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Review Article

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Changes in the Treatment Strategies for *Helicobacter pylori* Infection in Children and Adolescents in Korea

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ABSTRACT

The policies developed for the treatment of *Helicobacter pylori* infection in adults may not be the most suitable ones to treat children and adolescents. Methods used to treat children and adolescents in Europe and North America may not be appropriate for treating children and adolescents in Korea due to differences in epidemiological characteristics of *H. pylori* between regions. Moreover, the agreed standard guidelines for the treatment of *H. pylori* infection in children and adolescents in Korea have not been established yet. In this study, the optimal treatment strategy for *H. pylori* infection control in children and adolescents in Korea is discussed based on these guidelines, and recent progress on the use and misuse of antimicrobial agents is elaborated. Non-invasive as well as invasive diagnostic test and treatment strategy for *H. pylori* infection are not recommendable in children aged less than ten years or children with body weight under 35 kg, except in cases of clinically suspected or endoscopically identified peptic ulcers. The uncertainty, whether enough antimicrobial concentrations to eradicate *H. pylori* can be maintained when administered according to body weight-based dosing, and the costs and adverse effects outweighing the anticipated benefits of treatment make it difficult to decide to eradicate *H. pylori* in a positive non-invasive diagnostic test in this age group. However, adolescents over ten years of age or with a bodyweight of more than 35 kg can be managed aggressively as adults, because they can tolerate the adult doses of anti-*H. pylori* therapy. In adolescents, the prevention of future peptic ulcers and gastric cancers is expected after the eradication of *H. pylori*. Bismuth-based quadruple therapy (bismuth-proton pump inhibitor-amoxicillin/tetracycline-metronidazole) with maximal tolerable doses and optimal dose intervals of 14 days is recommended, because in Korea, the antibiotic susceptibility test for *H. pylori* is not performed at the initial diagnostic evaluation. If the first-line treatment fails, concomitant therapy plus bismuth can be attempted for 14 days as an empirical rescue therapy. Finally, the salvage therapy, if needed, must be administered after the *H. pylori* antibiotic susceptibility test.

Keywords: *Helicobacter pylori*; Therapeutics; Guideline; Children

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INTRODUCTION

The fifth edition of the Maastricht Consensus Report for the management of *Helicobacter pylori* infection (the Maastricht Consensus V) [1] reflects the Kyoto global consensus report in which *H. pylori* gastritis is defined as an infectious disease [2]. In the Maastricht Consensus V, it is recommended that the bacteria should be eradicated if discovered in the human gastric mucosa [1]. However, in guidelines revised in 2013 for the diagnosis and treatment of *H. pylori* infection in Korea (the Korean 2013 revised adult guidelines), eradication therapies were not recommended for all *H. pylori*-infected persons. Instead, these therapies were restricted to *H. pylori*-infected adult patients with particular gastroduodenal or systemic diseases [3].

The European Society for Paediatric Gastroenterology Hepatology and Nutrition/North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/NASPGHAN) guidelines updated in 2016 for the management of *H. pylori* in children and adolescents recommend against aggressive diagnostic or therapeutic approaches in children, except in cases of clinically suspected or endoscopically identified peptic ulcers. The guidelines do not recommend non-invasive diagnostic tests and treatment strategies for *H. pylori* infection in children [4].

However, the International Agency for Research on Cancer declared in 2014 that *H. pylori* eradication is necessary for preventing gastric cancer [5]. In Japan, eradication therapies for *H. pylori* gastritis in adults have been covered by insurance since 2013. This policy was expanded to set up a foundation for preventing gastric cancer through *H. pylori* eradication [6]. Adolescents, as well as adults, were included in the guidelines revised in 2016 for the management of *H. pylori* infection in Japan to prevent gastric cancer through *H. pylori* eradication. It is believed that the chances of preventing gastric cancer are high if *H. pylori* eradication therapy is administered at a relatively earlier stage to prevent gastric atrophy from progressing. In Japan, eradication therapy in adolescents is considered an effective method of preventing the transmission of *H. pylori* to future generations via intrafamilial infection [6]. The epidemiological features of *H. pylori* infection in Japan are as follows. *H. pylori* infection primarily occurs at infancy, and this is normally due to exposure to infected family members. *H. pylori* infection occurrences have been decreasing and the prevalence rates of the anti-*H. pylori* antibody among individuals born during the 1970s, 1980s, and 2000s were 20%, 12%, and 3.2%, respectively [6,7].

