UNDERSTANDING THE MULTIPLE FACETS OF HELICOBACTER PYLORI INFECTION IN CHILDREN

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ABSTRACT

Helicobacter pylori (*H. pylori*) is a bacterium that colonizes the gastric mucosa and which is known for its ability to survive in the acidic environment of the stomach, thanks to its unique spiral shape and the presence of multiple flagella. Thus, *H. pylori* infection may present under the shape of multiple clinical entities and understanding its various facets is crucial for effective diagnosis and treatment. The importance of *H. pylori* infection in children lies in its potential to cause significant morbidity and long-term complications. This article aims to provide an overview of the importance of *H. pylori* infection in children, including its epidemiology, clinical manifestations, and treatment. Through a better understanding of this common infection, healthcare providers can work towards improving the diagnosis and management of *H. pylori* infection in children, ultimately improving the long-term health outcomes of affected individuals.

Key words: Helicobacter pylori; infection; children; pediatrics

INTRODUCTION

Helicobacter pylori (*H. pylori*) represents a Gram-negative bacterium that colonizes the gastric mucosa of humans, and which is estimated to infect up to 50% of the population worldwide.

In recent decades, many studies have observed a downward trend in the prevalence of *H. pylori* infection among pediatric patients globally (1,2). Estimates suggest that the prevalence of this infection decreased by approximately one-third, from 39% prior to 2000 to 26% in 2010. This decline may be attributed to improvements in socioeconomic status, as well as advancements in environmental and living conditions that have resulted in better sanitation and reduced transmission of the infection over time (3). A study conducted in Romania described that the prevalence of *H. pylori* is higher in female patients and it is increased in children originating from rural areas (4). Although *H. pylori* infection is often asymptomatic, it can cause a range of gastrointestinal symptoms and complications, including gastritis, peptic ulcers, and gastric cancer (5).

While *H. pylori* infection is more commonly associated with adults, it can also manifest in children. The clinical manifestations of *H. pylori* infection in children can range from asymptomatic to severe symptoms such as abdominal pain, nausea, vomiting, loss of appetite, and even headache (6). In addition, *H. pylori* infection in children has been linked to growth retardation, iron deficiency anemia (similar with gastroesophageal reflux) (7), vitamin B12 deficiency, liver cytolysis, and autoimmune disorders (8,9).

On the other hand, there are some studies

that indicate *H. pylori* infection as a protective factor for the gastroesophageal reflux disease (GERD), fact that is still being argued in the literature. Studies have shown that the eradication of *H. pylori* has been found to decrease the contractions of the esophageal muscles, increase the amount of acid in the esophagus, and exacerbate symptoms of GERD, proven by a Boix-Ochoa score >11.99 (10-13).

Early recognition and management of *H. pylori* in children is important to prevent the development of complications and to improve long-term health outcomes. However, the diagnosis of *H. pylori* infection in children can be challenging due to the non-specific nature of the symptoms and the limitations of available diagnostic tests.

This article aims to provide an overview of the clinical manifestations of *H. pylori* infection in children, including the challenges of diagnosis and the importance of early recognition and treatment. By improving our understanding of the clinical manifestations of *H. pylori* infection in children, we can better identify and manage affected children, ultimately improving their long-term health outcomes.

PATHOGENESIS OF *H. PYLORI* INFECTION

The pathogenesis of *H. pylori* infection involves a complex interplay between the bacterium and the host's immune system. *H. pylori* is able to survive in the acidic environment of the stomach by producing urease, which breaks down urea into ammonia, thus neutralizing the acid (14). Additionally, *H. pylori* has multiple flagella that allow it to move along the stomach lining and to penetrate the mucous layer that lines the stomach, where it can determine a chronic infection.

Once *H. pylori* has colonized the gastric mucosa, it triggers an inflammatory response in the host. This inflammatory response involves the recruitment of various immune cells, such as neutrophils, macrophages, and T lymphocytes to the site of infection (15,16). These immune cells release cytokines and other mediators that promote inflammation and tissue damage (17).

Over time, chronic *H. pylori* infection can lead to the development of chronic gastritis which is characterized by inflammation of the gastric mucosa. In some cases, chronic gastritis can progress to peptic ulcer disease (Figure 1), which manifests through erosion of the mucosal lining of the stomach or duodenum (Figure 2).

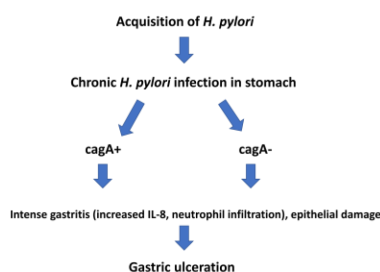

Figure 1. Pathogenesis of *H. pylori*-induced gastritis and peptic ulcer disease

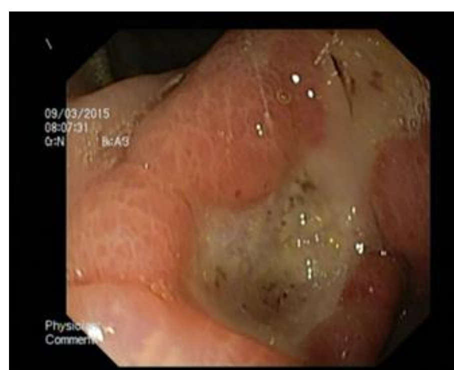

Figure 2. Upper digestive endoscopy: ovoid prepyloric ulcer (from hospital's archive)

MANIFESTATIONS OF *H. PYLORI* INFECTION

H. pylori infection is a common bacterial infection that can affect people of all ages, including children. The clinical manifestations of *H. pylori* infection in children can vary from asymptomatic to severe symptoms (18).

