD in comparison to PUD[26]. However, the long-term relief of dyspepsia has been shown in one of 12 patients with *H. pylori* and functional dyspepsia after *H. pylori* eradication, which is better than any other treatment[55].

Prolonged *H. pylori* infection is a well-recognized cause of different phenotypes of gastritis based on the topography of the colonization and inflammation in the stomach, including mild pangastritis, corpus, and antrum predominant gastritis, each with different clinical outcomes[2,26]. The antrum predominant gastritis, the most common form of *H. pylori* mediated gastritis, is usually associated with a normal to high secretion of gastric acid and an increased risk of duodenal ulcer disease[2,56]. On the other hand, the corpus predominant gastritis is usually associated with hypochlorhydria and results in an increased risk of developing gastric atrophy, intestinal metaplasia, and ultimately gastric carcinoma[2,48,57]. As the name implies, the patients with mild pangastritis do not have clinically significant disease. It needs to be noted that the different phenotypes are not completely separate entities, and antrum predominant gastritis may progress into the other types[2,56]. Regarding the effects of advancing age on gastritis, it has been shown that gastric acid secretion decreases with age only in *H. pylori* positive subjects[22]. This influence is probably due to the increasing prevalence of fundic atrophic gastritis in elderly[58]. Evidence suggests that eradication of *H. pylori* infection results in significant decrease in the activity of gastritis in elderly[59].

Gastric malignancies

H. pylori eradication may prevent gastric cancer[60]; however, its effects depend on the histological stage and gastric

localization. The progression of the premalignant lesions can be prevented with the eradication[61], whereas if intestinal metaplasia is established the eradication does not completely prevent the gastric cancer, although it might slow the progression[62,63]. A meta-analysis has shown that the eradication significantly improves corpus atrophy, but not antrum, and not intestinal metaplasia[64]. Therefore, the early diagnosis with endoscopy and treatment are important in elderly patients. For low grade MALTomas, *H. pylori* eradication is the first line treatment but the patients need to be followed up after the treatment in case the lymphoma fails to respond to the eradication[65].

Extragastric diseases

H. pylori has been associated not only with diseases of the gastrointestinal tract but also with extragastric diseases most of which are commonly seen in elderly population[6]. However, the causal or therapeutic links are stronger in some extragastric diseases than the others. The eradication is indicated in patients with unexplained iron deficiency anemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency with significantly clear evidence[66-70].

Multiple studies reported higher prevalence of *H. pylori* infection in patients with type 2 diabetes mellitus (DM), with one study analyzing the individuals older than 60 year old[6,71]. Some groups even propose an association between *H. pylori* infection and the metabolic syndrome, supported by the synergistic effect of *H. pylori* infection and higher body mass index (BMI) in increasing the level of glycosylated hemoglobin[72], the significant association of *H. pylori* seropositivity with both DM and insulin use, as well as the independent association of *H. pylori* positivity with microalbuminuria[73]. On the other hand, there are some other groups contesting these associations with opposite findings[74,75]. Therefore, for obesity and DM the evidence is unclear and further studies are warranted.

Some epidemiologic studies suggest the association of *H. pylori* infection and neurologic diseases such as stroke, Parkinson's and Alzheimer's diseases[6,76-78], as well as ischemic heart disease[79]. Nonetheless, the evidence is equivocal for *H. pylori* eradication and improvement of these diseases[26]. Lastly, the bioavailability of thyroxine and Capitalize L-dopa improves with *H. pylori* eradication, although there is no verification of direct clinical benefit to the patients[80,81].

ERADICATION THERAPY

The triple therapy of PPI, clarithromycin, and amoxicillin (or metronidazole) has been the standard for *H. pylori* eradication since 1997 when the first Maastricht conference report was published[82]. However, multiple studies have reported suboptimal efficacy of this regimen with cure rates of less than the initial aim of 80%[8-10,83-87]. The decrease in efficacy might be associated with increased resistance to clarithromycin, high bacterial load, strain types, high gastric acidity, and low compliance[26,88]. Among these factors, the clarithromycin resistance has been identified as the major contributor to the eradication failure. To improve the efficacy, different combinations of currently available antibiotics have been assessed[26,89,90]. Triple therapy with PPI, amoxicillin, and metronidazole has been proposed as an alternative to the standard therapy with cure rates of 82%-94%[91-94]. Sequential therapy including a 5-d period with PPI-amoxicillin, followed by a 5-d period with PPI, clarithromycin, metronidazole (or tinidazole) is another regimen that has been studied in different countries. A recent systematic review of 22 trials revealed that the sequential therapy is more effective than standard triple therapies, confirming that the sequential administration of drugs is a successful therapeutic intervention for *H. pylori* eradication. Whether the use of the modified sequential therapy with longer duration of sequential regimens is actually more advantageous than that of 10-d sequential therapy requires further studies[95,96]. Non-bismuth quadruple therapy, also called "concomitant therapy", has been offered as a more convenient regimen for the patient, which involves all three antibiotics to be taken simultaneously together with a PPI for a period of 10-14 d. A recent meta-analysis from 19 studies (2070 patients) on concomitant therapy revealed a mean of 88% cure rate, superior to standard triple therapy, with a safe and well-tolerated profile[97].

