Diagnostic and Treatment Practices for *Helicobacter Pylori* Infection in an Academic Pediatric Hospital

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ABSTRACT

BACKGROUND: In 2016, ESPGHAN/NASPGHAN issued revised guidelines for the management of *Helicobacter pylori* (*H. pylori)* infection in children and adolescents. Recommendations include performing antibiotic susceptibility testing to tailor therapy. The aim of our study was to evaluate the *H. pylori* treatment landscape in pediatric patients at our institution.

METHODS: We performed a retrospective study of patients diagnosed with *H. pylori* infection at a single academic children's hospital from 2015 to 2021. The frequency of each treatment regimen and their respective eradication rates were calculated. We compared trends in antibiotic prescriptions and eradication rates before and after 2016.

RESULTS: One hundred and ninety-six patients were included. Triple therapy with amoxicillin, clarithromycin, and a proton pump inhibiter (PPI) was the most often prescribed regimen (46.5%), followed by amoxicillin, metronidazole, and PPI (33%). Eradication rates were 70% for amoxicillin, clarithromycin, and PPI and 64% for amoxicillin, metronidazole, and PPI.

CONCLUSION: Our results show eradication rates for both regimens were comparable but suboptimal, highlighting the need to incorporate resistance testing into broader practice.

KEYWORDS: *Helicobacter pylori*, triple therapy, children, eradication

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative, microaerophilic, spiral organism, which colonizes the stomach, and which is present in almost half of the world population.[1] In North America, the overall prevalence of *H. pylori* is reported to be 37%,[1] but these rates vary depending on the geographic location, ethnicity, and socioeconomic profile. *H. pylori* infection can cause peptic ulcer disease, gastric cancer, and lymphoma. Early recognition offers an opportunity to prevent important clinical sequelae.

To eradicate *H. pylori* infection, a combination of two or more antibiotics with a proton pump inhibitor (PPI) is used for the duration of at least 10–14 days. For adult patients within the United States, bismuth-based quadruple therapy including tetracycline is first-line treatment for *H. pylori*, as evidence supports this regimen as the most effective.[2,3] There is no comparable study in pediatrics. Moreover, tetracycline is generally avoided in children due to potential adverse effects. In a retrospective study of treatment outcomes of 261 children with *H. pylori* infection from 2011–2015, 87% were treated with clarithromycin-based regimens.[4] Resistance rates for clarithromycin are increasing worldwide and in North America. A multi-center, retrospective study from different geographic regions within the U.S. reported clarithromycin resistance rates of up to 31% in North America with no significant difference among the regions[5]. The goal for *H. pylori* treatment is to achieve an eradication rate of at least 90%, which becomes less likely if antibiotic resistance is more than 20% in the community.[5-7]

In 2016, joint guidelines on the diagnosis and management of *H. pylori* were published by the European Society and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN/NASPGHAN), recommending tailored therapy through culture and sensitivity testing.[8] However, susceptibility testing is not readily available at most centers. In the absence of testing, selection of empiric antibiotic therapy should be based on national and local antibiotic resistance patterns. However, very little such data exists in United States, especially among pediatric patients. Given high resistance rates of *H. pylori* against clarithromycin, triple therapy based on amoxicillin, clarithromycin and PPI is not recommended as first line for *H. pylori* eradication when susceptibility of *H. pylori* against clarithromycin is unknown.

Given the paucity of information regarding the contemporary management of pediatric *H. pylori* infection in the US, we evaluated the *H. pylori* treatment landscape within our institution since 2015, focusing on prescribing patterns and eradication rates. Importantly, reviewing trends over this time period allowed us to examine the impact of the updated ESPGHAN/NASPGHAN guidelines on current clinical practice.

METHODS

We conducted a retrospective study of patients less than 21 years of age at the time of diagnosis, who were tested and treated for *H. pylori* infection at a single academic children's hospital from June 2015 to February 2021. Hasbro Children's Hospital is the only children's hospital in the state of Rhode Island with the catchment area of one million people. Electronic medical records (EMRs) of patients meeting the inclusion criteria were reviewed to collect basic demographic data including age, gender, ethnicity, race, and zip code. Frequency of different treatment regimens used for *H. pylori* eradication along with their dose, duration of therapy, and the eradication rate was calculated. We also looked at pre- and post-treatment symptoms, type of test used for diagnosis of *H. pylori* infection and the test of cure (TOC) ordered. EMRs were also reviewed for the documentation of noncompliance and loss to follow up. We compared the first-choice antibiotic regimen used before and after the publication of the 2016 ESPGHAN/NASPGHAN guidelines. This study was approved by local institutional review board. Data was collected and saved via REDCap data collection software and further analyzed using SPSS V28.0.

