How should *Helicobacter pylori* infected children be managed?

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It is now recognised that *Helicobacter pylori*, like most enteric infections, is mainly acquired in childhood.¹ Adults rarely become infected, with seroconversion rates varying between 0.33 and 0.5% per person year.²⁻³ The age at which children are most likely to become infected is still unclear, but findings in a number of cross-sectional studies suggest that infection is acquired before the age of five.⁴⁻⁶ The prevalence of infection is highest in children in the developing world where up to 75% of children may be infected by the age of 10.⁷ In the developed world the prevalence of infection is noticeably increased among socially deprived children.⁸⁻⁹

The diagnosis of *H pylori* infection in childhood is most often made at endoscopy, for which there are many indications. Symptoms such as abdominal pain, vomiting, and haematemesis may be associated with duodenal ulcer and *H pylori* infection. However, in the case of children undergoing endoscopy for assessment of oesophagitis, failure to thrive, coeliac disease, Crohn's disease, or portal hypertension, the finding of *H pylori* infection is likely to be incidental. How should we manage these children with a diagnosis of *H pylori* infection?

Currently, there are no consensus guidelines for the management of *H pylori* infected children. In 1994 the National Institutes of Health consensus statement recommended that adults with gastric or duodenal ulcer disease, who are infected with *H pylori*, should receive antimicrobial treatment.¹⁰ The European Maastricht Consensus Report suggested broader indications for treatment of infected adults.¹¹ It states that treatment is advisable for all *H pylori* infected dyspeptic patients diagnosed non-invasively under 45 years of age at a primary care level. Patients older than 45 years with dyspeptic symptoms should be treated for *H pylori* infection but only after endoscopy to rule out any other underlying pathology.¹¹ The European guidelines also recommend treatment for infected patients with mucosa associated lymphoid tissue lymphoma and patients who are found to have intestinal metaplasia and gastric atrophy.¹¹

Children with duodenal ulceration

In children, as in adults, long term healing of duodenal ulcer disease is achieved following eradication of *H pylori*.¹² All *H pylori* infected children with a duodenal ulcer should therefore have treatment to eradicate infection.

Possible indications for treatment of *H pylori* infected children

Duodenal ulcer disease associated with *H pylori* is the only definite indication to treat this infection in children. There is controversy as to other possible indications for the treatment of *H pylori* infection in children.

PREVENTION OF DUODENAL ULCER DISEASE

Duodenal ulcer disease is a rare condition in children under 10 years of age.¹³ It is estimated that 15% of individuals infected with *H pylori* will develop a duodenal ulcer as adults. Whether eradication of *H pylori* is justified in order to reduce the risk of developing duodenal ulcer disease is unknown at this point. In a recent study individuals infected with *H pylori* who had a family history of endoscopically verified ulcer had a much greater risk of developing ulcer disease.¹⁴ Although the study did not control for socioeconomic status, it may be reasonable to treat *H pylori* gastritis in a child whose father or mother has a definite history of peptic ulcer disease.

RECURRENT ABDOMINAL PAIN

Although most studies have found no association between *H pylori* infection and abdominal pain in children,¹⁵⁻¹⁶ a number have suggested that *H pylori* infection may be the cause of recurrent abdominal pain.¹⁷⁻¹⁸ However, it is vital that symptoms are only evaluated in a situation where the investigator is unaware of the *H pylori* status of the child. In a meta-analysis McArthur *et al* found that recurrent abdominal pain is not associated with an increased prevalence of *H pylori* associated gastritis.¹⁹ *H pylori* infected children cannot be differentiated from those who are not infected on the basis of their presenting symptoms.²⁰⁻²¹ *H pylori* eradication is associated with an improvement in symptoms in children who have duodenal ulcer disease but not in those with gastritis alone.²⁰ This suggests that the effect of *H pylori* eradication on symptoms in these children relates to healing of duodenal ulcer disease rather than clearing of gastritis.

Furthermore *H pylori* infection frequently occurs in asymptomatic children.⁴⁻⁹ Bode *et al*, in a large epidemiological study of healthy children, showed that *H pylori* is not a cause of gastrointestinal symptoms.²² In fact two studies suggest that children with symptoms of recurrent abdominal pain are less likely to be infected with *H pylori*.²²⁻²³ There is therefore no clear evidence that treatment of *H pylori* will alleviate symptoms in children with recurrent abdominal pain who have *H pylori* gastritis.

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IRON DEFICIENCY ANAEMIA

There have been a number of case reports describing children with refractory sideropaenic anaemia which only responded to treatment after eradication of *H pylori*.²⁴⁻²⁶ A recent report by Milman *et al* suggests that serum ferritin concentrations are reduced in *H pylori* infected adults.²⁷ They suggest that *H pylori* may interfere with iron metabolism in humans. This may be an important issue in children who have lower iron stores than adults and may be at a greater risk of developing anaemia. Further research is required to assess the contribution of socioeconomic status and dietary factors to low iron stores in *H pylori* infected individuals. However, based on our present knowledge, children with iron deficiency anaemia which is refractory to treatment should be screened for *H pylori* and treated if infection is present.

SHORT STATURE

Oderda *et al* have shown that *H pylori* infection is not associated with short stature.²⁸ Previous reports of such an association²⁹ failed to control for socioeconomic status as a risk factor for short stature. Short stature is therefore not an indication to treat *H pylori*.

