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THE PREVALENCE RATE OF ANTIBIOTIC RESISTANCE OF *HELICOBACTER PYLORI* AMONG CHILDREN: A SYSTEMATIC REVIEW

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ABSTRACT

The lack of information regarding antibiotic susceptibility and *H. pylori* resistance in children is considered a major obstacle for *H. pylori* eradication. This review is aimed at collecting a comprehensive information about antibiotic resistance of *H. pylori* in children, to increase awareness about this population group. An electronic MEDLINE search was conducted using keywords with filter of "human studies". The studies were screened for eligibility criteria such as studied population of children, the use of three or more antibiotics treatment, and the reporting antibiotic primary resistance for *H. pylori* as the outcomes of the study. The full texts of the eligible articles were retrieved and the secondary exclusion was done based on the full text reading by two independent evaluators from 2000-2018. The electronic search of the literature resulted in 98 studies. After exclusion of irrelevant, duplicated and review studies, 11 studies which met the inclusion criteria were selected. Included studies aimed to determine, from the best available evidence, the prevalence of antibiotics resistance towards H. pylori pathogen. The resistance rate of H. pylori to metronidazole ranged from 75.20% to 10.1%, while resistant rate for clarithromycin ranged from 84.9% to 11.9%, resistance rate for rifampicin ranged from 13.3% to 0.9%, for furazolidone it was 0.06%, and resistance rate for amoxicillin was 0.5% -3.9%. The highest resistance rate of H. pylori in children was reported for azithromycin followed by clarithromycin and metronidazole, while it was low for moxifloxacin, rifampicin, furazolidone, and very low for amoxicillin.

KEYWORDS: ***Antibiotic resistance, Children, Bacteria, H. pylori.***

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a spiral *gram*-negative bacterium, which has been recently emerged as a major public health concern for many reasons. *H. pylori* is considered to be a main factor in causing many gastric diseases like gastritis, and cancer of the stomach (adenocarcinoma). Globally, it is isolated from the gut of about half of the people, 25% of the population of developed countries, and 80% to 90% of humans in the developing countries[1,2]. The prevalence of infection in children is 10% in industrialized countries and over 50% in developing countries[3]. This high prevalence of *H. pylori* bacteria makes it the focus of so many studies resulting in shifting of the treatment guidelines for several diseases, which are considered infections caused by H. pylori [4]. The best recommendation of North American, Japanese and Canadian Helicobacter Study Groups regarding eradication of *H. pylori* in adults and pediatric groups, was that the best way is by using triple therapy. This contains one proton pump inhibitor (PPI) plus two antibiotics from different classes such as amoxicillin, metronidazole, clarithromycin, fluoroquinolones, tetracycline, and rifamycins for up to 14 days. These antibiotics might lose their eradication ability due to newly emerged antibiotic resistance of *H. pylori*[4-6]. When triple therapy failed to achieve its therapeutic goals practitioners may use quadruple, sequential and concomitant therapy, which showed better results even when they have been faced by resistance in various parts of the world[7]. Actually, we cannot deny the importance of *H. pylori* eradication among children,[1] yet the issue of antibiotics resistance has been considered as a major concern because of irrational use of antibiotics among patients[5]. The deficiency in information regarding antibiotic susceptibility and *H. pylori* resistance in children is considered a major obstacle for *H. pylori* eradication. Additionally, the majority of the eradication studies had methodological issues such as recruiting small sample size[8] or butting their effort on adult patients [6]. This review aims at gathering comprehensive information regarding primary antibiotic resistance of *H. pylori* in children, to increase the awareness about the *H. pylori* resistance in children .

METHODS

An electronic MEDLINE search using thekeywords "antibiotic resistance" AND (child*) AND (Helicobacter pylori OR *H. pylori*) with filter of “human studies”. The eligibility criteria including the studied population of children, the use of three or more antibiotic treatment, and the reporting primary antibiotic resistance for *H. pylori* as the outcomes of the study. The titles and abstracts of the studies were scrutinized for these criteria and the study that does not meet the criteria was excluded. Additionally, duplicated studies and reviews were excluded from the review. After that, the full texts of the eligible articles were retrieved and the secondary exclusion was done based on the full text reading by two independent evaluators. Both evaluators agreed about the studies which should be included in this review.

