REVIEW ARTICLE

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Helicobacter pylori Infection and Eradication in Paediatric Patients

Hoda M. Malaty

Department of Medicine, Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas, USA

Contents

Abstract

Helicobacter pylori is now recognised to be typically acquired during childhood. Studies also indicate that the infection is frequently lost in childhood; however, it is still unclear whether this is related to the use of antibacterials, the natural history of the infection, or both. *H. pylori* colonises gastric mucosa and is causally related to chronic gastritis and peptic ulcer disease in both children and adults.

Successful eradication of *H. pylori* has resulted in the healing of duodenal ulcers and the lowering of the ulcer relapse rate in children. Therapy to cure the infection should be started in all children with peptic (duodenal or gastric) ulcer who are still infected. The ideal anti-*H. pylori* regimen should be safe, cheap, easy to comply with, well tolerated by children and able to achieve a high cure rate. Although US data are lacking, it is anticipated that the treatment regimen for children should be similar to that in adults (a triple therapy regimen that combines a proton pump inhibitor with 2 antimicrobial agents for 14 days).

It is inappropriate to prescribe anti-*H. pylori* therapy without a firm diagnosis. The use of multiple antibacterials in a paediatric patient with an ulcer but without *H. pylori* infection cannot provide any benefit to the patient or the community. Such an approach only provides the possibility for adverse effects, for example development of antibacterial resistance among bystander bacteria.

It is very important to confirm the diagnosis of *H. pylori* infection. The [^{13}C]urea breath test is the noninvasive method of choice to determine *H. pylori* status in children and the ideal test for post-therapy testing. There is a need for post-therapy confirmation because of the likelihood of poor outcome for some treatment regimens, which is why post-therapy testing should be the standard of care.

There is weak and inconsistent evidence of an association between *H. pylori* infection and recurrent abdominal pain (RAP) in children, in part because of the unclear definition of RAP in the literature. Therefore, there is still considerable debate regarding the treatment of infected children with RAP.

Although *Helicobacter pylori* infection is now recognised to be typically acquired during childhood,[1-6] the natural history of the infection remains poorly understood. *H. pylori* is present in most cases of children with primary gastritis, implicating *H. pylori* as the aetiological agent in chronic antral gastritis in children.[7,8] Although the prevalence of peptic ulcer disease in children is very low, the association between *H. pylori* infection and peptic ulcer disease has been established in children as in adults.[8] Because *H. pylori* infection is most prevalent during childhood, there is a need for all physicians to become knowledgeable regarding the infection. The focus of the present article is on the epidemiology of *H. pylori* infection, symptoms and clinical manifestations associated with *H. pylori*, and diagnosis and management of the infection in children.

1. Epidemiology

H. pylori infection is a chronic infection. Early data suggests that, once acquired, it is often lifelong. The prevalence of *H. pylori* in a community depends on the rate of acquisition (i.e. incidence of the infection) and the rate of loss of the infection. Among children, the rate of acquisition of *H. pylori* varies between, and within, populations.[9-14] It has been established that the prevalence of *H. pylori* is inversely related to socioeconomic status,[9,12,15-17] with the major variable being socioeconomic status during childhood, the period of highest risk. Attempts to understand the different rates of infection in defined groups have focused on differences in socioeconomic status defined by occupation, family income level and living conditions. Each of these variables measures a different component of the socioeconomic complex.

Within the US, studies in a cohort of Blacks and White Hispanics examined the relationship between current and childhood socioeconomic status and the prevalence of *H. pylori* infection.[1] There was an inverse correlation between socioeconomic status during childhood and the prevalence of *H. pylori* infection, irrespective of the present social class. For populations in which the social class is more or less homogeneous, such as in China and Russia, the density of living conditions has been shown to be the most significant risk factor.[3,10] A study of the effect of childhood conditions in a sample of monozygotic and dizygotic twins, reared together or apart in different socioeconomic status, revealed that the strongest effects on the acquisition of *H. pylori* were the density of living and low household income during childhood.[18]

Cross-sectional studies have consistently indicated a gradual increase in *H. pylori* seroprevalence with age,[9-16] which has been interpreted as a reflection of the fall in the rate of acquisition in successive generations of children as sanitation improved and standards of living increased.[19,20] It is now apparent that the decrease in the prevalence of *H. pylori* infection in industrialised countries is related to improved living conditions during childhood.[5] Although *H. pylori* infection is a chronic, and possibly a lifelong, infection,[20] spontaneous elimination of the infection has been reported.[2] A recent longitudinal study that examined Black and White children living in the same community and attending the same schools over a 12-year period found that the rates of acquisition and disappearance of *H. pylori* were identical for the total population.[2] However, there were differences between the 2 races as more Black children remained infected while more White children lost the infection during the observation period. The study suggested that the higher rate of acquisition and the lower rate of loss of infection among Black children might be because of differences in access to healthcare facilities or a more intense exposure. Another 9-year

follow-up study conducted on children and adults from a typical mountain village in Japan also found that the rate of disappearance was greater than the rate of acquisition.[5] The study reported that there was a fall in the prevalence during the observation period which did not reflect changes in the rate of acquisition but rather the higher rate of loss of infection. These changes may be related to changes in medical practices leading to the more frequent use of antimicrobials for other common infections.

