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Original Article

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Prevalence, Management, and Outcomes of Non-Invasive *Helicobacter pylori* Testing in Children at a Tertiary Paediatric Hospital in Singapore

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ABSTRACT

Purpose: *Helicobacter pylori* infections differ between children and adults. The Pediatric society practice guidelines recommend against a test-and-treat approach, characterized by the use of non-invasive tests for diagnosis (e.g. urea breath test [UBT] or stool antigen test). However, significant variations exist in clinical practice. This study examined the use of non-invasive testing for the screening and diagnosis of *H. pylori* infection in children at a tertiary pediatric hospital in Singapore, reviewing both management decisions and patient outcomes.
Methods: A retrospective review was conducted on children between the ages of 0 and 18 years who were tested for *H. pylori* infection using either a stool antigen test or UBT between January 2018 and June 2020.
Results: Among the 1,397 children tested, 117 (8.4%) had a positive stool *H. pylori* antigen result, and 5 out of 85 tested (5.9%) had a positive UBT. Abdominal pain was the predominant symptom (n=98; 80.3%). Only 7 treatment-naïve children had biopsy-proven disease. Tissue biopsies for *H. pylori* culture were sent to 2 children, with 1 negative result. A total of 111 children (91.0%) received treatment, wherein proton pump inhibitor, amoxicillin, and clarithromycin for 14 days was the most common therapeutic regimen. Symptom resolution was observed in 62 children (50.8%).
Conclusion: A test-and-treat strategy was more widely utilized than endoscopy-based testing, showing a low compliance to existing guidelines for the management of *H. pylori* infections in children at our center and significant false-positive rates.

Keywords: Children; *Helicobacter pylori*; Diagnosis

INTRODUCTION

Helicobacter pylori is a common chronic bacterial infection worldwide [1] and an important cause of peptic ulcer disease (PUD) and gastric cancer [2]. The incidence of *H. pylori* infection in Southeast Asia is increasing, with a rising number of adults being tested and treated for this ubiquitous disease. In Singapore, the seroprevalence rate has been reported to be 31% [3]. However, studies on the prevalence and clinical presentation of *H. pylori* infection in children remain scarce.

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Current recommendations for pediatric treatment and management have mostly been adapted from adult practice. Compared to adults, children and adolescents develop PUD and gastric cancer infrequently. Symptoms generally appear only after a long-term infection, and the factors influencing the clearance of acute infection remain largely unknown [4].

The immune mechanisms against infection differ in children. Compared to adults, gastric biopsies obtained from children infected with *H. pylori* show reduced pathological inflammation [5]. In addition, an increase in the number of immunosuppressive T regulatory cells and anti-inflammatory interleukin (IL)-10 rather than a proinflammatory IL-17 cytokine response has been reported [6].

Therefore, diagnosis and treatment should not be conducted in the same way in children as in adults. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) recommend a test-and-treat approach [7]. Instead, invasive endoscopy-based testing is recommended for valid clinical indications. Studies on children do not support the role of *H. pylori* infection testing in functional disorders, such as recurrent abdominal pain [8]. The purpose of testing should be to investigate the cause of symptoms and not simply to determine whether *H. pylori* is present.

Despite the established guidelines, there is significant variation in clinical practice regarding the utilization of empiric treatment based on positive non-invasive *H. pylori* testing, such as the urea breath test (UBT), stool antigen test, and serology in children [9]. There are clinical challenges in compliance with these guidelines, from advising for invasive endoscopy to obtaining gastric biopsies for culture-directed treatment.

The aim of this clinical audit was to examine the frequency of non-invasive testing as the primary tool for the screening and diagnosis of *H. pylori* in children at a tertiary pediatric hospital in Singapore and to review management decisions and patient outcomes in patients with positive non-invasive *H. pylori* tests.

