Helicobacter pylori & beyond: pediatric peptic ulcer disease

The word peptic implies 'gastric-, pepsin- or acid-related'. Peptic ulcer disease (PUD) denotes the presence of gastric and/or duodenal ulceration or erosion. In clinical practice, the term encompasses gastric or duodenal inflammation due to any etiology, and may be more common in childhood than ulcerative disease. PUD occurs across the pediatric age group. Although etiopathology of PUD is typically related to that of *Helicobacter pylori* infection, other etiology for PUD is not uncommon in children and requires a different approach in evaluation and therapeutic decisions. Evaluation of PUD includes endoscopy with mucosal biopsy. Noninvasive testing, such as urea breath test, has a role in the follow-up of *H. pylori* eradication following therapy. Better understanding of pathogenic factors innate to *H. pylori* infection has enhanced our understanding of associated PUD. This review describes the management of both *H. pylori* and non-*H. pylori* PUD.

KEYWORDS: children, duodenal ulcer, gastric ulcer, gastroduodenitis, *Helicobacter pylori*, peptic ulcer disease

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Helicobacter pylori & peptic ulcer disease

Helicobacter pylori (*H. pylori*) is a common infection worldwide. The etiology of primary peptic ulcer disease (PUD) is mainly attributable to *H. pylori* infection. Other species of *Helicobacter* may also colonize the stomach, but are rarely implicated in PUD [1]. *H. pylori* is acquired in childhood and data from sero-prevalence surveys indicate that *H. pylori* incidence increases with the age of the children, the household size and with lower socio-economic status. The incidence also varies with ethnicity [2]. In regions endemic for *H. pylori* infection, longitudinal follow-up has shown that prevalence increases particularly when children are less than 10 years of age [3].

Epidemiological studies have utilized serology, the urea breath test (UBT) and stool testing for *H. pylori* antigen as screening tools. Several recent studies have shown that infection is prevalent even in the very young, especially in endemic regions. In the Pasitos Cohort Study conducted along the USA–Mexico border, subjects were recruited before birth and examined at age 6, 12, 18 and 24 months. The UBT demonstrated that, even at 6 months, prevalence of *H. pylori* infection had increased from 7 to 19%. Prevalence based upon serology was much lower [4]. Between 66 and 75% of Gambian infants studied by a combination of (13)C-UBT and fecal enzyme-linked immunosorbent assay showed *H. pylori* colonization by 12 months [5]. In an Italian study of symptomatic children under 5 years of age, 16.3% of consecutive endoscopy procedures tested positive for *H. pylori* [6]. In contrast, mean annual *H. pylori* infection upon endoscopy in symptomatic children decreased almost by half in the latter 6 years of a retrospective USA study spanning 13 years [7].

Although *H. pylori* infection almost invariably results in gastric inflammation, the degree, localization and severity of inflammation may vary. Several studies have addressed this variability in inflammatory response and symptoms, including risk of progression to gastric cancer [8]. If untreated, *H. pylori* gastritis may progress to gastric atrophy. Higher grades of gastritis are seen in the Chinese and Korean populations, who have a higher predilection for gastric cancer. Infants infected with *H. pylori,* have a lesser presence of gastric atrophy and intestinal metaplasia is absent, while moderate-to-severe gastric atrophy can be seen by 10–12 years; however, it is unclear if this progresses further to gastric cancer [9–11].

Divergent clinicopathological outcomes in *H. pylori* infection may be due to differences in host genotype and bacterial gene expression affecting the disease process. The host response to *H. pylori* differs in those with more severe disease. Several studies have evaluated specific parameters of host response. Children with a *H. pylori* ulcer, in comparison with infected children without an ulcer, demonstrated an increase in CD8(+)/HLA-DR(+) cells, and a decrease

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in CD8(+)/CD28(+) cells [12]. Expression of α-defensin was higher in a group of children positive for *H. pylori*, and was significantly associated with higher grades of acute and chronic inflammation [13]. A significant association was present between host TNF-α gene polymorphism (G to A polymorphism in position 238) and duodenal disease in children infected with *H. pylori* ice A1 strains, in contrast to gastritis [14]. A higher level of cytokine IL-1α, is associated with a lower risk of *H. pylori* infection among Jamaican children, indicating that an upregulation of proinflammatory cytokines may protect against persistent *H. pylori* colonization [15].