RESULTS

During our inclusion period, *H. pylori* was diagnosed in 196 patients, mean age 12.5 years. One hundred and twelve (57.1%) patients were female, and 84 (42.9%) were male. The predominant ethnicities were Hispanic (79, 40.3%), and White (68, 34.7%) followed by African American (32, 16.3%) and Asian (12, 6.1%) (**Table 1**). Patients reported abdominal pain as the most common symptom before *H. pylori* treatment (77%). Other symptoms included weight loss (28%), reflux (26%), vomiting (24%) and nausea (23%). Five percent of patients who were tested and treated for *H. pylori* infection were diagnosed incidentally (i.e., instances in which the *H. pylori* diagnosis was entirely unrelated to the indication for endoscopy, such as foreign body ingestion, esophageal food impaction, inflammatory bowel disease surveillance, percutaneous endoscopic gastrostomy tube placement, or confirmation of celiac disease). After *H. pylori* eradication, 81% of patients reported resolution or improvement in symptoms. All patients with hematemesis, melena and peptic ulcer disease had complete resolution of their symptoms following *H. pylori* eradication. Nine percent of patients reported ongoing abdominal pain after *H. pylori* eradication therapy. Only 0.9% of patients had persistent weight loss after the eradication therapy, compared to 28% before treatment.

Histopathology was the most common test used for the diagnosis of *H. pylori* infection (78% of cases). Stool antigen (29%) and urea breath testing (6%) were the other methods of diagnosis. Omeprazole was the most common PPI prescribed among eradication regimens, used in 90% of cases. A 14-day course of amoxicillin, clarithromycin and PPI was the most prescribed *H. pylori* eradication therapy (comprising 47% of regimens). Amoxicillin, metronidazole, and PPI was the second most common regimen, in 33% of cases. Other therapies used were metronidazole, clarithromycin, and PPI (6%), amoxicillin, metronidazole, bismuth, and PPI (3%), metronidazole, bismuth, tetracycline, and PPI (2%), and other combinations of different antibiotic regimens with PPI (9%).

A TOC was ordered by 82% of physicians and was performed in 59% of patients. Stool antigen (59%), and urea breath test (24%) were the most common TOC. TOC was negative in 70% overall, across all antibiotic regimens. We calculated individual eradication rates for *H. pylori* treatment regimens. Among all the empiric regimens, amoxicillin, clarithromycin, PPI therapy had the highest *H. pylori* eradication rate (70%) followed by amoxicillin, metronidazole, PPI therapy (64%) (**Fig. 1**).

We tracked treatment regimens over time. There was a consistent increase in prescribing metronidazole-based

Table 1. Demographics of study subjects

Patient demographics n=196	
Age (years)	
range	1.42–19.3 years
mean	12.5 year
median	13.1 year
Gender	
Female	112 (57.1%)
Male	84 (42.9%)
Ethnicity	
Hispanic	79 (40.3%)
Asian	12 (6.1%)
African American	32 (16.3%)
White	68 (34.7%)
Others/Unknown/not reported	5 (2.5%)

Figure 1. Eradication rates for each prescribed antibiotic regimen. Each regimen also included a PPI

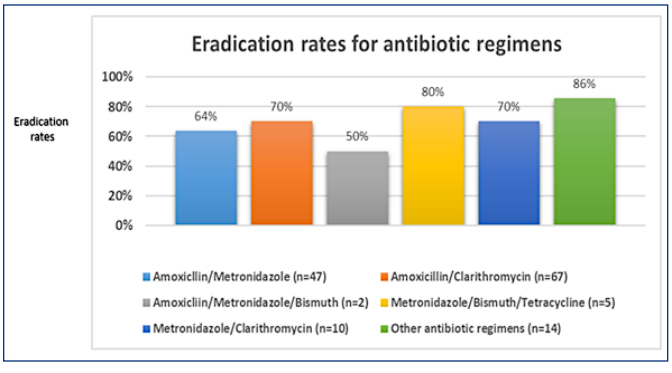


Figure 2. Prescribed antibiotic regimens over time. Each regimen used PPI (omeprazole in 90% of cases) in addition to the antibiotics listed.