MATERIALS AND METHODS

A retrospective clinical audit of non-invasive *H. pylori* testing was conducted in a tertiary pediatric hospital. Children between the ages of 0 and 18 years who were tested for *H. pylori* infection using either the stool antigen test (OXOID Rapid Immunochromatographic Assay) or the Urea Breath Test (^{13}C-UBT) between January 2018 and June 2020 were included. Electronic medical and laboratory records of children with abnormal stool antigen and/or ^{13}C-UBT results were accessed, and relevant information on their demographics, presenting complaints, investigations, treatments, and management plans were analyzed. For children who underwent endoscopy, 2 gastric biopsies from the antrum and 2 gastric biopsies from the corpus were obtained for histological evaluation, as recommended by the ESPGHAN/NASPGHAN guidelines for children. Standard hematoxylin and eosin staining of the gastric tissue was performed to detect *H. pylori* infection. Children diagnosed with *H. pylori* infection primarily by endoscopy were excluded. The empirical first-line treatment regimen used at our institution is a proton pump inhibitor (PPI), amoxicillin (AMO), and clarithromycin (CLA) for 14 days. Other regimens include PPI, AMO, and metronidazole (MET). Alternatively, in patients with a penicillin allergy, MET or tetracycline can be used with PPI and CLA, with or

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without bismuth. Ethics approval was obtained from the Centralized Institutional Review Board (CIRB) for this retrospective clinical audit (approval no. 2022/2574).

RESULTS

Patient characteristics and presenting symptoms

A total of 1,397 children who underwent stool *H. pylori* antigen testing and 85 children with ^{13}C-UBT performed between January 2018 and June 2020 were identified. Among them, 117 (8.4%) had a positive stool *H. pylori* antigen result, and 5 (5.9%) had a positive ^{13}C-UBT. The main indication for screening was the presence of abdominal pain. The characteristics of the patients with a positive screening test are described in **Table 1**. The children were aged 15–210 months (median, 132 months). Notably, 4 children had previously positive results from non-invasive *H. pylori* tests.

Abdominal pain was the predominant symptom (n=98, 80.3%), with the duration of pain varying between 1 and 1,095 days (median, 60 days). Other symptoms, such as nausea, vomiting, acid brash, heartburn, food impaction, hematemesis, blood in stools, and nocturnal awakening, were reported less frequently (**Table 1**). A total of 21 children (17.2%) had a positive family history of *H. pylori* infection, and 4 (3.3%) had a history of gastric cancer.

Investigation

Only 30 children (24.6%) underwent upper gastrointestinal (GI) endoscopy. Among these, 12 underwent endoscopy before the initiation of eradication therapy, 16 underwent at least

Table 1. Baseline patient characteristics of children with positive screening test

Baseline patient characteristics	Number of children (percentage of total)
Number of children with positive screening test	122
Male	58 (47.5)
Race	
Chinese	78 (64.0)
Malay	18 (14.7)
Indian	19 (15.6)
Others	7 (5.7)
Significant past medical history	20 (16.4)
Previous *Helicobacter pylori* infection	4 (3.3)
Asthma	3 (2.5)
Anorexia nervosa	1 (0.8)
Crohn's disease	1 (0.8)
Gitelman syndrome	1 (0.8)
Positive family history of *Helicobacter pylori*	21 (17.2)
Family history of gastric cancer	4 (3.3)
Presenting symptoms	
Abdominal pain	98 (80.3)
Nausea	48 (39.3)
Loss of appetite	40 (32.8)
Vomiting	37 (30.3)
Anemia	30 (24.6)
Loss of weight	26 (21.3)
Nocturnal awakening	24 (19.7)
Acid brash	13 (10.7)
Blood in stool	10 (8.2)
Heartburn	8 (6.6)
Hematemesis	6 (4.9)
Food impaction	2 (1.6)