Common symptoms of PUD and nonulcerative *H. pylori* infection include nausea, vomiting and abdominal pain (Table 1). Very young infants may also exhibit nonspecific symptoms including failure to thrive, weight loss or diarrhea and irritability [16]. Specific symptoms or symptom sets do not distinguish between *H. pylori* and other causes of PUD.

Diagnosis of *Helicobacter pylori*

Diagnosis of *H. pylori* incorporates both invasive and noninvasive testing (Table 2). Accurate noninvasive tests for *H. pylori* diagnosis is particularly necessary in the very young, and is an area of much interest at the present time.

Noninvasive testing for *Helicobacter pylori*

Routine serum antibody testing with ELISA is unreliable in children [17]. Recent serology tests incorporate a current infection marker (CIM), an antigenic protein homologous to a secreted protein of *H. pylori*. Presence of anti-CIM antibody may suggest active infection. A study utilizing an immunoblot with CIM indicates that this test may be a useful addition to available noninvasive tests. However, this particular study reported a wide variation in culture, rapid urease test (RUT) and histology positive rates ranging from 37.8 to 64.6% [18]. CIM tests may not accurately identify past or current infections within 6 months after therapy for *H. pylori*. [19]

Stool *H. pylori* antigen testing is shown to be more reliable. A meta-analysis has shown monoclonal stool antigen testing in children to be accurate for initial diagnosis of *H. pylori* infection and to confirm post-treatment eradication. The monoclonal test has higher sensitivity than the polyclonal-based assay, especially in the post-treatment setting [20]. Monoclonal antibody-based antigen in stool testing also showed a high sensitivity and specificity in a study of Vietnamese children [21].

(^{13})C-UBT is considered as the gold-standard diagnostic test, especially in confirmation of eradication. However, it may be difficult to perform and interpret in young children less than 5 years of age. Endogenous CO_2 production in this age group may lead to a higher false-positive result [6,22]. Recent studies involving younger children report improved accuracy by adapting different cut-off values and measurement of urea hydrolysis rate. UBT is a highly specific test; however, colonization of urease-producing non-*H. pylori* bacteria may produce false-positive results in the presence of gastric atrophy [23].

Diagnosis at endoscopy

Upper gastrointestinal endoscopy with biopsy is the modality of choice for diagnosis of PUD and *H. pylori* infection [24]. Although antral nodularity is clinically considered to be a diagnostic feature at endoscopy in children, evidence is conflicting regarding its association with the severity of gastritis [25,26]. Moreover, as many as half of the children with antral nodularity may have other diagnoses, including celiac disease [27]. Conversely, an absence of antral nodularity, along with regular arrangement of collecting venular pattern, is highly indicative of *H. pylori* uninfected gastric mucosa [28]. Although *H. pylori* infection causes symptomatic infection at all ages, peptic ulcer and erosions occur more commonly in later childhood [16,29]. A study of Israeli children found that *H. pylori*-positive gastric ulceration and erosions were commonly seen after 9 years of age, while duodenal erosive disease is more prevalent in adolescence [30].

RUT, a well-accepted rapid diagnostic test at endoscopy, may be less sensitive with a lower negative predictive value [31]. A number of factors affect the diagnostic efficacy of RUT. A positive association exists between RUT (CLO^R-test), and the density of *H. pylori* organisms on histology [32]. The number of biopsies obtained for

Table 1. Clinical symptoms in childhood peptic ulcer disease.

