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*Helicobacter pylori* infection and childhood

2009–2010

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ABSTRACT

Pediatric-based *Helicobacter pylori* research continues to contribute significantly to our understanding of both clinical and pathophysiological aspects of this infection. Here, we review the published pediatric *H. pylori* literature from April 2009–March 2010. Analysis of pediatric *H. pylori* strains continues to suggest that CagA+ and CagPAI competent strains are less prevalent than in adult isolates. Studies from the Middle East report a high *H. pylori* prevalence and intrafamilial transmission. Data continue to show a lack of association between *H. pylori* and recurrent abdominal pain of childhood, gastroesophageal reflux disease, and growth retardation.

Recent probiotic trials have not shown a benefit on *H. pylori* eradication in children, while sequential therapy remains an attractive therapeutic eradication strategy in children, which requires validation in different geographic regions.

PATHOPHYSIOLOGY

The relationship between apoptosis and *Helicobacter pylori* remains an important aspect of *H. pylori* pathogenesis research. In a Polish cohort of children with symptomatic *H. pylori* infection and gastritis, Fas receptor expression was increased in the CD4+T cell population in the lamina propria at diagnosis and Fas antigen expression was significantly decreased in both epithelial cells and mucosal lymphocytes following successful eradication. The authors speculate that apoptosis of CD4+ T cells could contribute to bacterial persistence in the mucosa.

Studies of the spectrum of *H. pylori* genetic variability between childhood and adult isolates may help to elucidate age-specific microbial genetic factors involved in pathogenesis. Rick et al. suggested that in situ hybridization techniques, which reflect in vivo gene transcription, may be superior to testing isolates for CagA in vitro and used this method to confirm the association between gastric mucosal *H. pylori* CagA expression and pediatric gastro-duodenal ulcer disease. While children had a higher prevalence of CagA+ strains compared to adults in one study from China, CagA was not shown to influence their disease phenotype. *H. pylori* strains from symptomatic children in the USA and Greece were more likely to be CagA- and lack a functional CagPAI, although the USA isolates were more likely to retain outer membrane protein (OMP) and adherence gene expression than adult strains, a possible microbial advantage for early life infection and colonization.

The adherence properties and expression profile of OMP genes of *H. pylori* isolates from 200 symptomatic patients were characterized by Odenbreit et al. Apart from AlpA and AlpB, the expression of other OMPs was variable. In vitro interleukin (IL)-8 expression was again shown to be increased by CagA+ strains, while co-expression of OipA, but not OipA alone, further enhanced IL-8 secretion. The presence of the putative virulence factor gene IceA, while common, was not predictive of the extent of inflammation on histology in Slovenian children; CagA and VacA s1 genotypes were associated with more severe gastritis and greater bacterial density.

Autophagy, an evolutionary conserved process in eukaryotic cells, is an integral component of our innate immune system and is implicated in the pathogenesis of a number of gastrointestinal diseases. *H. pylori* VacA toxin has recently been shown to induce autophagy in gastric cells in vitro, a potential host defense strategy to limit toxin damage, but auto-phagosome formation may also facilitate bacterial replication and survival. *H. pylori* has also been shown to multiply in autophagosomes in macrophages, suggesting that it may be subverting autophagy for its own benefit.

**Keywords:** Review, recurrent abdominal pain, resistance, sequential therapy.
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EPIDEMIOLOGY AND TRANSMISSION

The estimated 71% prevalence of *H. pylori* infection in asymptomatic children in the Czech Republic is among the lowest reported in Europe. Sykora et al found a positive association with increasing age; the number of children in the household (OR 4.26, CI 1.91–9.80), lack of formal education of the father (OR 0.23; CI 0.18–0.64), and institutionalization (OR 6.33; CI 2.25–26.50). Their findings are consistent with improving trends in living and housing conditions in recent years and with decreasing family size.

