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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Received on: 10-04-2018
Revised and Accepted on: 03-01-2019
DOI: http://dx.doi.org/10.22376/ijpbs/lpr.2019.9.1.P22-28
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. The prevalence of infection in children is 10% in industrialized countries and over 50% in developing countries. 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. 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. 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. Actually, we cannot deny the importance of H. pylori eradication among children, yet the issue of antibiotics resistance has been considered as a major concern because of irrational use of antibiotics among patients. 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 or butting their effort on adult patients. 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 the keywords "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 to 55 participants. 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 to 9 years. The time spent by the researchers in studying antibiotic resistance ranged from one year to 13 years. Only one article did not mention time length. Only three articles mentioned symptoms of H. pylori infection, such as peptic ulcer gastrointestinal hemorrhagic coeliac disease and inflammatory bowel disease. Dyspepsia, nausea or vomiting, epigastric pain and chronic abdominal pain/distress. 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% to 11.9%. Resistance rate for rifampicin ranged from 13.3% to 0.9%. Furazolidone was mentioned in one study with resistance rate of 0.06%. Studies
reported no resistance for tetracycline, but study of Vécsei et al. 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. and Liu et al. respectively. The resistance of *H. pylori* for ciprofloxacin and gentamycin were reported as 4.6% and 0% respectively, while resistance for levofloxacin reported by Li et al. and Liu et al. was 6.7% and 13.7% respectively. In addition, amoxicillin had no resistance profile as found by several included studies. However other included studies reported a resistance rate of 0.5% and 3.9% by Nguyen et al. and Karabiber et al., respectively. Moxifloxacin was studied by Liu et al. and reported a resistance rate of 15.1% (Table 1). In Liu et al. 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***

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Sample size</th>
<th>Age of patients</th>
<th>Signs and symptoms of <em>H. pylori</em> infection</th>
<th>Type of antibiotic (for which the resistance has developed)</th>
<th>Prevalence rate of antibiotic resistance for <em>H. Pylori</em> in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Li et al., 2017b)</td>
<td>A multicenter retrospective cohort study</td>
<td>1746 isolates of <em>H. pylori</em></td>
<td>Mean age of 14.0 years (collected from pediatric patients undergoing upper gastrointestinal endoscopy)</td>
<td>Not reported</td>
<td>Metronidazole Clarithromycin Levofoxacin Amoxicillin Furazolidone</td>
<td>75.20% Metronidazole 16.38% Clarithromycin 6.70% levofloxacin 0.06% Amoxicillin 0.06% Furazolidone</td>
</tr>
<tr>
<td>(Biernat et al., 2016)</td>
<td>A retrospective cohort analysis</td>
<td>(16.05%) were positive for <em>H. pylori</em></td>
<td>1.5-18 years old with mean age = 9.75 years</td>
<td>Chronic abdominal pain/distress, epigastric pain, nausea or vomiting</td>
<td>Amoxicillin Clarithromycin Metronidazole</td>
<td>The rate in 2009-2013 for Metronidazole, Clarithromycin, Clarithromycin with Metronidazole, and Amoxicillin were 36%, 26%, 22.7%, and 0% respectively</td>
</tr>
<tr>
<td>(Regnath et al., 2017a)</td>
<td>A retrospective cohort study</td>
<td>610 <em>H. pylori</em> isolates</td>
<td>Median age of 12 years</td>
<td>Not reported</td>
<td>Metronidazole Clarithromycin Rifampicin</td>
<td>Overall resistance to metronidazole, clarithromycin, and</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Age Description</td>
<td>Antimicrobial Activity</td>
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<tr>
<td>(Maçin et al., 2015b)</td>
<td>Cohort study</td>
<td>93 patients</td>
<td>5-19 years old with mean of 12 years</td>
<td>Amoxicillin (28.7%), Clarithromycin (23.2%), Metronidazole (13.3%), and Rifampicin was rare (0.8%)</td>
<td></td>
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<tr>
<td>(Karabiber et al., 2014)</td>
<td>Cohort study</td>
<td>98 patients</td>
<td>2-17 years old with mean of 9.5 years</td>
<td>Clarithromycin, Metronidazole, and Amoxicillin, Dyspepsia</td>
<td></td>
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<tr>
<td>(Nguyen et al., 2012)</td>
<td>A randomized, prospective, double-blind treatment trial with a parallel-group design</td>
<td>222 children</td>
<td>3-15 years old with mean of 9 years</td>
<td>Amoxicillin, Clarithromycin, Metronidazole</td>
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<tr>
<td>(Hojsak et al., 2012)</td>
<td>A retrospective cohort study</td>
<td>382 patients</td>
<td>1-18 years old with mean of 9.5 years</td>
<td>Amoxicillin, Clarithromycin, Metronidazole, Azithromycin</td>
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<tr>
<td>(Liu et al., 2011)</td>
<td>Cohort study</td>
<td>120 patients</td>
<td>3-16 years old with mean of 9.5 years</td>
<td>Clarithromycin, Azithromycin, Metronidazole, Levofoxacin, Moxifloxacin, Rifampicin, Amoxicillin, Gentamicin, Tetracycline</td>
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<tr>
<td>(Oleastro et al., 2011)</td>
<td>A multicentral prospective cohort study</td>
<td>1115 patients</td>
<td>Mean age 10.17 years</td>
<td>Clarithromycin, Metronidazole, Amoxicillin, Tetracycline, Ciprofloxacin</td>
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<tr>
<td>(Vécsei et al., 2010)</td>
<td>A retrospective cohort study</td>
<td>153 patients</td>
<td>Mean age of 11.5 years</td>
<td>Clarithromycin, Metronidazole, Tetracycline, Rifampicin, Amoxicillin</td>
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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. If the eradication failed, the susceptibility test should be done to ensure better action. Thus, every country should have their own list of antibiotics according to the need of the patients and the resistance profile. Regarding *H. pylori* resistance to antibiotic therapy, antibiotics with the highest resistance rate is azithromycin (87.7%), 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. Amoxicillin had a low resistance rate ranging from 3.9% to 0.5% as reported by Karabiber et al. and Naguyen et al. The high consumption rate of azithromycin and clarithromycin as a treatment for other conditions such as upper respiratory tract infection may have contributed to its high resistant rate. A strong recommendation stands by the use of susceptibility tests preceding eradication therapy, 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., 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. 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. 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...
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.

REFERENCES


CONFLICT OF INTEREST

Conflict of interest declared none.


