

Mini-review

Helicobacter Pylori in Children

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Abstract

Helicobacter pylori infection is the most common infection of the gastrointestinal system worldwide, with an estimated 50% of the world's population being infected. The infection is acquired early in childhood, with most pathological symptoms present in adulthood. Transmission is mainly fueled by overcrowding and poor sanitation. Diagnosis in children considers criteria that call for testing and further investigation to eradicate infection. Since this infection is common, one must consider a different approach when suspecting *Helicobacter pylori* infection in the pediatric population, from the definition of index case to the diagnostic approach and eradication.

Keywords: Helicobacter pylori, Children, Gastrointestinal infection, Pediatric gastritis

Introduction

Helicobacter pylori was discovered in 1982 by Barry Marshall and Robin Warren. It is a gram-negative microaerophile which thrives mainly in the stomach(1). *Helicobacter pylori* transmission is fueled by overcrowding and poor sanitation. The infection is transmitted oral-oral, fecal-oral, and gastric-oral. It mainly affects the adult population, with acquisition occurring in childhood(2). It is present mainly as nodular gastritis in children, with few developing peptic ulcers(3). Treatment in the pediatric population entails positive nodular gastritis or ulcer seen through endoscopy and a positive confirmatory test, whether invasive (biopsy) or non-invasive (*Helicobacter pylori* antigen test in the stool(4), with the current recommendation on the management of *Helicobacter pylori* in children being against the 'test and treat' approach as no benefits has been reported with risk of resistance but also complications related to antibiotic use(5).

Epidemiology

Helicobacter pylori infection is highly prevalent globally, with an estimated 50% affected. Most of the infections are found in the developing world(6). With early acquisition in childhood, with infection occurring before the age of 10 years, with a prevalence of 80% in developing countries and dropping to 50% in industrialized countries by the age of 60(7,8).

The prevalence of *Helicobacter pylori* in children has been fluctuating across the world, with the prevalence of 48%, 82%, 44%, 45%, and 37% in Nigeria, Mexico, Uganda, Kenya, and Cameroon respectively(9–11) and in Europe having the prevalence of 13.6%, 8.6% and 2.4% in Sweden, Irish and German(12,13). Poor socioeconomic status and high population have been identified as the leading risk factors in the transmission of the organism in the pediatric population(14–16).

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This resilient organism has managed to embark itself into humanity, making eradication futile, especially in the developing world. Poor living conditions facilitate the further spread of the disease within a household, namely overcrowding, bed-sharing, and scarcity of water(17). Transmission of the organism has been found to occur via oral-to-oral, fecal-oral, and gastric oral.

Pathology

The *Helicobacter pylori* infection has managed to thrive in gastric acidic conditions with its virulence factors. It is a gram-negative microaerophilic with a spiral shape. Its surface consists of two proteins, ring-shaped protease and urease heat shock(18). These proteins and adhesion molecules allow it to attach to gastric cells and ensure its proliferation. Pathogenicity possession of *Helicobacter pylori* includes urease, adhesins, γ glutamyl transferase, vacuolating cytotoxins, and lipopolysaccharides. These factors perpetuated the organism's existence in the harsh environment of the acidic gastric mucosa(18).

Urease converts the urea to bicarbonate and ammonia, which acts as a neutralizer of the acid within the stomach, allowing the bacteria to move fast with its flagella into the more neutral environment(19). Urease is stored in the organism's cytosol. The enzyme facilitates colonization by neutralizing the acid and evading the host system by binding immunoglobulin. It also causes detrimental damage to the tissue since it activates the inflammatory process via leucocytes and oxidative bursts in neutrophils(20). This can be substantiated when urease-negative strains are introduced to the gastric mucosa. They are unable to invade the epithelium of gnotobiotic piglets(21,22).

In addition, molecular mimicry exists between the organism's lipopolysaccharide and Lewis's body, creating a camouflage effect, thus evading the immune system. When the serum of an infected human was taken, it contained autoantibodies that cross-react with gastric mucosa. A similar observation was seen with murine monoclonal antibodies directed against the organism(23). Adhesins, namely Hop S, which facilitates attachment to Lewis body, Hop H, which catalyzes the activation of interleukin 8(IL 8), and Hop P, which mediates binding to glycoconjugate containing sialic acid (24–26), further reinforce the attachment and inflammation process.

