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Review

Diagnosis and treatment of *Helicobacter pylori* infections in children and elderly populations

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Abstract

Helicobacter pylori (*H. pylori*) infection is associated with various gastric and extra-gastric diseases. Importantly, this infection is the strongest known risk factor for gastric cancer (GC). *H. pylori* eradication can effectively prevent *H. pylori* infection-associated diseases in *H. pylori*-positive patients, including children and elderly subjects. However, a limited selection of antibiotics, a higher reinfection rate, and certain spontaneous clearance rates, to some extent, restrict the choice of *H. pylori* treatments in pediatrics. In addition, it is imperative to perform an accurate diagnosis of *H. pylori* infection in children by determining the presence of the *H. pylori* infection and the underlying cause of symptoms. In elderly patients, poor tolerance to drugs and higher sensitivity to adverse effects are major concerns during *H. pylori* therapy. Recent studies have demonstrated that *H. pylori* eradication could significantly lower the GC risk in the elderly population. The benefit and risk of *H. pylori* eradication in elderly patients should be comprehensively considered and balanced. If available, susceptibility-based tailored therapies may be preferable in eradicating *H. pylori*. In addition, to increase the eradication rate and reduce adverse effects, new therapeutic strategies (e.g., probiotic supplementation, berberine supplementation, dual therapy) for *H. pylori* infection are being extensively investigated. The impact of *H. pylori* eradication with antibiotics on the microbiota in children has been explored, but further high-quality studies are crucial to delineate the extent of *H. pylori* eradication affecting the microbial community in children. In this review, we summarize the current understanding of *H. pylori* diagnosis and treatment in children and the elderly population and aim to provide insights into the efficient management and treatment implementation in these populations.

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Introduction

Helicobacter pylori (*H. pylori*), a Gram-negative bacterium that colonizes the mucosa of the human stomach and infects over half the world's population, can induce chronic gastritis, peptic ulcers, and gastric mucosa-associated lymphoid tissue lymphoma.[1] The International Agency for the Research on Cancer (IARC) classified *H. pylori* as a Group 1 carcinogen in 1994.[2] *H. pylori* infection is the strongest risk factor for gastric cancer (GC), with at least 90% of GC attributed to *H. pylori* infection.[3] *H. pylori*-induced gastritis has been defined as an infectious disease in multiple guidelines.[4−6] The routes of *H. pylori* transmission are considered to be oral−oral, fecal-oral, or gastro-oral.[7] Furthermore, *H. pylori* prevalence varies in different geographic areas. High *H. pylori* prevalence is commonly considered to be associated with poor sanitary conditions and a low socioeconomic status. A meta-analysis indicated that among individual countries, the prevalence of *H. pylori* infection varied from as low as 18.9% in Switzerland to 87.7% in Nigeria.[1] The *H. pylori* prevalence remained high in most countries despite a decreasing trend observed for *H. pylori* infection rates in some developed countries.[1,8,9] Successful *H. pylori* eradication can effectively prevent *H. pylori*-associated diseases. The efficacy of standard triple therapy has been significantly decreased owing to increased antibiotic resistance.[10] Hence, the efficacy of novel regimens (e.g., concomitant therapy, sequential therapy, bismuth-quadruple therapy) has been extensively investigated in eradicating *H. pylori*.

Advanced age is an important risk factor for chronic gastritis and GC.[11,12] However, *H. pylori* infection can be primarily acquired during infancy and increases with aging.[13] The Kyoto consensus on *H. pylori* gastritis firstly proposed that *H. pylori*-infected individuals should be offered eradication therapy unless there are competing considerations.[5] Therefore, *H. pylori*-infected children and elderly patients are also included in the patient populations who require *H. pylori* treatment. The World Health Organization has defined people older than 60 years as elderly. People under 18 years are defined as children according to the "UN Convention on the Rights of the Child". However, there are still considerable controversies in clinical practice regarding the management of *H. pylori* infections in children and the elderly.

