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Antibiotics resistance of *Helicobacter pylori* and treatment modalities in children with *H. pylori* infection

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Pediatric infection with *Helicobacter pylori* may occur early in childhood and persist lifelong. Global pediatric clinical studies have reported a decreasing tendency in the overall rate of *H. pylori* eradication. In pediatric patients with *H. pylori* infection, pediatric patients with peptic ulcer, and the first-degree relatives of patients with a history of gastric cancer, it is commonly recommended that *H. pylori* strains be eradicated. Antibiotic drug resistance to *H. pylori*, which has been reported to vary widely between geographic regions, is mainly associated with treatment failure in these patients. It is therefore imperative that the antibiotic resistance rates of *H. pylori* in children and adolescents be meticulously monitored across countries and throughout geographic regions. This paper particularly focuses on the antibiotic drug resistance of *H. pylori* and the thearpy of pediatric *H. pylori* infection cases.

Key words: Helicobacter pylori, Drug resistance, Therapy, Child

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Introduction

Helicobacter pylori infection in young children and adolescents[1,2] is a chronic, persistent infection that may lead to chronic gastritis, atrophic gastritis, intestinal metaplasia, and even gastric adenocarcinoma[3]. As such, it is likely that eradication of *H. pylori* lowers the risk of developing gastric cancer[4-6]. International guidelines for the treatment of *H. pylori* infection recommend the use of a 7-day, triple-medication therapy consisting of clarithromycin, either metronidazole or amoxicillin, and either a proton pump inhibitor (PPI) or bismuth citrate as the first-line of treatment[7-10]. Nevertheless, antibiotic resistance remains problematic in the treatment of *H. pylori* infection[11,12], requiring careful monitoring of antibiotic resistance to *H. pylori* in children and adolescents throughout regions and countries[13].

This paper particularly focuses on the antimicrobial resistance of *H. pylori* and the treatment of pediatric *H. pylori* infection cases.

Antimicrobial resistance of *H. pylori* in children

A useful means of choosing the best treatment options and/or managing treatment failure[14] is obtaining a culture of *H. pylori* from the gastric mucosa, which helps in determining the antimicrobial susceptibility. However, as compared with other normal intestinal flora, the fragility of *H. pylori* at room and very low temperatures poses a therapeutic challenge for clinicians[15]. Further, data regarding the antimicrobial susceptibility of *H. pylori* in

children as compared with that in adults is scarce, owing to the lesser need to perform endoscopy in children as well as because endoscopy is rarely indicated for the treatment of children.

H. pylori resistance rates may vary among patients depending on age, sex, disease state, and regional location. In some countries, antimicrobial resistance has evolved with the use of antibacterial agents[3,16]. Table 1 shows recent the rates of *H. pylori* resistance to antimicrobials that are commonly administered to children in 10 countries[17-27]. The E-test has been established as a reliable modality for measuring antibiotic resistance to all antimicrobials, except for metronidazole for which it overestimates resistance. However, its results should be confirmed using the agar dilution method. Therefore, the agar dilution method has been recommended to test *H. pylori* resistance[28]. The serial 2-fold agar dilution method cannot be routinely used to examine the antimicrobial sensitivity because it is expensive and difficult to perform. To date, most of the studies in the antibiotic resistance of *H. pylori* have been conducted using the E-test method.

Amoxicillin is a β-lactam antibiotic used to treat numerous bacterial infections (e.g., acute otitis media, streptococcal pharyngitis, pneumonia, impetigo, cystitis, and acute bacterial enteritis). Once administered orally, it is absorbed better and is more effective against *H. pylori* than other β-lactam antibiotics. According to a meta-analysis of 6 published studies, there have been no reports of amoxicillin resistance (Table 1)[20,21,23-25,27]. In contrast, 2 South Korean studies reported a great discrepancy in the rate of amoxicillin resistance between the 2 main regional areas, with Seoul reported to have a rate of 0% and Jinju, of 24.2%[22,24]. This discrepancy might be due to differences in the prescription of antibiotics to patients by the medical doctors of these areas. In Jinju, the rate of amoxicillin resistance increased from 19.0% between 1990 and 1994 to 24.2% between 2005 and 2009[22], and has been estimated at more than 50% in Iran[18]. These findings suggest that administration of a course of amoxicillin is ineffective for the management of *H. pylori* infection. In contrast, there have been no reports of amoxicillin resistance in Israel, Portugal, Austria, Japan, China, or, as reported above, in Seoul, South Korea (Table 1), which indicates that amoxicillin administration is a recommended modality for the treatment of *H. pylori* infection. The causes of this great discrepancy in the rate of amoxicillin resistance among regions and countries remain unclear. This is because amoxicillin is one of the most commonly prescribed antibiotics for children. Further follow-up studies are therefore warranted to evaluate changing trends in the rate of amoxicillin resistance.