Infants and young children*	Older children and adolescents‡
Vomiting	Abdominal pain
Failure to thrive	Anorexia
Weight loss	Nausea/vomiting
Chronic diarrhea	Heartburn
Hematemesis	Hematemesis
Iron-deficiency anemia	Iron-deficiency anemia
Irritability	

Data from [16].
‡*Data from* [30.72].

Table 2. Diagnostic tests in *Helicobacter pylori* infection in children.

Noninvasive test	Remarks
Serology: anti *Helicobacter pylori* IgG antibody serology	Not recommended for clinical diagnosis in children Very low sensitivity [17] Recent serology incorporating current infection marker may detect active infection [18]
Stool *Helicobacter pylori* antigen assay [20,21]	Several commercial assay kits available Monocolonal assays are more sensitive than polyclonal tests High sensitivity and specificity shown in both diagnosis and after treatment testing
^{13}C urea breath test [6,22]	Well accepted test to confirm eradication. Recent studies have shown accuracy in children below 6 years of age
Diagnosis at endoscopy	
Rapid urease test	Acceptable specificity and sensitivity False-negative in atrophic gastritis, low-density infection Testing with two or more tissue samples increases detection rate [32–34]
Histology	Standard method of diagnosis for *Helicobacter pylori* gastritis
Microbial culture	Not routinely used Useful for susceptibility testing Recent studies report success with quicker culture method [37]

testing affects accuracy; over half the patients were positive in those with one antral biopsy compared with 96% in the group with four biopsies [33]. Rapid CLO^{R} tests also have a lower detection rate for *H. pylori* in the presence of a higher degree of mucosal atrophy and intestinal metaplasia [34].

Histology

Characteristic spiral organisms are identified on histology, with routine or special stains such as Warthin–Starry and modified Giemsa stains. Expertise in assessing histology may impact the accuracy of histology [35]. In low-density infection with *H. pylori*, RUT may have a lower yield, and a UBT test may be false-negative. When suspicion of *H. pylori* infection persists despite negative noninvasive testing, obtaining an adequate number of biopsies at endoscopy for histology may be important. Immunohistochemistry may provide an alternative method in this group of patients, although it is not as accurate as routine histochemical staining [36].

Microbial culture

In children, culture of tissue obtained at endoscopy appears to achieve comparable results with histology and stool antigen testing for *H. pylori* identification. *H. pylori* is a fastidious organism, and growth in culture is delayed; this renders its utilization for routine diagnosis impracticable. Modified Agar culture may yield *H. pylori* within 24 h, and may hold promise for widespread application [37].

Helicobacter pylori therapy

Expert consensus recommends treatment when PUD is present in *H. pylori* infection [24,38,39]. There is also a general agreement to treat nonulcerative *H. pylori* gastritis in children when the diagnosis is made at endoscopy carried out for investigation of PUD [38]. Eradication of *H. pylori* decreases PUD prevalence [40].

The multiple treatment regimens that are used for *H. pylori* eradication imply that eradication rates are far from optimal. Published findings from a European pediatrician registry study show that 27 different regimens were utilized in 518 children treated with an overall eradication rate of only 65.6%, although only six triple-therapy regimens were most often used [41]. This includes a combination of two antibiotics from amongst amoxicillin, metronidazole and clarithromycin, along with a proton pump inhibitor (PPI) or bismuth. Some of the common antibiotics and other medications used in *H. pylori* therapy are summarized in Table 3. Both the North American and the Canadian Consensus statements recommend triple therapy for 7–14 days with a PPI and clarithromycin, in combination with amoxicillin or metronidazole for primary eradication [24,39].

A recent meta-analysis further indicates that there is no single optimal regimen for primary therapy [42]. In the analysis of 80 studies including 4436 children, the most commonly tested regimen contained a combination of a proton pump inhibitor, clarithromycin and amoxicillin

Table 3. Common medications employed in treatment regimens for *Helicobacter pylori* infection.