Considering the poor tolerance to drugs, high sensitivity to adverse effects, relatively poor compliance, and antibiotic resistance, the management of *H. pylori* in children and elderly patients necessitates additional considerations than that in adult patients. Initial treatment failure makes selection of rescue therapy challenging due to the potential for *H. pylori* resistance to antibiotics included in the initial treatment. Furthermore, second-line therapy usually exert compromised efficacy and decreased tolerability.[14] The benefits and risks of eradication failure should be comprehensively balanced. Screening the appropriate patients for tests, and careful selection of diagnostic tests and initial therapies are pivotal for the effective management of *H. pylori* infection. The aim of this study was to provide a comprehensive review of the recent literature regarding the diagnosis and treatment of *H. pylori* infection in children and elderly patients.

Children

Indications for H. pylori eradication therapy in pediatric patients

The global *H. pylori* prevalence in children varies significantly, from 2.5% in Japan to 34.6% in Ethiopia.[15] A recent study indicated that the *H. pylori* prevalence among Chinese school children aged 7−12 years was high and the overall infection rates were 24.1%.[16] For the treatment of *H. pylori* infection in children, there is an urgent need to define which patients receive eradication treatment in *H. pylori*-positive children. In addition, it has been documented that distinct differences in immune responses and pharmacokinetics to medications exist between children and adults. In contrast to adults, children have a limited selection of antibiotics and low tolerance to the adverse effects of drugs. Additionally, children with *H. pylori* infection have a certain spontaneous clearance rate.[16,17] Furthermore, the reinfection rate may be higher in children than in adults after eradication.[18] These factors to some extent restrict the treatment of *H. pylori* in pediatrics. *H. pylori*-infected children have

reduced Th1 and Th17 responses and increased Treg responses compared to infected adults in accordance with a higher level of FOXP3, TGF-β, and IL-10.[19,20] These immune responses may partly contribute to the differences in gastrointestinal symptoms between *H. pylori*-infected children and adults. Therefore, *H. pylori* treatment guidelines for adults are not fully applicable to pediatric patients. Recent ESPGHAN (European Society for Pediatric Gastroenterology Hepatology and Nutrition) and NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition) guidelines for *H. pylori* infection in pediatrics recommend that the primary goal of clinical investigations of gastrointestinal symptoms should aim to determine the underlying cause of symptoms, and not solely the presence of *H. pylori* infection. Thus, "test and treat" strategies are not generally recommended for *H. pylori* infection in children.[21] However, in regions with a high incidence of GC (e.g., Eastern Asia),[22] this strategy may be appropriate in adolescents. In China, it is not recommended to detect *H. pylori* routinely in children under 14 years of age.[4] Similarly, a "screening and treatment" strategy for *H. pylori* infection in adolescents has been supported and considered as measures to decrease the lifetime GC risk in Japan. Besides, eradication therapies for adolescents have been an effective method of controlling the next generation infection by preventing intrafamilial infection.[13]

In the Chinese Expert Consensus regarding the management of *H. pylori* infection in children (2015), recommendations for diagnostic *H. pylori* test include children with peptic ulcer disease, gastric MALT lymphoma, chronic gastritis, family history of GC, iron deficiency anemia (IDA) of undetermined etiology or children requiring long-term NSAIDs treatment,[23] while diagnostic tests for *H. pylori* infection are strongly recommended in pediatric patients with peptic ulcer disease in ESPGHAN/NASPGHAN guideline.[21] To identify the risk factors for giant peptic ulcers (>2.0 cm) in children from Shanghai, Tang et al[24] retrospectively analyzed 19208 children who underwent gastroscopy and determined 83 patients with giant peptic ulcers. Among patients with giant peptic ulcers, 71.1% were positive for *H. pylori* infection, suggesting a strong association between peptic ulcer and *H. pylori* infection. In addition, diagnosis of *H. pylori* infection is recommended in patients with refractory IDA of undetermined etiology; in patients with chronic immune thrombocytopenic purpura of an unknown cause, the recommended level is low.[21] However, diagnostic *H. pylori* tests are not recommended as part of the initial investigation in children with IDA or functional abdominal pain disorders, or causes of short stature.[21] The majority of gastrointestinal symptoms in children are mainly due to functional dyspepsia, with only a small proportion classified as organic and associated with *H. pylori*-related diseases.[25] Consistently, recent studies failed to demonstrate the differences in gastrointestinal symptoms between *H. pylori*-positive and *H. pylori*-negative children with dyspepsia in some countries,[26,27] further supporting the recommendations of the ESPGHAN/NASPGHAN guidelines (2016). The association between *H. pylori* infection and extra-gastrointestinal symptoms in children is still controversial. A large prospective multicenter case–control study (808 subjects included) evaluating the associations between eosinophilic esophagitis and *H. pylori* infection failed to demonstrate the inverse association between them, in both children and adults.[28,29] Hence, future studies are imperative to clarify this association.