Clarithromycin, a macrolide antibiotic that has been commonly prescribed to South Korean children for the treatment of infectious disease since 1997, is the treatment of choice that may be alternatively used with chemotherapy regimens to treat *H. pylori* infection. A significant correlation has been reported between clarithromycin resistance and the rate of *H. pylori* eradication in pediatric patients[25]. The range of clarithromycin resistance that has been reported for 10 countries varies widely, from 13.9% to 84.9% (Table 1), and is higher in 7 countries than the rate previously reported in 14 European countries (<24.0%)[29]. Moreover, an increasing tendency in the rate of clarithromycin resistance has been observed in Bulgaria[17], South Korea[22,24], Austria[23], and Japan[25]. Presumably, this increase is due to the increased rate of prescription of clarithromycin for the treatment of respiratory tract infections in children. At the same time, an age-dependent decrease in the prevalence of clarithromycin resistance has been observed in Vietnam, decreasing from 62.7% in children aged 3–6 years to 54% in children aged 7–10 years and to 31.7% in children aged 11–15 years[19]. The marked increase in the rate of clarithromycin resistance in Vietnam over the past decade may be explained by the extensive administration of clarithromycin for the treatment of respiratory tract infections in children since

Table 1. Primary antimicrobial resistances of *Helicobacter pylori* in children according to a review of studies published since 2000

Country	Year	No. of strains	Method of testing	Resistance rate (%)				
				Amoxicillin	Clarithromycin	Metronidazole	Tetracycline	Quinolone
Bulgaria[17]	2003–2004	28	Limited agar dilution	1.4	13.9	13.9	NA	NA
Iran[18]	2003–2005	100	E-test and disk diffusion	59.0	16.0	95.0	7.0	7.0
Vietnam[19]	2005–2006	222	E-test	0.5	50.9	65.3	NA	NA
Israel[20]	2005–2007	53	E-test	0	25.0	19.0	0	0
Portugal[21]	2006–2009	1,115	E-test	0	34.7	13.9	4.6	4.6
Korea (Jinju)[22]	2005–2009	33	Agar dilution	24.2	18.2	27.3	15.2	15.2
Austria[23]	2002–2008	153	E-test	0	34.0	22.9	NA	NA
Korea (Seoul)[24]	2003–2009	28	E-test and disk diffusion	0	25.0	17.8	NA	NA
Japan[25]	2003–2007	27	E-test	0	40.7	7.4	NA	NA
Brazil[26]	2008–2009	77	Agar dilution	10.4	19.5	40.0	NA	NA
China[27]	2009–2010	73	E-test	0	84.9	61.6	13.7	13.7

NA, not available.

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its inexpensive generic version became commercially available[19]. It may also be partially explained by the widespread prescription of macrolides for the treatment of children aged 3–10 years.

In patients with *H. pylori* infection, clarithromycin resistance occurs as a result of mutations of domain V in the 23S ribosomal RNA (rRNA) gene[30]. Although such mutations have been identified in children in South Korea, China, and Japan (Table 2)[27,31,32], the type of mutation varies by country. Whereas the A2144G mutation is the most prevalent mutation in macrolide-resistant strains in South Korea and Japan, the A2143G is the most prevalent in those from China. It has also been reported that erythromycin and azithromycin resistance results from the point mutation of the 23S rRNA gene. However, no studies have reported the rate of cross-resistance among erythromycin, azithromycin, and clarithromycin in the management of *H. pylori* infection. It is presumed that the low resistance rate is associated with the widespread administration of a course of clarithromycin for the treatment of children with *H. pylori* infection in such countries as Bulgaria, Iran, Brazil, and South Korea (Jinju).

