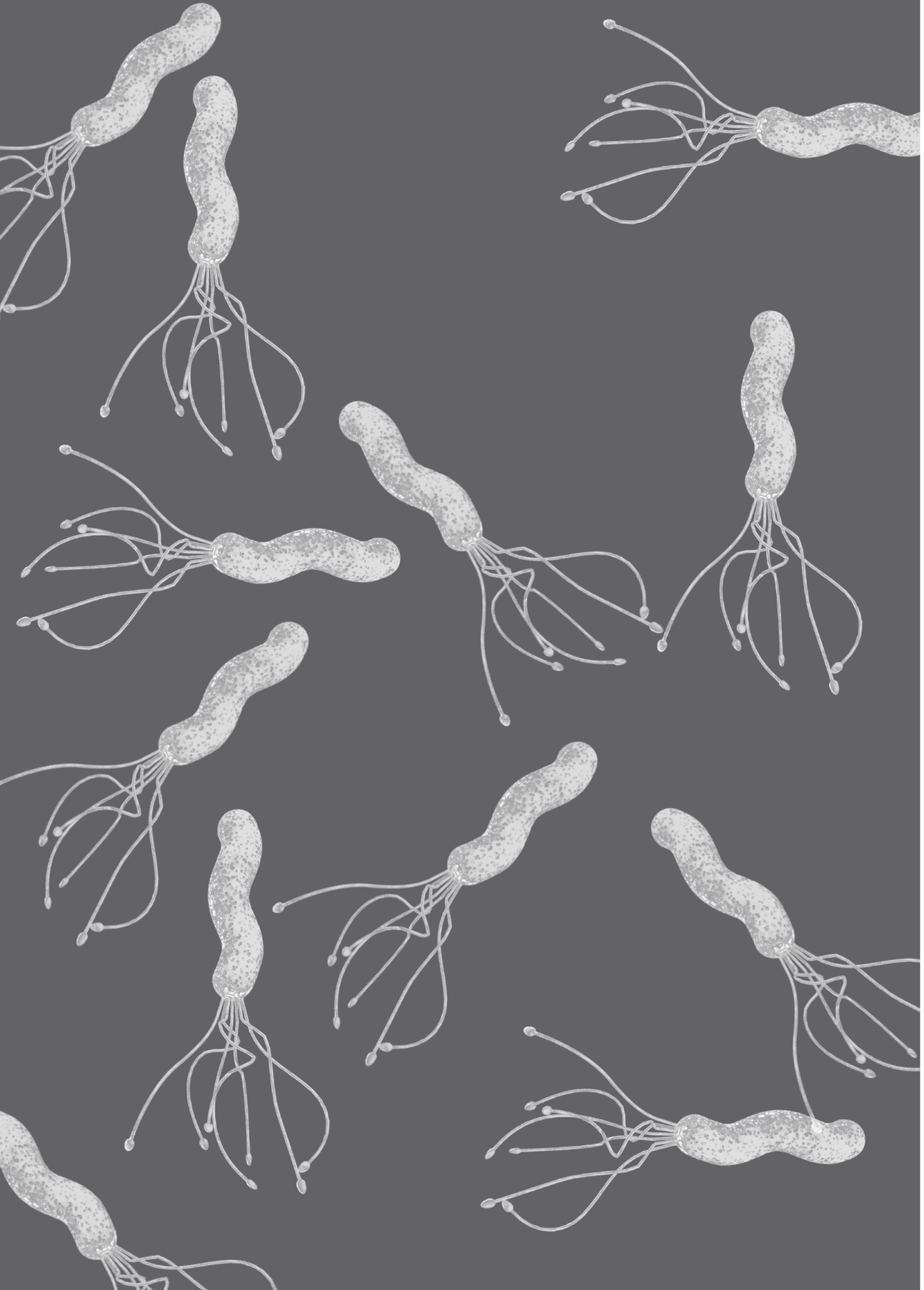