In most of the cases, *H. pylori* infection causes a range of gastrointestinal symptoms such as nausea, vomiting, loss of appetite or abdominal pain that can be mild or severe and can persist for several weeks or months (19).

On the other hand, a significant inverse association between *H. pylori* infection and pediatric asthma was described in the literature. Multiple theories explain the possible protective mechanism of *H. pylori* against allergic asthma (20), disease which increases the chances of gastroesophageal reflux by 2.86 (21).

In addition, *H. pylori* infection in children has been linked to autoimmune disorders such as idiopathic thrombocytopenic purpura (ITP) and autoimmune thyroiditis. ITP represents a bleeding disorder that is characterized by low platelet count and which can cause easy bruising and bleeding. Autoimmune thyroiditis is a condition in which the immune system attacks the thyroid gland, which can lead to hypothyroidism (22,23). A study on 1757 patients also indicated a potential correlation between liver cytolysis and *H. pylori* infection (24).

Along with dietary habits that are not conducive to good health and can compromise the structural integrity of the oral cavity (25), there is also evidence of the presence of viable *H. pylori* in the oral cavity that may adversely affect the eradication of gastric infection (26). The findings which indicate that *H. pylori* is present in the non-gastric cavitated area of children with severe caries, could potentially act as a source for spreading the microorganisms to other regions of the body (27). Also, the existence of *H. pylori* within these cavities may shift the equilibrium of the microbial community within dental plaque in favor of *Streptococcus mutans*, which is considered the primary bacterium involved in the development of dental caries (28). Similar to gastroesophageal reflux (29), *H. pylori* has been associated with a range of oral manifestations, including: glossitis, halitosis, angular cheilitis, gingivitis, and recurrent aphthous stomatitis. These clinical entities are thought to be caused by the direct contact of the bacterium with the oral mucosa or by the systemic inflammatory response to the infection. Treatment of *H. pylori* infection is considered to improve both gastrointestinal and oral symptoms in children (30).

Many studies have provided evidence that highlighted the impact of *H. pylori* infection on physical growth, particularly following the establishment of persistent infection (31,32). Rational consumption of nutrients is important in the development of a child (33), and especially in the context of *H. pylori* infection in children as it can affect the outcome of the infection. Adequate intake of essential nutrients is necessary to maintain the structural integrity and function of the gastrointestinal tract, which can help to prevent the colonization and overgrowth of *H. pylori*. Nutrient deficiencies, on the other hand, can compromise the immune response and the healing of the gastric mucosa, which may exacerbate the infection and lead to more severe disease. Therefore, a balanced and nutrient-rich diet is recommended as a part of the management and prevention of *H. pylori* infection in children (34,35). As for the gut microbiome, it was observed that after the successful eradication of *H. pylori*, the levels of normal stomach microbiota, including *Bacilliota, Bacteroidota, Actinomycetota, Cyanobacteria*, and *Fusobacteria,* increased

to levels similar to those observed in healthy individuals. However, it was observed that the baseline status of the microbiota was only fully restored after a period of two years following the completion of treatment (36-38).

DIAGNOSIS OF *H. PYLORI* INFECTION

The diagnosis of *H. pylori* infection in children can be challenging as the symptoms are non-specific and can overlap with other gastrointestinal disorders. Diagnostic tests for *H. pylori* infection in children include breath tests, stool antigen tests, and endoscopy with biopsy (39).

Although endoscopy, histology, culture and biopsy-based PCR are more accurate diagnostic tools for *H. pylori* infection, non-invasive methods are preferred due to their lower discomfort for patients. However, the selection of non-invasive diagnostic methods should be based on their accuracy and associated costs. The urea breath test and stool antigen are likely the best non-invasive options for diagnosing *H. pylori* infection in pediatric patients. In selected cases, molecular non-invasive techniques may also be useful in strengthening the diagnosis (40). Recently, a notable association between *H. pylori* infection and inflammation as measured by the neutrophil-to-lymphocyte ratio (NLR) -a dependable and straightforward marker of inflammation- was described. A progressive rise in NLR was highlighted as the severity of *H. pylori*-associated gastritis worsens. However, this elevated ratio can be normalized with appropriate treatment (41).

TREATMENT OF *H. PYLORI* INFECTION

The treatment of *H. pylori* infection in children typically involves a combination of antibiotics and proton pump inhibitors. The antibiotics used include clarithromycin, amoxicillin, and metronidazole, while PPIs such as omeprazole are used to reduce the acidity of the stomach, which can enhance the effectiveness of the antibiotics.

However, whilst there has been a global decline in the prevalence of *H. pylori* infection among pediatric patients, there has been a persistent increase in the rates of *H. pylori* antimicrobial resistance (42).

While the use of probiotics alone in eradicating *H. pylori* infection is generally not recommended, combining them with standard antibiotic-based regimens may enhance eradication rated and mitigate the most significant side effects associated with antibiotic use (43).

CONCLUSION

In summary, *H pylori* infection in children can cause a range of gastrointestinal symptoms and has been associated with growth retardation, iron deficiency anemia, headache, and autoimmune disorders. Early recognition and treatment of *H. pylori* infection in children is important to prevent the development of complications and improve long-term health outcomes. However, when considering the management of *H. pylori* infection in pediatric population, the decision to pursue diagnosis and treatment should be based on the likelihood of actual therapeutic benefits and this includes considering the infrequent incidence of complications, the possibility of recurrent infection, the potential inverse associations with allergic and immunological disorders or the emergence of antimicrobial resistance.

AUTHOR CONTRIBUTIONS

All authors have read and agreed to the published version of the manuscript. AAR, AMLB, TIL, GS, MAM, LSG, RAB, DCG contributed equally with ALC to this article.

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