ORIGINAL ARTICLE

PRIMARY ANTIBIOTIC RESISTANCE AND EFFECTIVENESS OF CLARITHROMYCIN VS METRONIDAZOLE BASED THERAPY FOR *HELICOBACTER PYLORI* INFECTION IN CHILDREN

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Background: NASPGHAN guidelines recommend regional antibiotic susceptibility profiling for *H. pylori* eradication treatment. Profiling local antibiotic resistance patterns is mandatory for successful *H. pylori* eradication in children. The aim of our study was to determine primary resistance to Clarithromycin and Metronidazole, most commonly used in the eradication regimens in children presenting with symptomatic *H. pylori* infection. This study was conducted at Children Hospital PIMS Islamabad from June 2020 to August 2021. **Methods:** The children of either gender age 2–14 years having symptomatic *H. pylori* infection (hematemesis, chronic abdominal pain) underwent stool for *H. pylori* Antigen. Children requiring urgent diagnostic endoscopy underwent rapid urease tests. Biopsies were taken from children having positive stool *H. pylori* Ag and rapid urease test for histological examination. The biopsy specimens were cultured and subsequently tested for antibiotic sensitivity. **Results:** Out of 54 children having *H. pylori* infection 40/54 (74.074%) children had strains susceptible to antimicrobials and 14/54 (25.92%) were having resistance to antimicrobials. According to the pattern of antimicrobial sensitivity, they were further grouped into three (a) Clarithromycin and Metronidazole sensitive group (18/40, 45%) (b) Clarithromycin sensitive and Metronidazole resistant group (12/40, 30%) (c) Metronidazole sensitive group (10/40 25%). **Conclusion:** Clarithromycin and Metronidazole cannot be used as1stline treatment for *H. pylori* eradication in children and can only be used with known antimicrobial susceptibility.

Keywords: Clarithromycin; Metronidazole; Resistance rate; *Helicobacter pylori*

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is rarely symptomatic in children, although they may acquire it early in childhood and keep it lifelong. Infected children have a risk of developing chronic active gastritis and peptic ulcer disease in 10% of cases.[1] Children with peptic ulcer need *H. pylori* strains eradication. It is a gram-negative rod and its successful eradication is dependent on the selection of susceptible antibiotics. In the paediatric population standard eradication regimens are based on amoxicillin, proton pump inhibitor and Clarithromycin or Metronidazole in two divided doses for a period of 14 days.[2] The same antibiotics are being used for other infections too, therefore primary resistance against these antibiotics is increasing. This significantly impairs the efficacy of any eradication regimen and poses the most critical factor affecting effectiveness.[3] In children ESPGHAN/NASPGHAN guidelines and Maastricht IV Conference recommend against the use of Clarithromycin if local resistance is greater than 20%.[4]Thus, it is recommended to know the *H. pylori* susceptibility pattern to determine developing primary resistance. This will help in the development of regional knowledge of the prevalence of antimicrobial resistance for local isolates and empirical antibiotic selection.[5]

In the paediatric population, the options of antibiotics that are being used in triple therapy for *Helicobacter pylori* eradication are limited. Since continuous use of specific antibiotics develops antibiotic resistance, it is of utmost importance to perform periodic antibiotic resistance assessments to help paediatricians in prescribing appropriate therapy.[6] The primary aim of our study was to evaluate primary resistance to commonly used antibiotics in triple therapy, i.e., Clarithromycin and Metronidazole in children presenting with symptomatic *H. pylori* infection, i.e., either gastritis or ulcer. Secondarily we will assess the effectiveness of a Clarithromycin-based eradication regimen versus a Metronidazole-based eradication regimen.

MATERIAL AND METHODS

It was a randomized control trial; the sample size was calculated according to the WHO calculator as 41 children. Prior approval was taken from the institutional review board; informed written consent was obtained from the guardians of all the children. Children of either gender aged 2–14 years having symptomatic *H. pylori* infection were enrolled in the study. This study was conducted at the paediatric gastroenterology department, Children hospital Pakistan Institute of Medical Sciences Islamabad from June 2020 to August 2021. Exclusion criteria was as follows: The children treated with proton pump inhibitors within 4 weeks, children treated with H2-receptor antagonists within 4 weeks, children treated with bismuth preparations within 4 weeks, and children have taken antibiotics in the 4 weeks before the endoscopy. The children having an allergy to proton pump inhibitors, and Clarithromycin or Metronidazole were excluded too. For each child sex, age, weight, height, socioeconomic status, and family education were collected.

All symptomatic children having either hematemesis and or chronic abdominal pain underwent stool for *H. pylori* Antigen. For the children with hematemesis requiring urgent diagnostic endoscopy, a rapid urease test (*Helicobacter pylori* Gastrex, Medical HealthCare France) was performed on the specimen from the antrum. All children having positive stool *H. pylori* Ag and rapid urease test underwent biopsies for histological examination.