Differences between the Japanese 2016 revised guidelines and the updated ESPGHAN/NASPGHAN Guidelines for the control of *H. pylori* infection in adolescents seem to originate from the differences in stomach cancer incidence between the two regions [6]. The incidence of gastric cancer in Korea is currently the highest in the world and gastric cancer remains the second most prevalent cancer in Korea after thyroid cancer, which is increasingly diagnosed via sonographic thyroid screening [8]. The prevalence rates of the anti-*H. pylori* CagA antibody among individuals born before and during the 1970s and during the 1980s, 1990s, and 2000s in Jinju, Korea were 80%, 60%, 20%, and 15%, respectively, which were significantly higher than those in Japan. There are still many infected adolescents in Korea (unpublished observation). Unlike in Korea, Japan utilizes screening test-endoscope-treatment strategy of *H. pylori* infection in adolescents to prevent gastric cancer in the future.

The eradication rate of the currently recommended anti-*H. pylori* therapeutic regimen is more than 90% [9]. However, the eradication rates of *H. pylori* in children and adolescents have been less than satisfactory in Korea. In addition, treatment failures are expected to increase

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both nationwide and worldwide owing to a general increase in antimicrobial resistance of *H. pylori* [1,10-12].

The methods used to treat *H. pylori* infection in adults may not be the most effective ones for treating children and adolescents. Methods used to treat children and adolescents in Europe and North America may not be appropriate for treating children and adolescents in Korea. Moreover, the agreed standard guidelines for the treatment of *H. pylori* infection in children and adolescents in Korea have not been established yet.

In this study, the optimal treatment strategy for *H. pylori* infection control in children and adolescents in Korea is discussed based on these guidelines, and recent progress on the use and misuse of antimicrobial agents is detailed.

WHO BENEFITS FROM ANTI-*H. PYLORI* ERADICATION THERAPY?

It is becoming a standard recommendation for all adults who have been tested positive for *H. pylori* infection to be administered eradication therapy [1,6]. Even in the U.S.A., non-invasive diagnostic tests and treat strategies are recommended for patients with uninvestigated dyspepsia who are below 60 years of age and with no other alarming features for gastric cancer [13]. However, the recommendations for *H. pylori* eradication therapy in adults in Korea are restricted to the following diseases: peptic ulcers, low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, resected early gastric cancer, chronic atrophic gastritis or intestinal metaplasia, a family history of gastric cancer, functional dyspepsia, long-term use of nonsteroidal anti-inflammatory drugs, previous long-term use of proton pump inhibitors (PPIs), and idiopathic thrombocytopenic purpura [3].

According to a nationwide survey of Japanese pediatricians on eradication therapy for *H. pylori*, it was found that 332 patients (mean age 11.6±3.4, 200 males) were treated from 1997 to 2013. The reasons for eradication therapy consisted of chronic gastritis (26.8%), iron deficiency anemia (25.0%), duodenal ulcers (24.7%), gastric ulcers (7.2%), idiopathic thrombocytopenia (8.8%), and MALT lymphoma (0.6%) [14]. Recently, serological screenings for *H. pylori* infection in middle-school students were implemented by some local governments in Japan. The middle school students with positive anti-*H. pylori* antibodies underwent endoscopies to confirm active *H. pylori* infections. Eradication therapy was administered to students with confirmed *H. pylori* infection to prevent the future possibility of stomach cancer [7].

In North America and Europe, the recommendations for *H. pylori* eradication in children and adolescents are limited to those with *H. pylori*-positive peptic ulcers, refractory iron deficiency anemia, and chronic idiopathic thrombocytopenic purpura. This is because the incidence of stomach cancer in these regions is lower than in far east Asia, and the prevalence of *H. pylori* infections is low in pediatric populations. In North America and Europe, even pediatric patients with functional abdominal pain, short stature, or first diagnosed iron deficiency anemia (of which associations with *H. pylori* infection are controversial) are not recommended to undergo diagnostic tests for *H. pylori* infection. If these patients are diagnosed as *H. pylori*-infected and treated during childhood and adolescence, there might be a greater chance of preventing peptic ulcers or gastric cancer later in life. However, this type

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of treatment in childhood can result in reinfections, the development of new allergies, no symptomatic improvement, treatment failure, abdominal pain, diarrhea, and the undesirable alteration of the gut microbiome. In North America and Europe, these possible undesirable effects of eradication therapy for *H. pylori* in children or adolescents may be considered as outweighing the potential prevention of future peptic ulcers or gastric cancer [4].

It remains uncertain whether enough anti-microbial concentrations to eradicate *H. pylori* can be maintained in the gastric mucosa of young children when anti-*H. pylori* therapeutic agents are administered according to body weight-based dosing. The treatment provided to eradicate *H. pylori* is not expected to improve symptoms in young children in developed countries, either. Therefore, Korean children under the age of ten should be managed by the updated ESPGHAN/NASPGHAN guidelines. However, if the cause of abdominal pain or dyspepsia is unknown, then even young children with body weights under 35 kg should undergo upper gastrointestinal endoscopy [15]. If they are diagnosed with *H. pylori* infection, they may be treated with aggressive countermeasures which can reduce active and chronic inflammation-mediated adverse effects until they are treated for eradication.

