Annals of Clinical and Analytical Medicine

Emerging of Antibiotic Resistance of Helicobacter pylori among Hospitalized Patients: A Systematic Review

Ali Nasser Ali ALHaydar (1) *, Saleh Salem Oshemah ALHendi (2), Ali Mana Mohammed ALQil (3), Mohammed Abdullah Ali ALQurayshah (4), Nasser Ali Saleh ALRawas (5), Bandar Mohammed Ahmed ALMorshed (6), Fahad Abdullah Hamad ALQurayshah (7), Hadi Hamad Ali ALZhoof (8)

(1) Paramedic, Najran Health Administration, Saudi Arabia.
(2) Nursing Technician, Najran General Hospital, Saudi Arabia.
(3) Health Administration Specialist, Najran General Hospital, Saudi Arabia.
(4) Saudi Board Certificate in Internal Medicine, King Khalid Hospital, Najran, Saudi Arabia.
(5) X Ray Technician, Najran General Hospital, Saudi Arabia.
(6) Health Information Technician, Najran General Hospital, Saudi Arabia.
(7) Health Information Technician, Rare PHCC, Najran, Saudi Arabia.
(8) Nursing Technician, Najran Health Administration, Saudi Arabia.

Received 7/8/2022; revised 29/10/2022; accepted 14/12/2022

*Corresponding author

Abstract

Introduction: The deficiency in information regarding anti biotic susceptibility and H.pylori resistance in children group is considered a massive problem. Additionally, the majority of the studies contain small sample size putting their effort on adult patients. This review aiming at collecting comprehensive information regarding antibiotic resistance of H.pylori in children, to increase the awareness about this important population group.

Methods: The systematic review was conducted with specific inclusion and exclusion criteria in mind. Inclusion criteria involved studies published in the English language, focused on antibiotic susceptibility or resistance in Helicobacter pylori (H. pylori) infections among children aged 0-18 years, and encompassed various study designs such as observational studies. A robust and comprehensive search strategy was formulated to identify relevant studies in five major electronic databases: PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library. The search strategy incorporated combinations of keywords related to "H. pylori," "antibiotic resistance," "children," and "pediatric population." Boolean operators were utilized to refine and optimize search results.

Results: The search of the literature, after exclusion of irrelevant, duplicated and review studies, revealed 11 studies met the inclusion criteria. Included studies aimed to determine, from the best available evidence from different cohort studies that pointed out to the epidemiology of antibiotics resistance only towards Helicobacter pylori pathogen.

Conclusions: The findings underscore the substantial variability in resistance rates among different antibiotics, with metronidazole and clarithromycin exhibiting particularly high resistance levels in certain studies. Moreover, the wide age range and the diverse clinical presentations of H. pylori infection in children were notable, highlighting the complexity of diagnosing

and managing this condition in this population. The evidence presented here emphasizes the urgent need for continued research and surveillance on antibiotic resistance in pediatric H. pylori infections, particularly in the context of evolving resistance patterns and varying clinical presentations.

Keywords: ***Antibiotic Resistance, Helicobacter pylori, Pediatric Infections, Systematic Review, Children's Health.***

Introduction

Helicobacter pylori (H.pylori) is a spiral gram negative bacterium, recently it is became a major concern due to so many reasons the most important of them is that its considered to be a main factor in developing many gastric diseases like peptic ulceritis, and cancer of the stomach (adenocarcinoma). Also it is founded in the gut of 25% of developed countries population and 80% to 90% of humans in the developing countries and 50% of the people in the world [1, 2]. However, the prevalence of infection in children is 10% in industrialized countries and over 50%in developing countries [3]. This massive presence of H.pylori bacteria in the world's population makes it the focus of so many studies resulting in shifting of the treatment guide lines of many diseases which after that are considered infections caused by H.pylori, antibiotic use is mandatory [4].

The best recommendation of North American, Japanese and Canadian Helicobacter Study Groups regarding the matter of H.pylori eradication in adult and pediatric groups, agreed on that the best way is by using triple therapy contains one proton pump inhibitor (PPI) plus two antibiotics from different classes like amoxicillin, metronidazole, clarithromycin, fluoroquinolones, tetracycline, and rifamycin for up to 14 days, these antibiotics might lose their eradication ability due to the resistance that's why we need susceptibility tests. [4-6].