Currently, metronidazole is widely administered to treat anaerobic bacterial infection, amebic infection, and gynecologic infection. As shown in Table 1, the range of metronidazole resistance in *H. pylori* isolated from children ranges from 7.4%[25] to 95.0%[18]. This relatively wider range, than that of amoxicillin and clarithromycin, might be due to the differences in the epidemic diseases (e.g., amebic infections) prevalent in different countries. It has been reported that a course of metronidazole might be effective against *H. pylori* infection in countries such as Iran[18], Vietnam[19], Brazil[26], and China[27]. In contrast, according to 2 Korean studies, the prevalence of metronidazole resistance has decreased over time in both major regions of South Korea, from 32.8% between 1990 and 1994 to 27.3% between 2005 and 2009 in Jinju[22] and from 44.4% between 2003 and 2006 to 5.3% between 2006 and 2009 in Seoul[24], which may be attributable to the decreased administration of metronidazole in the treatment of South Korean children.

Several studies regarding the administration of other antimicrobials, such as tetracycline, quinolone, rifabutin, and furazolidone, for the treatment of patients with *H. pylori* infection have reported tetracycline or quinolone resistance. However, tetracycline is contraindicated for children aged ≤8 years and quinolone for children aged ≤18 years. Review of the findings indicates that children might become vertically infected with tetracycline- or quinolone-resistant *H. pylori*. The rates of tetracycline and quinolone resistance have both been reported to range from 0% to 15.2%, depending on the regional area (Table 1)[18,21,22,27].

Dual antimicrobial resistance is another problem in the management of *H. pylori* infection. The rate of dual resistance to clarithromycin and metronidazole has been reported as 5.7% in Bulgaria[17], 42.0% in Iran[18], 28.8% in Vietnam[19], 13.0% in Israel[20], 4.9% in Portugal[21], 15.2% in Jinju, South Korea[22], 33.3% in Seoul, South Korea[24], 10.9% in Austria[23], 7.8% in Brazil[26], and 38.4% in China[27]. A 7-day triple-therapy regimen of a PPI, amoxicillin, and either clarithromycin or metronidazole remains the first-line therapy in regional areas where primary clarithromycin resistance is estimated to range between <15% and 20%[14]. Use of a clarithromycin-metronidazole regimen should be considered after the antimicrobial sensitivity test in Iran, Vietnam, China, and Seoul, South Korea.

Table 2. The point mutation of the 23S rRNA gene associated with clarithromycin resistance

Country	Mutation in 23S rRNA gene	Frequency
Korea[31]	A2143G	1/27 (3.7%)
	A2144G	4/27 (14.8%)
Japan[32]	A2144G	11/12 (92.0%)
China[33]	A2142C	1/65 (1.5%)
	A2142G	4/65 (6.2%)
	A2143G	55/65 (84.6%)

Treatment of *H. pylori* infections in children

H. pylori infection in pediatric patients is characterized by mild gastritis, normal gross appearance of the stomach, and lower incidence of peptic ulcer than that in adults[33,34]. In the treatment of these patients, as well as that of pediatric patients with peptic ulcer and that of the first-degree relatives of patients with a history of gastric cancer, eradication of *H. pylori* strains is commonly recommended[13]. *H. pylori* infection should also be suspected in children with iron-deficiency anemia who are refractory to iron therapy, and treatment should be provided as appropriate[35].

Four studies comparing the effectiveness of different treatment modalities for *H. pylori* infection in South Korean children all found that a bismuth-based triple therapy was more effective against *H. pylori* as the first-line of treatment than a PPI-based therapy (Table 3)[36-39]. Other studies in South Korea have reported a decreasing tendency in the rate of *H. pylori* eradication by the administration of omeprazole with amoxicillin and clarithromycin, specifically a decrease from 81.0% between 1998 and 2000[37], to 74.0% between 1999 and 2000[38], and to 67.7% between 2004 and 2012[39]. Moreover, it has been reported that the quadruple therapy showed a higher rate of *H. pylori* eradication than the triple therapy[39]. Presumably, these results might be due to the inhibitory effects of bismuth on *H. pylori* growth and the low rate of resistance to amoxicillin or metronidazole in patients in Seoul[24].

