Review Article

Helicobacter pylori in childrenPeter B. Sullivan¹ and Julian E. Thomas²¹Department of Child Health, Westminster Children's Hospital, Vincent Square, London SW1P 2NS, and²Department of Child Health, University of Newcastle on Tyne, UK

Summary: The clinical manifestations of *Helicobacter pylori* (formerly *Campylobacter pylori*) infection in children overlap with those encountered in adults but there are some important differences. The aim of this review is to describe the range of manifestations of this infection in children, together with means of diagnosis and treatment.

Background

Within the last decade there has been increasing recognition of the role of *Helicobacter pylori* in disease in the upper gastrointestinal tract. Although spiral organisms were recognized on the gastric mucosa nearly a century ago it was not until 1983 that the relationship between non-auto-immune gastritis and *H. pylori* infection was identified.¹ The association between *H. pylori* infective gastritis and peptic ulceration in adults is very strong; the prevalence for duodenal ulcer is around 90%^{2,3} and for gastric ulcer around 70%.^{4,5} The concept that there may be an infective component to peptic ulcer disease has important implications for treatment; abolition of gastric acid secretion with H₂-receptor antagonists will heal most duodenal ulcers⁶ but 70–80% of healed ulcers relapse within the next year.⁷ Eradication of *H. pylori* infection is probably a prerequisite of successful anti-ulcer therapy.⁸

Methods of diagnosis

The accepted 'gold standard' for the diagnosis of *H. pylori* infection in adult life is the demonstration of bacteria in gastric biopsies.⁹ They can be seen on fixed sections, using selective stains such as Warthin Starry silver or Giemsa stains, or they can be cultured from biopsies.¹⁰

The bacterium is capable of rapid hydrolysis of urea, a property utilized in rapid urease tests (CLO-test).¹¹ Preformed bacterial urease on a gastric biopsy specimen will convert urea into

ammonia and carbon dioxide in a small volume of substrate, sufficient to change a pH indicator within 1 h in more than 90% of adult cases. All these techniques, however, depend on upper gastrointestinal endoscopy, which is usually only available for children in specialized referral centres.

The urease activity of *H. pylori* can also be utilized in non-invasive diagnostic tests. An oral dose of urea, labelled with either ¹³C or ¹⁴C, is followed in infected individuals by a rise in labelled exhaled CO₂.^{12,13} Unfortunately, neither technique is suitable for routine use in paediatric populations; ¹⁴C compounds are radioactive and detection of ¹³C compounds requires a dedicated mass spectrometer.

Active infection is accompanied by a systemic IgG response that can be detected by an enzyme-linked immunosorbent assay (ELISA).^{14,15} Recent work suggests that the diagnosis of *H. pylori* infection in childhood may be made by measuring systemic IgG antibodies directed against a crude whole cell bacterial antigen.¹⁶

Clinical manifestations

Recurrent abdominal pain (RAP) is a frequent presenting complaint in paediatric practice. RAP with or without recurrent vomiting is a common initial manifestation of *H. pylori* infection in children.^{17–19} Tolia *et al.*¹⁹ reported *H. pylori* to be a causative factor in 7/37 children with RAP. They, and others, have observed that histological gastritis is often confirmed when gastric antral mucosal appearances, viewed endoscopically, are normal and that gastric antral biopsy is necessary to exclude *H. pylori* infection. As in adults, *H. pylori* in children has been shown to be specifically

associated with primary antral gastritis and some affected children may also be anaemic.^{17,20} Surveys of RAP in childhood have shown that a history of RAP in siblings and a family history of peptic ulcer disease are more common in affected children than in those without RAP, and an infective link through *H. pylori* will account for this association in a proportion of cases. Identification of infection in children with RAP is important as it renders treatable a condition that, in many cases, was previously resistant to therapy.

Peptic ulcer, although less common than in adults, does occur in children^{21,22} and may present with non-specific symptoms. The association between *H. pylori* gastritis and gastric or duodenal ulcer in children is recognized.^{17,18,23–25} Drumm *et al.*²⁵ showed that 10/16 children with *H. pylori*-associated gastritis had a duodenal ulcer. This emphasizes the need for upper gastrointestinal endoscopic examination in children with dyspeptic symptoms.

It has recently been shown that children (age 5–36 months) with chronic diarrhoea and malnutrition in West Africa have a high prevalence of *H. pylori* infection.²⁶ In an endoscopically validated serological study, 41/77 (53%) of such children had significantly raised anti-*H. pylori* antibody levels compared with only 18/70 (26%) of age-matched healthy controls ($P < 0.01$). The significance of these findings is that gastric *H. pylori* infection may predispose to bacterial overgrowth in the upper small intestine – a commonly observed feature of children with chronic diarrhoea in the tropics.²⁷ *H. pylori* has been shown to be associated with hypochlorhydria and achlorhydria.^{28,29} Compromise, even if transient, of the gastric acid barrier could predispose to small bowel bacterial contamination, particularly in areas where food is highly polluted with faecal micro-organisms. Further investigations are required to clarify the role of *H. pylori* infection in small bowel bacterial overgrowth in children with chronic diarrhoea. If the relationship is proved, this may have important implications for the treatment of children with diarrhoeal disease in developing countries.