While the prevalence in Western countries and America is decreasing, the high prevalence in Asia remains. Malekzadeh et al using stool antigen and serology testing, reported a high prevalence of *H. pylori* infection in 592 Iranian children from Shiraz and 386 children from Rafsanj (82% and 47%, respectively). Iran and Iraq have a high prevalence of CagA+ *H. pylori*. In a study from Pakistan, a seroprevalence of 47% among 1976 children (1–15 years) was reported. The father’s educational status, crowding, and increasing age, were the main factors influencing sero-positivity.

Understanding the intrafamilial spread of *H. pylori* is an important aspect of transmission research. A study of 100 children with abdominal symptoms (*H. pylori*) found a higher percentage of *H. pylori* infected siblings, mothers, and fathers, tested by urea breath test (UBT), among *H. pylori*+ than *H. pylori*- index cases (p < .001, p < .001 and p < .035, respectively). Each *H. pylori*+ child had at least one infected family member, implicating the family as the source of *H. pylori* infection in children. Nahar et al found evidence of intrafamilial transmission of *H. pylori* by characterizing *H. pylori* in 35 families, including 38 family members, using DNA fingerprinting. Forty-six percent of strains from the mothers shared related genotype with strains from their children. Only 6% of parents shared a related genotype, suggesting mother-child transmission as the most probable transmission route.

In a study from Iran, Amini et al described the association between *H. pylori* infection and eating habits (sharing plates, glasses, and spoons) and found a significantly higher prevalence of *H. pylori* infection in families where common dishes were used.

Travis et al used UBT at 6-month intervals from birth to 24 months to describe possible water-borne transmission of *H. pylori* in a cohort study of 472 children from Mexico and Texas. Their results provide some support for water-borne transmission. On the other hand, Vale and Vitor reviewed water- and food-borne transmission of *H. pylori* and concluded that the principal transmission route remains to be clearly defined.

SYMPTOMS

Recurrent Abdominal Pain

The discussion about the association between recurrent abdominal pain (RAP), epigastric pain, unspecified abdominal pain, and *H. pylori* infection in children continues. Thakkar et al published a retrospective study on upper digestive endoscopy in 1991 children with abdominal pain; 55 children (2%) were diagnosed with *H. pylori* infection, the second most common diagnosis after reflux esophagitis (23%). They agreed that earlier studies did not show a causal relation between *H. pylori* infection and abdominal pain in absence of ulcer disease, but conceded that there is a trend to offer eradication therapy once the *H. pylori* infection has been diagnosed. In a meta-analysis, Spee et al found no association between RAP and *H. pylori* infection in children and limited evidence for an association between unspecified abdominal pain and *H. pylori* infection, but not in primary care patients. Although current evidence does not support infection as a significant cause of common symptoms in children, guidelines on *H. pylori* screening in children are contradictory. For example, discrepancies exist between the earlier European Pediatric Task Force on *H. pylori* report and the more recent Maastricht III statement, which suggests that although RAP is not an indication for a test-and-treat strategy in children, those with upper gastrointestinal symptoms should be tested after exclusion of other causes of symptoms.

Peptic Ulcer

*H. pylori* infection is the most important cause of primary duodenal ulcers in children. A retrospective study of differences between *H. pylori*+ and *H. pylori*- primary ulcers in 43 Chinese children diagnosed >8 years showed that boys vs. girls (91.3 vs. 50%) and older children (12 vs. 10 years) were more likely to have *H. pylori-* ulcers (53.5%) in the *H. pylori*-group, ulcer recurrence was more common. In an editorial comment, Oderda et al noted the emergence of ‘a new disease’. *H. pylori*-negative gastric or duodenal ulcer, occurring more frequently in younger children, without gender preference and tending to have a higher recurrence rate. Rick et al investigated 51 children, of whom six had gastric ulcers (all *H. pylori*+) and 11 had duodenal ulcers (10 *H. pylori*+), and found *H. pylori* by 165 rDNA and CagA PCR significantly higher in children with ulcer compared with normal children.