Diagnosis of H. pylori infection in pediatrics

The ESPGHAN/NASPGHAN guideline emphasizes the importance of endoscopy in the initial diagnosis of *H. pylori* infection in children. Moreover, positive culture or *H. pylori* gastritis on histopathology with at least one other positive biopsy-based test such as the rapid urease test (RUT), molecular-based assays when available, including polymerase chain reaction (PCR), or fluorescent *in situ* hybridization are recommended in the initial diagnosis of *H. pylori* infection.[21] Cultured *H. pylori* strains can be used for performing antibiotic susceptibility tests, which could guide the selection of anti-*H. pylori* treatments. In addition, the determination of initial infection should not be solely based on noninvasive tests (e.g., urea breath test (UBT), *H. pylori* stool antigen test, serological test). It has been reported that ^{13}C-UBT may present false-positive results in children younger than 6 years due to the lower volume of distribution and different CO_2 production rates.[30] These diagnostic criteria for *H. pylori* infection in children are relatively strict and aim to largely avoid the excessive detection of *H. pylori* infection, improving the accuracy of detection. In addition, serological tests are not recommended for the diagnosis of *H. pylori* infection in both initial tests and confirmation of *H. pylori* eradication in children.[21]

In contrast, the guideline for determining *H. pylori* infection in Chinese children recommended both invasive and noninvasive tests.[23] *H. pylori* culture with a specificity of 100% is accepted as a "gold standard" for

diagnosing current *H. pylori* infections. However, it is difficult to use this technique as a routine diagnostic method as its sensitivity to detect *H. pylori* is relatively low (55%–96%).[31] The accuracy of diagnostic tests rapidly decreases in populations with a low infection prevalence. Therefore, it appears reasonable that the ESPGHAN/NASPGHAN guidelines recommend the positive diagnosis of *H. pylori* infection be based on at least two biopsy-based tests and not solely on positive histology.[21] Due to special technical requirements, *H. pylori* culture is challenging to perform in many regions. In Japan, a highly accurate UBT is recommended as a test for *H. pylori* infection in adolescents.[13]

Additionally, evaluation of the *H. pylori* status in adults or children should be performed at least 2 weeks after stopping proton pump inhibitors (PPIs) and 4 weeks after stopping antibiotic treatment. Reportedly, PPIs and antibiotics can suppress bacterial growth and replication, which may present a false-negative diagnostic result when testing for *H. pylori* infection.[31,32] ^{13}C-UBT or monoclonal stool antigen test has been proposed to assess the *H. pylori* eradication, whereas invasive tests are rarely needed to verify *H. pylori* eradication in children with uncomplicated peptic ulcer diseases.[21]

Treatment of H. pylori infection in pediatrics

Treatment of *H. pylori* in pediatric patients remains challenging in clinical practice. Eradication failure is usually associated with several factors such as an inappropriate treatment regimen, poor compliance, and antibiotic resistance. In the latest Chinese guidelines for the management of *H. pylori* infection, eradication regimens against *H. pylori* infection are not distinguished as first-line, second-line, or third-line (except levofloxacin-containing therapy).[4] The most efficient regimen should be chosen as the initial therapy. However, the selection of antibiotic classes for *H. pylori* eradication in children is extremely limited. Amoxicillin, clarithromycin, and metronidazole are recommended to eradicate *H. pylori* in pediatric patients.[21,23] Currently, clarithromycin- and metronidazole-resistant *H. pylori* strains are prevalent worldwide,[33] decreasing eradication rates in children. Zhou et al[16] reported that treatment of *H. pylori*-infected children with standard triple therapy (PPI, amoxicillin, and clarithromycin) only achieved a 60.0% eradication rate. A prospective cohort study in Portuguese patients demonstrated a 97.8% eradication rate in *H. pylori*-infected children with a susceptibility-based therapy for 14 days.[34] Thus, antimicrobial susceptibility-based tailored therapies are recommended for *H. pylori* treatment in pediatrics.[21]