There have been reports of protein-losing enteropathy in children with *H. pylori* gastritis; Hill *et al.*³⁰ reported 3 children less than 4 years of age, 2 of whom had had a previous diarrhoeal illness, with a transient protein-losing enteropathy in association with acute *H. pylori* gastritis. However, Sullivan *et al.*³¹ were unable to confirm this finding in 30 children with chronic diarrhoea and malnutrition and evidence of *H. pylori* infection.

Prevalence of *H. pylori* infection

On the basis of serological studies in western Europe and Australia the prevalence of *H. pylori*

infection in the general population appears to be 20–30%;^{32,33} however, this is both age and geographically dependent. Prevalence of *H. pylori* infection appears to be linked to the degree of industrialization and economic development of the populations studied. Studies in adults in Ethiopia, El Salvador and Samoa indicate a higher prevalence ($\approx 40\%$) in the general population than in western Europe.³⁴ Even in developed countries the prevalence of *H. pylori* infection is related to socio-economic status; Fiedorek *et al.*,³⁵ in Arkansas, demonstrated a prevalence of 67% in asymptomatic teenage blacks from low-income families compared with a prevalence of 26% in more affluent white teenagers. The incidence of both *H. pylori* infection and gastritis increases throughout life to reach a maximum in the 6th decade, with over 60% of the population affected.³² *H. pylori* infection is rare in healthy children in developed countries. Thomas *et al.*²⁰ in a serological study reported 5% of 150 well school children in Newcastle to have *H. pylori* infection. Jones *et al.*³² found 1/109 children aged 6–14 years and 9/151 of 15–20 year olds to be seropositive for *H. pylori*. The situation in the developing world is different,³⁶ and Sullivan *et al.*²⁶ studying healthy Gambian children found the age-related prevalence of anti-*H. pylori* antibody titres to be 15% in those aged < 19 months, rising to 46% in children between 40 and 60 months of age.

Management

As in adults, a combination of a colloidal bismuth preparation and an antibiotic has been shown to be effective in eradication of *H. pylori* infection in children²⁵ and most courses of treatment are used for at least 6 weeks. Oderda³⁷ has shown that a single antibiotic is not associated with successful clearance of infection, although a combination of tinidazole and amoxycillin produces clearance rates as effective as regimes utilizing bismuth.

Several authors have shown that eradication of bacteria with bismuth and an antibiotic is accompanied by healing of gastritis and duodenal ulceration, and resolution of symptoms.^{25,37} Currently, 2 separate regimes, one utilizing 2 antibiotics and one utilizing colloidal bismuth and one antibiotic, have proved successful and acceptable in children.

A possible management strategy in children suspected of being infected would be to offer *H. pylori* seropositive children a course of specific therapy. Upper gastrointestinal endoscopy should be reserved for *H. pylori* seronegative cases, and for children whose symptoms do not respond to appropriate antibacterial treatment. This approach requires access to serodiagnosis of *H. pylori* infection and until recently this has been available

only in centres with a special research interest. This situation is now changing with the appearance of commercially available serodiagnostic kits (e.g. HELICO-G, Porton Cambridge, UK). There is no evidence to suggest that prolonged asymptomatic *H. pylori* infection poses a health risk to children in developed countries, and, therefore, there is no indication to screen for *H. pylori* infection in children except those whose symptoms may be directly related to gastritis or peptic ulceration.

The main problem as regards treatment of children infected with *H. pylori*, especially in developing countries, is the high likelihood of re-infection after treatment. Eradication of acute infection may not be sufficient under circumstances where rapid re-infection is likely. Vaccination against *H. pylori* urease has been suggested.³⁸ Although this is an attractive idea, especially as *H. pylori* infection is arguably the commonest infectious disease in man,³⁹ it is unlikely to be effective as there is no evidence that the host immune response

either effects clearance or confers immunity to infection.

The problem of relapse of peptic ulcer after treatment is similar in children to that in adults; in children treated for peptic ulcer with ranitidine, Oderda *et al.*⁴⁰ demonstrated a 45% relapse rate and *H. pylori* was present on the antral mucosa in 85% of these patients. Successful treatment of peptic ulcer in children, as in adults, depends on eradication of *H. pylori* from the mucosa.

Return of symptoms may occur after treatment of RAP secondary to *H. pylori*, and this is likely to be due to re-infection from affected relatives.⁴¹ Therefore, an effort to simultaneously treat *H. pylori* carriers in the family could improve the success rate in eliminating the organism from the gastric mucosa.⁴² Failure to eradicate *H. pylori* infection in children with RAP may be one of the reasons why, in the time-honoured phrase of John Apley, 'little belly achers grow up to be big belly achers'.⁴³

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