Currently, anti-*H. pylori* therapeutic agents recommended for use in pediatric patients can be administered at adult doses in adolescents aged over 10–12 years with body weights over 35 kg [4]. Moreover, the recommended dosages and durations of eradication therapy have been increased recently to eradicate *H. pylori* infection efficiently. Therefore, it is more advantageous only to treat children and adolescents who weigh more than 35 kg. Drug compliance in this patient group can be improved by providing a detailed explanation of why the treatment is being administered and the effects it may have before commencing treatment. As a result, reluctance to comply to treatment instructions can be overcome, and the side effects of high doses of antimicrobial agents and the inconvenience of having to take a relatively large number of medications can be tolerated. However, when a diagnostic test confirms *H. pylori* infection, the decision to treat or not should be determined after in-depth discussions with patients and their guardians in relation to the advantages and disadvantages of anti-*H. pylori* therapy. This strategy may help prevent peptic ulcers and gastric cancer later in life. Therefore, Korean adolescents with dyspepsia or a family history of stomach cancer may be managed using the Korean 2013 revised adult guidelines [15].

Middle school-aged students may also be an ideal target for *H. pylori* eradication to prevent stomach cancer in Korea, as in Japan, because gastric atrophy begins to advance in this age group. If the prevalence of *H. pylori* infection in adolescents further decreases to less than 5% and a nationwide consensus is made with regards to gastric cancer prevention via *H. pylori* eradication therapy in adolescents, a serological screening test-endoscope-treatment strategy could be implemented, as in Japan.

EXPERIENCES AND LESSONS LEARNED FROM FAMILY THERAPY

In the early 1990s, the authors of this study's research team believed that reinfection of pediatric patients from their untreated parents might frequently occur if they received anti-*H. pylori* eradication therapy alone because most Korean adults were identified as being infected with *H. pylori* at that time [16]. Therefore, it was hypothesized that all family members living together should be treated simultaneously to eradicate *H. pylori* in pediatric patients successfully.

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There were several reports of successful regimens of anti-*H. pylori* eradication therapy before family therapy was designed. In 1989, Borody's bismuth (BIS)-tetracycline (TET)-metronidazole (MET) triple therapy (BIS qid 28 d, TET qid 28 d, MET qid 10 d) in adults demonstrated a high initial eradication rate of *H. pylori* and a rare recrudescence over one to three years of follow-up [17]. In the meantime, BIS-ampicillin (AMP) dual therapy (BIS qid 42 d, AMP qid 42 d) and AMO-tinidazole (TIN) dual therapy (AMO 42 d, TIN 42 d) were used in pediatric patients with an immediate *H. pylori* eradication rate of 75% and 94%, respectively [18,19]. BIS-AMO-MET triple therapy (BIS qid 42 d, AMO tid 42 d, MET bid 28 d) was also attempted when BIS-AMO dual therapy failed to eradicate the infection in pediatric patients who were *H. pylori* (+) with duodenal ulcers [20]. In pediatric eradication therapies only, TET was replaced with AMO because its use in children aged below eight is contraindicated.

BIS-based triple therapy is considered first, with the second consideration being that antimicrobial agents and the method of administration should be the same for both children and adults. AMO was chosen instead of TET because it could be administered relatively safely to both children and adults (**Table 1**). Antimicrobial doses in children under 30 kg were adjusted according to their body weight.

From 1992 to 1993, families with a child who previously underwent an endoscopy due to various upper gastrointestinal symptoms and were confirmed *H. pylori*-infected at the Gyeongsang National University Hospital were recruited for a study. All family members who lived together with the *H. pylori*-infected child were treated simultaneously with anti-*H. pylori* eradication therapy after confirmation of *H. pylori* infection via endoscopy. At first, 165 participants (141 from 33 families and 24 individual participants) were treated with chemotherapy I and a further 25 participants (23 from four families and two individual participants) were treated with chemotherapy II (**Table 1**) [21,22].