The human is the only known host reservoir for *H. pylori* infection.[20] The mode of transmission is probably person-to-person, but whether the route is oral-oral or faecal-oral transmission is still unclear.[21-28] *H. pylori* can reach the oral cavity via reflux of gastric juice and can be found in saliva and dental plaque;[29,30] however, dental workers are not at high risk of acquiring the infection.[31] The organism may also survive in faeces[32-33] which could be the vehicle of transmission through anything contaminated by them (e.g. food or water). Studies have reported that unclean water supplies in Peru[34] and consumption of fresh vegetables grown using human wastes for fertiliser in Chile[35] have both been associated with acquisition of *H. pylori* infection. Although water-borne sources of *H. pylori* infection may be important in some developing countries,[34] it does not play a significant role in transmission of the infection in developed countries.[16]

Genetic differences in susceptibility to acquire *H. pylori* infection and outcome of the infection have also been reported.[36-38] A study on monozygotic and dizygotic twins investigated the importance of genetic and environmental factors on the acquisition of *H. pylori*.[36] The results of the twin study confirmed that there was a genetic influence for susceptibility to acquire the infection, but that environmental factors are more important.

There are conflicting results regarding the relationship between *H. pylori* infection, nutritional factors and growth in children. A study from Colombia indicated that children infected with *H. pylori* were significantly shorter than their uninfected peers.[39] However, 2 well designed studies, 1 from Nicaragua[40] and the other from South Africa,[41] failed to confirm such associations. Literature on *H. pylori* and breast-feeding practices is limited. Few studies have hinted at the protective effect of breast milk on acquiring *H. pylori* infection.[42,43] A prospective study of infants from a Gambian village found that a high level of immunoglobulin A in mothers' breast milk may protect against infection during the first year of life.[42] A very recent study from the US has provided additional evidence in support of an association between breast-feeding practices and the prevention of acquisition of *H. pylori* infection (Malaty HM, Graham DY, Logan ND, unpublished data). Although in that study breast-feeding practice was significantly associated with the mother's education, children who were breast-fed consistently had a lower rate of *H. pylori* infection than children who were not breast-fed, regardless of the mother's education (fig. 1).

2. Clinical Manifestations

Primary gastritis is uniformly associated with *H. pylori* infection, which implicates *H. pylori* as an aetiological agent in chronic gastritis in adults and children.[7,8] As in adults, most infected children who have gastritis are asymptomatic. A study from Arkansas reported a 30% infection rate among

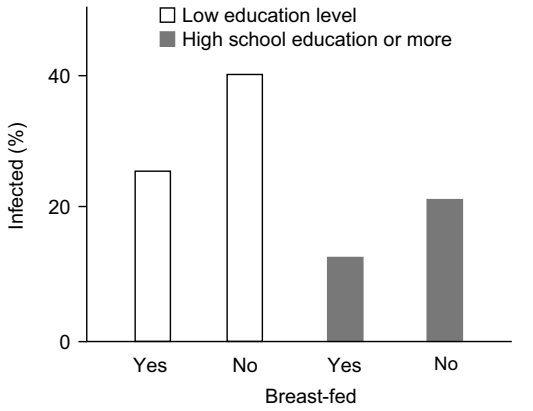

Fig. 1. Effects of maternal factors on *Helicobacter pylori* infection in children. Each pair of bars represents the prevalence of *H. pylori* infection in children in relation to breast-feeding practices and maternal education (Malaty HM, Graham DY, Logan ND, unpublished data).

healthy children with no upper gastrointestinal symptoms.[12] The endoscopic appearance of gastric mucosa in children with *H. pylori* colonisation can vary from completely normal to erosions, ulceration and nodularity.[44]

