

Comparison of the Different Protocols for the Eradication of Pediatric Helicobacter Pylori Infection in Iran

Ameneh Lamsehchi¹, *Hosein Alimadadi¹, Moeinadin Safavi²

¹MD, Department of Pediatrics, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

²MD, Molecular Pathology and Cytogenetic Ward, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Background

Helicobacter pylori has become very important recently due to infecting around 50% of the population worldwide. This infection can cause peptic ulcer disease and gastric cancer. This study aimed to evaluate the efficacy of common triple treatment, sequential treatment, and other regimens for Helicobacter pylori eradication in children.

Materials and Methods: In this retrospective cohort study, 40 children who were diagnosed with Helicobacter pylori infection by endoscopic and pathologic features in the Children's Medical Center of Tehran, Iran, in 2018 were included. The questionnaire was completed by telephone interview. Types of protocols include triple therapy (proton pump inhibitors with clarithromycin and amoxicillin or metronidazole for 2 weeks), sequential therapy (proton pump inhibitors with amoxicillin for 5 days followed by proton pump inhibitors with clarithromycin and metronidazole for 5 days), and other treatments (every protocol except triple and sequential regimens). At the end, we compared the efficacy of the different protocols for eradicating this infection by urea breath test or stool antigen test 8 weeks after therapy.

Results: The age of patients with and without successful eradication was 8.12 and 7.8 years, respectively ($p=0.8$). There was no significant difference between both sexes ($p=0.999$) in the frequencies of eradication. The eradication rate of Helicobacter pylori was 95.5% in sequential therapy, 100% in conventional triple therapy, and 87.5% in other regimens. There was no significant difference between different protocols ($p=0.422$).

Conclusion

Determining first-line treatment for eradicating Helicobacter pylori infection is important to increase treatment success and reduce rate of secondary antimicrobial resistance. Our study showed that sequential treatment is as effective as conventional treatment in eradication of this infection in children.

Key Words: Children, Conventional triple therapy, Sequential therapy, Stool antigen test.

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*Corresponding Author:

Hosein Alimadadi, MD, Address: Gharib Street, Pediatric Gastroenterology and Hepatology Research Center, Tehran, Iran. Postal code: 1275894241

Email: dr.hosein.alimadadi@gmail.com

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1- INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral-shaped, catalase, and urease positive spirochete that is associated with a wide range of GI and non-GI diseases. *H. pylori* has recently become very important due to infecting around 50% of the world population (1). The overall prevalence of *H. pylori* infection is strongly linked to socioeconomic conditions (2). The prevalence of this infection in developing countries is 50.8%, while the prevalence in the developed countries is 34.7%. The prevalence of *H. pylori* infection in children is notably lower than in adults (32.6% vs. 48.6%) (3).

According to a meta-analysis study in Iran, the prevalence of *H. pylori* is 54% in all populations and 42% vs. 62% in children and adults respectively (4). The distribution of *H. pylori* seems to vary according to the age, race, and socio-economic condition of patients, these factors are important for the quality of nutrition and health in childhood (5). Although most of the patients with *H. pylori* infection have no clinical manifestations, some conditions are associated with the presence of this bacterium such as peptic ulcer disease, gastric cancer, dyspepsia, and other extraintestinal diseases (4, 6). As is known, the pathogenesis of duodenal ulcer and chronic gastritis in children depends on the role of *H. pylori* infection (7).

Many studies have evaluated different regimens as the first-line and second-line treatments for eradicating *H. pylori* infection in children in Iran; however, to date, it remains controversial (5). Protocols for eradicating *H. pylori* contain a proton pump inhibitor (PPI), and several antibiotics. In addition, for raising eradication rate and reducing secondary antimicrobial resistance, treatment success rate should be over 90% per-protocol analysis (8). However, various studies

showed low success rate for conventional therapy, which is probably due to increasing antibacterial resistance especially to clarithromycin, other factors include poor compliance with treatment, non-adherence to medication, short treatment period, drug complications, bacterial load, and underlying illnesses (9, 10). According to (The European and North American Societies for Pediatric Gastroenterology Hepatology and Nutrition) ESPGHAN/NASPGHAN Guidelines, treatment of this infection should be chosen based on susceptibility testing. If access to antibiotic susceptibility tests does not exist, high-dose conventional triple therapy (proton pump inhibitors (PPI) with clarithromycin (CLA), and amoxicillin (AMO) or metronidazole (MET) for 2 weeks) are used to treat *H. pylori* infection.