STATISTICAL ANALYSIS

The data were extracted regarding items of study design, sample size, mean age of patients, reported signs and symptoms of *H. pylori* infection, type of antibiotic (for which the resistance has developed), and prevalence rate of antibiotic resistance for *H. pylori* in children. The narrative discussion of the extracted data was conducted.

RESULTS

The electronic search of the literature resulted in 98 studies. After exclusion of irrelevant, duplicated and review studies, 11 studies met the inclusion criteria (Figure 1). The included studies aimed to determine the prevalence of antibiotics resistance towards *H. pylori* pathogen. The number of patients recruited ranged from 1746 patients[9] to 55 participants[10]. A total of 5984 pediatric patients (better term is children) were included in this study with mean age ranged from 14 years to 9 years.. The age of the children was in the range from 14 years [9], to 9 years[11]. The time spent by the researchers in studying antibiotic resistance ranged from one year[11,12] to 13 years[13,14]. Only one article did not mention time length[15]. Only three articles mentioned symptoms of *H. pylori* infection, such as peptic ulcer gastrointestinal hemorrhagic coeliac disease and inflammatory bowel disease[10], dyspepsia[15], nausea or vomiting, epigastric pain and chronic abdominal pain/distress[13]. The included studies have discussed the resistance rate of 11 antibiotics that has been used to treat *H. pylori* infections. The investigators listed the resistance rate of *H. pylori* to metronidazole which ranged from 75.20% to 10.1%, while resistant rate for clarithromycin ranged from 84.9% [12] to 11.9% [16]. Resistance rate for rifampicin ranged from 13.3% [14] to 0.9% [17], furazolidone was mentioned in one study with resistance rate of 0.06%. Studies

reported no resistance for tetracycline [13,15,18], but study of Vécsei *et al.* [17] documented a dual resistance of 0.9% for *H. pylori* against tetracycline and rifampicin. The resistance to azithromycin was reported in two studies with resistance rate of 17.9% and 87.7% in Hojsak *et al.*[16] and Liu *et al.*[12] respectively. The resistance of *H. pylori* for ciprofloxacin and gentamycin were reported as 4.6% and 0% respectively [12], while resistance for levofloxacin reported by Li *et al.* [9] and Liu *et al.*[12] was 6.7% and 13.7% respectively. In addition, amoxicillin had no resistance profile as found by several included studies [10,12,13,17-19]. However other included studies reported a resistance rate of 0.5% and 3.9% by Nguyen *et al.* and Karabiber *et al.* [15], respectively. Moxifloxacin was studied by Liu *et al.* [12] and reported a resistance rate of 15.1% (Table 1). In Liu *et al.* [12] study conducted in Austria between 2002-2008 on 153 children, it was found that clarithromycin, metronidazole, tetracycline, rifampin and amoxicillin with clarithromycin were having the highest resistance rate (34%), and the only risk factor associated with clarithromycin resistance was the origin of a child from Austrian parents.