Vacuolating cytotoxin has a significant role in pathogenicity; it is hypothesized that the vacuolating cytotoxin A (Vac A) insertion into the gastric epithelium causes an ionic change, which results in cell swelling secondary to osmotic swelling and apoptosis(27,28).

The γ glutamyl transpeptidase (GGT) partakes in tissue injury by facilitating mitochondria-mediated apoptosis in gastric mucosa cells in an experimental model done in mice and gerbils. It induces IFN γ inflammatory response upon infection by *Helicobacter pylori*(29). Another study that involved a comparative knockout strain of GGT showed similar results with high levels of GGT found in gastric cancer patients with concurrent helicobacter pylori infection compared to patients with chronic gastritis or ulcer(30).

The most potent virulence factor hosted by *Helicobacter pylori* infection is having the cytotoxin A associated gene (CagA); the oncogene is located on the CagA pathogenicity island (PAI)(31,32). Studies have shown that this interaction with the host gastric epithelium increases the severity of gastroduodenal diseases, including adenocarcinoma(33). The bacteria inject itself into the host epithelium mucosa cells using the type 4 secretion system (T4SS). Once it is inserted into the host cells, it follows either the dependent phosphorylation or independent phosphorylation pathways leading to mitogenic signal interruptions, disruption of the cell-to-cell junctions, an overactive inflammatory pathway with the dependent phosphorylation pathway forming the CagA-SHP-2 complex which is the culprit in the dysregulation of cell growth, with pro-inflammatory, pro-proteins and pro-mitogenic overexpression coupled with the cytoskeleton and cell junctions change (34,35).

Transmission

Currently, humans are the only identifiable host with the transmission of this organism requiring direct contact. In vitro, the organism survives in seawater, saline, and cold water if kept cool, with survival dropping to one to three days if fluids are at room temperature(36). Risk or susceptibility to infection has been linked with poor sanitation, overcrowding, gastric acid production, disease, malnutrition, genetic susceptibility, and age(36–39).

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Transmission is speculated to be fecal-oral, oro-oral, and gastric oral with the detection of the organism in the dental plaque(40,41). Although detection of dental plaque has been found, the prevalence is low in transmission(42). The reinfection rate is similarly lower once the organisms have been eradicated(43). Vertical transmission from mother to infant has been speculated, with horizontal transmission suspected in family members, including the horizontal transmission of mother to child. A study that investigated vertical transmission in *Helicobacter pylori*-infected women, whereby follow-up of the newborns to five years of age through stool antigen test and serology test was done, showed a transmission of mother-to-child transmission. This is probably the most common cause of intrafamilial transmission(44).

Diagnosis

Diagnosing *Helicobacter pylori* entails whether the patient falls into conditions or guidelines for testing. The ACG (American College of Gastroenterology) embraces testing for those for whom treatment is planned as in gastric MALT lymphoma, an active or past peptic ulcer, patients younger than the age of 55 years with dyspepsia even with no alarming features with consideration of the availability of endoscopy, cost, and quality of the test ensue(45).

Testing can be discussed as invasive and noninvasive methods. The urease biopsy test is one of the invasive methods being done; several kits are available in the market; the CLO test kit (Campylobacter-like organism test kit) is a urease contained agar that constitutes urea-based agar and pH monitor that changes color when urea is broken down to ammonia and thus raises the pH content of the agar. This is the most inexpensive biopsy method compared to the histology test, with a high sensitivity and specificity(46,47). In addition, rapid urease test (RUT) kits give results within an hour(48).

Apart from the tests above using biopsy as the sample, histology also has a role in identifying the organism and the consequential impact of the disease, such as gastritis and mucosa-associated lymphoid tissue. Despite the benefit of using tissue biopsy as the RUT, histology, and urease biopsy test sample, the tissue sample collection site affects the results as the organism's density changes with location. The recommendation is to take multiple tissue samples from the antrum and the body of the stomach. Also, the sensitivity of the histological method, including the RUT and urease biopsy method, is affected by antisecretory therapy and bleeding(47). For patients with bleeding disorders, brush cytology can be employed with a high sensitivity of 95% and specificity of 96%(49).