Medications	Remarks
Antibiotics	
Amoxicillin 50 mg/kg/day up to 1 g b.i.d. [24]	Primary resistance is minimal [54,57,58]
Clarithromcyin [56,82,83] 15 mg/kg/day up to 500 mg b.i.d. [24]	Increasing resistance. May determine treatment failure
Nitroimidazoles – metronidazole 20 mg/kg/day 500 g b.i.d. and tinidazole 20 mg/kg/day [44]	Increased resistance in regions where these antibiotics are used for other infections such as amebic infections Used in sequential therapy [44]
Furazolidine [48] Nifuratel [47] Levofloxacin	Vomiting is a significant side effect
Proton pump inhibitors	
Omeprazole (1 mg/kg/day up to 20 mg bid) and esomeprazole Lansoprazole Pantoprazole	All have equal efficacy [49]
Others	
Probiotics (*Lactobacillus reuterii*, *Lactobacillus casei*, *Bacillus clausii*) [45,61,62]	Primarily to reduce side effects of multidrug regimen
Bismuth (colloidal bismuth subcitrate or bismuth subsalicylate) 1 tablet (262 mg) or 15 ml four-times a day (17.6 mg/ml).	As part of triple or quadruple therapy; both in first- or second-line regimens. PERTH registry analysis favored bismuth regimens [41]

b.i.d.: Twice daily; PERTH: Pediatric European Register for Treatment of Helicobacter pylori.

(PPI-CA) and the eradication rate varied from 29 to 100%. The treatment response also differed in different geographic locations thought to mirror metronidazole resistance. In addition, quadruple regimens did not offer improved cure rates. The authors point out that a major limitation of this study was the poor quality of clinical trials available in the pediatric literature.

Very few studies address retreatment after eradication failure in children. A recent study of interest explored this issue. Of 275 children, 113 who received primary therapy with 1- or 2-week triple therapy failed to eradicate *H. pylori*. A total of 89 of these children were then given a quadruple therapy with bismuth, doxycycline and metronidazole (7 days) and omeprazole (14 days), with successful eradication in only 66.7% [43]. Sequential therapy has attracted attention as an attempt to improve eradication rates [44,45]. The regimen involves omeprazole plus amoxicillin for 5 days, followed by a combination of omeprazole, clarithromycin and tinidazole for another 5 days. Both of these studies reported eradication rates between 80 and 97.3% in the sequential arm with good compliance. In contrast to the metronidazole resistance that impacts the efficacy of conventional regimens, primary resistance to clarithromycin appears to reduce the efficacy of sequential therapy [46].

Primary triple therapy regimens containing nifuratel or furazolidine appear to have no added advantage in children [47,48]. Moreover, furazolidine caused vomiting in a third of children. The cost–effectiveness of various *H. pylori* regimens in the pediatric age group has not been studied. Choice of proton pump inhibitor does not alter the efficacy of treatment regimens [49].

Compliance and antibiotic resistance are the most significant factors in failure of anti-*H. pylori* therapy [50]. Resistance to the various antibiotics utilized in anti-*H. pylori* therapy is widespread, but variable across regions and ethnic groups. A study conducted in Italy found a resistance rate of 16.9% for clarithromycin, 29.4% for metronidazole and 19.1% for levofloxacin. Resistance to metronidazole was also higher in non-Italian subjects [51]. Metronidazole resistance is very high in certain geographic regions, as studies from Iran and Kenya suggest [52,53]. Development of resistance to antimicrobials is a dynamic process, and alters over time depending upon the geographic location [54,55]. Prevalence of clarithromycin resistance, as high as 24% in a multicenter European study [55], is important, as it appears to determine treatment failure regardless of virulence genes [56]. Amoxicillin-resistant *H. pylori* strains are unusual [54,57,58]. Resistance rates may differ in those who received prior therapy from treatment-naïve subjects. This is especially true for clarithromycin and metronidazole [59]. Strains with clarithromycin resistance may spread within family members [60].