Sometimes when triple therapy fails to achieve its therapeutic goals practitioners may use different was like quadruple, sequential and concomitant therapy, which shows better results, although they have also been faced by resistance in various part of the world [7]. Naturally, we cannot deny the importance of H.pylori eradication among children, [1] yet the antibiotics resistance issue raise a major concern because of irrational use of them among patients [5]. 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 this criteria due to the dramatic increase in antibiotic resistance [7] and if it failed susceptibility test should be done to ensure better action [8]. That's how every country will have their own list of antibiotics according to every patients need [9].

The deficiency in information regarding anti biotic susceptibility and H.pylori resistance in children group is considered a massive problem. Also the majority of the studies contain small sample size [10] butting their effort on adult patients [6]. This review aiming at collecting comprehensive information regarding antibiotic resistance of H.pylori in children, to increase the awareness about this important population group.

Methods

The systematic review was conducted with specific inclusion and exclusion criteria in mind. Inclusion criteria involved studies published in the English language, focused on antibiotic susceptibility or resistance in Helicobacter pylori (H. pylori) infections among children aged 0-18 years, and encompassed various study designs such as observational studies (e.g., cross-sectional, cohort, case-control), clinical trials, and systematic reviews. The review aimed to be inclusive of studies conducted across different geographical regions. Exclusion criteria consisted of non-English publications, studies lacking adequate data on antibiotic susceptibility or resistance, investigations solely centered on adult populations or non-human subjects, and studies with sample sizes below a predefined threshold, if applicable. A robust and comprehensive search strategy was formulated to identify relevant studies in five major electronic databases: PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library. The search

strategy incorporated combinations of keywords related to "H. pylori," "antibiotic resistance," "children," and "pediatric population." Boolean operators were utilized to refine and optimize search results. A two-step process was employed for study selection. Initially, two independent reviewers screened studies based on their titles and abstracts to assess their relevance to the research objectives. Subsequently, potentially relevant studies underwent a full-text review to determine their eligibility based on the pre-established inclusion and exclusion criteria.

A standardized data extraction form was utilized to systematically collect information from the selected studies. This information encompassed crucial aspects such as study characteristics (authors, publication year, and study design), patient demographics (including age, geographic location, and sample size), antibiotics tested and their susceptibility/resistance rates, the methodology utilized for antibiotic susceptibility testing, and primary outcomes along with key findings pertaining to antibiotic resistance.
Data collected from the selected studies were synthesized using both narrative techniques. The synthesis aimed to identify prevalent trends and patterns related to antibiotic susceptibility and resistance in children with H. pylori infections. The findings of this systematic review was be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The results were summarized, and implications for clinical practice and future research directions were discussed in detail.

Results and discussion

The classification of Helicobacter pylori (H. pylori) as a class 1 carcinogen by the World Health Organization underscores its significance due to its direct link with various gastric lymphomas. Given the global interconnection in disease transmission, studying antimicrobial resistance across regions is imperative. In our review, the highest antibiotic resistance was observed with azithromycin (87.7%), as reported in [18], followed closely by clarithromycin with a resistance rate of 84.9%, also noted in [18] as demonstrated in the table 1. Metronidazole, as studied by [11], showed a resistance rate of 75.20%. Interestingly, a study in Italy revealed elevated metronidazole and clarithromycin resistance rates but lower resistance in the case of tetracycline and ampicillin [22]. Amoxicillin, on the other hand, displayed a relatively low resistance rate, ranging from 0.5% to 3.9% as reported in studies [15] and [16], with six studies finding no resistance towards it [15]. The widespread use of azithromycin and clarithromycin for conditions beyond H. pylori infections, such as upper respiratory tract infections, may contribute to the high resistance rates [23]. Countries like France have managed to lower these rates by implementing antimicrobial restriction policies for various infections [24]. Differences in breakpoints may account for the relatively high resistance rates against clarithromycin and metronidazole observed in [13]. Metronidazole's extensive use as a first-line therapy for various infections, including oral, gynecological, and parasitic diseases, in both developed and developing countries, may contribute to its elevated resistance rate [12, 25].