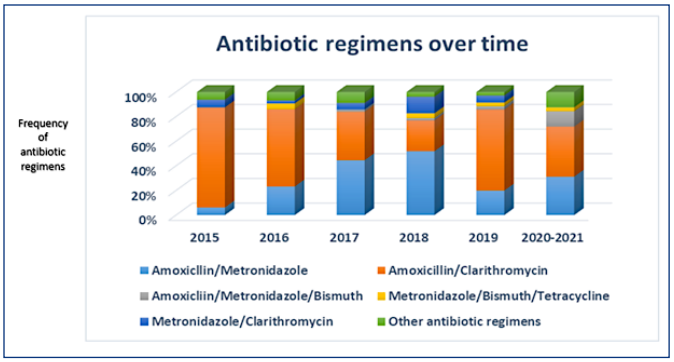
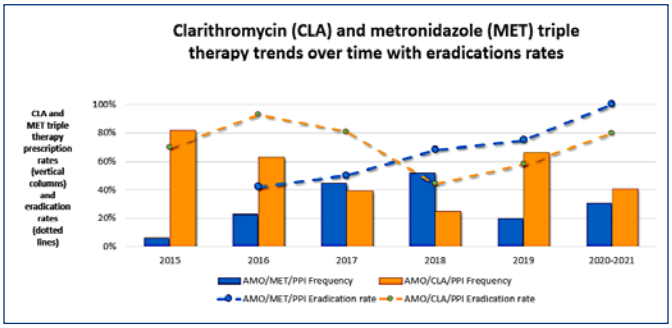


Figure 3. Clarithromycin and metronidazole triple therapy trends with respective eradication rates over the years



regimens from 2015 (6%) through 2018 (52%), a trend that reversed in 2019 (20%). In 2020, use of metronidazole-based regimens rose again. Clarithromycin-based therapies were more common before 2016 (81.3%) and aside from 2019, trended down over subsequent years (**Fig. 2**).

Individual eradication rates of *H. pylori* therapies varied by year. Clarithromycin-based regimens had eradication rates of 70%, 93% and 81% in 2015, 2016, and 2017 respectively. The eradication rate of amoxicillin, clarithromycin, PPI was the lowest in 2018–2019 (44–58%) (**Fig. 3**).

DISCUSSION

This retrospective analysis documents the management of *H. pylori* at a single pediatric academic institution from June 2015 to February 2021. All our patients were treated empirically for *H. pylori* eradication. No cultures or sensitivities were performed before treatment in contrast to joint ESPGHAN/NASPGHAN guidelines[8] that recommended their use routinely before selecting a treatment regimen. A triple regimen of amoxicillin, clarithromycin, PPI was the most commonly used before 2016. After 2016, clarithromycin prescribing trended down while the use of metronidazole increased. This observation likely reflects growing awareness of the ESPGHAN/NASPGHAN 2016 guidelines since there were no new locally reported data to support or refute the use of clarithromycin-based therapies. Indeed, the eradication rates for clarithromycin-based therapies were highest from 2015–2017.

The trend away from clarithromycin- towards metronidazole-based regimens unexpectedly reversed in 2019. Though speculative, perhaps this shift reflects providers' subjective impression of the relative efficacy of amoxicillin, clarithromycin, PPI compared to amoxicillin, metronidazole, PPI triple therapy. Indeed, in 2015–2017, the eradication rate for amoxicillin, clarithromycin, PPI was > 80%. It is also possible that variation in provider preference accounts for the unexpected increase in clarithromycin prescribing in 2019. In our academic practice of approximately 12–15 providers at one time, one outlier could have had outsized effect on our data.

It has been previously reported that in the absence of peptic ulcer disease (PUD), the presence of *H. pylori* infection alone does not generally cause symptoms[9-11] and *H. pylori* eradication will not improve symptoms for these patients.[12-13] However, conflicting results demonstrate improvement in abdominal pain with *H. pylori* eradication among children.[14] The Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition (JSPGHAN) recently published updated guidelines and recommend *H. pylori* eradication therapy in symptomatic children with chronic gastritis, in the absence of peptic ulcers.[15] Adult studies suggest a noninvasive test-and-treat strategy for dyspepsia in young adult patients depending on local prevalence.[16-19] Noting a small but statistically significant improvement in dyspeptic symptoms with *H. pylori* eradication (NNT=14) investigators propose excluding *H. pylori* before diagnosing functional dyspepsia.[16,20] These strategies have not been adopted for pediatric patients and the current ESPGHAN/NASPGHAN guidelines recommend against a test and treat strategy.