The culture and sensitivity test is another invasive method mainly recommended in patients with a disease recurrence. It allows the identification of antibiotic-resistant strains. Metronidazole is identified for high resistance, especially in tropical countries, with a study done in the United States showing women are most affected(50,51).

Noninvasive testing procedures include stool antigen, urea breath test (UBT), and serology. The urea breath test encompasses either a radioactive or non-reactive carbon isotope urea, which is given to the patient orally and enables hydrolysis of ammonia and marked carbon isotope carbon dioxide, which can be detected by breath(52,53). The UBT has a high sensitivity of 88 to 95% with a specificity of 99 to 100%, meaning false negatives can occur, especially in patients taking antisecretory medication, bismuth, or antibiotics(54). If one needs to improve sensitivity, the patient should be off the medicines above for about four weeks(55).

Another noninvasive method for testing *Helicobacter pylori* is serology. Serological testing by ELISA allows the detection of IgG antibodies against the organism. This test has many flaws, and its practicability has been reduced in exceptional cases and circumstances with a good sensitivity of 90 to 100% but poor specificity of 76 to 96% (45,56). In addition, stool antigen assay and rapid stool antigen test are additional noninvasive tests that can detect *Helicobacter pylori* with slightly lower specificity than the invasive method. These tests are also affected by proton pump inhibitors and bismuth; therefore, analysis for eradication post-treatment should be delayed up to four weeks post-treatment (57–59).

Other tests available but not routinely practiced are polymerase chain reaction, salivary assay, urinary assay, and 13C urea blood test.

Pediatric *helicobacter pylori* infection

Presentation in children is vague since studies have shown no correlation between symptoms (heartburn, abdominal pain, vomiting, or nausea) and infection compared to adults(60). The infection is related to idiopathic thrombocytopenic purpura, vitamin B12 deficiency, and iron deficiency anemia(61). Endoscopically nodular gastritis and chronic inflammation suggest *Helicobacter pylori* infection(62).

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There are several guidelines regarding testing, treatment, and eradication of *Helicobacter pylori* in children, considering diseases associated with *Helicobacter pylori*. The guideline is based mainly on the local prevalence of infection and the pattern of associated diseases. For example, the Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition (JSPGHAN), with a high prevalence of gastric cancer in Japan, the guideline in adults, employs a 'test and treat' policy. Such a policy has been rejected in the pediatric population(63).

The guideline further rejects eradication therapy in *Helicobacter pylori*-infected children who underwent endoscopy for abdominal symptoms since most of the symptoms do not resolve with treatment. In addition, for children presenting with protein-losing enteropathy, *Helicobacter pylori* infection should be sought and eradicated only when other causes are ruled out, such as cytomegalovirus infection, Menetrier's disease, Eosinophilic gastroenteritis and intestinal lymphangiectasia(63). The Japanese guideline also advocated against eradication therapy in asymptomatic children whose first or second-degree relatives have a history of gastric cancer unless the family is concerned.

The joint North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend that the root cause of the abdominal symptoms should be sought rather than focusing only on *Helicobacter pylori* infection(64). The joint guideline emphasizes biopsy sample collection during endoscopy for RUT and culture in patients for whom treatment is planned and confirmation of infection has been made.

It should be made clear that in children, eradication of *Helicobacter pylori* may not improve the symptoms, and the endoscopic accidental discovery of *Helicobacter pylori* in children investigated for other pathologies should not warrant treatment since it rarely causes improvement clinical presentation(65). The reinfection rate correlates to the prevalence, with rates ranging from 11% after a year of eradication in Latin America to as low as 2.3% per year in Germany(66).

The guideline recommends treatment and eradication for children with endoscopic peptic ulcer disease, whether duodenal or gastric. This also prevents recurrence of the ulcer(64). On the other hand, the guideline rejects *Helicobacter pylori* testing in children presenting with functional abdominal pain with no other alarming signs and who comply with the Rome criteria for functional abdominal pain(67–69). With all being said, one should take precautions and not perform an *H pylori* test in the first-time presentation of iron deficiency anemia, short stature, or immune thrombocytopenic purpura but rule out primary causes first.