Notably, adequate acid suppression improves the efficacy of *H. pylori* eradication regimens. If available, esomeprazole and rabeprazole, whose properties were less affected by *CYP2C19* genetic polymorphisms, may be preferably chosen in populations with a high proportion of rapid metabolizers (e.g., Caucasians).[21] Recently, a study examined the genotypes of *CYP2C19* in 1083 Chinese patients and found that over 53% of patients were heterozygous extensive metabolizers (EM), 38.04% were homozygous fast type and only 8.96% were poor metabolizers.[35] These results suggested that the ability to metabolize drugs varies in Chinese patients, and the determination of *CYP2C19* genetic polymorphisms should receive adequate importance to achieve sufficient acid suppression in Chinese patients requiring *H. pylori* eradication. Potassium-competitive acid blockers (P-CABs) are a new class of gastric acid-suppressing agents. P-CABs inhibit H^+/K^+ ATPase-mediated gastric acid secretion in a reversible and potassium-competitive manner. Furthermore, P-CABs are thought to possess stronger inhibitory effects than PPIs. Thus, P-CABs are predicted to be more effective than PPI in *H. pylori* eradication therapies.[36,37] Current data assessing the usefulness and safety of P-CAB in *H. pylori* eradication is primarily available from studies conducted in Japan. A retrospective study in Japan reviewed the medical records of 661 consecutive patients who received first-line *H. pylori* eradication treatment. The results suggested that 7-day P-CAB-based triple therapy (vonoprazan 20 mg + amoxicillin 750 mg + clarithromycin 200 mg twice/day) was generally well-tolerated and was more effective than a 7-day PPI-based triple therapy (lansoprazole 30 mg/rabeprazole 20 mg + amoxicillin 750 mg + clarithromycin 200 mg twice/day) in both intention-to-treat (89.1% vs. 70.9%; $P < 0.001$) and per-protocol analyses (91.2% vs. 71.7%; $P < 0.001$).[37] Furthermore, another two Japanese studies evaluated the efficacy and safety of P-CAB-based triple therapy for *H. pylori* eradication in children and reported eradication rates of 81.3% and 85.1%. These findings indicated that a 7-day P-CAB-containing triple therapy is safe and well-tolerated in children.[38,39] Vonoprazan is acid-stable and water-soluble, allowing the peak plasma concentration to be rapidly reached after administration. Compared to PPIs, vonoprazan demonstrates fast-onset, effective acid suppression, and a long-lasting effect.[40] Notably, vonoprazan was also reportedly effective in clarithromycin-resistant *H. pylori* strains. In a clinical

trial (420 patients included), the eradication rates of clarithromycin-resistant strains were 76.1% in the vonoprazan group and only 40.2% in the PPI group (amoxicillin, clarithromycin, vonoprazan or PPI).[41]

Sufficient antibiotic dosages and treatment durations contribute to the success of *H. pylori* eradication. More than a 90% eradication rate with primary treatment in per-protocol analysis should be achieved, which can avoid repeated treatments and the induction of secondary resistance by the infecting *H. pylori* strains.[42] The ESPGHAN/NASPGHAN guideline (2016) recommends a 14-day eradication therapy containing PPI and two antibiotics in *H. pylori*-infected children. Metronidazole- and clarithromycin-resistant *H. pylori* strains are prevalent worldwide. Metronidazole resistance could be overcome with prolonged treatment duration and increased metronidazole dosage,[43] while clarithromycin resistance often results in eradication failure due to challenges in therapy. Hence, the evaluation of clarithromycin resistance prior to treatment could help optimize the selection of *H. pylori* eradication therapies.[34] In addition to culture-based susceptibility tests, PCR can be utilized to detect clarithromycin-resistant *H. pylori* strains.[44]