Notably, in our population, 57% of patients had complete resolution of symptoms, and 24% reported improvement after *H. pylori* eradication. Only 3% of these patients had peptic ulcer disease, the remainder were only with gastritis on pathology. Our findings are similar to those from a recent retrospective study in which 58% of patients had resolution of symptoms after treatment[21] and stand in contrast to data from multiple studies which refute an association between *H. pylori* gastritis without PUD and gastrointestinal symptoms.[9-11] Recognizing the limitations of our retrospective review and the known potential placebo effect of any treatment, future work with a more rigorous, prospective design may help to clarify this relationship between uncomplicated *H. pylori* infection and gastrointestinal symptoms.

Over the last three decades, evidence demonstrates declining eradication rates for first-line *H. pylori* eradication therapies from more than 90% to 70–80%, which is consistent with reports of emerging antibiotic resistance.[22] Clarithromycin-resistance rates of greater than 15–20% have been reported in the US and throughout the world, leading to

the recommendations of susceptibility testing before using clarithromycin-based regimens. In keeping with guideline recommendations, clarithromycin was commonly substituted with metronidazole at our institution.

Interestingly, we observed that the treatment success rate with amoxicillin, clarithromycin, PPI therapy was 70% compared to amoxicillin, metronidazole, PPI rate of 64%. To our knowledge, this finding has not been previously reported in a pediatric study in the US. These results may indicate emerging metronidazole resistance in the community, which has been demonstrated in a multi-center, randomized, double-blind, placebo-controlled trial among an adult population within the US, where resistance rates for metronidazole (43.6%) were higher than for clarithromycin (17.4%).[7] Recent meta-analysis of *H pylori* antibiotic resistance in US from 2011–2021, has also reported high resistance rates for both metronidazole (42%) and clarithromycin (31%).[23]

Our study was limited due to lack of TOC results in 41% of patients and loss to follow-up in 18% of patients. Patients who reported symptom resolution – a possible surrogate for successful treatment – yet who did not submit a TOC were also excluded from analysis of eradication rates. This may account for our low *H. pylori* eradication rates relative to the other reports.[4,21]

We found lower eradication rates for both clarithromycin- and metronidazole-based triple therapies, compared to goal eradication rates of more than 90–95%, emphasizing the need to incorporate susceptibility testing into our practice. Doing so will also help fill the knowledge gap for local antibiotic resistance against *H. pylori*. The ESPGHAN/NASPGHAN recommendation to perform susceptibility testing was not embraced by our physicians. Barriers include the absence of a local culture and sensitivity capabilities, cumbersome logistics involved in handling and sending tissue specimens to a distant, out-of-state facility within the required time frame, and weeks-long lag time in receiving results before prescribing therapy. Other barriers include the lengthy process of assuring insurance coverage for susceptibility testing, which may otherwise be too costly for families.

In recent years, this process has been eased by increasing availability of newer molecular techniques and next generation sequencing for susceptibility testing. A practical guide to help clinicians find such resources has recently been published[24] and may aid in the adoption of society recommendations. Our study demonstrates a disconnect between practice guidelines and the current reality of clinical practice, but with easier access to susceptibility testing and a greater understanding of local resistance patterns, we expect to bridge that divide.