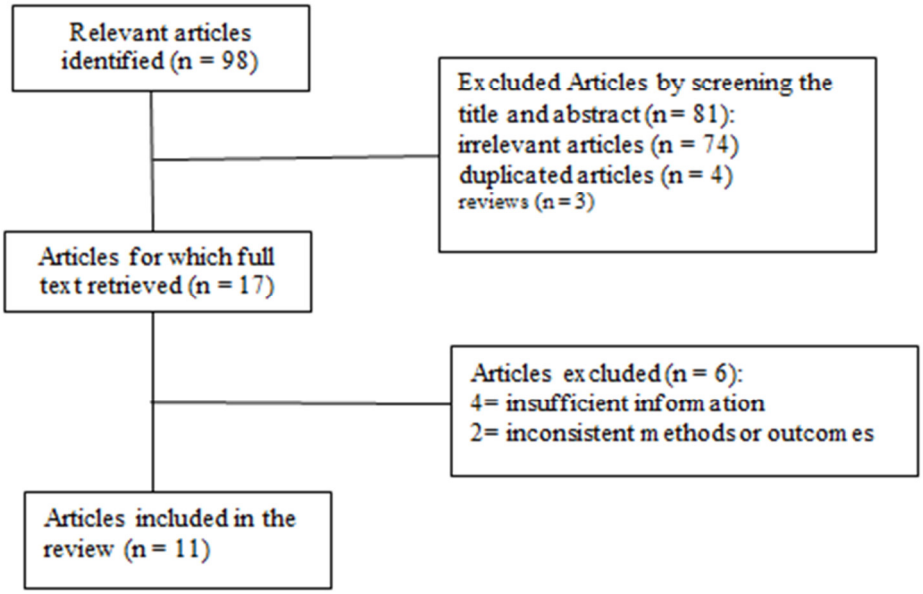

Figure 1
Flow diagram of the included studies in the systematic review

Table 1
Characteristics and the outcomes of included studies regarding antibiotic resistance of H. pylori

Study	Study design	Sample size	Age of patients	Signs and symptoms of H. pylori infection	Type of antibiotic (for which the resistance has developed)	Prevalence rate of antibiotic resistance for H. Pylori in children
(Li et al., 2017b) [9]	A multicenter retrospective cohort study	1746 isolates of H. pylori	Mean age of 14.0 years (collected from pediatric patients undergoing upper gastrointestinal endoscopy)	Not reported	Metronidazole Clarithromycin Levofloxacin Amoxicillin Furazolidone	75.20% Metronidazole 16.38% Clarithromycin 6.70% levofloxacin 0.06% Amoxicillin 0.06% furazolidone
(Biernat et al., 2016) [13]	A retrospective cohort analysis	1390 (16.05%) were positive for H. pylori	1.5-18 years old with mean age = 9.75 years	Chronic abdominal pain/distress, epigastric pain, nausea or vomiting	Amoxicillin Clarithromycin Metronidazole	The rate in 2009-2013 for Metronidazole, Clarithromycin, Clarithromycin with Metronidazole, and Amoxicillin were 36%, 26%, 22.7%, and 0% respectively
(Regnath et al., 2017a)	A retrospective cohort study	610 H. pylori isolates	Median age of 12 years	Not reported	Metronidazole Clarithromycin Rifampicin	Overall resistance to metronidazole, clarithromycin, and

[14]					Amoxicillin	rifampicin was 28.7%, 23.2%, and 13.3%, respectively, while resistance to amoxicillin was rare (0.8%)
(Maçin et al., 2015b) [19]	Cohort study	93 patients	5-19 years old with mean of 12 years	Not reported	Clarithromycin Metronidazole Amoxicillin Tetracycline	Tetracycline and amoxicillin 0% prevalence, Clarithromycin resistance was detected in 28 (30.1%) and metronidazole resistance in 45 (48.4%) patients' strains.
(Karabiber et al., 2014) [15]	Cohort study	98 patients	2-17 years old with mean of 9.5 years	Dyspepsia	Clarithromycin, Metronidazole, and Amoxicillin	Resistance rates to clarithromycin, metronidazole, and amoxicillin were 23.5%, 11.7%, and 3.9%, respectively And 0% tetracycline resistance
(Nguyen et al., 2012) [11]	A randomized, prospective, double-blind treatment trial with a parallel-group design	222 children	3-15 years old with mean of 9 years	Not reported	Amoxicillin Clarithromycin Metronidazole	Overall resistance to clarithromycin, metronidazole, and amoxicillin was 50.9%, 65.3%, and 0.5%, respectively
(Hojsak et al., 2012) [16]	A retrospective cohort study	382 patients	1-18 years old with mean of 9.5 years	Not reported	Amoxicillin Clarithromycin Metronidazole Azithromycin	Azithromycin (17.9%), followed by clarithromycin (11.9%), metronidazole (10.1%) and amoxicillin (0.6%)
(Liu et al., 2011) [12]	Cohort study	120 patients	3-16 years old with mean of 9.5 years	Not reported	Clarithromycin, Azithromycin, Metronidazole, Levofloxacin, Moxifloxacin, Rifampicin Amoxicillin, Gentamicin, Tetracycline	The resistance rate to clarithromycin, azithromycin, metronidazole, levofloxacin, moxifloxacin, and rifampicin was 84.9%, 87.7%, 61.6%, 13.7%, 15.1%, and 6.8%, respectively. No resistance to amoxicillin, gentamicin, and tetracycline was observed
(Oleastro et al., 2011) [18]	A multicentral prospective cohort study	1115 patients	Mean age 10.17years	Not reported	Clarithromycin, Metronidazole, Amoxicillin, Tetracycline Ciprofloxacin	Overall, the primary resistance rate was 34.7% to clarithromycin, 13.9% to metronidazole and 4.6% to ciprofloxacin, while 6.9% were resistant to two of these antibiotics simultaneously. Resistance to amoxicillin and to tetracycline was not detected.
(Vécsei et al., 2010) [17]	A retrospective cohort study	153 patients	Mean age of 11.5 years	Not reported	Clarithromycin Metronidazole Tetracycline Rifampin, Amoxicillin	Primary resistance to clarithromycin and metronidazole were 34% and 22.9%, respectively; dual resistance was found in 9.8% of the strains; 0.9% was resistant to tetracycline and rifampin,