A total of 45 children and adolescents were given chemotherapy I during the initial period of study, and 21 of them (46.7%) had the infection eradicated. Fifteen of the children who retained the *H. pylori* infection were repeatedly administered chemotherapy I once more, and ten of the children (66.7%) became *H. pylori*-negative. The eradication rate of chemotherapy I was unexpectedly low, so the same regimen with doubled dosages (chemotherapy II) were administered to 11 adult participants. Six of them (54.5%) became *H. pylori*-negative. There were no significant differences between the eradication rates of chemotherapy I and II. The reason for low eradication rates in family therapy was thought to be due to family members not taking the anti-bacterial medication properly as prescribed. From the end of the family

Table 1. Anti-*Helicobacter pylori* chemotherapy regimens in pediatrics of Gyeongsang National University Hospital

Study periods		Chemotherapy I	Chemotherapy II
1992–1993	>30 kg adults	MET 250 mg tid for 14 d AMO 500 mg tid for 28 d DeNol® 1T tid for 42 d	MET 500 mg tid for 14 d AMO 1,000 mg tid for 28 d DeNol® 2T tid for 42 d
1995–2008	>30 kg	MET 250 mg tid for 14 d AMO 750 mg tid for 28 d DeNol® 1T tid for 42 d	
2008–present	>30 kg	lansoprazole 30 mg bid for 28 d MET 500 mg tid for 14 d AMO 750 mg tid for 28 d DeNol® 1T tid for 42 d	

MET: metronidazole, AMO: amoxicillin.
DeNol® 1T: tripotassium dicitrato bismuthate 300 mg (bismuth 120 mg).

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therapy study to 2008, the authors used standard BIS-based triple therapies for pediatric patients in which the AMO dose was increased to 750 mg (**Table 1**).

MET resistance is overcome by increasing the dose and treatment duration and by adding PPIs to maintain a stomach pH of >6 [23]. The BIS-based modified quadruple therapy (MET 500 mg tid 14 d, AMO 750 mg tid 28 d, lansoprazole 30 mg bid 28 d, DeNol® 300 mg tid 42 d; Greencross Co., Seoul, Korea) has been used as a first-line therapy since 2008 (**Table 1**).

However, if this therapy failed to eradicate *H. pylori*, it was thought that the high prevalence rates of clarithromycin (CLA) - or fluoroquinolone-resistant strains in Korea would make it difficult to select antimicrobial agents for the rescue or salvage therapy [10]. Therefore, *H. pylori* eradication therapy is administered to children and adolescents whose body weight is over 30 kg and can tolerate adult dosages and the adverse effects of medication. These patients are also able to understand the importance of taking the drugs according to the instructions given. If the pediatric patient's body weight is less than 30 kg, conservative treatment will be provided until their body weight is over 30 kg.

PEDIATRIC *H. PYLORI* ERADICATION THERAPY IN KOREA

In a study comparing the efficacy of BIS-based eradication therapy for children and adolescents between 1993 and 1996, triple therapy with BIS 28 d-AMO 14 d-MET 14 d or BIS 14 d-AMO 14 d-MET 14 d showed improved *H. pylori* eradication rates than dual therapy with BIS 28 d-AMO 14 d (about 90% vs. 60%, respectively) [24]. Retrospective analysis of the results of the triple therapies in a relatively large number of pediatric patients from 1999 to 2004 with PPI-AMO-CLA 7 d and BIS-AMO-MET 7 d revealed that PPI-AMO-CLA is inferior to BIS-based triple therapy (74% vs. 85%, respectively) in terms of *H. pylori* eradication rate [25]. BIS-based triple therapy is the old regimen, but its eradication rate is better than that of PPI-CLA-based triple therapy. In a study comparing PPI-AMO-CLA 14 d to BIS-PPI-AMO-MET 7 d from 2004 to 2012, BIS-based quadruple therapy for seven days was more effective than PPI-CLA triple therapy for 14 days in terms of the eradication rate (83.9% vs. 67.7%, respectively) (**Table 2**) [24-27].

Few studies have investigated the differences in eradication rates according to treatment duration for children and adolescents. In one comparison study of PPI-AMO-CLA 7 d and 14 d, there was no significant difference in eradication in terms of treatment duration (81.0% vs. 84.6%, respectively) (**Table 2**) [27].

Table 2. Anti-*Helicobacter pylori* chemotherapeutic trials in Korean children

Authors	Year	Treatment	Eradication rate
Bae et al. [24]	1993–1996	BIS 28d-AMO 14 d	61.4 (35/57)
		BIS 28d-AMO 14 d-MET 14 d	88.9–90.9 (16/18, 10/11)
Choi et al. [27]	1998–2000	PPI-AMO-CLA 7 d	81.0 (17/21)
		PPI-AMO-CLA 14 d	84.6 (11/13)
Choi et al. [25]	1999–2004	PPI-AMO-CLA 7 d	74.5 (105/141)
		BIS-AMO-MET 7 d	84.8 (78/92)
Hong and Yang [26]	2004–2011	PPI-AMO-CLA 14 d	67.7 (42/62)
		BIS-PPI-AMO-MET 7 d	83.9 (47/56)

Values are presented as % (number/total number).
BIS: bismuth, AMO: amoxicillin, MET: metronidazole, PPI: proton pump inhibitor, CLA: clarithromycin.
BIS 7–8 mg/kg/d, AMO 50 mg/kg/d, MET 20 mg/kg/d, PPI (omeprazole) 0.7–1 mg/kg/d, CLA 15–25 mg/kg/d.