Gastroesophageal Reflux Disease (GERD)

The role of *H. pylori* in GERD remains controversial, limited by sufficient published data in children. Both a positive and negative association between *H. pylori* and GERD was reported recently. Moon et al found reflux esophagitis in 13 of 16
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_H. pylori_-positive patients, but in only 38.1% of 404 _H. pylori_-negative children and concluded a positive association. However, the prevalence of _H. pylori_ in the study was low, and they did not address CagA status in _H. pylori_-positive patients in the study. On the other hand, researchers in Turkey did not find a positive association between _H. pylori_ infection and the severity of esophagitis 34.

**DIAGNOSIS**

Guaner et al published a ten-year review on diagnostic tests in children between 1999 and 2009, concluding that most commercial noninvasive tests now have adequate sensitivity and specificity for detecting the presence of _H. pylori_. They again emphasized that endoscopy with histopathology is the only method that can diagnose and confirm _H. pylori_ infection, its lesions and other causes of symptoms; UBT test and monoclonal stool antigen test being good tests for post-treatment control 31.

The same rapid office-based stool test using an immunoassay with monoclonal antibodies was tested in young children in Germany and in France. Prell et al compared it to biopsy tests considered as reference in the setting of pre-and post eradication of _H. pylori_ and found a sensitivity of 85.5–90.8% and a specificity of 91.0–97.6% 30. Results of Kalach et al were similar, showing a sensitivity of 87.5% and a specificity of 97.8% 31. She et al confirmed the lack of clinical utility of serology testing in children and adults, including an unacceptably low IgM sensitivity of just 6.8% 32.

**EXTRA-INTESTINAL MANIFESTATIONS**

Iron Deficiency and Growth

The link between _H. pylori_ infection and anemia or sub-optimal growth remains tenuous. Ferrara et al presented retrospective data on a heterogeneous group of 102 Italian children aged between 10 and 12 years with iron deficiency anemia, suggesting that children with both _H. pylori_ infection (positive stool antigen test) and iron deficiency anemia were more likely to have a reduced height standard deviation score (SDS) in comparison with children with other causes of anemia 33. However, the data spanning an 8-year period lacked growth velocity assessments, case-matched controls, and details regarding the etiological work-up. A cross-sectional study of children from a low socio-economic background from Mexico found an association between _H. pylori_ infection and reduced height compared to uninfected matched controls and suggested that the risk was cumulative per annum above the age of 7 years 34. In a contrasting study from Turkey, Gulcan et al did not find a significant association between anemia and growth retardation; a subgroup analysis did suggest an association between endoscopic mucosal disease and lower height SDS (p = .02) 35. Chi et al did not find an association between _H. pylori_ infection and growth failure in their cross-sectional study from Taiwan, albeit of high-school children and based again on height SDS rather than growth velocity 36. An Australian cross-sectional study of refugee children from Africa also failed to find an association between _H. pylori_ infection and subnormal anthropometric measurements 37.

A series of cross-sectional studies from Latin America did not find significant evidence linking _H. pylori_ infection and anemia 38. Children with a positive UBT in Cuba, Argentina, Bolivia, and Venezuela did not have a statistically increased risk of associated anemia in comparison with their UBT negative counterparts. In a study among Arab-Israeli children, a population with a high prevalence of both _H. pylori_ infection and anemia, Muhsen et al only found a statistically significant association between low ferritin levels and positive _H. pylori_ serology in children less than 5 years of age but not among older age groups 39. Unfortunately, it remains difficult to extrapolate a causal inference from studies of such design.

**Idiopathic Thrombocytopenic Purpura (ITP) and Platelet Dysfunction**

A multi-center randomized controlled trial of _H. pylori_ eradication in children with chronic ITP failed to show an effect of _H. pylori_ eradication on platelet recovery 40. Ferrara et al reported a positive effect of _H. pylori_ eradication on the outcome of children with chronic ITP with a positive stool antigen test, although their study was not a randomized controlled trial 41. One translational study described platelet aggregation dysfunction in children with symptomatic _H. pylori_ infection, which improved post-eradication 42.