						respectively. No case of amoxicillin resistance was detected
(Zevit et al., 2010) [10]	A prospective case-series design was used	55 patients	median age of 13 years	Abdominal pain, coeliac disease, gastrointestinal, hemorrhage, inflammatory, bowel disease, and peptic ulcer	Amoxicillin, Clarithromycin, Metronidazole, Tetracycline, Levofloxacin	In treatment-naïve children, the prevalence rate of primary resistance to clarithromycin was 25% and to metronidazole, 19%. 56% no resistance. No resistance was found to amoxicillin, tetracycline or levofloxacin

DISCUSSION

According to World Health Organization, *H. pylori* is considered a class 1 carcinogen associated with different gastric lymphomas. Studying antimicrobial resistance for every region in the world is a mandatory issue, because it is not just affecting one part of the world, but the world is inter-connected in this matter. The Kyoto Global Consensus declared that any empirical therapy for *H. pylori* eradication should have more than 90% eradication rate, unfortunately the majority of the world could not meet these criteria due to the dramatic increase in antibiotic resistance [7]. If the eradication failed, the susceptibility test should be done to ensure better action [20]. Thus, every country should have their own list of antibiotics according to the need of the patients and the resistance profile [21]. Regarding *H. pylori* resistance to antibiotic therapy, antibiotics with the highest resistance rate is azithromycin (87.7%) [12], followed by clarithromycin with resistance rate of 84.9%, then metronidazole as found by Li *et al*. with a resistance rate of 75.2%. This is supported by a study conducted in Italy having high metronidazole and clarithromycin resistance rate in contrary to tetracycline and ampicillin [22]. Amoxicillin had a low resistance rate ranging from 3.9% to 0.5% as reported by Karabiber *et al*. [15] and Naguyen *et al*. [11]. The high consumption rate of azithromycin and clarithromycin as a treatment for other conditions such as upper respiratory tract infection may be considered as a reason for this high resistant rate [23]. Countries such as France reduced this rate by issuing an antimicrobial restriction policy for treating *H. pylori* infections [24]. In a study conducted by Regnath *et al*.[14], a relatively high rate of resistance against clarithromycin and metronidazole was observed, which may be attributed to the difference in the breakpoints. The massive spread of metronidazole usage as a first line therapy for many infections like oral, gynecological and parasitic throughout both developed and developing countries, may have contributed to its high resistance rate [13,25]. A strong recommendation stands by the use of susceptibility tests preceding eradication therapy [16], as this will preserve time and effort that is exerted in the empirical treatment giving more precise therapeutic scheduling and less drug adverse effects. Better hygienic environment and clearer, broader understanding of bacterial infection and how antibiotics work decreased the *H. pylori* prevalence in all over the world with its different socioeconomic status. Moreover, improvement in the diagnostic procedure like endoscopy was aimed at high eradication rate therapy in the children. In a study of Liu *et al*. [12], clarithromycin had the highest resistance rate (34%) and the only risk factor associated with it is the origin of a child from Austrian parents. This assumption is supported by Regnath *et al*. [14] who found that children with Arabic background risk factor for high metronidazole resistance rate and this is might attributed to irrational use of antibiotics in Arabic countries [26]. Furthermore, the noncompliance of the patients and lack of commitment towards the right medicament regimen are limitations. Many questions raised about risk factors leading to antibiotics resistance and how to prevent it have not been answered yet so, extensive and more detailed studies are needed in this area.

