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CHAPTER 2

*Helicobacter pylori*

infection in pediatrics

2005–2006

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ABSTRACT

This review summarizes the literature on Helicobacter pylori infection in childhood between April 2005 and March 2006, and includes guidelines of the Canadian Helicobacter Study Group Consensus Conference, non-invasive tests, optimum therapy regimens and problems with resistance, and reviews on immune mechanisms in the gastric mucosa that may lead to the development of an effective vaccine.

INTRODUCTION

In 2005 “the Nobel Prize in Medicine or Physiology” was awarded to Marshall and Warren for the discovery in 1982 that most peptic ulcers are caused by an infection with Helicobacter pylori [1-3]. It took a further 10 years before literature about H. pylori infection in children was published. It is now well accepted that the bacterium is usually acquired during childhood, mainly from the mother via vomitus or fecal oral route [4-9]. Great strides have been made since. In July 2005, the Canadian Helicobacter Study Group published an evidence-based Consensus Update on the approach to H. pylori infection in children and adolescents, adopted in 2006 by members of the H. pylori Pediatric Task Force in the U.S.A [10]. We hope to reach a combined NASPGHAN-ESPGHAN consensus before the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition meeting in Brazil in 2008.

BASIC RESEARCH

Peeters published an excellent overview about the peptide ghrelin, related to motilin which has been suggested to have “saginary” effect in H. pylori infection. H. pylori infection could influence ghrelin-secreting cells, and impairs the secretion of histamine, pepsin and gastric acid [11]. Eradicating H. pylori can lead to a rise in plasma ghrelin, which could promote the development of obesity, increasing the risk of reflux disease and subsequent risks of Barrett’s esophagus and esophageal adenocarcinoma. The suggestion that H. pylori-eradication may contribute to the obesity epidemic in industrialized countries is an interesting hypothesis to ponder! Ernst highlighted an article of Velin et al about the essential role of mast cells as mediators in experimental Helicobacter clearance by vaccination because mast cells-deficient mice could not be protected by immunization; this could be changed by reconstituting them with bone marrow-derived mast cells [12,13]. Ceponis and Jones summarized in the Canadian H. pylori Update the current knowledge of specific H. pylori factors. H. pylori infection can modulate signal transduction pathways in multiple host cell types and specific bacterial factors can activate certain cascades in the mucosa. The bacterium can also lead to opposing effects: anti-apoptotic by inducing NF-kB activity and can suppress interleukin (IL)-4 induced signal transduction [14].

PREVALENCE, INCIDENCE AND TRANSMISSION

The prevalence of H. pylori infection is declining in developed countries. Nevertheless, immigrants and indigenous people continue to carry a high burden of

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H. pylori infection and disease in their children. In Canada, the immigrant population comprises 200,000 individuals per year. The prevalence in children undergoing gastrointestinal endoscopy from 1990 to 1994 was 26-43%; it has now decreased to about 5%. Jacobson also highlights the study by Miller (2003), in which adopted children have a seroprevalence of 16%, 20% and 49% respectively. He suggests more studies in children with different geographic, socioeconomic and ethnic backgrounds using validated screening tools to see whether eradication is associated with reduced H. pylori-related diseases or with significant benefit in adulthood 15.

New data on prevalence come from Asia: Nizami found that early colonization in 148 children showed a decreasing trend with increasing age (80% at 1 month of age, 67% at 9 months). The researchers did not, however, study children over 1 year of age 9. Singh et al. determined prospectively the prevalence of H. pylori in 58 children with upper abdominal pain (UAP) and 182 controls. In the UAP-group, the prevalence of H.pylori was 53.4%, in the group children without UAP, 28%. The overall prevalence increased with age; 82% of the children with UAP were negative after eradication, with a further 18% after second eradication therapy. All treated children with UAP remained symptom-free for two years. They concluded to a strong link between H. pylori infection and UAP 16. Alborzi et al. collected stool samples from children from different age groups in Shiraz and found prevalence rates of H. pylori of 82, 98, 88, 89 and 57% in age groups of 9 months, and 2, 6, 10, and 15 years, respectively. There was a significant decrease in the 15 year old teenagers 17. Wong et al. studied the prevalence of H. pylori in symptomatic Chinese children retrospectively from 1997-2004 to assess the impact of an aggressive eradication program. From 159 patients undergoing gastroscopy, 119 had gastritis, 13 had peptic ulcer disease (overall rate of proven H. pylori infection 25.6%). They did not find a significant decrease of overall prevalence (33% in 1997, 27.7% in 2004), but reported that increasing age was significantly associated with a higher risk of infection. Their hypothesis was that eradication efforts were unsuccessful, possibly due to Chinese eating habits (cross infection from sharing chopsticks).