H. pylori is also an established organism for both duodenal ulcer and gastric ulcer disease in children and adults.[8,9,20] However, among infected children with *H. pylori,* peptic ulcer disease is uncommon.[45] There is a distinction between primary and secondary ulcer in children. Secondary ulcers are usually caused from severe stress or medication and patients usually present with acute haematemesis. Primary ulcer is very rare, particularly before adolescence, and mostly occurs in the duodenum.[45] *H. pylori* infection accounts for 90 to 100% of paediatric duodenal ulcers.[8] Kilbridge et al.[46] reported an 89% infection rate among 9 paediatric patients with duodenal ulcers. If *H. pylori* is not effectively treated, duodenal ulcers in infected children can persist or relapse with long term morbidity.[47,48] There are no significant studies that have reported an association between *H. pylori* and gastric ulcer disease in children because of the very low rate of gastric ulcers in this population. A study conducted by Prieto et al.[49] investigated 270 children who underwent endoscopy; 12 had gastric ulcers, of whom 75% were infected with *H. pylori*.

Worldwide, *H. pylori* infection may affect up to 50% of children with recurrent abdominal pain (RAP).[50,51] Apley's criteria for RAP are still considered the gold standard, defining it as 'the occurrence of 3 separate pain episodes over a 3-month period which are severe enough to interfere with normal activity'.[52] RAP affects approximately 10 to 15% of children and adolescents.[53] However, there is weak and inconsistent evidence of an association between RAP and *H. pylori* infection. Although a study from Germany[54] found no difference regarding abdominal pain between infected and noninfected children, a study from Peru[55] found a significant association between *H. pylori* infection and RAP among young children enrolled in the study. A study that evaluated 80 children with RAP reported a 54% infection rate among these children.[51] At 2 months after anti-*H. pylori* therapy, they observed that all of the children cured of *H. pylori* became asymptomatic compared with those with persistent infection who still had symptoms. Interestingly, another study reported that a course of triple therapy improved RAP symptoms significantly in children, irrespective of the elimination of the infection.[56]

Because of the conflicting results of the association between RAP and *H. pylori* in childhood, there is considerable debate regarding the treatment of infected children with RAP, and as yet there are no uniform guidelines regarding this issue. Therefore, clinicians and primary care physicians should make all possible efforts to convey to parents that RAP in their child may have a multifactorial origin and that *H. pylori* infection may be only one of the possible contributing elements to their symptoms. Testing for *H. pylori* infection in children with RAP is appropriate only when treatment is planned if the test is positive. Well controlled multicentre prospective studies on eradication of *H. pylori* from infected children with RAP, with long term follow-up, are required to answer these questions.

3. Diagnostic Methods

The link between *H. pylori* and a number of important gastrointestinal diseases prompted development of a variety of methods to detect the presence of the infection. The same tests to diagnose *H. pylori* infection in adults are applied to children. Diagnostic tests for *H. pylori* can be categorised into 2 groups; noninvasive tests and invasive tests that require endoscopy. As in adults, the gold standard procedure for the diagnosis of *H. pylori* infection is the histological examination of mucosal biopsies using special stains (Diff-Quick, EL-Zimaity or Genta stains).[57,58] An additional specimen could be taken, during the endoscopy procedure, from the greater curvature of the prepyloric antrum for rapid urease testing ('CLO Test'). Obtaining gastric biopsies requires the child to have an endoscopy procedure under deep sedation or general anaesthesia. Although a study from Ireland reported concerns

regarding the small biopsy specimen obtained from paediatric endoscopy,[7] others have reported that biopsy size was not as critical for the diagnosis of *H. pylori* infection.[59]

Noninvasive tests for the diagnosis of *H. pylori* infection are desirable in the paediatric setting. However, these tests cannot distinguish between *H. pylori* gastritis and peptic ulcer disease. Serological tests and the urease breath test fall into this category.

Laboratory-based immunoglobulin G (IgG) tests are typically done using multiwell enzyme-linked immunosorbent assays (ELISA) [e.g. 'HM-CAP'], which have proven to be accurate in symptomatic children.[60] ELISA is a technique that measures IgG antibodies to *H. pylori* and is an indicator of current or past infection. However, there is still an argument for its use as a screening test to preselect patients for endoscopy. There are also a number of rapid office-based IgG kits using serum, including 'QuickVue' and 'FlexSure HP'. Rapid whole blood–based IgG tests have also become available but their sensitivity and specificity may be lower than those of serum-based methods.[61] Although the rapid tests are reliable in adults, their use in children remains controversial because of their low sensitivity.[61,62] Children who have recently acquired *H. pylori* will test negative in serological tests because of the delay in developing a sufficient humoral immune response.[61] Several studies are still investigating the validation of tests based on measuring antibodies in children.