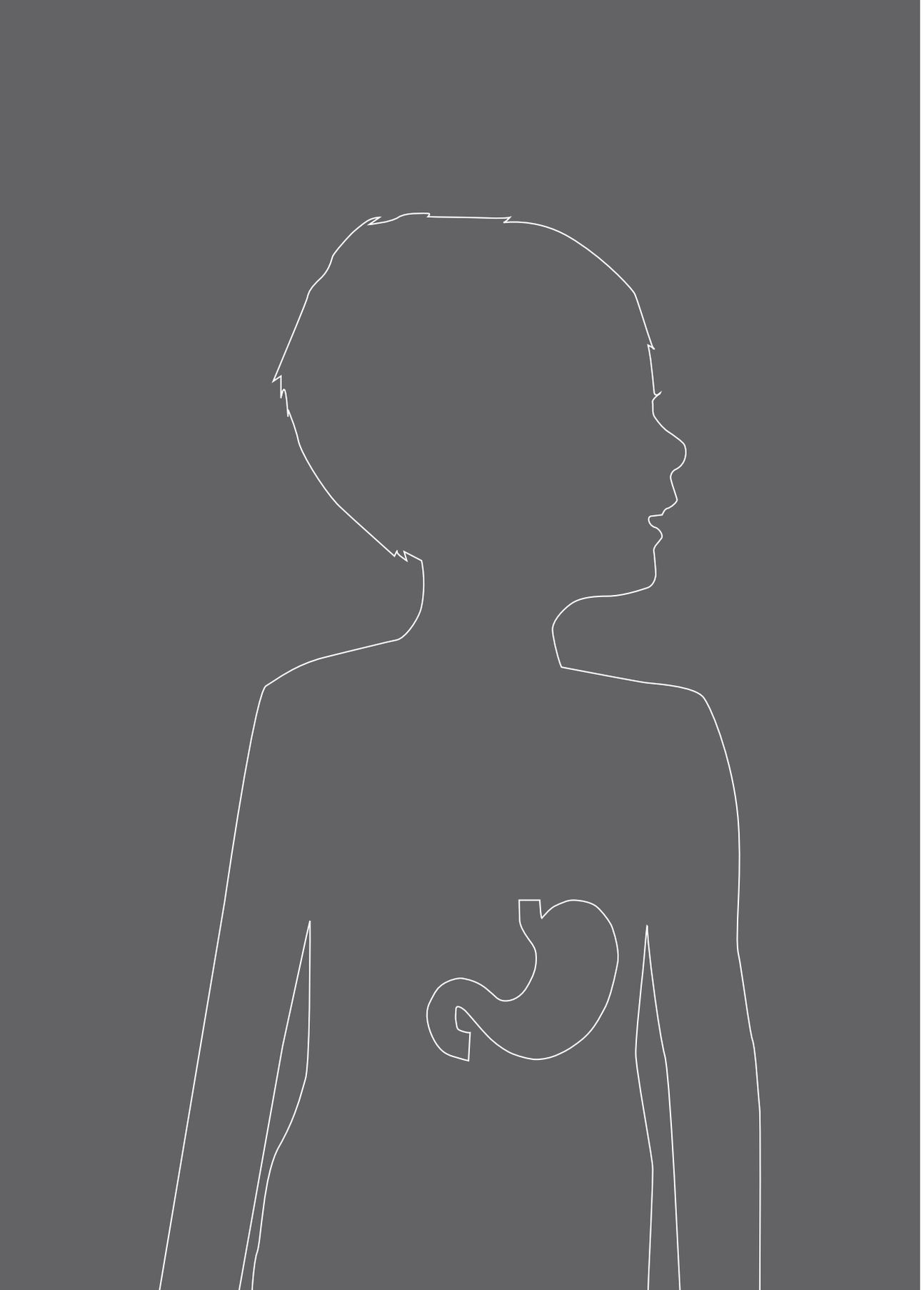