Recently, Rowland et al. published a prospective study of age-specific incidence of H. pylori infection in children between 24 and 48 months of age, by using 13C-urea breath test (13C-UBT). They found a positive test in 28 of 327 index children (8.6%) at baseline assessment; during the next 4 years 20 children became infected. As in previous studies, the infection was acquired at a very young age with a declining risk after 5 years of age. Risk factors were having an infected mother, an infected older sibling, and delayed weaning from a feeding bottle 8.

MOTHER TO CHILD TRANSMISSION

The role of infected mothers has been described in 2002 4 and stated by Konno et al in a 5-year follow-up study of 44 children. They collected gastric juice samples for culture and DNA-analysis from 69 H. pylori-positive mothers. None of the children acquired H. pylori during the first year of life. Five children were tested positive within 5 years by serology and stool antigen test. Strains of the 5 positive children exhibited DNA fingerprinting patterns identical to those of their mothers. In a follow-up of children up to 36 months old using monoclonal stool test, infected mothers were the main source of H. pylori infection of their children, as the mother, being primary carer, has closer contact with the infant than the father in the first year of life 8.

SYMPTOMS

Abdominal pain

The association between chronic abdominal pain and H. pylori infection is still hotly debated.

Tindberg et al investigated the association between type-specific H.pylori infection and gastrointestinal symptoms in a cross-sectional study of Swedish schoolchildren. Infection was investigated by IgG-antibodies in serum and confirmed by immunoblot and UBT. Abdominal pain was reported by 63% of the children and recurrent abdominal pain (RAP) by 13%; 16% were infected; 73% of these children had CagA antibodies and 59% VacA antibodies. The authors did not find a positive association between H. pylori-status and occurrence of abdominal pain: RAP was unrelated to the infection (OR 1.0; 95% CI 0.5-2.1), when adjusted for sex, age and family background. The prevalence of RAP was lower in children with CagA+ and VacA+ infections than among uninfected children 21. Yang et al investigated 1271 children with questionnaires to define RAP or short-term RAP (SRAP) with pain duration from 2 weeks to 3 months. All children with RAP, SRAP or a combination were tested for H. pylori by serology. Prevalence rates of RAP and SRAP were 9.8 and 5.5%, respectively. Children with SRAP had a higher anti-H. pylori seropositivity rate than those with RAP and controls. One year later 71% of the seropositive children became symptom-free, regardless of persistence of H. pylori. Infection was more frequently found in children with SRAP 18.

The subcommittee on chronic abdominal pain reviewed the predictive value of laboratory tests. The authors conclude that the coexistence of abdominal pain and an abnormal test result for H. pylori infection does not necessarily indicate a causal relation between the two 22.
Non-ulcer dyspepsia (NUD)
Kalach et al investigated 101 children older than 6 years with NUD, by endoscopy for epigastric pain in a prospective double-blind study; 26 children were infected. No differences in age or symptom characteristics between infected and non-infected children was found, except for epigastric pain during meals, which was more frequent in non-infected children. They concluded that *H. pylori*-infected NUD-children had no specific symptoms. At the end of 2005 Talley et al published a review on the evaluation of dyspepsia in adults. As is the case in adults, the test-and-treat strategy is not recommended in children with dyspepsia: endoscopy is mandatory in this age group.

Gastroesophageal reflux disease
The question is whether testing for *H. pylori* is necessary in infants with gastroesophageal reflux disease (GERD). Moayyedi reviewed the literature about the association between GER and *H. pylori* infection. His conclusion is that *H. pylori*-induced hypochlorhydria is frequent in adults, but rare in children and that therefore eradication is unlikely to have an important impact on GERD or proton pump inhibitor (PPI) efficacy in this age group. His advice is that children with GERD, diagnosed clinically or by pH studies, do not need to be tested for *H. pylori*, unless they have endoscopy and have proven infection.

As GERD has been suggested as a contributing factor to otitis media, Bitar et al investigated the possibility of a role of *H. pylori* in middle ear disease in children, however, all 28 middle ear fluid cultures and polymerase chain reaction (PCR) were negative; also 13 adenoids were negative for *H. pylori* by PCR. Seven of 18 patients had symptoms suggestive of GERD preceding the study, but this had no impact on the results of the study.