Sequential therapy consists of PPI with AMO for 5 days followed by PPI with CLA and MET for 5 days. This regimen is as effective as triple therapy in fully susceptible strains of *H. pylori* bacterium (11). Although, sequential therapy seems to be superior to conventional triple regimen in children in some studies (12, 13). Rescue therapy for *H. pylori* eradication consists of a PPI, quinolone, and amoxicillin as an option (11). This study aimed to evaluate the efficacy of common triple treatment, sequential treatment, and other regimens for *Helicobacter pylori* eradication in children.

2- MATERIALS AND METHODS

2-1. Study design and population

This retrospective cohort study was carried out on 40 children who were diagnosed with *H. pylori* infection by endoscopic and pathologic features in the Children's Medical Center of Tehran, Iran, in 2018. After contact with the parents of patients, informed consent was obtained from them, and the questionnaire was completed by telephone interview, and if

they were interested, an appointment was made for a one-hour interview, and no intervention or clinical assessment was done. In this study triple therapy describes as PPI with CLA and AMO or MET for 2 weeks and sequential regimen consists of PPI with AMO for 5 days followed by PPI with CLA and MET for 5 days. In addition, rescue therapy for *H. pylori* eradication is made up of a PPI, quinolone, and amoxicillin as an option. The history of confirmed *H. pylori* eradication by C-urea breath test (C-UBT) or stool antigen test was taken in the telephone interview. Exclusion criteria were an unknown treatment regimen, unknown *H. pylori* status after eradication therapy, and missed questionnaire data.

2-2. Ethical consideration

Written informed consent for publication was obtained from parents of patients. This survey was approved by the Medical Ethics Committee of Tehran University of Medical Sciences, Iran (IR.TUMS.MEDICINE.REC.1396.4649).

2-3. Statistical analyses

All Categorical data were shown as frequency (%) and compared using the Chi-square test. Continuous data were expressed as Mean \pm SD. All P-values were two-tailed, with the level of statistical significance specified as 0.05. The statistical analysis was performed using the IBM SPSS ver. 18.0 Statistics for windows.

3- RESULTS

Forty patients treated for *H. pylori* infection were analyzed. Children were aged between 2 and 16 years old with a mean and standard deviation (SD) of 8.0 ± 3.8 years. Of these, 19 (47.5%), and 21 (52.5%) were boys and girls, respectively. Furthermore, 22 (55%) were treated with sequential therapy, 10 (25%) with triple therapy, and eight (20%) with other treatment regimens (**Table.1**). At diagnosis, the age of patients with and without successful eradication was 8.12 and 7.8 years, respectively ($p=0.8$). Also, the age of patients who received conventional triple therapies was 8.1 years compared to 8.2 in sequential therapy, and 7 in other regimens, which had no significant difference ($p=0.852$),(**Table.2**).

The frequencies of eradication were 94.7% in boys, and 95.2% in girls and there was no significant difference between both sexes ($p=0.999$). Accurate result of eradication was achieved in 7 patients with C-urea breath test (C-UBT), and 31 patients with stool antigen ($p=0.364$). Eradication was not successful in only two cases (5%), and the eradication rate was 95.5% for the sequential therapy, 100% for the triple therapy, and 87.5% for other treatments. No significant difference in eradication rate was observed between the various treatments ($p=0.422$), (**Table.3**). Results of the endoscopic examination of patients are demonstrated in Table.3. No significant difference was found between the patients with successful and unsuccessful eradications.

Table-1: General characteristics of patients, n=40.

Protocols	Mean	Standard Deviation
Triple therapy	8.09	3.448
Sequential therapy	8.18	3.907
Other treatment	7.00	4.967
Total	8.04	3.803

Table-2: The association between different treatment protocols and eradication rate in patients with H. pylori infection.

Eradication	Triple therapy (10 patients)	Sequential therapy (22 patients)	Other regimes (8 patients)	*P-value
	Number (%)	Number (%)	Number (%)	
Successful	10 (100.0)	21 (95.5)	7 (87.5)	0.422
Unsuccessful	0 (0.0)	1 (4.5)	1 (12.5)	

* Chi-Square test.