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1 course of eradication therapy, and 2 underwent ongoing eradication therapy. In order of decreasing prevalence, the most common findings in children after biopsy were stomach erythema, stomach nodularity, duodenal erythema, stomach erosions, mucosal friability, and esophageal erythema. The most common histopathological finding was chronic gastritis, followed by *H. pylori* inclusion bodies and lymphoid follicles. One child developed active duodenitis. No children had gastric or duodenal ulcers, metaplasia, or carcinomatous changes. The endoscopic and histopathological findings are described in **Table 2**. In the treatment-naïve group of 12 children, only 7 showed evidence of biopsy-proven disease, with the remainder having false-positive stool antigen test results (**Fig. 1**). The tissue biopsies for *H. pylori* culture were sent to 2 children, 1 of whom had a negative result without prior treatment, and the other of which showed *H. pylori* sensitivity to AMO and MET and resistance to CLA. Among the 6 patients who presented with hematemesis, 3 had previously undergone endoscopy with findings of gastric erosions.

Treatment

A total of 111 children (91.0%) received triple therapy, 7 (5.7%) were treated with only PPIs, and 4 (3.3%) received no treatment. Overall, 97 children (79.5%) received 1 course, 13 children (10.7%) received 2 courses, and 1 child (0.8%) received 3 courses of triple therapy. The indication for more than 1 course was the persistence of *H. pylori* infection on non-invasive testing. All 7 treatment-naïve patients with endoscopy-proven disease received only 1 course of AMO/CLA/omeprazole. The various combinations of triple therapies prescribed are detailed in **Table 3**. One child with Crohn's received ciprofloxacin/MET/omeprazole, and 1 child with inflammatory abdominal phlegmon received augmentin/CLA/omeprazole.

Table 2. Endoscopic and histopathological findings in children who underwent endoscopy

Endoscopic findings	Number of children, n=30 (%)
Rapid urease test	
Positive	7 (5.7)
Negative	16 (12.8)
Not done/unknown	7 (5.7)
Esophagus erythema	1 (3.3)
Stomach erythema	13 (43.3)
Stomach nodularity	10 (33.3)
Stomach erosions	2 (6.7)
Mucosal friability	2 (6.7)
Duodenal erythema	4 (13.3)
Histopathological findings	
Chronic gastritis	27 (90.0)
Helicobacter pylori inclusion bodies	13 (43.3)
Lymphoid follicles	1 (3.3)
Active duodenitis	1 (3.3)

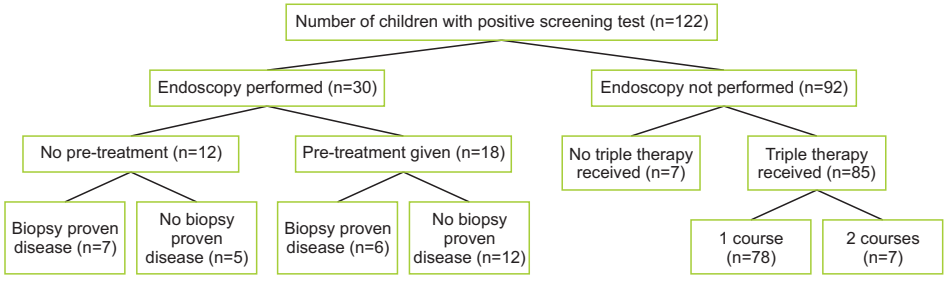

Fig. 1. Distribution of endoscopic evaluation and treatment of children with positive screening test for *Helicobacter pylori*.

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Table 3. Number of courses and types of triple therapy administered

Number of courses of triple therapy	Number of children (%)
One course	97 (79.5)
AMO/CLA/omeprazole	84 (68.8)
AMO/MET/omeprazole	7 (5.7)
CLA/MET/omeprazole	4 (3.3)
Ciprofloxacin/MET/omeprazole	1 (0.8)
Augmentin/CLA/omeprazole	1 (0.8)
Two courses	13 (10.7)
AMO/CLA/omeprazole+AMO/MET/omeprazole	8 (6.6)
Two courses of AMO/CLA/omeprazole	4 (3.3)
AMO/CLA/omeprazole+tetracycline/bismuth/MET/omeprazole	1 (0.8)
Three courses	1 (0.8)
AMO/CLA/omeprazole+AMO/MET/omeprazole+bismuth/AMO/MET/omeprazole	1 (0.8)

AMO: amoxicillin, CLA: clarithromycin, MET: metronidazole.