SECTION A

REVIEWS



CHAPTER 2

Helicobacter pylori infection in pediatrics 2005-2006

P.E.C. Mourad-Baars and S. Chong

Helicobacter 2006; 11 (Suppl 1): 40-45

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.

Keywords: ***Helicobacter pylori***; pediatrics; recurrent abdominal pain, stool antigen test.

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

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 [16]. 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 [17]. 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 [18].

Wong *et al* [19] 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 ^{13}C-urea breath test (^{13}C-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 [9].

MOTHER TO CHILD TRANSMISSION

The role of infected mothers has been described in 2002 [4] and stated by Konno *et al* [5] 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 school-children. 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 [20].

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 [21].

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* [23] investigated 100 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 dypepsia: endoscopy is mandatory in this age group [24].

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 protonpump 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 [25].

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 [26].

Gastritis

Leung *et al* emphasized the diagnostic role of macroscopic observation of the gastric mucosa at endoscopy [27]. Ricuarte *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 [28].

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, some without sufficient evidence [29].

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 [30,31]. 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 [29].

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 [32].

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 [33]. 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 [34].

In the Canadian Consensus Report, Sherman and Lin did not find firm evidence for the role of *H. pylori* infection in growth [29].

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. ^{13}C-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 [10]. 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 [35].

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 [10,36].

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) [37].

The polyclonal antibody-based stool antigen test (HpSA) is not as reliable as UBT, neither pre-treatment nor after eradication [35], 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 [36]. 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% [38].

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 [39].

Hauser *et al* compared a multi-step polyclonal versus one-step monoclonal enzyme immunoassay in stool with ^{13}C-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 [41].

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% [42].

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 [36].

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 [43].

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 [44].

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% [45].

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 [46,47].

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) [10].

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 [48].

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 [49].

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%) [50]; Boyanova *et al* found primary clarithromycin resistance in 12.5% and metronidazole resistance in 15% of Bulgarian children [51]. 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 [52].

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 [53].

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 [54].

REFERENCES

1. Parsonnet J. Clinician-Discoverers- Marshall, Warren, and H.pylori. *N Engl J Med* 2005;353:2421-3
2. Zetterström R. The Nobel Prize in 2005 for the discovery of *Helicobacter pylori*: Implications for child health. *Acta Paediatrica* 2006;95:3-5
3. Kuehn BM. Nobels Honor Research on Ulcer Microbe, "Green" Drug Production Method. *JAMA* 2005;294:2289-90
4. Rothenbacher D, Winkler M, Gonser T, Adler G, Brenner H. Role of infected parents in transmission of *Helicobacter pylori* to their children. *Pediatr Infect Dis J* 2002;21:674-9
5. Konno M, Fujii N, Yokota S, Takahashi M et al. Five-Year Follow-Up Study of Mother-to-Child Transmission of *Helicobacter pylori* Infection Detected by a Random Amplified Polymorphic DNA Fingerprinting Method. *J.Clin. Microbiol.* 2005; 43:2246-50
6. Kivi M, Johansson AL, Reilly M, Tindberg Y. *Helicobacter pylori* status in family members as risk factors for infection in children. *Epidemiol Infect.* 2005; 133:645-52
7. Kivi M, Johansson ALV, Salim A, Tindberg Y, Reilly. Accomodation of additional non-randomly sampled cases in a study of *Helicobacter pylori* infection in families. *Statistics in Medicine* 2005;24:4045-54
8. Weyerman M, Adler G, Brenner H, Rothenbacher D. The Mother as Source of *Helicobacter pylori* Infection. *Epidemiology* 2006;17: 1-3
9. Rowland M, Daly L, Vaughan M, Higgins A, Bourke B. Age-specific Incidence of *Helicobacter pylori*. *Gastroenterology* 2006;130:65-72
10. Jones NL, Sherman P, Fallone CA, Flook N, Smaill F, Veldhuyzen van Zanten S, Hunt R, Thomson A. Canadian Helicobacter Study Group Consensus Conference: Update on the approach to *Helicobacter pylori* infection in children and adolescents—an evidence-based evaluation. *Can J Gastroenterol* 2005;19;7;399-408
11. Peeters TL. Ghrelin: a new player in the control of gastrointestinal functions. *Gut* 2005;54:1638-49
12. Ernst PB. Understanding Immunity to *Helicobacter pylori*: Unraveling the Riddle, Wrapped in a Mystery, Inside an Enigma. *Gastroenterology* 2005;129:380-3
13. Ernst PB, Peura DA, Crowe SE. The translation of *Helicobacter pylori* Basic Research to Patient Care. *Gastroenterology* 2006;130:188-206
14. Ceponis PJM, Jones NL. Modulation of host cell signal transduction pathways by *Helicobacter pylori* infection. *Can J Gastroenterol* 2005;19;415-20
15. Jacobson K. The changing prevalence of *Helicobacter pylori* infection in Canadian children: Should screening be performed in high-risk children? *Can J Gastroenterol* 2005;19;7;412-4
16. Nizami SQ, Bhutta ZA, Weaver L, Preston T. *Helicobacter pylori* Colonization in Infants in a Periurban Community in Karachi, Pakistan. *J Pediatr Gastroenterol Nutr* 2005;41:191-4
17. Singh M, Prasad KN, Yachcha K, Saxena A, Krishnani N. *Helicobacter pylori* infection in children:

prevalence, diagnosis and treatment outcome. *Roy Soc Trop Med Hyg* 2006;100: 227-33
18. Alborzi A, Soltani J, Pourabbas B, Oboodi B, Haghighat M, HayatiM, Rashidi M. Prevalence of *Helicobacter pylori* infection in children (south of Iran). *Diagn Microbiol Infect Dis* 2006;54:259-261
19. Wong KY, Chung PHY, Lan LCL, Lin SCL, Tam PKH. Trends in the prevalence of *Helicobacter pylori* in symptomatic children in the area of eradication. *J Ped Surgery* 2005;40:1844-7
20. Tindberg Y, Nyrén O, Blennow M, Granstrőm M. *Helicobacter pylori* Infection and Abdominal Symptoms Among Swedish School Children. *J Pediatr Gastroenterol Nutr* 2005;41:33-38
21. Yang YJ, Sheu BS, Lee SC, Wu JJ. Short-term recurrent abdominal pain related to *Helicobacter pylori* infection in children. *J Gastroenterol Hepatol* 2005; 20(3): 395-400
22. Di Lorenzo C et al. Subcommittee on Chronic Abdominal Pain. Chronic Abdominal Pain in Children. *Pediatrics* 2005;115:370-81
23. Kalach N, Mention K, Guimber D, Michaud L, Spyckerelle C, Gottrand F. Helicobacter pylori Infection Is Not Associated With Specific Symptoms in Nonulcer-Dyspeptic Children. *Pediatrics* 2005;115:17-21
24. Talley NJ, Vakil NB, Moayyedi P.American Gastroenterological Association Medical Position Statement: Evaluation of Dyspepsia. *Gastroenterology* 2005;129:1753-5
25. Moayeddi P. Should we test for *Helicobacter pylori* before treating gastroesophageal reflux disease? *Can J Gastroenterol* 2005;19;7;425-7
26. Bitar M, Mahfouz R, Soweid A, Racoubian E, Ghasham M, Zaatari G, Fuleihan N. Does *Helicobacter pylori* colonize the nasopharynx of children and contribute to their middle ear disease? *Acta Oto-Laryngologica* 2006;126:154-9
27. Leung WK, Chan FKL, Graham DY. Ulcers and Gastritis. *Endoscopy* 2006;38:2-4
28. Ricuarte O, Gutierrez O, Cardana H, Kim JG, Graham DY, El-Zimaity HMT. Atrophic gastritis in young children and adolescents. *J Clin Pathol* 2005;58: 1189-93
29. Sherman PM, Lin FYH. Extradigestive manifestations of *Helicobacter pylori* infection in children and adolescents. *Can J Gastroenterol* 2005;19:421-4
30. Jaing TH, Yang CP, Hung IJ et al. Efficacy of *Helicobacter pylori* eradication on platelet recovery in children with chronic idiopathic thrombocytopenic purpura. *Acta Paediatr* 2003;92:1153-57
31. Jaing T-H, Tsay P-K, Hung I-J, Chiu C-H et al. The Role of *Helicobacter pylori* Infection in Children With Acute Immune Thrombocytopenic Purpura. *Pediatr Blood Cancer* 2005;1-3
32. Mahalanabis D, Islam MA, Shaik S, Chakrabarty M et al. Haematological response to iron supplementation is reduced in children with asymptomatic *Helicobacter pylori* infection. *Br J Nutr.*2005; 94:969-75
33. Sood MR, Joshi S, Akobeng AK, Mitchell J, Thomas AG. Growth in children with *Helicobacter pylori* infection and dyspepsia. *Arch Dis Child* 2005;90:1025-28
34. Mera RM, Correa P, Fontham EE, Reina JC, Pradilla A et al. Effects of a new *Helicobacter pylori* Infection on Height and Weight in Colombian Children. *Ann Epidemiol* 2006;16:347-51
35. Megraud F, on behalf of the European Paediatric Task Force on *Helicobacter pylori.* Comparison of non-invasive tests to detect *Helicobacter pylori* infection in children and