Little is known regarding the pharmacokinetics of antimicrobial agents in children. In a study of 238 *H. pylori*-infected children comparing the rate of *H. pylori* eradication using clarithromycin-

Table 3. Correlation between the rate of *Helicobacter pylori* eradication and the optimal treatment modalities in Korean children

Author	Year	Treatment	Duration	Follow-up	Eradication rate	*P* value
Bae et al.[36]	1993–1996	BA	2 Weeks	Urease test, culture and a modified Giemsa stain	35/57 (61.4%)	0.012
		BAM	2 Weeks		16/18 (88.9%)–10/11 (90.9%)	
Choi et al.[37]	1998–2000	OAC OAC	1 Week 2 Weeks	Urease test and histologic examination	17/21 (81.0%) 11/13 (84.6%)	0.785
Choi et al.[38]	1999–2004	OAC BAM	1 Week 1 Week	Urea breath test	105/141 (74.0%) 78/92 (85.0%)	0.07
Hong and Yang[39]	2004–2012	OAC OAMB	2 Weeks 1 Week	Urea breath test or endoscopic biopsy-based method	42/62 (67.7%) 47/56 (83.9%)	0.041

B, bismuth subsalicylate; A, amoxicillin; M, metronidazole; O, omeprazole; C, clarithromycin; NA, not available.

and metronidazole-based triple therapies between a once daily (q.d.) regimen group, which consisted of patients weighing 13–22 kg, and a twice daily (b.i.d.) regimen group, which consisted of patients weighing 23–45 kg, the rate of *H. pylori* eradication was found to be lower in the q.d. group than in the b.i.d. group (45.7% vs. 70.9%, respectively)[40]. This finding suggests that weight-based dosages might be based on either suboptimal dosing recommendations or, because some medications are not available as pediatric formulations, suboptimal dosing itself, unless the medication is adjusted for administration to children[14]. One study of 62 children, aged <18 years weighing <15 kg, with *H. pylori* infection who were refractory to metronidazole and clarithromycin found the rate of *H. pylori* eradication to be 66%–73% after a 2-week course of high-dose amoxicillin, metronidazole, and esomeprazole therapy[41]. In these children, the most common adverse events were nausea, diarrhea, and vomiting[41]. Further studies are therefore warranted to determine the appropriate doses of antimicrobials and PPI or bismuth in children weighing <30 kg. Host factors, such as bacterial burden and cytochrome P450 genotype, are mainly associated with treatment outcomes. In addition, the proportion of *H. pylori* is another factor that is associated with the treatment efficacy as a proportion of the bacteria become attached to the gastric mucosa, where they produce a biofilm[28]. The *H. pylori* present are then protected by the thick mucosal layer in the acidic environment, likely greatly reducing the efficacy of many antimicrobials in the acidic pH environment. In light of these findings, antisecretory agents, such as PPIs, have been used to increase the bioavailability of amoxicillin and metronidazole in the treatment of *H. pylori* infection[28]. Based on the findings of dose-related studies, it may also be beneficial to prescribe doses of medications higher than those currently recommended for children, such as the doses prescribed for a 14-day course for adults, for children weighing >30 kg[40,41].

Recent studies have reported on sequential therapy and concomitant use of probiotics[14]. In this regimen, a 10-day course comprises a 5-day course of PPI and amoxicillin and a 5-day course of clarithromycin and metronidazole[42]. Probiotics are used to resolve the treatment-emergent adverse effects and to increase the efficacy of *H. pylori* eradication[14,43]. Further studies are therefore warranted to assess the efficacy of sequential therapy and concomitant use of probiotics in children.

Conclusions

Great variability exists in the antimicrobial resistance of *H. pylori* in children by regional location. Clinicians should therefore consider performance of continuous and serial antimicrobial sensitivity testing and the eradication rate when determining the optimal treatment regimen (e.g., a PPI or bismuth-based regimen), use of antimicrobial agents, and the timing, dosage, and duration of the agents.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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