Outcomes

Ninety children (73.8%) were referred to a pediatric gastroenterologist for further assessment. The eradication of *H. pylori* was documented in 56 children (45.9%), among which 12 (9.8%) underwent endoscopy, 28 (23.0%) stool antigen testing, and 16 (13.1%) ^{13}C-UBT. A total of 48 children (39.3%) did not undergo any eradication testing done as they had default follow-up. Symptom resolution was only observed in 62 children (50.8%). Of the 92 children who received treatment based on positive non-invasive testing alone, 32 (34.8%) had documented eradication, mostly via stool antigen test. Fourteen (15.2%) of these children had persistent of symptoms, despite documented eradication in half of them. The majority of the children (n=110, 90.1%) were no longer being followed-up at the time of this publication.

DISCUSSION

This study represents the experience of a single large pediatric tertiary care center in the management of *H. pylori* infection in Singapore, and is the first known local audit in Singapore to study the non-invasive testing of *H. pylori*, which has only become readily available and increasingly used in the pediatric population in recent years.

The audit showed that the "test-and-treat" strategy was more widely utilized than endoscopy-based invasive diagnostic testing, with only a small subset of patients having had a gastric biopsy culture. This mirrors the physician management patterns reported in the literature, which highlights a low compliance with existing guidelines [9].

These non-invasive tests may have been favored over endoscopy because they are easily administered with a short turnaround time. The advantages of stool antigen testing include easy sample collection, no need for fasting, and no dependence on operator or clinician experience. There are also fewer risks to patients than endoscopy, which is a highly specialized procedure that requires a referral to a pediatric gastroenterologist and the administration of intravenous sedation for pediatric patients. This makes endoscopy less appealing for caregivers and attending physicians.

Notably, almost half of the treatment-naïve children with a positive screening test who underwent endoscopy did not have biopsy-proven disease, raising concerns about the significantly high false-positive rate of non-invasive screening tests. Different methods of *H. pylori* stool antigen testing exist and differ in their performance. The conventional

stool antigen test using an enzyme-linked immunosorbent assay detects *H. pylori* antigen using polyclonal or monoclonal antibodies, and the rapid stool antigen test uses immunochromatography [10]. The reported sensitivity ranges from 87% to 100%, with the specificity ranging from 82% to 100% [11,12]. Tests using monoclonal antibodies have been reported to have a higher diagnostic accuracy [13,14].

^{13}C-UBT has a reported sensitivity and specificity of approximately 95% in children [15]. As ^{13}C-UBT easures the isotopic ratio of $^{13}CO_2/^{12}CO_2$ and endogenous CO_2 production differs according to age, sex, body weight, and height, the isotopic ratio may be higher in children despite ingesting an amount of ^{13}C-urea identical to that in adults. Therefore, the ^{13}C-UBT may give false-positive results in children younger than 6 years of age [16,17]: 8.3% in children younger than 6 years of age compared to 0.85% in children older than 6 years [18]. There are also technical difficulties in performing ^{13}C-UBT in young children because they are often unwilling to swallow the substrate.

Abdominal pain was the most common symptom among our cohort of patients who underwent non-invasive *H. pylori* testing. No association was found between the presence of *H. pylori* infection and the frequency of functional abdominal pain disorders [19]. Moreover, at present, definitive evidence of the improvement or resolution of symptoms after eradication therapy is lacking [20,21]. This was also evident in the cohort of the present study, in which symptom resolution was observed in only half of patients after *H. pylori* treatment. Therefore, in cases of abdominal pain in which an organic cause is considered, diagnostic upper endoscopy, rather than non-invasive testing for *H. pylori*, should be performed.