Dysbiosis of gut microbiota is associated with various diseases (e.g., metabolic diseases, cardiovascular diseases, cancer).[45] Therefore, eradication therapy-induced disturbance of gut microbiota is also an important concern associated with *H. pylori* treatments. Recent studies have indicated that the gastrointestinal microbiota could be restored after *H. pylori* eradication in healthy teenagers and young adults.[46,47] A large sample study conducted in Taiwan reported that *H. pylori* eradication had minimal disruption of the microbiota.[48] In addition, Serrano et al[49] reported that the eradication of *H. pylori* in infected children was associated with the restoration of the gastric microbiota to the community structure observed in the non-infected children in a cohort of 16 patients (≤13 years) presenting nausea and abdominal discomfort. However, this study was performed in a relatively small sample size, necessitating additional studies to define the impact of eradication therapy on the gut microbial composition in children. Several meta-analyses have examined the efficacy and safety of probiotic supplementation in children receiving *H. pylori* eradication therapy. Probiotic supplementation during eradication therapy could significantly decrease the incidence of adverse events and could increase the eradication rate during therapy.[50,51] However, it is difficult to draw meaningful conclusions since studies included in these meta-analyses used different strains and concentrations of probiotics. Moreover, it has been reported that probiotic-containing yogurts could restore *Bifidobacterium* spp./*E. coli* ratio in the gut microbiota of children with *H. pylori* infection.[52] The benefit of probiotic supplementation in *H. pylori* eradication therapy needs further investigation.

The elderly

Concerns regarding H. pylori treatment in elderly patients

Notably, with increased global aging, a high *H. pylori* prevalence has been observed among the elderly population. Concurrently, many gastrointestinal disorders (e.g., peptic ulcer disease, GC) occur much more common in the elderly.[53] The eradication of *H. pylori* infection in elderly patients can prevent the development of *H. pylori*-associated diseases and significantly decrease GC incidence. However, elderly patients frequently demonstrate lower tolerance and poor compliance with anti-*H. pylori* eradication medication, and thus have an increased risk for drug side effects.[14] Therefore, concerns regarding *H. pylori* treatment in the elderly need to be carefully addressed in clinical practice. Currently, there are no special consensus reports in this regard. A comprehensive benefit/risk assessment and individualization of treatments should be performed when eradicating *H. pylori* in the elderly population.[4]

In aging patients, the benefits of treating *H. pylori* infections remain controversial. As emphasized in the fourth and fifth *H. pylori* guidelines in China, *H. pylori* eradication before gastric mucosal atrophy and/or the absence of intestinal metaplasia can reduce the risk of GC more effectively.[4,54] A prospective, randomized, placebo-controlled, population-based primary prevention study in 1630 *H. pylori*-infected individuals reported that *H. pylori* eradication could significantly decrease the GC risk in patients with precancerous lesions during a follow-up of 7.5 years after eradication treatment.[55] In addition, another retrospective study in Hong Kong, China revealed that the treatment of *H. pylori* infection was associated with a lower GC risk, particularly in older subjects, 10 or more years after treatment.[56] A blinded randomized factorial placebo-controlled trial (3365 residents included) in Linqu assessed the effects of *H. pylori* treatment, vitamin supplementation, and garlic supplementation in GC prevention. After a follow-up of 22 years, the inhibitory effect of *H. pylori* treatment on the GC risk was more significant in elderly patients compared to young or middle-aged subjects. Furthermore, *H. pylori* treatment could significantly reduce the GC incidence and

mortality in subjects with intestinal metaplasia or dysplasia rather than in those with less severe gastric lesions.[57] These results indicate that the eradication of *H. pylori* can be beneficial at various stages of GC. Moreover, NSAIDs and *H. pylori* infections are two risk factors for the development of peptic ulcers. Notably, NSAIDs are recommended as an indication for *H. pylori* treatment.[58] Furthermore, it was reported that *H. pylori* infection was associated with an increased risk of neurodegeneration diseases (Alzheimer's disease, Parkinson's disease, etc.),[59,60] commonly observed in an elderly population. Reportedly, *H. pylori* eradication in these patients was associated with improvements in symptoms associated with Alzheimer's disease[61] or Parkinson's disease,[62] further supporting the benefits of *H. pylori* treatment in the elderly.

Drug–drug interactions are also a great concern during *H. pylori* treatment in elderly patients.[14] The potential for drug interactions should be taken into consideration when choosing a PPI to manage gastric acid-related diseases,[63,64] especially in elderly patients taking multiple prescriptions.