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A national survey on the state of *H. pylori* eradication therapy in children among doctors who were members of the Korean Society for Pediatric Gastroenterology, Hepatology, and Nutrition in 2016 revealed that the most commonly used first-line eradication therapies were PPI-CLA-based triple therapy (75%) and BIS-based quadruple (AMO) therapy (25%). Most pediatric gastroenterologists had experienced treatment failures, and they frequently chose sequential therapy for rescue therapy [28]. Treatment regimens or eradication rates were not different from those of previous studies.

HOW TO OVERCOME DIFFICULTIES IN ERADICATION

The eradication rate of anti-*H. pylori* therapy should be more than 90% [9]. However, the reported rates of eradication of *H. pylori* infection among children and adolescents have not been satisfactory in Korea.

Substantial bacterial burdens exist when diagnosing *H. pylori* infection because it can begin as early as infancy. These bacteria are found within gastric mucus, with some being attached to gastric epithelial cells and seated deep in gastric pits. Sometimes, the bacteria invade gastric mucous cells in the *H. pylori*-infected patients. These characteristics of the living environment may contribute to forming the sanctuary for *H. pylori* against antibiotics. Moreover, *H. pylori* rarely replicate and only grow slowly below pH 6. Therefore, it is relatively resistant to antimicrobial agents, and the antimicrobial-resistant strains or dormant bacteria showing phenotypic antibiotic resistance may exist before the start of treatment. The acid pH of the stomach is also known to reduce the efficacy of most antibiotics. In addition, BIS drugs are diluted and washed out because of gastric acid secretion and peristaltic movement of the stomach [23,29].

There have been therapeutic trials to overcome eradication difficulties using the following suggestions. Combination therapy with several antimicrobials may help to overcome the pre-existing resistant strains. The maximal tolerable doses and optimized dosing intervals of antimicrobial drugs with sufficient PPI doses for strong acid suppression and the reduction of gastric secretion are expected to increase and maintain the antimicrobial gastric concentration to help overcome the sanctuary in which *H. pylori* are protected. PPI would also help to kill *H. pylori* directly via anti-*H. pylori* toxicity and indirectly by inducing the growth phase of *H. pylori*, improving the antimicrobial activity, and increasing the antibiotic stability at a higher pH. A longer duration of antimicrobial use and the addition of MET, which targets the bacterial DNA, and of BIS, which kills bacteria by direct coating, to combination therapy would assist in killing any dormant or infrequently replicating organisms [29,30]. Therefore, effective treatment may include a potent PPI, several antimicrobials, and BIS. The antimicrobial agents should be administered together for a longer duration. However, CLA or fluoroquinolone resistance are all or none phenomena that cannot be overcome by increasing doses or the duration of therapy. In contrast, AMO and MET resistance can be overcome using these measures along with strong gastric acid suppression [30].

BIS alone is not effective in eradicating *H. pylori*, but the addition of BIS increases the cure rate of a non-BIS containing triple regimen by 20–30% despite the high prevalence of antimicrobial resistance used for eradication therapy [31]. First, BIS coats the bacteria and exerts their action through binding to the key enzymes of *H. pylori*, which subsequently shows decreased urease and catalase activity, and increased lipid peroxide with reduced

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adherence [32]. BIS can be added to any combination of non-BIS containing triple therapies and can be repeatedly administered without inducing the resistance of *H. pylori*. It has also been suggested that BIS be administered with meals to increase distribution throughout the stomach. The low uptake of BIS by the human gastrointestinal tract might explain the relatively low reports on systemic adverse effects. BIS causes only reversible nephrotoxicity or encephalopathy at extreme dosages or physical conditions [33].

FIRST-LINE THERAPY

The updated ESPGHAN/NASPGHAN guidelines recommend the bacterial culture and antibiotic sensitivity test of *H. pylori* at the initial endoscopic evaluation for *H. pylori* infection in pediatric patients. They are given tailored treatments, as recommended in **Table 3** [4], according to the antibiotic sensitivity test results. However, bacteria culture is not practicable as well as not recommended at the initial diagnostic evaluation of *H. pylori* infection in Korea. When treating *H. pylori* infection in pediatric as well as adult patients, anti-*H. pylori* eradication therapy should be determined without knowledge of antibiotic susceptibility.