It is strongly recommended to conduct susceptibility tests before initiating eradication therapy [17], as this approach not only saves time and effort spent on empirical treatment but also results in more precise therapeutic scheduling and fewer adverse drug effects [14]. Improved hygiene and a deeper understanding of bacterial infections, antibiotic mechanisms, and advancements in diagnostic procedures like endoscopy have led to a reduction in H. pylori prevalence worldwide, regardless of socioeconomic status. Additionally, efforts to achieve higher eradication rates in pediatric populations have played a crucial role [12]. In [18], clarithromycin displayed the highest resistance rate (34%), with the only identified risk factor being a child's Austrian parental background. This observation is supported by [13], which found that children with Arabic backgrounds exhibit a high metronidazole resistance rate, possibly due to irrational usage. Noncompliance with treatment regimens and patient commitment issues may also contribute to resistance [14]. Many questions remain regarding the risk factors leading to antibiotic resistance and how to prevent it, highlighting the need for extensive and detailed studies in this area. As The world health organization categorize H.pylori as a class 1 carcinogen After the direct relationship

between it and different gastric lymphomas studying antimicrobial resistance for every region in the world is a mandatory issue, because it's not just affecting one part but the world is inter connected in this matter [14].

In our review, antibiotics with the highest resistance rate is azithromycin (87.7%) mentioned in [18] study, followed by clarithromycin with resistance rate of 84.9% also founded in [18] study, then metronidazole studied by [11] with a resistance rate of 75.20%. This is supported by a study done in Italy having high metronidazole and clarithromycin resistance rate in contrary to tetracycline and ampicillin [22]. Amoxicillin have had a low resistance rate ranging from 3.9% to 0.5% in [15] and [16] studies and six of the studies founded that bacteria have no resistance towards it. Studies are ranged between 0.5% -3.9% in [16] and [15] studies. The high consumption rate of azithromycin and clarithromycin as a treatment for another conditions such as upper respiratory tract infection may be considered as a reason for this high resistant rate [23]. Countries for example like France decreased this rate by issuing an antimicrobial restriction policy for many infections [24]. In [13] study a relatively high rate of resistance against clarithromycin and metronidazole was observed, this is 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 [12, 25]. A very strong recommendation stands by the use of susceptibility tests preceding eradication therapy [17], as this will preserve time and effort that is exerted in the empirical treatment giving us more precise therapeutic scheduling and less drug adverse effects [14]. 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, Also Improvement in the diagnostic procedure like endoscopy and aiming for high eradication rate therapy in the children population [12]. In [18] study clarithromycin had the highest resistance rate (34%), the only risk factor associated with it is the origin of a child from Austrian parents. This assumption is supported by [13] study that found children's Arabic background is the reason for high metronidazole resistance rate and this is might be attributed to irrational use of them. Not only that but also the noncompliance of the patients and lack of commitment towards the right medicament regimen [14].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

In conclusion, this systematic review has provided a comprehensive overview of antibiotic susceptibility and resistance in pediatric Helicobacter pylori (H. pylori) infections. Through an extensive literature search and meticulous data extraction, we identified 11 studies that met the inclusion criteria, collectively shedding light on the epidemiology of antibiotic resistance in H. pylori infections in children. The findings underscore the substantial variability in resistance rates among different antibiotics, with metronidazole and clarithromycin exhibiting particularly high resistance levels in certain studies. Moreover, the wide age range and the diverse clinical presentations of H. pylori infection in children were notable, highlighting the complexity of diagnosing and managing this condition in this population.

The evidence presented here emphasizes the urgent need for continued research and surveillance on antibiotic resistance in pediatric H. pylori infections, particularly in the context of evolving resistance patterns and varying clinical presentations. Future studies should further investigate risk factors and strategies for tailored treatment approaches, taking into account the significant impact of antibiotic resistance on clinical outcomes. This systematic review contributes to a deeper understanding of this critical issue and provides valuable insights for clinicians and researchers working in the field of pediatric gastroenterology and infectious diseases.

Conflict of interests

The authors declared no conflict of interests.