Gastritis
Leung et al emphasized the diagnostic role of macroscopic observation of the gastric mucosa at endoscopy. Ricarte et al studied the prevalence of atrophic gastritis in childhood with this hypothesis. Of 173 children, atrophic mucosa near the antrum-corpus border was present in 16% of the positive children, primarily as pseudo pyloric metaplasia (median age 15 years). As gastric atrophy occurs in infected children living in countries with a high incidence of gastric cancer they recommend that biopsies be taken near the lesser and greater curvature just proximal to the anatomical antrum-corpus border as well.

EXTRADIGESTIVE MANIFESTATIONS
In the pediatric age group the following have been reported: anemia, idiopathic thrombocytopenic purpura (ITP), short stature, diarrhea, food allergy and sudden infant death syndrome, same without sufficient evidence.

Idiopathic thrombocytopenic purpura
Although the same author in an earlier study in 2003 reported an increased incidence of *H. pylori* in patients with chronic ITP, in a prospective study, Jaing et al did not find evidence of an association. Sherman and Lin mentioned the potential for molecular mimicry with antiplatelet antibodies, recognizing the CagA protein of *H. pylori* as a possible explanation for an association. The Canadian group did not include ITP as extradigestive manifestation in the recent guidelines.

Anemia
The Canadian Consensus Group concluded that there is sufficient evidence available to consider unexplained sideropenic anemia as an extradigestive manifestation and to consider test-and-treat strategy in such cases.

One recent study from India reported reduced hematological response to iron supplementation in asymptomatic children with *H. pylori* compared to children without infection. The mean serum ferritin was similar at admission and improved in both groups of children, but infection had a significant adverse effect on response to iron therapy.

Growth
In 2005 two studies have been published about the relationship between growth and *H. pylori* infection: Sood et al compared height, weight and body mass index (BMI) of 97 positive children with dyspeptic symptoms to 160 children with dyspepsia without infection. They found no significant difference between mean weight and height SD score in the infected and not infected group. Mera et al investigated, whether a newly acquired infection affects height and weight within 16 months by performing UBT and anthropometry every 2-4 months. Authors observed a significant decrease in growth velocity during the first 4 months after infection and the children showed no height catch-up. Infected children had a small decrease in weight, in comparison to non-infected children. Their conclusion is that *H. pylori* infection causes a non-transient negative effect on height and weight in Colombian children.

In the Canadian Consensus Report, Sherman and Lin did not find firm evidence for the role of *H. pylori* infection in growth.
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Other reported manifestations such as food allergy, diarrhea and sudden infant death syndrome were not added to the list of extra intestinal symptoms by the Canadian group.

DIAGNOSTIC TOOLS

None of the non-invasive tests are 100% specific and sensitive. 13C-Urea breath test is reliable for detecting infection in children older than 6 years of age but can give false-positive results in younger children 35. There was a small number of very young H. pylori-positive patients in these studies, making it difficult to validate new diagnostic tests in this age group.

Mégraud et al reported in a multinational study on four non-invasive tests that UBT had the best sensitivity in all age groups, followed by serology, stool antigen test and antibody detection in urine. In all tests, except the stool test, better sensitivity was observed with increasing age. The urine office test exhibited a very low sensitivity 36. The Canadian Consensus group concluded that UBT is currently the best available noninvasive diagnostic test in children and published a list of variables that may influence the results of the test 37,38.

Recently Nugalieva et al raised attention to the problem of false-positive UBT and recommended confirmation of a single positive test in low-prevalence populations by using a test that measures a different parameter (UBT confirmed by stool test) 39. The polyclonal antibody-based stool antigen test (HpSA) is not as reliable as UBT, neither pre-treatment nor after eradication 39, but monoclonal stool antigen tests perform as well as UBT. The Canadian group judged that it was too premature to recommend stool antigen testing as an alternative to UBT, but in settings where the breath test is not available for children, the monoclonal test is an excellent alternative to assess H. pylori status pre-and post-treatment 39. Raguza et al evaluated 127 children to compare the accuracy of a modified polyclonal stool antigen test with the gold standard. However, there were no H. pylori positive infants below the age of 2 years in his study. Three patients showed false-positive results and two false-negative results for the HpSA. The sensitivity of the HpSA test was higher in children in the age of 6–18 years (100%) than in 2–6 years (80%). The specificity was respectively 95-100% and 96.4% 39.

Haggarty et al also used the polyclonal HpSA test in a study of stool samples from children at two time points, 3 months apart; PCR was performed on all 26 pairs reverting from positive to negative (transient positives), all four persistent positive pairs and 10 randomly selected persistent antigen-negative pairs. In 15 of 26 transient positive stools H. pylori was sequenced and identified in 12 and other

Helicobacter spp. were identified in three. They suggested that transient positive stool tests are common and represent H. pylori in majority of cases; however some positive stools may represent other Helicobacter species 40.