CONCLUSIONS

The primary antibiotic resistance for *H. pylori* was varied according to the antibiotic type. The highest resistance rate of H. pylori in children was reported for azithromycin followed by clarithromycin and metronidazole, while it was low for Moxifloxacin, rifampicin, furazolidone, and very low for amoxicillin.

AUTHORS CONTRIBUTION STATEMENT

Mohammed Ashi, Anas Alzahrani, and Abdullah Alghamdi planned and conceived the concept of the

review. Marwan Aljohani and Omer Maimsh, and Mohammed Alhalabi conducted the systematic search and extracted the results of included studies. All authors contributed in manuscript writing and rectification.

CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. Yousefi-Avarvand A, Vaez H, Tafaghodi M, Sahebkar AH, Arzanlou M, Khademi F. Antibiotic Resistance of Helicobacter pylori in Iranian Children: A Systematic Review and Meta-Analysis. Microb Drug Resist . 2018;24(7):980–6. DOI: 10.1089/mdr.2017.0292
2. Safaei H, Khademi F, Faghri J, Moghim S, Esfahani B, Fazeli H, et al. The study of mutation in 23S rRNA resistance gene of Helicobacter pylori to clarithromycin in patients with gastrointestinal disorders in Isfahan - Iran. Adv Biomed Res. 2014;3(1):98. DOI: 10.4103/2277-9175.129368
3. K N. Prevalence of Helicobacter pylori infection in asymptomatic children in Birjand, Eastern Iran. Int J Pediatr. 2014;2(4.2):55–63.
4. Megraud F. H pylori antibiotic resistance: prevalence, importance, and advances in testing. Gut . 2004;53(9):1374–84. DOI: 10.1136/gut.2003.022111
5. Maleknejad S, Mojtahedi A, Safaei-Asl A, Taghavi Z, Kazemnejad E. Primary Antibiotic Resistance to Helicobacter pylori Strains Isolated From Children in Northern Iran: A Single Center Study. Iran J Pediatr. 2015;25(6). DOI: 10.5812/ijp.2661
6. 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. DOI: 10.1111/hel.12481
7. Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. Gut. 2010;59(8):1143–53. DOI: 10.1136/gut.2009.192757
8. Prechtl J, Deutschmann A, Savic T, Jahnel J, Bogiatzis A, Muntean W, et al. Monitoring of Antibiotic Resistance Rates of Helicobacter pylori in Austrian Children, 2002–2009. Pediatr Infect Dis J. 2012;31(3):312–4. DOI: 10.1097/inf.0b013e31823d9490
9. Li L, Ke Y, Yu C, Li G, Yang N, Zhang J, et al. Antibiotic resistance of Helicobacter pylori in Chinese children: A multicenter retrospective study over 7 years. Helicobacter. 2017;22(3):e12373. DOI: 10.1111/hel.12373
10. Zevit N, Levy I, Shmuely H, Samra Z, Yahav J. Antibiotic resistance ofHelicobacter pyloriin Israeli children. Scand J Gastroenterol. 2010;45(5):550–5. DOI: 10.3109/00365521003663688
11. Nguyen TVH, Bengtsson C, Yin L, Nguyen GK, Hoang TTH, Phung DC, et al. Eradication of Helicobacter pylori in Children in Vietnam in Relation to Antibiotic Resistance. Helicobacter. 2012;17(4):319–25. DOI: 10.1111/j.1523-5378.2012.00950.x
12. Liu G, Xu X, He L, Ding Z, Gu Y, Zhang J, et al. Primary Antibiotic Resistance of Helicobacter pylori Isolated from Beijing Children. Helicobacter . 2011;16(5):356–62. DOI: 10.1111/j.1523-5378.2011.00856.x
13. Biernat M, Iwańczak B, Bińkowska A, Grabińska J, Gościniak G. The Prevalence of Helicobacter pylori Infection in Symptomatic Children: A 13-Year Observational Study in the Lower Silesian Region. Adv Clin Exp Med. 2016;25(2):303–8. DOI: 10.17219/acem/44372
14. Regnath T, Raecke O, Enninger A, Ignatius R. Increasing metronidazole and rifampicin resistance ofHelicobacter pyloriisolates obtained from children and adolescents between 2002 and 2015 in southwest Germany. Helicobacter. 2017;22(1):e12327. DOI: 10.1111/hel.12327
15. Karabiber H, Selimoglu MA, Otlu B, Yildirim O, Ozer A. Virulence Factors and Antibiotic Resistance in Children With Helicobacter pylori Gastritis. J Pediatr Gastroenterol Nutr. 2014;58(5):608–12. DOI: 10.1097/mpg.0000000000000273
16. Hojsak I, Kos T, Dumančić J, Mišak Z, Jadrešin O, Jaklin Kekez A, et al. Antibiotic resistance of Helicobacter pylori in pediatric patients — 10 years' experience. Eur J Pediatr. 2012;171(9):1325–30. DOI: 10.1007/s00431-012-1722-8