References

1. Yousefi-Avarvand, A., et al., Antibiotic Resistance of Helicobacter pylori in Iranian Children: A Systematic Review and Meta-Analysis. Microbial Drug Resistance, 2017.
2. Khademi, F., et al., The study of mutation in 23S rRNA resistance gene of Helicobacter pylori to clarithromycin in patients with gastrointestinal disorders in Isfahan—Iran. Advanced biomedical research, 2014. 3.
3. Namakin, K., Prevalence of Helicobacter pylori infection in asymptomatic children in Birjand, Eastern Iran. International Journal of Pediatrics, 2014. 2(4.2): p. 55-63.
4. Megraud, F., H pylori antibiotic resistance: prevalence, importance, and advances in testing. Gut, 2004. 53(9): p. 1374-1384.
5. Maleknejad, S., et al., Primary antibiotic resistance to Helicobacter pylori strains isolated from children in Northern Iran: a single center study. Iranian journal of pediatrics, 2015. 25(6).
6. Shu, X., et al., Antibiotics resistance of Helicobacter pylori in children with upper gastrointestinal symptoms in Hangzhou, China. Helicobacter, 2018.
7. Graham, D.Y. and L. Fischbach, Helicobacter pylori treatment in the era of increasing antibiotic resistance. Gut, 2010. 59(8): p. 1143-1153.
8. Koletzko, S., et al., Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. Journal of pediatric gastroenterology and nutrition, 2011. 53(2): p. 230-243.
9. Malfertheiner, P., et al., Management of Helicobacter pylori infection—the Maastricht IV/Florence consensus report. Gut, 2012. 61(5): p. 646-664.
10. Prechtl, J., et al., Monitoring of antibiotic resistance rates of Helicobacter pylori in Austrian children, 2002–2009. The Pediatric infectious disease journal, 2012. 31(3): p. 312-314.
11. Li, L., et al., Antibiotic resistance of Helicobacter pylori in Chinese children: a multicenter retrospective study over 7 years. Helicobacter, 2017. 22(3).
12. Biernat, M.M., et al., The Prevalence of Helicobacter pylori Infection in Symptomatic Children: A 13-Year Observational Study in the Lower Silesian Region. Advances in clinical and experimental medicine: official organ Wroclaw Medical University, 2016. 25(2): p. 303-308.
13. Regnath, T., et al., Increasing metronidazole and rifampicin resistance of Helicobacter pylori isolates obtained from children and adolescents between 2002 and 2015 in southwest Germany. Helicobacter, 2017. 22(1).
14. Maçin, S., et al., Determination of Helicobacter pylori antibiotic resistance patterns in pediatric gastroenterology patients: the Hacettepe experience. Turk J Pediatr, 2015. 57(3).
15. Karabiber, H., et al., Virulence factors and antibiotic resistance in children with Helicobacter pylori gastritis. Journal of pediatric gastroenterology and nutrition, 2014. 58(5): p. 608-612.
16. Nguyen, T.V.H., et al., Eradication of Helicobacter pylori in children in Vietnam in relation to antibiotic resistance. Helicobacter, 2012. 17(4): p. 319-325.
17. Hojsak, I., et al., Antibiotic resistance of Helicobacter pylori in pediatric patients—10 years' experience. European journal of pediatrics, 2012. 171(9): p. 1325-1330.
18. Liu, G., et al., Primary antibiotic resistance of Helicobacter pylori isolated from Beijing children. Helicobacter, 2011. 16(5): p. 356-362.
19. Oleastro, M., et al., Primary antibiotic resistance of Helicobacter pylori strains isolated from Portuguese children: a prospective multicentre study over a 10 year period. Journal of antimicrobial chemotherapy, 2011. 66(10): p. 2308-2311.
20. Vécsei, A., et al., Time trends of Helicobacter pylori resistance to antibiotics in children living in Vienna, Austria. Helicobacter, 2010. 15(3): p. 214-220.
21. Zevit, N., et al., Antibiotic resistance of Helicobacter pylori in Israeli children. Scandinavian journal of gastroenterology, 2010. 45(5): p. 550-555.
22. Sustmann, A., M. Okuda, and S. Koletzko, Helicobacter pylori in children. Helicobacter, 2016. 21(S1): p. 49-54.
23. Boyanova, L., et al., Two-decade trends in primary Helicobacter pylori resistance to antibiotics in Bulgaria. Diagnostic microbiology and infectious disease, 2010. 67(4): p. 319-326.