Hauser et al compared a multi-step polyclonal versus one-step monoclonal enzyme immunoassay in stool with 13C-UBT in 43 children; 18 children were positive (positive UBT). The polyclonal stool test had a comparatively good sensitivity, but lower specificity compared to UBT. The one-step monoclonal rapid test also had a comparable sensitivity and specificity, when a weakly positive test (visual interpretation) was considered negative 40.

Kalach et al tested the rapid monoclonal stool test in 128 children and observed the highest performance of the test in children older than 10 years (sensitivity 100%), in contrast with 75% in those younger than 5 years; in this study he found 11 discordant results of the test compared with gold standard 40.

Antos et al evaluated a novel rapid monoclonal one-step immunochromatographic assay for detection of stool antigen and concluded that this quick test shows a good interobserver agreement, but equivocal results in 5% 41. More studies with quick tests in stools are needed; however, in settings without possibilities for UBT or enzyme immunoassay, the immunochromatographic test could become an alternative to assess H. pylori status pre- or post-treatment in children 41.

A study from Thailand evaluated the performance of a rapid office-based serologic test (Assure™, Genelabs Diagnostics, Singapore) and the immunoblotting for the diagnosis in symptomatic children. The sensitivity of the test was 96%, specificity 94.6% versus immunoblot, 100 and 96.2% respectively, so the test seems to be reliable for the diagnosis of infection in Thai children 42.

The above Assure test was also evaluated in 130 children by Pelerito et al. They found a lower sensitivity (75.7%) and a specificity of 95.0%, which increased to 98.6 and 95% when a longer reading time of 45 minutes was considered 43. The use of serology-based tests could not be advocated by the Canadian Consensus group anymore because of their low accuracy in young children. In a study from Lithuania a seroprevalence of 57% was found; following gold standard it was 79% 44.

Invasive diagnostic methods require endoscopic biopsies and include rapid urease testing, histology and culture. When used in combination, these tests are still considered the “gold standard” for the diagnosis of H. pylori in children. The added advantage of this approach is the detection of upper gastrointestinal pathologies including complications of the infection, such as nodular gastritis, peptic ulcer disease, gastric cancer and MALT-lymphoma. Biopsies are necessary for determination of antibiotic resistance and virulence factors 45,46.
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TREATMENT

Based on the data in pediatric literature and in adults the Canadian Consensus group decided that the recommended first-line eradication therapy should include a PPI and clarithromycin, combined with either amoxicillin or metronidazole. Higher eradication rates may be achieved by a longer treatment regimen (triple therapy 14 days instead of 1 week) 46.

A randomized clinical trial from Italy showed that a novel 10-day sequential treatment (omeprazole plus amoxicillin for 5 days, followed by omeprazole plus clarithromycin plus tinidazole for another 5 days) achieves a significantly higher eradication rate than standard triple therapy (omeprazole, amoxicillin and metronidazole) for one week 47.

Khurana et al summarized data from studies that have examined treatment efficacy, safety, drug resistance and reinfection rates. Treatment efficacy was reduced in the presence of metronidazole and/or clarithromycin resistance. Resistance to metronidazole and/or clarithromycin is common and no therapy has yet been identified as safe and consistently effective to eradicate H. pylori infection 48.

Elitsur et al assessed the resistance rate against clarithromycin in 16 positive children by the FISH technique in gastric biopsies; the primary resistance rate in this small group was very high (31-38%) 49; Boyanova et al found primary clarithromycin resistance in 12.5% and metronidazole resistance in 15% of Bulgarian children 50. Recently Koletzko et al assessed the bacterial resistance in children from 14 European countries. She reports an overall resistance to clarithromycin of 24%, to metronidazole 25%; and to amoxicillin 0.6%, the last being very low 51.

A Russian group investigated failure of triple therapy; patients were randomized to receive a 2-week course of bismuth, amoxicillin with either nifuratel or furazolidone plus omeprazole. Both schemes produced good cure rates, but nifuratel is preferred because of lower frequency of side-effects. Antibiotics susceptibility tests have not been carried out in this study 52.

The Canadian group discussed whether treatment of H. pylori in childhood will alter the two-to sixfold increased risk of developing gastric cancer among infected patients. A population-based test-and-treat policy in children is not justified, except in groups with a high risk of developing gastric cancer (Japanese or those with a strong positive family history) regarding negative cost-benefit analysis 53.
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