Table-3: The association between eradication rate with Endoscopic and histopathology findings of patients with H. Pylori infection.

Findings		Eradicated	Not eradicated	Total	P-value
		Number (%)	Number (%)	Number (%)	
Endoscopy	Esophagus erythema	12 (31.6)	1 (50.0)	13 (32.5)	0.419
	Antrum nodularity	4 (10.5)	1 (50.0)	5 (12.5)	
	Gastric erythema	15 (39.5)	0 (0.0)	15 (37.5)	
	Duodenal ulcer (D1)	1 (2.6)	0 (0.0)	1 (2.5)	
	Esophagus erythema + Antrum nodularity	1 (2.6)	0 (0.0)	1 (2.5)	
	Esophagus erythema + Gastric erythema	2 (5.3)	0 (0.0)	2 (5.0)	
	Duodenal ulcer (D1) + Antrum nodularity	1 (2.6)	0 (0.0)	1 (2.5)	
	Duodenal ulcer (D1) + Gastric erythema	1 (2.6)	0 (0.0)	1 (2.5)	
	Duodenal ulcer (D1) + Antrum nodularity + Gastric erythema + Esophagus erythema	1 (2.6)	0 (0.0)	1 (2.5)	
Histopathology	Esophagitis	10 (26.3)	1 (50.0)	11 (27.5)	0.269
	Gastritis	20 (52.6)	0 (0.0)	20 (50.0)	
	Duodenitis	1 (2.6)	0 (0.0)	1 (2.5)	
	Esophagitis + Gastritis	4 (10.5)	1 (50.0)	5 (12.5)	
	Gastritis + Duodenitis	3 (7.9)	0 (0.0)	3 (7.5)	

4- DISCUSSION

In this study, we compared different regimens for eradicating H. pylori in children. According to our analysis, there was no significant difference in eradication rate of different protocols and sequential therapy was as effective as conventional triple therapy. According to the Guidelines eradication of H. pylori is proven to be beneficial for the prevention of gastric cancer, therefore indications of H. pylori eradication are increasing in the area with a higher prevalence of H. pylori infection. This highlights the need for proper treatment of H. pylori and selection of the

first-line therapy for the eradication of this infection, which is still challenging for physicians. In this study, 40 patients with positive pathology of H. pylori were included and there was no significant association between age at diagnosis and the rates of H. pylori eradication. The age of patients who received conventional triple therapies was 8.1 years and 8.2 in sequential therapy, which is lower than the mean age in the Francavilla et al. study (9.9 and 11 years, respectively), probably because our patients are more likely to have an infection in lower ages (13). The frequencies of eradication in our study

were 94.7% in boys and 95.2% in girls, and there was no significant difference between sex and eradication rates similar to the systematic review of Zamani et al. (3). In addition, the most frequent endoscopic finding in *H. pylori* positive children was gastric erythema (39.5%), and the least frequent was duodenal ulcer (2.6%), while in the study of Francavilla et al., the antrum nodularity was found to be the most frequent, 70%, and the lowest was similar to our finding (13). Moreover, in the study of Kotilea et al., nodular gastritis was cardinal endoscopic finding in children with *H. pylori* infection (8).

In the current study, the endoscopic findings in patients with successful eradication were gastric erythema in 39.5%, esophageal erythema in 31.6%, antrum nodularity in 10.5%, and duodenal ulcer in 2.6%, however, there is no significant difference between the endoscopic findings and the eradication of *H. pylori*. Additionally, histopathologic findings in biopsies of patients with successful eradication was gastritis in 60.9%, esophagitis in 30.4%, and 8.7% in duodenitis, similarly, no significant difference between histopathologic findings and eradication of the infection were observed. Our study showed eradication rate was 95.5%, 100%, 87.5% for the sequential therapy, triple therapy and other treatments respectively.