The updated ESPGHAN/NASPGHAN guidelines recommend that the first-line antimicrobial treatment of *H. pylori* for pediatric patients in this circumstance can be selected from one of PPI-high dose AMO-MET 14 d, BIS-PPI-AMO/TET-MET 14 d, and PPI-AMO-MET-CLA (concomitant therapy) 14 d [4]. PPI-high dose AMO-MET 14 d and PPI-AMO-MET-CLA (concomitant therapy) 14 d have been evaluated as relatively effective in eradication therapy for adult *H. pylori* infection. Clinical studies of their therapeutic abilities in young children and adolescents are limited but may be used as empirical rescue therapy in patients who have failed first-line eradication therapy.

In Korea, epidemics of Mycoplasma pneumoniae pneumonia, occurring periodically every three to four years and lasting for between one and one and a half years, have occurred since the mid-1980s [34]. Therefore, pediatricians have become accustomed to prescribing CLA or azithromycin for respiratory infections in children and adolescents during cyclic epidemics. These practices might have resulted in a CLA-resistant *H. pylori* frequency of more than 30% in Korea. The incidence of CLA resistance of *H. pylori* isolated from pediatric patients in Jinju, Korea increased from 6.9% in 1990–1994 to 18.2% in 2005–2009 [11].

Table 3. Recommended options for first-line therapy for *Helicobacter pylori* infection

H. pylori antimicrobial susceptibility	Suggested treatment
Known	
Susceptible to CLA and to MET	PPI-AMO-CLA 14 d or Sequential therapy 10 d
Resistant to CLA, susceptible to MET	PPI-AMO-MET or BIS-PPI-AMO (TET)-MET 14 d*
Resistant to MET, susceptible to CLA	PPI-AMO-CLA or BIS-PPI-AMO (TET)-MET 14 d*
Resistant to CLA and to MET	PPI-high dose AMO-MET 14 d or BIS-PPI-AMO (TET)-MET 14 d* or concomitant therapy 14 d
Unknown	PPI-high dose AMO-MET 14 d or BIS-PPI-AMO (TET)-MET 14 d* or concomitant therapy 14 d

CLA: clarithromycin, MET: metronidazole, PPI: proton pump inhibitor, AMO: amoxicillin, BIS: bismuth, TET: tetracycline.
Sequential therapy: PPI-AMO 5 day→PPI-CLA-MET 5 day.
Concomitant therapy: PPI-AMO-MET-CLA 14 day.
*In the case of penicillin allergy: if the strain is susceptible to CLA and MET, use standard dose triple therapy with MET in place of AMO; if the strain is resistant to CLA, then use BIS-based quadruple therapy with TET instead of AMO if older than 8 years.
Modified from Jones et al. (J Pediatr Gastroenterol Nutr 2017;64:991-1003) [4].

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The prevalence rate of CLA resistance in cultured *H. pylori*s from adults in Bundang-gu, Seongnam, Gyeonggi-do has increased steadily from 22.9% in 2003–2005 to 25.5% in 2006–2008 and 37.0% in 2009–2013 [35].

The Maastricht Consensus V recommends the BIS-based quadruple therapy instead of the CLA-based triple therapy in areas where the frequency of CLA resistance exceeds 15–20% [1]. Given the recommendations of the updated ESPGHAN/NASPGHAN guidelines and the Maastricht Consensus V, the BIS-based quadruple therapy (BIS-PPI-AMO/TET-MET 14 d), which is formed by the addition of PPI to the classic BIS-based triple therapy (BIS-AMO-MET), may be considered as the ideal first-line therapy for pediatric *H. pylori* eradication in Korea.

Use of the conventional BIS-based quadruple therapy (BIS 120 mg qid, PPI standard dose bid, TET 500 mg qid, MET 500 mg tid) is recommended for seven to 14 days as the first-line therapy if CLA resistance is expected in Korean adults [3]. The modified BIS-based quadruple therapy for 14 days, in which TET was replaced with AMO and all medication was taken twice a day to increase compliance (BIS 240 mg, rabeprazole 20 mg, AMO 1,000 mg, MET 750 mg bid), showed an eradication rate of 88.1% in Korean adults [36].

BIS-based quadruple therapy with AMO as per the updated ESPGHAN/NASPGHAN guidelines includes Pepto Bismol® 2T qid (Procter & Gamble, Cincinnati, OH, USA), omeprazole (PPI) 40 mg bid, AMO 1,000 mg bid, and MET 500 mg bid and is administered for 14 days. Patients over the age of 12 and weighing more than 40 kg may be treated with TET instead of AMO. This treatment includes Pepto Bismol® 2T qid, omeprazole (PPI) 40 mg bid, TET 500 mg tid, and MET 500 mg bid administered for 14 days (**Table 4**) [3,4].