The management of *Helicobacter pylori* in the pediatric population is very complex, with utmost consideration required to avoid overuse, increased cost, and treatment catered only to those who will benefit from it.

Treatment in children is the same as in adults. The therapeutic regimen is chosen with consideration of local epidemiological data, cost, and side effects. The triple therapy regimen entails a proton pump inhibitor, amoxicillin, and clarithromycin for 14 days(5,45). Metronidazole can be used instead of amoxicillin for those with a penicillin allergy. A resistance of more than twenty percent in metronidazole and clarithromycin warrants initiation of a quadruple therapy, which can be administered similarly for those who have used these drugs (metronidazole and clarithromycin) recently.

The quadruple regimen includes bismuth, proton pump inhibitor (PPI), metronidazole, and tetracycline(70). The duration of therapy is one week, which has shown to be effective(71). Lastly, a sequential regimen of ten days has demonstrated efficacy, especially in areas having resistance against clarithromycin. The regimen consists of a five-day course of PPI and amoxicillin followed by a combination of PPI, clarithromycin, and tinidazole for another five days, with studies showing higher efficacy than triple therapy and in clarithromycin resistance (72). In the pediatric population, efficacy is limited for sequential regimens (73,74).

Eradication and Treatment failures

Eradication can be confirmed four weeks post-treatment by urea breath test, stool or fecal antigen test, or endoscopy(45). The eradication test should be performed in patients who have persisting symptoms, in those in whom an ulcer was found with *Helicobacter pylori* infection, in MALT, or those in resection for gastric cancer (70).

Treatment failure in the first-line drugs (PPI, amoxicillin, and clarithromycin) occurs in about 20% of the patients (75). And when the 'rescue' therapy (PPI, tetracycline, bismuth, and metronidazole) is employed. Still, 20 to 30 percent have persistent treatment failure(76). A third line of treatment comprising moxifloxacin, levofloxacin, or rifabutin combined with amoxicillin and PPI can be employed. These combinations are effective by 50% in treatment failure groups(77). Further failure entails microbial sensitivity stewardship by conducting culture and sensitivity.

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First line regimen

PPI (1-2mg /kg/day), metronidazole 20mg/kg/day, amoxicillin 50mg/kg/day

OR

PPI, amoxicillin, clarithromycin (20mg/kg/day) if the resistance is lower than 15% in the region.

OR

Bismuth salts (substrate or subsalicylate) 8mg/kg/day, amoxicillin, and metronidazole(78)

Second line regimen

Bismuth subsalicylate one-tab (262mg) QID or 15ml (17.6mg/mL QID), metronidazole 20mg/kg/day 500mg BID, PPI 1mg/kg/day up to 20mg BID, amoxicillin (1g BID) OR tetracycline (50mg/kg/day up to 1 g BID) or clarithromycin (15mg/kg/day up to 500mg BID)

Sequential regimen

The sequential regimen comprises two phases, each consisting of a five-day course. The first phase is Amoxicillin (50mg/kg/day with a maximum dose of 2 g) and PPI (1mg/kg/day maximum is 40mg) BID then followed by a second phase of metronidazole (50 mg/kg/day with a maximum dose of 2 g), clarithromycin (15mg/kg/day with a maximum dose of 1g) and a PPI(79,80).

Summary

Helicobacter pylori is a common infection and a leading cultured organism in the pediatric population. It has virulent factors that have aided it in surviving in the gastric mucosa and evading the immune system.

Transmission is fueled by poor sanitation, overcrowding, and low socioeconomic status. The presentation is nonspecific in the pediatric population. Nonetheless, endoscopy reveals chronic inflammation and gastritis.

Diagnosis can be invasive (urease biopsy test, culture and sensitivity, histology, and rapid urease test from the gastric mucosa sample collected during endoscopy) or noninvasive, namely urease breath test, stool antigen test, and the least preferred serology.

In the pediatric population, testing correlates with guideline recommendations to avoid cost and unnecessary exposure since most abdominal symptoms, when present, do not improve with medication such as functional abdominal pain. *Helicobacter pylori* in children can present with iron deficiency anemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency.

Treatment comprises combination regimens with 20% failure in the first line of drugs. Second, sequential, and third-line regimens can be followed if failure erupts. Eradication is crucial to prevent complications.

Footnotes.

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