No significant difference was found between rates of eradication in different treatments, which is like the results of two review studies of Kalach and Roma (14, 15). Also, Kefeli et al., evaluated different regimens in eradication of *H. pylori* in adults in Turkey and there was no significant difference between quadruple, sequential, and concomitant therapy (16). Unlike our results, some studies found sequential therapy superior to conventional therapies including the study of Huang and Zhan (12), the study of Albrecht et al. in Poland (17), and the study of Francavilla et

al. in Italy (13). However, in a study in 2014, the standard triple treatment could not eradicate *Helicobacter pylori* infection and sequential therapy was a little superior to triple therapy (18). Nonetheless, it has been suggested that antibiotic susceptibility test is required for eradication therapy (19). Moreover, Dehghani et al. in Shiraz (20), and Seo et al. in Korea have introduced the Bismuth treatment regimen as the first-line therapy in their area (21). In addition, in two studies in Iran that evaluated the effectiveness of the sequential therapy on the eradication of *H. pylori* in adults (22, 23), triple and quadruple therapies for eradication of *H. pylori* in Iranian population were considered superior to sequential therapy. Similarly, Masjedizadeh et al. showed that standard triple therapy is the most effective strategy for eradicating *H. pylori* in adults in Ahvaz, Iran (24).

However, most of these studies have been conducted in Europe and other countries, and there is little data from developing countries. It seems that studies in Iran have not confirmed the superiority of sequential therapy. Besides, the 2016 guideline of ESPGHAN & NASPGHAN emphasizes the need for treatment based on antibiotic susceptibility, and if cultures or antibiotic sensitivity tests are not available, triple therapy containing clarithromycin should not be used as the first line of treatment, due to the increasing prevalence of clarithromycin resistance (11). The superiority of sequential therapy as first-line therapy in children and adults has already been discussed in various studies. Furthermore, antimicrobial susceptibility testing is required for increasing treatment success rate of different regimens.

4-1. Study Limitations

We had some limitations that restricted our study. First, we did not have facilities for testing antimicrobial susceptibility for all patients. Second, a long time was needed

to gather more cases with inclusion criteria for evaluating efficacy of different regimens. Third, it was a retrospective study and we had some unknown eradication status because of missing data by parents.

5- CONCLUSION

Due to the high prevalence of H. pylori worldwide, especially in developing countries, selecting first-line treatment for eradication H. pylori infection is crucial. The results of this study showed that sequential therapy is as effective as conventional triple therapy. It seems that further studies are needed to determine the first-line treatment for eradication of H. pylori in Iran due to a lack of sufficient infrastructural facilities for antibiotic susceptibility tests of H. pylori before eradication and increasing resistance of H. pylori strains to clarithromycin in the world. It is believed that reducing eradication failure at first-line treatment may lead to lower secondary antimicrobial resistance and decreasing health care burden. Therefore, it is suggested to establish a registry system for recording the clinical, histopathological, laboratory and demographic data of H. pylori-positive children, and type of therapies and precise follow-up for these patients by creating a multi-center database in Iran.

6- AUTHOR'S CONTRIBUTIONS

Hossein Alimadadi contributed to the literature review, participated in the design and drafting the manuscript. Ameneh Lamsehchi was responsible for interviewing patients, involved in designing and revising the manuscript and gave the final approval of the version to be published. Moeinadin Safavi was the pathologist of this study and we gathered a list of children with positive H. pylori infection in his laboratory and with his confirmation.

7- CONFLICT OF INTEREST: None.

8- REFERENCES

1. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, et al. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. *Gastroenterology*. 2017;153(2): 420–9.
2. Hu Y, Wan J, Li X, Zhu Y, Graham DY, Lu N. Systematic review with meta-analysis: the global recurrence rate of Helicobacter pylori. *Aliment Pharmacol Ther*. 2017;46(9):773–9.
3. Zamani M, Ebrahimitabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J, et al. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. *Aliment Pharmacol Ther*. 2018;47(7):868–76.
4. Moosazadeh M, Lankarani KB, Afshari M. Meta-analysis of the prevalence of Helicobacter pylori infection among children and adults of Iran. *Int J Prev Med*. 2016;7.
5. Fakhri H, Firoozi MS, Bari Z. Eradication of Helicobacter pylori in Iran: a review. *Middle East J Dig Dis*. 2018;10(1):5.
6. Crowe SE. Helicobacter pylori infection. *N Engl J Med*. 2019;380(12):1158–65.
7. Sabbagh P, Javanian M, Koppolu V, Vasigala VR, Ebrahimpour S. Helicobacter pylori infection in children: an overview of diagnostic methods. *Eur J Clin Microbiol Infect Dis*. 2019;1–11.
8. Kotilea K, Kalach N, Homan M, Bontems P. Helicobacter pylori infection in pediatric patients: update on diagnosis and eradication strategies. *Pediatr Drugs*. 2018;20(4):337–51.
9. Wang B, Lv Z-F, Wang Y-H, Wang H, Liu X-Q, Xie Y, et al. Standard triple therapy for Helicobacter pylori infection in China: a meta-analysis. *World J Gastroenterol WJG*. 2014;20(40):14973.
10. Peng C, Hu Y, Ge Z-M, Zou Q-M, Lyu N-H. Diagnosis and treatment of Helicobacter pylori infections in children and

elderly populations. *Chronic Dis Transl Med.* 2019;5(4):243–51.