adolescents: results of a multicenter European study. *J Pediatr* 2005;146:198-203
36. Koletzko S. Noninvasive diagnostic tests for *Helicobacter pylori* infection in children. *Can J Gastroenterol* 2005;19:433-9
37. Nugalieva ZZ, Opekun AR, Graham DY. Problem of distinguishing false-positive tests from acute or transient *Helicobacter pylori* infections. *Helicobacter* 2006;11:69-74
38. Raguza D, Granato CFH, Kawakami E. Evaluation of the Stool Antigen Test for *Helicobacter pylori* in Children and Adolescents. *Dig Dis Sci* 2005;50:453-7
39. Haggarty TD, Perry S, Sanchez L, Perez-Perez G, Parsonnet J. Significance of Transiently Positive Enzyme-Linked Immunosorbent Assay Results in Detection of *Helicobacter pylori* in Stool Samples from Children. *J. Clin. Microbiol.* 2005; 43:2220-3
40. Hauser B, Wybo I, Tshibuabua G, Pierard D, Vandenplas Y. Multiple-step polyclonal versus one-step monoclonal enzyme immunoassay in the detection of *Helicobacter pylori* antigen in the stools of children. *Acta Paediatrica* 2006;95: 297-301
41. Kalach N, Nguyen VB, Bergeret M, Boutros N, Dupont C, Raymond J. Usefulness and influence of age of a novel rapid monoclonal enzyme immunoassay stool antigen for the diagnosis of *Helicobacter pylori* infection in children. *Diagn Microbiol Inf Dis* 2005;52:157-60
42. Antos D, Crone J, Konstantopoulos N, Koletzko S. Evaluation of a Novel Rapid One-Step Immunochromatographic Assay for Detection of Monoclonal *Helicobacter pylori* Antigen in Stool Samples from Children. *J Clin Microbiol* 2005;43:2598-2601
43. Treepongkaruna S, Nopchinda S, Taweewongsounton A, Atisook K et al. A Rapid Serologic Test and Immunoblotting for the Detection of *Helicobacter pylori* Infection in Children. *J Trop Pediatric*s 2006; Jan 9 (Epub ahead of print)
44. Pelerito A, Oleastro M, Lopes AI, Ramalho P, Cabral J, Monteiro L. Evaluation of rapid Assure® *Helicobacter pylori* for diagnosis of H pylori in pediatric population. *J Microbiol Methods* 2006 (in press)
45. Janulaityte-Gunther D, Kucinskiene R, Kupcinskas L, Pavilonis A et al. The humoral immunoreponse to *Helicobacter pylori* infection in children with gastrointestinal symptoms. *FEMS Immunology and Medical Microbiology* 2005; 44;205-12
46. Kato S, Sherman pM. What is new related to *Helicobacter pylori* Infection in children and teenagers? *Arch Pediatr Adolesc Med.* 2005;159:415-21
47. Huynh HQ. Invasive tests for *Helicobacter pylori* in children. *Can J Gastroenterol* 2005;19:429-32
48. Francavilla R, Lionetti E, Castellaneta SP, Magista AM et al. Improved Efficacy of 10-day Sequential Treatment for *Helicobacter pylori* Eradication in Children: A Randomized Trial. *Gastroenterology* 2005;129:1414-9
49. Khurana R, Fischbach L, Chiba NC, Veldhuyzen van Zanten S. An update on anti-*Helicobacter pylori* treatment in children. *Can J Gastroenterol* 2005;19: 441-5
50. Elitsur Y, Lawrence Z, Rüssmann H, Koletzko S. Primary Clarithromycin Resistance to *Helicobacter pylori* and Therapy Failure in Children: The Experience in West Virginia. *J Pediatr Gastroenterol Nutr.* 2006;42:327-8

51. Boyanova L, Nikolov R, Lazarova E, Gergova G, Katsarov N, Kamburov V, Spassova Z, Derejian S, Jelev C, Mitov I, Krastev Z. Antibacterial resistance in *Helicobacter pylori* strains isolated from Bulgarian children and adult patients over 9 years. *J Med Microbiol* 2006;55:65-8
52. Koletzko S, Richy F, Bontems P, Crone J, Kalach N, Monteiro ML,Gottrand F et al. Prospective multicentre study on antibiotic resistance of *Helicobacter pylori* strains obtained from children living in Europe. *Gut* 2006 (in press) (on line April 7, 2006)
53. Nyevitch AA, Shcherbakov PL, Sataev VU, Khasanov RSh. Al Khashash R, Tuygunov MM. *Helicobacter pylori* eradication in childhood after failure of initial treatmentr: advantage of quadruple therapy with nifuratel to furazolidone. *Aliment Pharmacol Ther* 2005;22:881-7
54. Bourke B. Will treatment of *Helicobacter pylori* infection in childhood alter the risk of developing gastric cancer? *Can J Gastroenterol* 2005;19:409-11