The use of probiotics such as *Lactobacillus reuteri* and *Bacillus clausii* is an emerging trend. Although their use appears to reduce adverse effects of antibiotic therapy with improved compliance, the eradication rate is not improved [45,61]. A randomized, control study with addition of *Lactobacillus casei* DN-114 001 fermented milk to triple therapy with omeprazole, amoxicillin and clarithromycin reported an enhanced eradication rate in the probiotic group [62]. Other studies have not demonstrated a clear-cut benefit either in reducing symptoms during therapy or eradication rate [63,64].

H. pylori eradication improves histology and gastritis, but mild chronic gastritis persists despite eradication even in asymptomatic children [65].

Other *Helicobacter* infections

Helicobacter heilmannii (*H. heilmannii*) is the best studied of the other *Helicobacter* species that infect gastric mucosa. Pediatric case reports describe this infection in the presence of failure to thrive and epigastric abdominal pain [66]. The incidence of *H. heilmannii* is reported to be as high as 6% in Chinese adults [67]. The long, tightly coiled corkscrew appearance of *H. heilmannii* permits diagnosis on hematoxylin and eosin stains at higher magnification. Although gastritis is less severe and ulceration is rare, *H. heilmannii* gastritis has been linked with gastric mucosa-associated lymphoid tissue lymphoma in adults [68].

Helicobacter felis was present in approximately half of 90 subjects in a South African population tested for its presence by PCR. Co-infection with *H. pylori* occurred in a quarter of the group, but did not augment severity of gastritis or atrophy. Intrafamilial clustering was noted [69]. Other *Helicobacter* species reported in the gut and liver tissue from pediatric patients are beyond the scope of this review [70,71].

Non-*Helicobacter pylori* peptic ulcer disease

There is limited data on PUD caused by etiology other than *H. pylori*. Non-*H pylori* peptic disease is not uncommon: 112 of 152 symptomatic infants less than 2 years of age did not have *H. pylori* infection at endoscopy. Although gastritis was more common in the *H. pylori*-infected infants, histological duodenitis was equally prevalent between the two groups. Moreover, three of the four infants with ulcers did not have *H. pylori* infection [16]. In a study from Israel, a third of older children and adolescents who underwent endoscopy for peptic symptoms did not have *H. pylori* infection. Even amongst 51 children with peptic ulcer at endoscopy, 23 (45%) did not have *H. pylori* infection. Of children with non-*H. pylori* PUD, 72% had no identifiable etiology [30]. This data is all the more compelling as these two studies are from regions with significant prevalence of *H. pylori*. In general, non-*H. pylori* PUD is more common in the younger children compared with older children and adolescents.

As apparent from the studies cited above, a significant proportion of non-*H. pylori* PUD is idiopathic, and a varied etiology accounts for the rest (Table 4). A total of 17% of duodenal ulcers in a Japanese study were found in *H. pylori*-negative children and with no identifiable cause [72]. Non-steroidal anti-inflammatory drug (NSAID) use is a well described cause of gastro–duodenal ulcers [16,30]. NSAID use is associated with both gastric or duodenal ulcers and erosions. NSAID PUD is typically dose-dependent or associated with long-term use, but has been reported in children with febrile illness even after one or two therapeutic doses [73].

Eosinophilic gastroenteritis may cause isolated or multiple ulcers [74,75]. Interestingly, eosinophilic gastric or duodenal inflammation appears to be common on histopathology, even in idiopathic PUD [16,76]. The significance of this is unclear. PUD is described in various systemic illnesses [77–79]. In critically ill children, 'stress-related' ulcers and significant bleeding occur, especially in association with mechanical ventilation [80]. Upper gastrointestinal lesions occur in pediatric inflammatory bowel disease. Duodenal ulceration and bleeding in acute pancreatitis, complicated by gastroduodenal artery aneurysm, and gastric erosion in association with adenoviral tonsillitis, caused significant bleeding in the authors' own experience.