**THERAPEUTIC ISSUES**

Drug Resistance

Drug resistance is a growing problem in adults as well as in children. Kato and Fujimura studied 61 strains from Japanese children 4–18 years old from 1999–2007 and reported high primary resistance of clarithromycin (36.1%) and metronidazole (14.8%) with consequences for the eradication rate 43. Double resistance was detected in 6.6% of the strains. In Bulgaria, resistance to clarithromycin and metronidazole was 19% and 16.2%, respectively; multidrug resistance was 1% 44. Both authors did not find resistance to amoxicillin and recommend susceptibility tests before treatment. Other studies on resistance came from Asia and South America; a low clarithromycin resistance rate was found in Malaysia (2.1%), Taiwan...
of Lactobacillus GG (n = 44) or placebo (n = 39). Subjects were recruited over a 40-month period, and complete data were only available in 34 of 44 children in the probiotic group and 32 of 39 children in the placebo group. No statistically significant benefit of probiotic supplementation over placebo was evident in terms of either eradication (69% versus 68%) or side effects. There was a no significant trend toward less regimen-associated diarrhea in probiotic treated children (6% versus 20%), although the study may have been underpowered to detect such differences with significance. In a study using functional food to deliver probiotics (cheese containing Lactobacillus gasseri OLL2716), Boonyaritichakij et al studied the effects of probiotic supplementation in two groups of asymptomatic kindergarten children in Thailand – with or without H. pylori as determined by stool antigen testing (n = 132 and 308, respectively). The eradication arm of the study was single-blinded and nonrandomized, whereas the prevention arm was randomized and stratified for age and gender. Compliance was evaluated by the children’s teachers. No statistically significant difference was detected between placebo and probiotic treatments in either the eradication or prevention arm of the study.

**RE-INFECTION AND SPONTANEOUS BACTERIAL CLEARANCE**

The extent of spontaneous clearance of H. pylori infection in childhood remains unclear. The Pasitos cohort study was established in 1998 to prospectively study H. pylori infection in Hispanic children 13. A recent follow-up report from this study examined the effect of incidental antibiotic exposure on subsequent H. pylori clearance, based on 13C-UBT changes and parental documentation of medication exposure 14. Medication dose and duration were not recorded. A remarkable 78% of 218 children with a previously positive UBT subsequently tested negative, especially those between ages 1–3. Of the 205 children with complete medication exposure data, 36% received at least one antibiotic course following the initial positive UBT, while 68% had a subsequent negative UBT. Notwithstanding the number of significant limitations of this study, incidental antibiotic exposure in this study cohort seemed to account for a relatively limited proportion of ‘spontaneous clearance’ of H. pylori infection.

**VACCINATION**

A recent editorial questioned the benefit of eliminating H. pylori, as only 10–15% of hosts develop ulcers and only 1% gastric adenocarcinoma. Vaccination can not yet be recommended, as our understanding of the bacterium is too
preliminary to make complete eradication a feasible option. Several studies have suggested the merits of prophylactic immunization. Rupnow et al quantified the cost-effectiveness of a prophylactic vaccine in the USA, using variables including costs of vaccine, vaccine administration, gastric cancer treatment, efficacy, quality adjustment caused by gastric cancer, and discount rate for periods of 10–75 years. They concluded that with a time horizon beyond 40 years, the use of such a vaccine could be cost-effective in the USA, especially if administered to infants or newborns. However, the problem is that the efficacy is unknown. This strategy would be different in less developed countries, where rates of \textit{H. pylori} prevalence remain high. If prevention of ulcer disease is included in the calculation, vaccination may also have some shorter term cost-benefits. In Australia, Hickey et al reported that transcutaneous immunization (TCI) with a lipid-based formulation against \textit{H. pylori} infection in mice partially protected them against challenge with live \textit{H. pylori}; this was not associated with development of gastric inflammation. Successful vaccination strategies in mice have not proven effective in human subjects. However, TCI may be effective as a route for inducing protection against \textit{H. pylori} colonization and warrants further study.

REFERENCES