Attempts have been made to provide diagnostic testing that does not require blood sampling. The [^{13}C]urea breath test is the noninvasive method of choice to determine *H. pylori* status in both children and adults.[63,64] This test is based upon the urease activity of the organism, which splits CO_2 from ingested urea. Ingestion of labelled urea allows for the labelled CO_2 produced in this reaction to be detected in the breath. The [^{13}C]urea breath test is nonradioactive and it is an easy and safe test to perform in children. Klein et al.[65] recently determined a single cutoff value for children of all ages by calculating the urea hydrolysis rate (UHR) independently of the differences in anthropometric measurements.

4. Management

Several different regimens have been evaluated for the treatment of *H. pylori* infection in adults, but to date there is no standard treatment or guidelines for the management of *H. pylori* infection in children. It is still debatable whether treating infected asymptomatic children is beneficial, since the reinfection rate and the exact age of acquisition of *H. pylori* infection have not been identified. However, therapy to cure the infection should be started in all children with peptic (duodenal or gastric) ulcer who are still infected. Successful eradication of *H. pylori* with antibacterial therapy has resulted in the cure of duodenal ulcers and lowering of the ulcer relapse rate in children.[66,67] The ideal anti-*H. pylori* regimen should be safe, cheap, easy to comply with, well tolerated by children and able to achieve a high cure rate.

Studies involving children have investigated different treatment regimens (monotherapy and dual or triple therapies) for durations ranging from 1 to 6 weeks. There was a wide variation in eradication rates in these paediatric studies, ranging from 27% to 94% when the treatment regimen lasted 4 to 6 weeks.[67-69] Triple therapy yielded a higher cure rate than dual therapy or monotherapy. 1-week and 2-week regimens of triple therapy that aim to optimise compliance and cure rates are summarised in table I.

Walsh et al.[73] in Ireland evaluated a 1-week treatment regimen of bismuth subcitrate, metronidazole and clarithromycin (at dosages adapted for a 1-week course), and reported a 95% cure rate among 22 children infected with *H. pylori*. Concern has been expressed about the use of bismuth in the treatment of *H. pylori* gastritis in children because of reports of bismuth toxicity in adults.[72,74] However, De Giacomo et al.[69] could not confirm these reports; no children who received colloidal bismuth subcitrate with amoxicillin for treatment of *H. pylori* gastritis displayed toxicity attributable to bismuth administration. Another study used a

Table I. Clinical trials of *Helicobacter pylori* eradication regimens in paediatric patients

Country	Treatment regimen	Duration of therapy	Cure rate	Reference
Spain	Colloidal bismuth subcitrate 8 mg/kg/day bid Amoxicillin 50 mg/kg/day tid Metronidazole 20 mg/kg/day tid	2 weeks	81% (35/43)	70
Spain	Colloidal bismuth subcitrate 8 mg/kg/day bid Amoxicillin 50 mg/kg/day tid Metronidazole 20 mg/kg/day tid	1 week	79% (31/39)	70
Canada	Metronidazole 250 or 500mg bid[a] Clarithromycin 250 or 500mg bid[a] Omeprazole 20mg od or bid[a]	2 weeks	93% (14/15)	71
Ireland	Colloidal bismuth subcitrate 480 mg/1.73 m^2/day qid Metronidazole 20 mg/kg/day tid Clarithromycin 7.5 mg/kg/day bid	1 week	95% (21/22)	72

a The first stated dosage relates to children <10 years, whilst the second dosage relates to children ≥10 years.

bid = twice daily; **od** = once daily; **qid** = four times daily; **tid** = three times daily.

2-week regimen of metronidazole and clarithromycin with omeprazole to achieve a 93% cure rate of infection in 15 Canadian children.[75]

Dual therapy yields a relatively better cure rate of *H. pylori* infection in children than in adults, perhaps because of the lower rate of antimicrobial resistance in children. In 3 earlier studies conducted in Italy, Oderda et al.[67,71,76] investigated the combination of amoxicillin and tinidazole for 6 weeks in the treatment of *H. pylori*–associated gastritis. Among the total of 67 children who completed the 6-month follow-up in the 3 studies combined, 54 (81%) were cured of the infection. For long term cure of infection, the combination of amoxicillin and tinidazole for 6 weeks appears to be more effective than using amoxicillin alone. Combination of amoxicillin with H_2-antagonists or omeprazole is not recommended to treat children with *H. pylori* infection because of the low cure rate.[77,78]

There are several important factors influencing the efficacy of therapy in paediatric patients, including poor compliance, adverse effects and development of antimicrobial resistance. Although prospective studies have examined the effect of such factors on the efficacy of treatment regimens in the adult population,[79] there is a lack of such studies in the paediatric setting. There is a great need for well designed and controlled clinical trials on large numbers of *H. pylori*–infected children to evaluate different regimens for treatment. Follow-up studies to measure reinfection rates are also needed.