In summary, *H. pylori* treatment in elderly patients should be governed by the benefit/risk assessment. *H. pylori* eradication can effectively prevent *H. pylori*-related diseases. Longer duration, higher doses of eradication therapy, selection of appropriate drugs and PPIs can contribute to higher eradication rates. In the absence of competing factors, *H. pylori* eradication is recommended in the elderly population.

Diagnosis and treatment of H. pylori infection in the elderly population

The recommended diagnostic *H. pylori* tests in the elderly are comparable to those in adults. UBT is the most popular noninvasive test to diagnose the *H. pylori* initial infection and is the best method to assess the efficacy of *H. pylori* eradication.[4] RUT is recommended among patients who require gastroscopy and is not recommended for the detection of *H. pylori* after eradication therapy. Due to the increased GC risk with aging,[53] elderly subjects may have a greater urgency for gastroscopy than younger patients. Similarly, there are no specific contraindications to the recommended eradication therapies. The selection of an eradication therapy should be based on local antibiotic-resistant patterns and the patient's history of antibiotic exposure. If the susceptibility-based test is unavailable, a validated eradication therapy with optimal efficacy should be chosen. Longer treatment durations and higher dosage are recommended to overcome antibiotic resistance, thereby increasing the efficacy of *H. pylori* treatment strategies. The longer duration of treatment, recommended in the American Gastroenterological Association guidelines for a general population, is also preferred among the elderly due to the high eradication rates.[58] Furthermore, the lack of data indicates that increased dosage can cause more severe side effects in the elderly. If the initial therapy fails, both the determination of *CYP2C19* genetic polymorphisms and susceptibility test can be used as effective methods to increase the eradication rate with a rescue therapy. Reportedly, several studies in Japan have demonstrated a superior efficacy with P-CAB in *H. pylori* treatment compared to PPI-contained triple therapy.[36] However, further clinical trials are required to assess the efficacy and safety of P-CAB-containing regimens in different local populations.

The exploration of new therapies remains an active focus in *H. pylori*-related research and might further illuminate *H. pylori* eradication strategies. Probiotic supplementation can be considered an effective measure to reduce the incidence of adverse effects in the elderly population receiving *H. pylori* eradication therapy.[65,66] In addition, a randomized controlled clinical trial including 232 *H. pylori*-infected patients (18–65 years) demonstrated that a modified dual therapy at a high dose is equally effective, safer, and less costly compared to bismuth-containing quadruple therapy.[67] It is medically imperative to investigate the efficacy and safety of dual therapies in elderly patients with *H. pylori* infections. The role of berberine, a traditional Chinese medicine, in *H. pylori* treatment has also been investigated. Several lines of evidence from a meta-analysis indicated that berberine in combination with triple therapy increased *H. pylori* eradication rates and also reduced the overall incidence of therapy-related adverse effects.[68] Additionally, a randomized, non-inferior trial conducted in China demonstrated that a berberine-quadruple regimen (PPI, amoxicillin, clarithromycin, and berberine) was comparable to the bismuth-containing quadruple regimen (PPI, amoxicillin, clarithromycin, bismuth).[69] Additional studies are crucial to define the role of berberine in *H. pylori* eradication.

Summary

H. pylori infection is associated with various gastrointestinal diseases. Eradication of *H. pylori* is an effective method to prevent *H. pylori*-related diseases. Due to the variabilities in physiological functions and pharmacokinetics, additional evaluations and

considerations in children and elderly patients should be implemented in *H. pylori* treatments. Gastroscopy-based tests are recommended for the diagnosis of *H. pylori* infection in children. According to the ESPGHAN/NASPGHAN guideline, the "test and treat" strategy for *H. pylori* infection is not recommended in pediatric patients. In countries with a high GC incidence, this strategy may be appropriate for adolescents. To reduce the GC risk, elderly patients should be offered *H. pylori* eradication therapies, unless there are competing factors. Moreover, owing to the reduced efficacy of current standard therapies, the exploration of newer regimens is urgently needed for the development of novel and efficient strategies with better eradication rates and lower adverse effects.

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Conflict of interest

None.

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