It is recommended for most antimicrobial medications that treat *H. pylori* infection that they are taken twice a day to improve compliance with children and adolescents, but BIS must be taken four times a day. However, there has been an analysis of the effects of BIS being administered two times a day as with other anti-*H. pylori* therapeutic agents [37].

Table 4. Antimicrobial standard and high dosing regimen

Drug	Body weight	Morning dose (mg)	Evening dose (mg)
PPI*	15–24 kg	20	20
	25–34 kg	30	30
	>35 kg	40	40
AMO	15–24 kg	500	500
	25–34 kg	750	750
	>35 kg	1,000	1,000
CLA	15–24 kg	250	250
	25–34 kg	500	250
	>35 kg	500	500
MET	15–24 kg	250	250
	25–34 kg	500	250
	>35 kg	500	500
Pepto Bismol®†	<10 yr	1T qid	
	>10 yr	2T qid	
TET‡	>12 yr, >40 kg	500 qid	
High dose AMO	15–24 kg	750	750
	25–34 kg	1,000	1,000
	>35 kg	1,500	1,500

PPI: proton pump inhibitor, AMO: amoxicillin, CLA: clarithromycin. MET: metronidazole, TET: tetracycline.
*Esomeprazole or omeprazole (1.5–2.5 mg/kg/d). †Pepto Bismol® 1T: BIS subsalicylate 262 mg (BIS 150 mg). ‡TET dose: adpated from Kim et al. (Korean J Gastroenterol 2013;62:3-26) [3].
Modified from Jones et al. (J Pediatr Gastroenterol Nutr 2017;64:991-1003) [4].

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Table 5. Suggested and hypothetical BIS-based quadruple therapy

Regimen	Comment
Double dose PPI bid-AMO 1,000 mg bid-MET 500 mg bid-Pepto Bismol® 2T qid 14 d	Recommended in Jones et al. [4]; low dose of MET
Double dose PPI bid-AMO 1,000 mg bid-MET 750 mg bid-DeNol® 4T bid 14 d	Modified from Choe et al. [36]; increased dose of PPI and BIS
Double dose PPI bid-TET 500 mg tid-MET 500 mg tid-Denol® 2T qid 14 d	Modified Kim et al. [3]; increased dose of PPI and BIS
Double dose PPI bid-TET 750 mg bid-MET 750 mg bid-Denol® 4T bid 14 d	Modified Kim et al. [3]; increased dose of PPI and BIS with bid dosing
Double dose PPI bid-AMO 750 mg tid-MET 500 mg tid-Denol® 2T tid 14 d	Modified from the author's regimen; increased dose of PPI and BIS

PPI: proton pump inhibitor, AMO: amoxicillin, MET: metronidazole, TET: tetracycline, BIS: bismuth.

Although AMO is administered twice daily for convenience, this antibiotic should be dosed three to four times daily in triple therapies because tid or qid dosing is more effective in eradication than bid dosing [38]. If MET is administered with AMO in a triple or quadruple therapy in combination with other antimicrobial agents, reasonable eradication rates occur with tid dosing.

The antibiotics used in PPI-AMO-CLA/MET triple therapy may be more effective if higher doses are used unless it has been shown that lower doses are equally effective. The AMO being administered in lower amounts four times a day is more effective than in higher amounts two or three times a day due to its pharmacokinetics. Double-dose PPI is recommended for triple therapy and increases the efficacy of AMO, CLA, or MET. The efficacy of triple therapies in the presence of resistance may be significantly improved through the addition of BIS. Tolerable higher doses and pharmacokinetically optimal dose intervals of antibiotics and doubling doses of PPI with the addition of BIS for more than 14 days may be optimal for increasing the *H. pylori* eradication rate [29].

It is recommended in the updated ESPGHAN/NASPGHAN guidelines that PPI is taken as twice the standard dose twice a day for *H. pylori* eradication therapy. Standard adult PPI dosages for *H. pylori* eradication therapy are omeprazole 20 mg bid, lansoprazole 30 mg bid, pantoprazole 40 mg bid, rabeprazole 20 mg bid, and esomeprazole 20 mg bid [2].

For the BIS-based quadruple therapy recommended in the Korean Pediatric Textbook, the recommended dose of BIS is 8 mg/kg/d [39]. The calculated dose of BIS 120 mg (DeNol® 1T) bid at 30 kg of body weight, as per the Korean Pediatric textbook, is only 20% compared to that of BIS 300 mg qid (Pepto Bismol® 2T qid) recommended for children and adolescents above 35 kg by the updated ESPGHAN/NASPGHAN guidelines.

Based on the theoretical background presented so far, five types of BIS-based quadruple therapies are described in **Table 5** [3,4,36] which consider the gastric acid suppression, the additive effects of BIS on cure rates of *H. pylori*, the total amount of antibiotics to be taken in at least one day, medication adherence, and the adverse effects of the medication.