17. Vécsei A, Kipet A, Innerhofer A, Graf U, Binder C, Gizci H, et al. Time Trends of Helicobacter pylori Resistance to Antibiotics in Children Living in Vienna, Austria. Helicobacter. 2010;15(3):214–20. DOI: 10.1111/j.1523-5378.2010.00753.x
18. Oleastro M, Cabral J, Ramalho PM, Lemos PS, Paixao E, Benoliel J, et al. Primary antibiotic resistance of Helicobacter pylori strains isolated from Portuguese children: a prospective multicentre study over a 10 year period. J Antimicrob Chemother. 2011;66(10):2308–11. DOI: 10.1093/jac/dkr293
19. Maçin S, Demir H, Özen H, Yüce A AY. Determination of Helicobacter pylori antibiotic resistance patterns in pediatric gastroenterology patients: the Hacettepe experience. Turk J Pediatr. 2015;57(3):254–7.
20. Koletzko S, Jones NL, Goodman KJ, Gold B, Rowland M, Cadranel S, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr [Internet]. 2011;53(2):230-43. DOI: 10.1097/mpg.0b013e3182227e90
21. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon ATR, Bazzoli F, et al. Management ofHelicobacter pyloriinfection—the Maastricht IV/ Florence Consensus Report. Gut. 2012;61(5):646–64. DOI: 10.1136/gutjnl-2012-302084
22. Sustmann A, Okuda M, Koletzko S. Helicobacter pyloriin children. Helicobacter. 2016;21:49–54. DOI: 10.1111/hel.12341
23. Boyanova L, Nikolov R, Gergova G, Evstatiev I, Lazarova E, Kamburov V, et al. Two-decade trends in primary Helicobacter pylori resistance to antibiotics in Bulgaria. Diagn Microbiol Infect Dis. 2010;67(4):319–26. DOI: 10.1016/j.diagmicrobio.2010.03.010
24. Raymond J, Lamarque D, Kalach N, Chaussade S, Burucoa C. High Level of Antimicrobial Resistance in FrenchHelicobacter pyloriIsolates. Helicobacter. 2010;15(1):21–7. DOI: 10.1111/j.1523-5378.2009.00737.x
25. Hunt RH, Xiao SD, Megraud F, Leon-Barua R, Bazzoli F, et al. Helicobacter pylori in developing countries. World gastroenterology organisation global guideline. J Gastrointestin Liver Dis. 2011;20(3):299–304. DOI: 10.1097/MCG.0b013e31820fb8f6
26. Otoom SA, Sequeira RP. Health care providers' perceptions of the problems and causes of irrational use of drugs in two Middle East countries. Int J Clin Pract. 2006;60(5):565–70. DOI: 10.1111/j.1742-1241.2005.00808.x