5. Vaccine Development

Extensive research has been directed towards the development of vaccination against *H. pylori* for prevention and possibly treatment of an existing infection. Czinn and Nedrud[80,81] reported the possibility of oral immunisation in animal models. Several animal models have been used over the past few years and many *H. pylori* antigens have been tested, but no single antigen has been fully successful. Examination of mixtures of antigens is under way, but the final formulation of a vaccine is not yet fully defined. The target population for prophylactic vaccination is children residing in areas with a high incidence of gastric carcinoma. In developing countries and areas with a high rate of infection among children, vaccination may be a valuable treatment regimen. Establishing the value of therapeutic immunisation alone or combined with anti-*H. pylori* treatment remains an important objective for research.

6. Conclusions

H. pylori infection is common in both adults and children, and *H. pylori*–associated gastritis and peptic ulcer disease have been reported in both age

groups. *H. pylori* infection causes 90 to 100% of paediatric duodenal ulcers. If *H. pylori* is not effectively treated, duodenal ulcers in infected children can persist or relapse with long term morbidity. There is still only weak and inconsistent evidence for an association between RAP in children and *H. pylori* infection. Evidence to date indicates that routine investigation for *H. pylori* infection in children with RAP is not warranted. Therefore, testing for *H. pylori* infection in children with RAP is appropriate only when treatment is planned if the test is positive. Current *H. pylori* eradication treatment for children is based on regimens for adults, using triple therapy or dual therapy with a proton pump inhibitor. An ideal treatment for *H. pylori* infection in children has yet to be determined.