In idiopathic PUD in children, ulcer perforation is unusual and appears to be mostly confined to the adolescents with PUD. In a 20-year study of Taiwanese children, 90% of ulcer perforations occurred in that age group [81]. Non-*H. pylori* PUD is almost always effectively treated with acid suppression, although prospective studies are lacking. Complete healing and resolution of symptoms requires appropriate therapy for the underlying etiology, as in eosinophilic gastroenteritis. Therapy for ulcer disease in children with intestinal transplantation depends upon the direct causative factors: lymphoproliferative disorders, acute graft rejection or viral infections.

Conclusion

In children, PUD is broadly attributable to *H. pylori* and non-*H. pylori* etiologies. A *H. pylori*

Table 4. Common causes of non-*Helicobacter pylori* peptic ulcer disease in children.

Category	Examples
Idiopathic	
Drug induced	NSAIDs, aspirin
Inflammatory	Eosinophilic gastroenteritis Inflammatory bowel disease Graft versus host disease Behcet's disease [84]
Vasculitides	Henoch–Schonlein purpura
'Stress related'	Critically ill children Mechanical ventilation
Viral infections	Cytomegalovirus, Herpes simplex
Systemic disease	Renal failure, cystic fibrosis [85]

NSAID: Nonsteroidal anti-inflammatory drug.

infection which is acquired in childhood, may persist throughout life. Endoscopy is the best initial investigation to evaluate PUD. Triple therapy is the most common regimen for *H. pylori* eradication and treatment regimens are suboptimal in eradication rate. Acid suppressive therapy and appropriate management for underlying cause will effectively treat non-*H. pylori* PUD.

Future perspective

Current treatment regimens for *H. pylori* eradication in children are suboptimal, and more effective treatment regimens of shorter duration are required. Improved techniques applicable in a clinical laboratory setting to evaluate microbial susceptibility of *H. pylori* strains is necessary to develop targeted, effective regimens. Increased availability of standardized techniques for noninvasive tests in diagnosis and assessment of eradication of *H. pylori* will facilitate their use in the pediatric population. The effort to reduce the incidence of gastric cancer will require recognition of the factors present in high-risk groups with *H. pylori* infection and strategies to conduct long-term surveillance of these groups. Socio–economic improvement will reduce infection incidence consistent with the paradigm of any chronic infectious illness.

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Executive summary

- *Helicobacter pylori* (*H. pylori*) is the predominant cause of peptic ulcer disease (PUD) in children, although non-*H. pylori* PUD is not uncommon. No identifiable etiology exists for a significant proportion of non-*H. pylori* peptic ulcers. Identifiable causes include use of nonsteroidal anti-inflammatory drugs, inflammatory or eosinophilic bowel disease or stress-related ulcers. Therapy for non-*H. pylori* depends upon the underlying cause, and acid suppressive therapy is effective.
- Symptoms of PUD are similar, regardless of *H. pylori* or non-*H. pylori* etiology and symptoms in very young children may be nonspecific, including failure to thrive, diarrhea and irritability. Noninvasive testing, such as stool *H. pylori* antigen testing and urea breath test are shown to be specific and sensitive in children including the very young. The *H. pylori* density, atrophic gastritis, adequacy of biopsy determines rapid urease test accuracy. Histological identification requires experience and expertise.
- *H. pylori* infection results in gastritis; however, severity of gastritis varies, and divergent clinical outcomes may be related to host gene polymorphisms and interaction with bacteria.
- Multiple regimens with variable eradication rates are used in treatment of *H. pylori* infection; triple therapy with a proton pump inhibitor, and two antibiotics from clarithromycin, amoxicillin or metronidazole, is the most widely used. Sequential anti-*H. pylori* therapy holds promise.

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