At least two specimens were taken from the antrum, corpus and incisura. Endoscopic findings were recorded, hyperaemic gastric mucosa as gastritis, hyperemic duodenal mucosa as duodenitis, mucosal breaks with a diameter <5 mmas Gastric or duodenal erosions and mucosal breaks with a diameter ≥5 mmas gastric or duodenal ulcers. The 13CUreaBreath Test was used to assess eradication at 4 weeks after discontinuation of therapy. The biopsy sample for the culture were transported via Portagerm-Pylori medium (BioMérieux, France) and cultured on Pylori agar and 10% horse blood agar. Then incubated for seven days at 37°C under microaerophilic conditions. Catalase and oxidase-positive colonies were tested for Metronidazole and Clarithromycin antibiotic sensitivity. The study was performed according to guidelines for Good Clinical Practice and the Declaration of Helsinki (1996 version, amended October 2000).

RESULTS

Total sixty-eight children were suspected of *H. pylori* induced peptic ulcer disease, and 54 of them were confirmed to have *H. pylori* infection. Overall, 40/54 (74.074%) children had strains susceptible to antimicrobials and 14/54 (25.92%) were having resistance to antimicrobials. (Amoxil, clarithromycin & Flagyl). The demographic data and clinical manifestation of patients having *H. pylori* induced peptic ulcer disease are shown in Table-1.

According to the pattern of antimicrobial sensitivity, they were further grouped into three (a) Clarithromycin and Metronidazole sensitive group (18/40, 45%) (b) Clarithromycin sensitive and Metronidazole resistant group (12/40, 30%) (c) Metronidazole sensitive group (10/40 25%).

The minimal inhibitory concentration (MIC) values against Clarithromycin ranged: ≤0.25mg/L (n = 26), 1–48mg/L (n = 10), and 64–256 mg/L (n = 4). Among the 26 Metronidazole-resistant strains, 30.76% (8/26) had high-level resistance with MIC ≥256mg/L.

Overall, 37 (92.5%) children had confirmed eradication, and 3 (7.5%) had positive urease breath tests. Two of them had susceptibility to both Clarithromycin and Metronidazole, while one had susceptibility to Clarithromycin. The children susceptible to Clarithromycin and Metronidazole were given options to take one. Eleven children opted for Clarithromycin, two of them developed a skin rash and three had gastrointestinal upset.

Table-1: Demographic, Clinical and laboratory characteristics of children with *H. pylori* infection

Parameters	Percentage, Mean± SD
Age	10.71 ± 2.448 years
Gender Male: Female:	 55% 45%
Clinical symptoms	
Hematemesis	55%
Persistent vomiting	52.5%
Abdominal pain	50%
Skin rash	12.5%
Culture Positivity	54/68 (79.41%)
Antimicrobial sensitivity	40/54 (74.04%)
Sensitive to both Clarithromycin & Metronidazole	18 (45%)
Sensitive to Clarithromycin	12 (30%)
Sensitive to Metronidazole	10 (25%)
Confirmed eradication	37 (92.5%)
Clarithromycin eradication	20/23 (86.95%)
Metronidazole eradication	17/17 (100%)

DISCUSSION

This is the first study in Pakistan to profile antibiotic resistance in *H.pylori*among paediatric patients. Overall, 40/54 (74.074%) children had strains susceptible to antimicrobials and 14/54 (25.92%) were having resistance to antimicrobials.

We obtained a significant resistance to clarithromycin and metronidazole (25.92%), while individually the Clarithromycin resistance was lesser than Metronidazole (44.44% vs 48.18%) though with no statistically significant value (P0.75). The primary Clarithromycin resistance in our cohort was much higher than documented in literature among paediatric patients.[8] Recently in Southwest China high primary Clarithromycin resistance has been reported and its use as empiric treatment for paediatric patients.[9] However, other studies recommend that if Clarithromycin susceptibility is known by antimicrobial susceptibility testing, only then it can be prescribed for successful *H. pylori* eradication.[10] Therefore ESPGHAN/NASPGHAN recommends in recent guidelines that antibiotic sensitivity testing should be performed before starting Clarithromycin-based triple therapy.[11]

Our study revealed that among the paediatric population,48.18% had primary Metronidazole resistance which was comparable to the primary Metronidazole resistance reported in the literature.[12] Resistance to Clarithromycin and Metronidazole simultaneously was present in (25.92%) this is comparable to a study conducted in China in which 28.3% of patients were having dual resistance.[13] This suggests that the eradication regimen composed of proton pump inhibitor, Amoxicillin, Clarithromycin and Metronidazole is not appropriate as empiric therapy in paediatric patients.[14] There are other studies suggesting Metronidazole resistance can be overcome either by increasing the dose of Metronidazole or the dose of Amoxicillin to achieve an excellent eradication.[15]

Nearly one-third of patients with poor adherence to Clarithromycin-based therapy for Helicobacter Pylori infection develop first-line treatment failure.[16]Our study revealed treatment failure in 3/23(13.04%) was due to poor adherence to clarithromycin-based therapy.

Limitations: Our study has limitations; it was conducted in a single tertiary care hospital, so our findings cannot be generalized to all paediatric patients in Pakistan. Future studies with more paediatric patients and factors e.g., age, race, and gender that are likely to influence antibiotic resistance profiles are needed.

CONCLUSION

Clarithromycin and Metronidazole should not be used in the empiric treatment of *H. pylori* eradication therapy in Pakistan and should be used only on children with known antimicrobial susceptibility to limit therapeutic failures.

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AUTHORS' CONTRIBUTION

NW: Conceptualization, data collection, write-up. NH, MS, RW: Data collection, data analysis, interpretation. MW: Write-up, data collection. AR: Data analysis, data interpretation.

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