24. Raymond, J., et al., High level of antimicrobial resistance in French Helicobacter pylori isolates. Helicobacter, 2010. 15(1): p. 21-27.

25. Hunt, R., et al., Helicobacter pylori in developing countries. J Gastrointestin Liver Dis, 2011. 20(3): p. 299-304.

Table (1): Summary of the findings related to antibiotic resistance for H. pylori

Study	Study design	Sample size	Age of patients (Mean, SD)	Type of antibiotic (for which the resistance has developed)	Prevalence of antibiotic resistance of H. Pylori in children
(Li et al., 2017)	A multicenter retrospective study cohort study	1746 isolates of H. pylori	Mean age of 14.0 years (collected from pediatric patients undergoing upper gastrointestinal endoscopy)	Metronidazole Clarithromycin Levofloxacin Amoxicillin Furazolidone	*The pattern of H. pylori antibiotic resistance demonstrated no significant changes in the rates of resistance to clarithromycin, amoxicillin, furazolidone, and metronidazole over 7 years. *A significant trend of increasing resistance to metronidazole was observed as children aged, but a downward trend in clarithromycin resistance was observed as children aged.
(Biernat et al., 2016)	A retrospective cohort analysis	1390 (%16.05) were positive for H. pylori	1.5-18 years 9.75 years	Amoxicillin (AM), Clarithromycin (CH) And Metronidazole (MZ)	The prevalence of infection increased with age and was highest in patients aged 12–18 years. Comparison of the resistance rates of H. pylori strains to antibiotics in the periods 2000–2004 and 2009–2013.
(Regnath et al., 2017)	A retrospective cohort study	610 H.pylori iso lates	Median age of 12 years	Metronidazole Clarithromycin Rifampicin Amoxicillin	*Overall resistance to metronidazole, clarithromycin, and rifampicin was 28.7%, 23.2%, and 13.3%, respectively, while resistance to amoxicillin was rare (0.8%) *From 2002-2008 to 2009-2015, resistance to metronidazole increased from 20.8% to 34.4% (P=.003) and to rifampicin from 3.9% to 18.8% (P=.0001)
(Karabiber et al., 2014)	A cohort study	98 patients	2 to 17 years 9.5 years	Clarithromycin, Metronidazole, And Amoxicillin	Resistance rates to clarithromycin, metronidazole, and amoxicillin were 23.5%, 11.7%, and 3.9%, respectively 0% tetracycline resistance

(Maçin et al., 2015)	A cohort study	93 patients	5-19 years 12 years	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.
(Hojsak et al., 2012)	A retrospective cohort study	382 patients	1 to 18 years 9.5 years	Azithromycin Clarithromycin Metronidazole Amoxicillin	Azithromycin (17.9%), followed by clarithromycin (11.9%), metronidazole (10.1%) and amoxicillin (0.6%)
(Liu et al., 2011)	A cohort study	120 patients	3-16 years Mean age of 9.5 years	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)	A prospective multicenter cohort study	1115 patients	Mean age 10.17±4.03 years	Clarithromycin, Metronidazole Ciprofloxacin, Amoxicillin Tetracycline	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.
(Zevit et al., 2010)	A prospective case-series design was used. The study group included 174 patients	55 patients	median age of 13 years	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
(Vécsei et al., 2010)	A retrospective cohort study	153 patients	11.5 years	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.
(Nguyen et al., 2012)	A randomized, ,prospective double-blind treatment trial with a parallel-group design	222 children	3-15 years 9 years	Clarithromycin, Metronidazole, And Amoxicillin	*overall resistance to clarithromycin, metronidazole, and amoxicillin was 50.9%, 65.3%, and 0.5%, respectively


Emerging Sources Citation Index (ESCI)
Clarivate
Analytics
WEB OF SCIENCE™
THOMSON
REUTERS