PERSISTENT DIARRHOEA

In developing countries some investigators have suggested that *H pylori* may be associated with chronic diarrhoea.³⁰ It is speculated that infection with *H pylori* at a young age may induce hypochlorhydria which interferes with the normal acidic barrier in the stomach. This acidic barrier is important in preventing infection with many gastrointestinal organisms.³⁰ Further studies are required in this group of children to determine whether eradication of *H pylori* reduces the prevalence of chronic diarrhoea.

GASTRIC CANCER

H pylori has been classified as a group I carcinogen by the World Health Organisation.³¹ The relative risk of gastric carcinoma is 2.3–8.7 times greater in infected adults compared with uninfected controls.³² However, only about 1% of *H pylori* infected individuals will develop gastric cancer.

H pylori is possibly only one risk factor in the cascade which leads to gastric cancer. Its importance in this cascade is unknown. If it is considered justified to eradicate *H pylori* in order to reduce the risk of gastric cancer, treatment in early life is likely to be most effective. Correa's model for the development of gastric cancer proposes a progression from gastritis to gastric atrophy and intestinal metaplasia followed by dysplasia.³³ Development of gastric atrophy is related to the duration of infection with *H pylori*² rather than a direct result of ageing. Treatment of *H pylori* infection in adult life may therefore be too late to reduce the risk of developing gastric cancer as atrophy may have already developed. If we consider atrophy to be present only when there is evidence of fibrosis and thinning of the lamina propria with replacement of the gastric

epithelium with intestinal type epithelium, then it is unlikely that the process is reversible.³⁴ Intestinal metaplasia has never been shown to regress.

In order for any intervention strategy to be calculated to be cost effective, the time period between intervention measures and the occurrence of gastric cancer must be relatively short.³⁵ A decision analysis model has shown that treatment of individuals in the 50–55 age group is potentially cost effective.³⁶ However in clinical practice treatment of people over the age of 50 years is unlikely to reverse the progression from *H pylori* gastritis to gastric cancer in susceptible individuals. Treatment at a much younger age may be effective but this would be prohibitively expensive.

A consensus has yet to be reached on the need to treat infected children because of the increased risk of developing gastric cancer at some time in the future. Furthermore, if we decide to treat these children it implies that we should also be screening all children for this infection.

Treatment of children

Compliance is a very important factor in achieving high eradication rates in children.³⁷⁻³⁸ Recently, a one week treatment regimen comprising colloidal bismuth subcitrate 480 mg/1.73 m²/day (maximum 120 mg qid), clarithromycin 7.5 mg/kg/day (maximum 250 bid), and metronidazole 20 mg/kg/day (maximum 200 mg tid) eradicated *H pylori* in 21 of 22 children.³⁸ Only two children experienced diarrhoea and vomiting. The short duration of treatment probably improved compliance as did the use of a redidose box with individual compartments for each dose of medication. It is questionable whether this level of compliance could be achieved in routine practice and the effectiveness of a one week regimen needs to be assessed under such circumstances.

Gormally *et al* reported eradication of the organism in 84% using metronidazole and bismuth for two weeks.²⁰ The strong taste of ammonia associated with liquid bismuth may reduce compliance. Regimens using a proton pump inhibitor instead of bismuth may therefore be more attractive. Two weeks' treatment with metronidazole, omeprazole and clarithromycin was successful in 93% (14/15) of children.³⁹ A one week treatment regimen using omeprazole (20 mg bid), clarithromycin (250 mg bid) and tinidazole or metronidazole (500 mg bid) eradicated *H pylori* in 24 (89%) of 27 patients who were treated for the first time.⁴⁰ However, in children in whom treatment for *H pylori* infection had failed previously this regimen was ineffective.

SIDE EFFECTS

Although concern has been expressed about the use of bismuth salts in children, none of the potential toxic side effects has been reported in children treated for *H pylori* infection. Few side effects have been reported associated with the use of clarithromycin. There

has been a recent report of *Clostridium difficile* colitis associated with clarithromycin, metronidazole and omeprazole triple therapy in a 54 year old man.⁴¹

The emergence of metronidazole resistant strains is a concern. Raymond *et al* detected metronidazole resistance in 26% (six of 23) of children in France using an E-test.⁴² Only one in six children with a metronidazole resistant strain was successfully treated for *H pylori* infection. This is in contrast to studies in adults which suggest that even if metronidazole resistance is detected, eradication rates with triple metronidazole based therapy are higher than expected.⁴³

Reinfection

H pylori infection is clustered within families and in institutions for the mentally handicapped. However, reinfection in adults⁴⁴ and older children⁴⁵ following successful treatment is rare. Therefore, there is no need to treat the entire family to prevent reinfection.

H pylori testing following treatment

In adults there is debate on the need to assess whether treatment has been successful or not because of the high success rates achieved. The success of treatment regimens for children in a primary care setting is unknown. If we decide to treat a child for *H pylori* infection we should assess whether that treatment has been successful. This can now be achieved non-invasively using the ¹³C-urea breath test which is 100% sensitive and specific for the diagnosis of *H pylori* following treatment.⁴⁷

Conclusions

All children with a duodenal ulcer who have *H pylori* infection should receive treatment for the infection. If infected children have a strong family history of duodenal ulcer disease or gastric cancer, treatment should be considered. Children with sideropaenic anaemia which is refractory to treatment with iron should be screened for *H pylori* infection and if infected, treatment may be of benefit.

There is no indication to screen children with recurrent abdominal pain for *H pylori* infection. Eradication of infection in such individuals has, in most studies, resulted in no improvement in the pain. Consensus is required on the need to treat *H pylori* infected children in relation to the possible risk of developing gastric cancer. We need to decide whether a screening programme for the identification and treatment of *H pylori* infected children is justified in terms of reducing the prevalence of gastric cancer.

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