11. Jones NL, Koletzko S, Goodman K, Bontems P, Cadranel S, Casswall T, et al. Joint ESPGHAN/NASPGHAN guidelines for the management of *Helicobacter pylori* in children and adolescents (update 2016). *J Pediatr Gastroenterol Nutr.* 2017;64(6):991–1003.

12. Huang Y, Zhan X. Sequential therapy is superior to triple therapy for *Helicobacter pylori* infection in children: a meta-analysis. *Indian J Pediatr.* 2016;83(4):307–15.

13. Francavilla R, Lionetti E, Castellaneta SP, Magistà AM, Boscarelli G, Piscitelli D, et al. Improved efficacy of 10-day sequential treatment for *Helicobacter pylori* eradication in children: a randomized trial. *Gastroenterology.* 2005;129(5):1414–9.

14. Roma E, Miele E. *Helicobacter pylori* infection in pediatrics. *Helicobacter.* 2015; 20: 47–53.

15. Kalach N, Bontems P, Raymond J. *Helicobacter pylori* infection in children. *Helicobacter.* 2017;22:e12414.

16. Kefeli A, Basyigit S, Yeniova AO, Kefeli TT, Aslan M, Tanas O. Comparison of three different regimens against *Helicobacter pylori* as a first-line treatment: A randomized clinical trial. *Bosn J basic Med Sci.* 2016;16(1):52.

17. Albrecht P, Kotowska M, Szajewska H. Sequential therapy compared with standard triple therapy for *Helicobacter pylori* eradication in children: a double-blind, randomized, controlled trial. *J Pediatr.* 2011;159(1):45–9.

18. Kutluk G, Tutar E, Bayrak A, Volkan B, Akyon Y, Celikel C, et al. Sequential therapy versus standard triple therapy for *Helicobacter pylori* eradication in children:

any advantage in clarithromycin-resistant strains? *Eur J Gastroenterol Hepatol.* 2014;26(11):1202–8.

19. Shu X, Yin G, Liu M, Peng K, Zhao H, Jiang M. Antibiotics resistance of *Helicobacter pylori* in children with upper gastrointestinal symptoms in Hangzhou, China. *Helicobacter.* 2018;23(3):e12481.

20. Dehghani SM, Erjaee A, Imanieh MH, Haghghat M. Efficacy of the standard quadruple therapy versus triple therapies containing proton pump inhibitor plus amoxicillin and clarithromycin or amoxicillin-clavulanic acid and metronidazole for *Helicobacter pylori* eradication in children. *Dig Dis Sci.* 2009;54(8):1720–4.

21. Seo J-H, Woo H-O, Youn H-S, Rhee K-H. Antibiotics resistance of *Helicobacter pylori* and treatment modalities in children with *H. pylori* infection. *Korean J Pediatr.* 2014;57(2):67.

22. Aminian K, Farsad F, Ghanbari A, Fakhreih S, Hasheminasab SM. A randomized trial comparing four *Helicobacter pylori* eradication regimens: standard triple therapy, ciprofloxacin based triple therapy, quadruple and sequential therapy. *Trop Gastroenterol.* 2011;31(4):303–7.

23. Sardarian H, Fakheri H, Hosseini V, Taghvaei T, Maleki I, Mokhtare M. Comparison of Hybrid and Sequential Therapies for *Helicobacter pylori* Eradication in Iran: A Prospective Randomized Trial. *Helicobacter.* 2013;18(2):129–34.

24. Masjedizadeh A, Zaeemzadeh N, Mard SA, Vanani GS. Comparing the efficacy of four different protocols for eradicating of *Helicobacter pylori* infection in Ahvaz, southwest Iran. *Prz Gastroenterol.* 2015;10(2):94.