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References

1. Malaty HM, Graham DY. Importance of childhood socioeconomic status on the current prevalence of *Helicobacter pylori* infection. Gut 1994; 35: 742-5
2. Malaty HM, Graham DY, Wattigney WA, et al. Natural history of *Helicobacter pylori* infection in childhood: a 12-year follow-up cohort study in a bi-racial community. Clin Infect Dis 1999; 28: 279-82
3. Mendall MA, Goggin PM, Molineaux N, et al. Childhood living conditions and *Helicobacter pylori* seropositivity in adult life. Lancet 1992; 339: 896-7
4. Mitchell HM, Li YY, Hu PJ, et al. Epidemiology of *Helicobacter pylori* in southern China: identification of early childhood as the critical period for acquisition. J Infect Dis 1992; 166: 149-53
5. Kumagai T, Malaty HM, Graham DY, et al. Acquisition vs. loss of *Helicobacter pylori* infection in Japan: results from 8-year Birth Cohort Study. J Infect Dis 1998; 178: 717-21
6. Roosendaal R, Kuipers EJ, Buitenwerf J, et al. *Helicobacter pylori* and birth cohort effect: evidence of a continuous decrease of infection rates in childhood. Am J Gastroenterol 1997; 92: 1480-2
7. Drumm B. *Helicobacter pylori* in the pediatric patient. Gastroenterol Clin North Am 1993; 22: 169-82
8. Blecker U. *Helicobacter pylori*-associated gastroduodenal disease in childhood. South Med J 1997; 90: 570-6
9. Malaty HM, Kim JG, Kim SD, et al. Prevalence of *Helicobacter pylori* infection in Korean children: inverse relation to socioeconomic status despite a uniformly high prevalence in adults. Am J Epidemiol 1996; 143: 257-62
10. Malaty HM, Paykov V, Bykova O, et al. *Helicobacter pylori* and socioeconomic factors in Russia. Helicobacter 1996; 2: 82-7
11. Graham DY, Adam E, Reddy GT, et al. Seroepidemiology of *Helicobacter pylori* infection in India: comparison of developing and developed countries. Dig Dis Sci 1991; 36: 1084-8
12. Fiedorek SC, Malaty HM, Evans DG, et al. Factors influencing the epidemiology of *Helicobacter pylori* infection in children. Pediatrics 1991; 88: 578-82
13. Teh BH, Lin JT, Pan WH, et al. Seroprevalence and associated risk factors of *Helicobacter pylori* infection in Taiwan. Anticancer Res 1994; 14: 1389-92
14. Radhakrishnan S, al Nakib B, Kalaoui M, et al. *Helicobacter pylori*-associated gastritis in Kuwait: endoscopy-based study in symptomatic and asymptomatic children. J Pediatr Gastroenterol Nutr 1993; 16: 126-9
15. Malaty HM, Evans DG, Evans Jr DJ, et al. *Helicobacter pylori* in hispanics: comparison with blacks and whites of similar age and socioeconomic class. Gastroenterology 1992; 103: 813-6
16. Graham DY, Malaty HM, Evans DG, et al. Epidemiology of *Helicobacter pylori* in an asymptomatic population in the United States: effect of age, race, and socioeconomic status. Gastroenterology 1991; 100: 1495-501
17. Sitas F, Forman D, Yarnell JW, et al. *Helicobacter pylori* infection rates in relation to age and social class in a population of Welsh men. Gut 1991; 32: 25-8
18. Malaty HM, Graham DY, Isaksson I, et al. A Cotwin study of the effect of environment on *Helicobacter pylori* acquisition. Am J Epidemiol 1998; 148: 793-7
19. Banatvala N, Mayo K, Megraud F, et al. The cohort effect and *Helicobacter pylori*. J Infect Dis 1993; 168: 219-21
20. Tytgat GNJ, Lee A, Graham DY, et al. The role of infectious agents in peptic ulcer disease. Gastroenterol Int 1993; 6: 76-89
21. Graham DY, Klein PD, Evans DG, et al. *Helicobacter pylori*: epidemiology, relationship to gastric cancer and the role of infants in transmission. Eur J Gastroenterol Hepatol 1992; 4 Suppl. 1: S1-6
22. Klein PD, Gilman RH, Leon-Barua R, et al. The epidemiology of *Helicobacter pylori* in Peruvian children between 6 and 30 months of age. Am J Gastroenterol 1994; 89: 2196-200
23. Guelrud M, Mujica C, Jaen D, et al. Prevalence of *Helicobacter pylori* in neonates and young infants undergoing ERCP for diagnosis of neonatal cholestasis. J Pediatr Gastroenterol Nutr 1994; 18: 461-4
24. Granstrom M, Tindberg Y, Blennow M. Seroepidemiology of *Helicobacter pylori* infection in a cohort of children monitored from 6 months to 11 years of age. J Clin Microbiol 1997; 35: 468-70
25. Malaty HM, Graham DY, Klein PD, et al. Transmission of *Helicobacter pylori* infection: studies in families of healthy individuals. Scand J Gastroenterol 1991; 26: 927-32
26. Mitchell HM, Bohane TD, Berkowicz J, et al. Antibody to *Campylobacter pylori* in families of index children with gastrointestinal illness due to *C. pylori*. Lancet 1987; II: 681-2
27. Bamford KB, Bickley J, Collins JS, et al. *Helicobacter pylori*: comparison of DNA fingerprints provides evidence for intrafamilial infection. Gut 1993; 34: 1348-50
28. Drumm B, Perez-Perez GI, Blaser MJ, et al. Intrafamilial clustering of *Helicobacter pylori* infection. N Engl J Med 1990; 322: 359-63
29. Krajden S, Fuksa M, Andersen J, et al. Examination of human stomach biopsies, saliva, and dental plaque for *Campylobacter pylori*. J Clin Microbiol 1989; 27: 1397-8
30. Ferguson DA, Li C, Patel NR, et al. Isolation of *Helicobacter pylori* from saliva. J Clin Microbiol 1993; 31: 280-4