References

1. Hooi JK, Lai WY, Ng WK, et al. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. Gastroenterology. 2017 Aug 1;153(2):420-9
2. Fallone CA, Moss SF, Malfertheiner P. Reconciliation of recent Helicobacter pylori treatment guidelines in a time of increasing resistance to antibiotics. Gastroenterology. 2019 Jul 1;157(1): 44-53.
3. Alsamman MA, Vecchio EC, Shawwa K, et al. Retrospective Analysis Confirms Tetracycline Quadruple as Best Helicobacter pylori Regimen in the USA. Digestive diseases and sciences. 2019 Oct 1;64(10):2893-8.
4. Mathews J, Malik P, Rai A, et al. A single centre experience of treatment outcomes for Helicobacter pylori infection among inner-city children and adolescents. Acta Paediatrica. 2020 Sep; 109(9):1860-6.
5. Park JY, Dunbar KB, Mitui M, et al. Helicobacter pylori clarithromycin resistance and treatment failure are common in the USA. Digestive diseases and sciences. 2016 Aug;61(8):2373-80.
6. Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. Gut. 2010 Aug 1; 59(8):1143-53.
7. Hulten KG, Lamberth LB, Kalfus IN, et al. National and Regional US Antibiotic Resistance to Helicobacter pylori: Lessons From a Clinical Trial. Gastroenterology. 2021 Jul 1;161(1):342-4.
8. Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN guidelines for the management of Helicobacter pylori in children and adolescents (update 2016). Journal of pediatric gastroenterology and nutrition. 2017 Jun 1;64(6):991-1003.
9. Bode G, Brenner H, Adler G. Helicobacter pylori and abdominal symptoms: a population-based study among preschool children in southern Germany. Pediatrics. 1998 Apr 1;101(4):634-7.
10. Macarthur C. Helicobacter pylori infection and childhood recurrent abdominal pain: lack of evidence for a cause and effect relationship. Canadian Journal of Gastroenterology. 1999 Sep 1; 13(7):607-10.
11. Dore MP, Fanciulli G, Tomasi PA, et al. Gastrointestinal symptoms and Helicobacter pylori infection in school-age children residing in Porto Torres, Sardinia, Italy. Helicobacter. 2012 Oct; 17(5):369-73.
12. Levine A, Milo T, Broide E, et al. Influence of Helicobacter pylori eradication on gastroesophageal reflux symptoms and epigastric pain in children and adolescents. Pediatrics. 2004 Jan;113(1): 54-8.
13. Ashorn M, Rägö T, Kokkonen J, et al. Symptomatic Response to Helicobacter Pylori Eradication in Children With Recurrent Abdominal Pain: Double Blind Randomized Placebo-controlled Trial. Journal of clinical gastroenterology. 2004 Sep 1;38(8): 646-50.
14. Özen H, Dinler G, Akyön Y, et al. Helicobacter pylori infection and recurrent abdominal pain in Turkish children. Helicobacter. 2001 Sep;6(3):234-8.
15. Kato S, Shimizu T, Toyoda S, et al. The updated JSPGHAN guidelines for the management of Helicobacter pylori infection in childhood. Pediatrics International. 2020 Dec;62(12):1315-31.
16. Malfertheiner P, Megraud F, O'morain CA, et al. Management of Helicobacter pylori infection—the Maastricht V/Florence consensus report. Gut. 2017 Jan 1;66(1):6-30
17. Suzuki H, Moayyedi P. Helicobacter pylori infection in functional dyspepsia. Nature reviews Gastroenterology & hepatology. 2013 Mar;10(3):168-74.
18. Ford AC, Tsipotis E, Yuan Y, et al. Efficacy of Helicobacter pylori eradication therapy for functional dyspepsia: updated systematic review and meta-analysis. Gut. 2022 Jan 11.
19. Moayyedi P. Helicobacter pylori test and treat strategy for young dyspeptic patients: new data. Gut. 2002 May 1;50(suppl 4):iv 47-50.

20. Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on Helicobacter pylori gastritis. Gut. 2015 Sep 1;64(9):1353-67.
21. Bonilla S, Mitchell PD, Mansuri I. Low adherence to society guidelines for the management of Helicobacter pylori among pediatric gastroenterologists. Journal of Pediatric Gastroenterology and Nutrition. 2021 Aug 1;73(2):178-83.
22. Savoldi A, Carrara E, Graham DY, et al. Prevalence of antibiotic resistance in Helicobacter pylori: a systematic review and meta-analysis in World Health Organization regions. Gastroenterology. 2018 Nov 1;155(5):1372-82.
23. Ho JJ, Navarro M, Sawyer K, et al. Helicobacter pylori Antibiotic Resistance in the United States Between 2011-2021: A Systematic Review and Meta-Analysis. The American Journal of Gastroenterology. 2022 May 5.
24. Graham DY, Moss SF. Antimicrobial Susceptibility Testing for Helicobacter pylori Is Now Widely Available: When, How, Why. Official journal of the American College of Gastroenterology| ACG. 2022 Apr 1;117(4):524-8.

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Disclosures

None

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