The “test-and-treat” approach is a reasonable option for adult patients presenting with dyspepsia without alarming features, such as weight loss, dysphagia, overt GI bleeding, abdominal mass, or iron deficiency anemia [22-24]. The age threshold depends on the local prevalence of gastric malignancies, ranging from 40 to 60 years [25]. For the evaluation of dyspepsia in adults, this approach showed an economic advantage of cost savings, which was weighed against the relatively lesser benefits of symptom improvement and patient satisfaction with the endoscopy-based strategy [26]. Hence, this “test-and-treat” approach would be more feasible in clinical practice, particularly for primary care physicians who have an important role in the first line management of such adult patients. However, as most children with *H. pylori* infection remain asymptomatic, empirical treatment is unlikely to outweigh the potential side effects.

A significant proportion of our patients were treated with CLA-based triple therapy based on a positive non-invasive screening test. The disadvantages of empiric therapy for *H. pylori* include potentially unnecessary treatment, a lack of definitive documentation of the organism and pathology, and most importantly, the use of incorrect antibiotic regimens, with higher treatment failure rates and declining microbial susceptibility [9].

An understanding of the local antibiotic resistance rates is important guideline for empirical therapy. The recommendation includes a 2-week period of first-line therapy, to be guided by antibiotic susceptibility testing or based on local susceptibility data [27,28]. Nonetheless, in Singapore, CLA-based triple therapy has continued to be effective as the first line treatment option, with an eradication rate exceeding 90% reported in adults. Although these numbers seem to favor the use of empirical CLA as a first-line therapy, a lower eradication success rate

among native Singapore children (76.7%) has been reported, with non-compliance cited as the most likely contributing factor [29].

Therefore, antibiotic resistance remains a major concern. In many countries, primary CLA resistance has increased to levels above the recommended threshold (15%) for use as a first-line treatment for *H. pylori* infection [30]. The data indicate that the prevalence of *H. pylori* infections resistant to CLA in children varies between 10% and 40% depending on the geographical region [31]. Similarly, in Singapore, rising rates of CLA and MET resistance have been reported in both adult and paediatric populations [3]. Immigration factors have also been shown to influence *H. pylori* antibiotic resistance patterns in children, with non-natives at a higher risk of antimicrobial-resistant strains and poorer eradication outcomes [29].

Singapore has a significant proportion of non-native population, which may come from regions with higher prevalence rates and different antibiotic resistance patterns. This, coupled with the growing *H. pylori* antibiotic resistance rate, adds to management challenges. Thus, culture-based, susceptibility-guided therapy and a reinforcement of the importance of compliance are becoming crucial in achieving the successful eradication of *H. pylori*. However, we should also acknowledge possible unique factors, including the inherent differences between patient populations in terms of their acceptance of invasive procedures and their associated healthcare costs, which impact clinical management. Further longitudinal observations and the collection of clinical data on *H. pylori* infection in children, both regionally and globally, are needed to optimize testing methods for this insidious infection.

The limitations of this study include the inherent verification bias due to the retrospective method of data collection and the high loss-to-follow-up rate, resulting in incomplete data on the patient outcomes, particularly pertaining to eradication rates. In addition, only a small number of gastric biopsy cultures were performed; hence, we were unable to study antibiotic susceptibility in our cohort. However, the findings presented in this study provide an important snapshot of our current real-world practice, allowing us to reflect on the current management challenges and guide the development of future quality improvement processes.

In summary, this study documents the widespread use of the "test-and-treat" approach, highlighting a low compliance to existing guidelines in the management of *H. pylori* infections in children at our center. More importantly, significant false positive rates were observed in patients who underwent confirmatory endoscopic evaluation, and only modest success was observed in terms of symptom improvement in children with the "test-and-treat" approach based on non-invasive testing. The findings of this audit provide a basis for hospital-wide quality improvement initiatives that seek to improve the testing and treatment of *H. pylori* infections in children.

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