RESCUE THERAPY

In Korea, BIS-based (BIS-PPI-AMO/TET-MET) quadruple therapy over 14 days is most likely used as the first-line therapy because the antibiotic susceptibility test of *H. pylori* is not routinely performed before eradication therapy. If the eradication therapy fails, rescue therapy can be conducted by following the recommendations of the updated ESPGHAN/NASPGHAN guidelines based on the results of the antibiotic susceptibility test (**Table 3**) [4]. If an endoscopy is not feasible, either high-dose AMO therapy or concomitant therapy can be selected for an empirical rescue therapy (**Table 6**) [4].

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Table 6. Rescue therapies in pediatric patients who failed therapy

Initial antibiotic susceptibility	Past treatment regimen	Rescue treatment
1. CLA and MET susceptible	Triple therapy using AMO and CLA	Triple therapy using AMO and MET
	Triple therapy using AMO and MET	Triple therapy using AMO and CLA
2. CLA and MET susceptible	Sequential therapy	Consider performing a second endoscopy and use a tailored treatment for 14 d; or treat like double resistance (**Table 3**)*
3. CLA resistant	Triple therapy using MET	Treat like double resistance (**Table 3**)*
4. MET resistant	Triple therapy using CLA	Consider performing a second endoscopy and use a tailored treatment for 14 d or treat like double resistance (**Table 3**)*
5. Primary antimicrobial susceptibility unknown	Triple therapy or sequential therapy	Consider performing a second endoscopy to assess secondary antimicrobial susceptibility; or treat like double resistance (**Table 3**)*

CLA: clarithromycin. MET: metronidazole, AMO: amoxicillin.
*In adolescents levofloxacin or tetracycline may be considered.
Modified from Jones et al. (J Pediatr Gastroenterol Nutr 2017;64:991-1003) [4].

High-dose AMO therapy (double dose PPI bid, AMO 1,500 mg bid, MET 500 mg bid 14 d), which has components included in the BIS-based quadruple (BIS-PPI-AMO-MET) therapy, used as first-line therapy, does not seem to be effective as rescue therapy, although the dose of AMO was increased 1.5-fold. However, TET instead of MET in high-dose AMO therapy with the addition of BIS (double dose PPI bid, AMO 1,500 mg bid, TET 750 mg bid, Denol® 2T qid 14 d) may be considered as empirical rescue therapy.

CLA and MET are administered simultaneously for 14 days as a concomitant therapy (double dose PPI bid, AMO 1,000 mg bid, MET 500 mg bid, CLA 500 mg bid 14 d). The addition of CLA, which is not present in BIS-based quadruple therapy, may be valuable as an empirical rescue therapy after its failure if the infection-causing *H. pylori* are susceptible to it.

Cyclic epidemics of *M. pneumoniae* pneumonia and the increased use of oral extended-spectrum macrolides have caused more than 80% frequency of macrolide-resistant *M. pneumoniae* occurrence in children [40]. Recently, the increased number of prescriptions of TET or fluoroquinolone to the macrolide-unresponsive *M. pneumoniae* pneumonia in children and adolescents has caused concerns over potential increases in fluoroquinolone-resistant *H. pylori* infections in adolescents. A recent nationwide survey found that the prevalence of fluoroquinolone-resistant *H. pylori* isolated from adult patients from 2017 to 2018 in Korea was 37% [12]. Therefore, fluoroquinolone should be selected as one of the components of an empirical rescue therapy only after the antimicrobial susceptibility test has been carried out.

SALVAGE THERAPY

If eradication fails after the first-line and rescue therapies, an endoscopy should be performed for antibiotic susceptibility tests. The selection of two susceptible antibiotics is advised for the administration of maximal tolerable doses with the double dose PPI bid and DeNol® 2T qid for at least 14 days.

The frequency of furazolidone resistant *H. pylori* isolated from pediatric and adult patients in Jinju was found to be 9.9% (9/91) from 1990 to 2009 and 7.0% (12/170) from 1986 to 1999, respectively [10,11]. However, furazolidone is not permitted for use on animals or humans in Korea. Therefore, It cannot currently be included in Korea as a rescue or salvage therapy.

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Rifabutin can be included in a rescue or salvage therapy for *H. pylori* eradication because rifabutin resistant *H. pylori* are rare in both pediatric and adult patients in Korea. The resistant rates in pediatric and adult patients in Jinju were found to be 7.7% (7/91) and 2.9% (5/170), respectively [10,11]. However, the occurrence of myelosuppression and the development of rifamycin-resistant *Mycobacterium tuberculosis* should be monitored if therapy containing rifabutin is used.

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