31. Malaty HM, Evans Jr DJ, Abramovitch K, et al. Seroepidemiology of *Helicobacter pylori* infection in clinical dental workers. Am J Gastroenterol 1992; 87: 1728-31
32. Thomas JE, Gibson RB, Darboe MK, et al. *Helicobacter pylori* from the human feces. Lancet 1992; 340: 1194-5
33. Leverstein van Hall MA, van der Enfe A, van Milligan de Wit M, et al. Transmission of *Helicobacter pylori* via feces. Lancet 1993; 342: 1419-20
34. Klein PD, Graham DY, Gaillour A, et al. Water source as a risk factor for *Helicobacter pylori* infection in Peruvian children. Lancet 1991; 337: 1503-6
35. Hopkins RJ, Vial PA, Ferreccio C, et al. Seroprevalence of *Helicobacter pylori* in Chile: vegetables may serve as one route of transmission. J Infect Dis 1993; 168: 222-6
36. Malaty HM, Engstrand L, Pedersen NL, et al. Genetic and environmental influences of *Helicobacter pylori* infection: a twin study. Ann Intern Med 1994; 120: 982-6
37. Graham DY, Malaty HM, Go MF. Are there susceptible hosts to *Helicobacter pylori* infection? Scand J Gastroenterol 1994; 205 Suppl.: 6-10
38. Fraser AG, Scragg R, Metcalf P, et al. Prevalence of *Helicobacter pylori* infection in different ethnic groups in New Zealand children and adults. Aust NZ J Med 1996; 26: 646-51
39. Goodman KJ, Correa P, Tengana AH, et al. Nutritional factors and *Helicobacter pylori* infection in Colombian children. J Pediatr Gastroenterol Nutr 1997; 25: 507-15
40. Kehrt R, Becker M, Brosicke H, et al. *Helicobacter pylori* infection in Nicaraguan children with persistent diarrhea diagnosed by the ^{13}C-urea breath test. J Pediatr Gastroenterol Nutr 1997; 25: 84-8
41. Pelser HH, Househam KC, Joubert G, et al. Prevalence of *Helicobacter pylori* infection in children in Bloemfontein, South Africa. J Pediatr Gastroenterol Nutr 1997; 24: 135-9
42. Thomas JE, Austin S, Dale A et al. Protection by human milk IgA against *Helicobacter pylori* infection in infancy [letter]. Lancet 1993; 342: 121
43. Weaver LT. Aspects of *Helicobacter pylori* infection in the developing and developed world: *Helicobacter pylori* infection, nutrients and growth of West African children. Trans R Soc Trop Med Hyg 1995; 347-50
44. Mitchell HM, Bohane TD, Tobias V, et al. *Helicobacter pylori* infection in children: potential clues to pathogenesis. J Pediatr Gastroenterol Nutr 1993; 16: 120-5
45. Hassall E, Dimmick JE. Unique features of *H. pylori* disease in children. Dig Dis Sci 1991; 36: 417-23
46. Kilbridge PM, Dahms BB, Czinn SJ. *Campylobacter pylori* associated gastritis and peptic ulcer disease in children. Am J Dis Childhood 1988; 142: 1149-52
47. Chang KL, Tam PK, Saing H. Long term follow-upon childhood duodenal ulcers. J Pediatr Surg 1997; 32: 1609-11
48. Bujanover Y, Reif S, Yahav J. *Helicobacter pylori* and peptic disease in the pediatric patient. Pediatr Clin North Am 1996; 43: 213-34
49. Prieto G, Polanco I, Larrauri J, et al. *Helicobacter pylori* infection in children: clinical, endoscopic, and histologic correlations. J Pediatr Gastroenterol Nutr 1992; 14: 420-5
50. Vaira D, Oderda G. Treatment of *Helicobacter pylori* in children. In: Fan XG, Xia HX, editors. *Helicobacter pylori*: basic principles and clinical practice. Changsha: Hunan Science and Technology Press, 1997: 284-9
51. Heldenberg D, Wahner Y, Heldenberg E, et al. The role of *Helicobacter pylori* in children with recurrent abdominal pain. Am J Gastroenterol 1995; 90: 906-9
52. Apley J. The child with abdominal pains. London: Blackwell Scientific Publication, 1975
53. Boyle JT. Chronic abdominal pain. In: Walker WA, Durie PR, Hamilton JR, et al., editors. Pediatric gastrointestinal disease. Philadelphia (PA): BC Decker, 1991: 45-54
54. Bode G, Rothenbacher D, Brenner H, et al. *Helicobacter pylori* and abdominal symptoms: a population based study among preschool children in southern Germany. Pediatrics 1998; 101: 634-7
55. Begue RE, Gonzales JL, Correa GH, et al. *Helicobacter pylori* in children with abdominal ailments in a developing country. Am J Med Sci 1997; 314: 279-83
56. Cucchiara S, Salvia G, Az-Zeqeh N, et al. *Helicobacter pylori* gastritis and non-ulcer dyspepsia in childhood: efficacy of one-week triple antimicrobial therapy in eradicating the organism. Ital J Gastroenterol 1996; 28: 430-5
57. Genta RM, Robason GO, Graham DY. Simultaneous visualization of *Helicobacter pylori* and gastric morphology: a new stain. Hum Pathol 1994; 25: 221-6
58. el-Zimaity HM, Wu J, Graham DY. Modified genta triple stain for identifying *Helicobacter pylori.* J Clin Pathol 1999; 52: 693-4
59. Yousfi MM, el-Zimaity HM, Cole RA, et al. Detection of *Helicobacter pylori* by rapid urease tests: is biopsy size a critical variable? Gastrointest Endosc 1996; 43: 222-4
60. Chong SK, Lou Q, Asnicar MA, et al. *Helicobacter pylori* infection in recurrent abdominal pain in childhood: comparison of diagnostic tests and therapy. Pediatrics 1995; 96: 211-5
61. Malaty HM. The effect of combination of tests on the prevalence of *Helicobacter pylori* infection in preschool and school age children [abstract]. Gut 1998; 43 Suppl. 2: A74-5
62. Elitsur Y, Hill I, Lichtman SN, et al. Prospective comparisons of rapid urease tests (PyloriTek, CLO) for the diagnosis of *Helicobacter pylori* infection in symptomatic children: a pediatric multicenter study. Am J Gastroenterol 1998; 93: 217-9
63. Rowland M, Lambert I, Gormally S, et al. Carbon 13-labeled urea breath test for diagnosis of *Helicobacter pylori* infection in children. J Pediatr 1997; 131: 815-20
64. Klein PD, Malaty HM, Martin RF, et al. Noninvasive detection of *Helicobacter pylori* infection in clinical practice: the ^{13}C urea breath test. Am J Gastroenterol 1996; 91: 690-4
65. Klein PD, Malaty HM, Czinn SJ, et al. Normalizing results of ^{13}C urea breath testing for CO_2 production rates in children. J Pediatr Gastroenterol Nutr 1999; 29: 297-301
66. Drumm B, Sherman P, Chiasson D, et al. Treatment of *Campylobacter pylori*-associated antral gastritis in children with bismuth subsalicylate and ampicillin. J Pediatr 1988; 113: 908-12
67. Oderda G, Vaira D, Holton G, et al. Amoxicillin plus tinidazole for *Campylobacter pylori* gastritis in children: assessment by serum IgG antibody, pepsinogen I, and gastrin levels. Lancet 1989; I: 690-2
68. Oderda G, Dell'Olio D, Morra I, et al. *Campylobacter pylori* gastritis: long term results of treatment with amoxicillin. Arch Dis Child 1989; 64: 326-9
69. De Giacomo C, Fiocca R, Villani L, et al. *Helicobacter pylori* infection and chronic gastritis: clinical, serological, and histologic correlations in children treated with amoxicillin and colloidal bismuth subcitrate. J Pediatr Gastroenterol Nutr 1990; 11: 310-6
70. Urruzuno P, Cilleruelo ML, Martinez MJ, et al. One week vs. two weeks triple therapy for *Helicobacter pylori* eradication in children [abstract]. Gut 1996; 39 Suppl. 2: A49
71. Oderda G, Vaira D, Dell'Olio D, et al. Serum pepsinogen I and gastrin concentration in children positive for *Helicobacter pylori.* J Clin Pathol 1990; 43: 762-5