The rate of the clarithromycin resistance is variable in different regions, with a threshold of 15%-20% prevalence to classify low or high clarithromycin resistance[26]. The clarithromycin resistance determines the approach to *H. pylori* eradication. In regions with low resistance, the standard triple therapy including clarithromycin is still recommended as first line regimen[26]. Different ways of improving the effectiveness of PPI-clarithromycin-containing regimens have been proposed including increasing the dosage and timing. Significant evidence from multiple studies suggests that high-dose PPIs increase in the cure rates up to 10% in comparison with standard doses[98]. Extension of PPI-clarithromycin-containing triple therapies from 7-d to 10-14 d has been shown to increase the eradication rate by about 5% without significant difference in the rate of side effects[99,100]. Bismuth-containing quadruple therapy may be either the first line regimen in a low clarithromycin resistance region or the second line therapy if PPI-clarithromycin containing triple therapy fails. An alternative second line treatment in this population is levofloxacin-containing triple therapy. After two treatment failures, third line treatment should be guided by antimicrobial susceptibility testing[26].

In regions with high clarithromycin resistance, bismuth-containing quadruple treatment has been suggested as the first line regimen[26]. This regimen achieved a significantly better eradication rate compared to standard triple therapy (82% *vs* 62%) in a population with high clarithromycin resistance[101]. If the bismuth-containing quadruple therapy is not available, sequential treatment or a non-bismuth quadruple therapy is may be administered. Similar to the low clarithromycin resistance regions, if the first line treatment fails in a high resistance region, it may be followed by levofloxacin-containing triple therapy as

the second line, and antibiotic susceptibility guided treatment as the third line therapy[26].

In the light of above-mentioned guidelines for *H. pylori* eradication, there are several issues to be emphasized in elderly population. Firstly, antibiotic resistance is particularly important in elderly due to increased prevalence of drug consumption and lower compliance potential in this population[102,103]. The health care providers should be especially cautious about the emerging levofloxacin resistance primarily in patients with chronic infectious bronchopneumopathy as they may have already received fluoroquinolones[26]. Structured patient counseling and follow-up might improve the patient compliance and efficacy of the therapy[104] and therefore, assist preventing antibiotic resistance. Secondly, the drug interaction is of significant importance in elderly population in whom polypharmacy is a common occurrence. Although the choice of PPI in *H. pylori* eradication does not affect the treatment success when used in standard doses[87], different PPIs might have different drug interactions. Omeprazole is the PPI that is most likely to have drug interactions particularly with cardiovascular drugs and clopidogrel, both of which commonly used in elderly. On the other hand, pantoprazole is the least likely PPI to interact with clopidogrel[105]. Similarly, frequently used antibiotics for eradication such as clarithromycin, amoxicillin, metronidazole, and tetracycline may also have important drug interactions with commonly used medications in elderly[106]. Although it is not easy to determine the effects of a particular drug's interaction in the large number of variables, cardiovascular drugs such as statins, antiarrhythmic drugs, and warfarin are among the well-established drugs which may interact with these antibiotics[106]. If the risk of interaction outweighs the benefit, the eradication treatment should be avoided or suspended. In addition, some co-morbidities in the elderly might require additional modification in the treatment plan. For example, while metronidazole can be used without dosage alteration in patients with renal failure, amoxicillin and clarithromycin require dose adjustment in patients with creatinine clearance less than 30 mL/min. These antibiotics may cause transient and mild elevation in the liver enzymes, but severe hepatotoxicity is unusual particularly in short term usage. Dosage adjustments for PPIs are not necessary in elderly patients or those with renal failure or mild hepatic impairment[106].

Last but not least, as the complications of *H. pylori* infection are increased with age, the proper follow-up testing needs to be conducted after eradication therapy to prevent further progression of the disease. While patients with gastric ulcer or gastric MALToma, or severe gastritis should be evaluated by endoscopy after therapy, the remaining situations may be followed-up with noninvasive methods (UBT or laboratory-based validated monoclonal SAT)[26,106].

CONCLUSION

H. pylori infection is a prevalent health problem in the older patients due to multiple factors increasing the potential damage of bacteria to gastric mucosa. The comorbidities and multidrug therapy can lead to increased and severe complications of *H. pylori* infection. The invasive tests using upper GI endoscopy should be preferred for the diagnosis of infection. The therapeutic approach suggested by the Maastricht IV Consensus Report is also suitable for older patients; however, the eradication failure may be a more significant problem due to high antibiotic resistance and low compliance rate. The expectation from eradication therapy in these patients should meet the therapeutic goals and therefore, the health care providers should take into account the specific characteristics of geriatric population.

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