72. Taylor EG, Klenerman P. Acute renal failure after colloidal bismuth subcitrate overdose. Lancet 1990; 335: 670-1
73. Walsh D, Goggin N, Rowland M, et al. One week treatment for *Helicobacter pylori* infection. Arch Dis Child 1997; 76: 352-5
74. Hudson M, Mowat NA. Reversible toxicity in poisoning with colloidal bismuth subcitrate. BMJ 1989; 299: 159
75. Dohil R, Israel DM, Hassell E. Effective 2-week therapy for *Helicobacter pylori* disease in children. Am J Gastroenterol 1997; 92: 244-7
76. Oderda G, Vaira D, Ainley C, et al. Eighteen months follow up of *Helicobacter pylori* positive children treated with amoxicillin and tinidazole. Gut 1992; 33: 1328-30
77. Yeung CK, Fu KH, Yuen KY, et al. *Helicobacter pylori* and associated duodenal ulcer. Arch Dis Child 1990; 65: 1212-6
78. Martinez MJ, Urruzuno P, Cilleruelo ML, et al. Failure of omeprazole plus amoxicillin therapy in *H. pylori* infected Spanish children [abstract]. Gut 1996; 39 Suppl. 2: A48
79. Graham DY, Lew G, Malaty HM, et al. Factors influencing the eradication of *Helicobacter pylori* with triple therapy. Gastroenterology 1992; 102: 493-6
80. Czinn SJ, Nedrud JG. Oral immunization against *Helicobacter pylori*. Infect Immun 1991; 59: 2359-63
81. Nedrud JG, Czinn SJ. Oral immunization for the prevention and treatment of infection with *Helicobacter*. In: Ernst P, Michetti P, Smith PD, editors. The immunobiology of *H. pylori* from pathogenesis to prevention. Philadelphia (PA): Lipincott-Raven, 1997: 273-86

Correspondence and offprints: Dr *Hoda M. Malaty,* Veterans Affairs Medical Center (111D), 2002 Holcombe Boulevard, Houston, TX 77030, USA.
E-mail: hmalaty@bcm.tmc.edu