

Management of *Helicobacter pylori* infection in children

G Oderda

Summary

When trying to decide which children with *Helicobacter pylori* infection should be treated and at what stage they should be tested, we should take into account the fact that eradication of the infection may be useful both to induce symptom remission and to prevent later complications in adulthood. However, well designed studies to identify those infected children who are at risk of developing complications or have symptoms due to the infection are still lacking. Current literature only gives information on how to treat children with *H pylori* infection. Treatment regimens that include two drugs are usually more effective than in adults, and produce an eradication rate of 70–80%, but they should be given for at least two weeks, shorter treatments being less effective. Antibiotic resistance can impair eradication rate and the frequency of resistant strains in children should be studied. Combinations of antibiotics with antisecretory drugs are highly effective in adults, but triple therapy with two antibiotics and an antisecretory drug has been seldom tried in children; compliance is often poor so that the eradication rate is often similar to that produced by dual therapy. Compliance strongly influences eradication, and short simple treatment regimens that produce rapid symptom remission with few side effects are needed to optimise patient compliance. After treatment, eradication must be proved. Serological tests can help, provided that pretreatment serum is available and three to six months have passed since the treatment. A ¹³C-urea-breath test (¹³C-UBT) should be performed at least six weeks after treatment, but false negative results can occur and cut-off must be adjusted.

H pylori infected children: who and when to treat?

Guidelines for the management of *H pylori* infection in children are urgently required, but a consensus is lacking, because sound data on the role of *H pylori* infection in children are not available. The infection is usually acquired in childhood,¹ and an early age of acquisition seems to be critical for development of severe complications later in life.^{2,3} As far as management of *H pylori* in children is concerned, one of the main issues is prevention of complications in adulthood, such as development of peptic ulcer and/or gastric atrophy and cancer. However, even though the prevalence of infection in children is lower than in adults, at least in developed countries, not all infected children can be tested and treated. Furthermore, if eradication is to be aimed at prevention of later complications, other risk factors associated

with them need to be more extensively studied to identify children at highest risk. Such risk factors would include environmental ones, such as a diet rich in salt and nitrites and poor in fresh vegetables, *H pylori* strain characteristics, such as *cagA* positivity, and host characteristics, such as age at acquisition, gastric acid secretion, and family history of gastric cancer. If the hypothesis that subjects infected with a cytotoxic *cagA*⁺ *H pylori* strain are at higher risk of developing duodenal ulcer or gastric cancer proves to be correct,⁴ then children infected with this strain of *H pylori* in early life should be considered a high risk population. Furthermore, children infected with a cytotoxic *cagA*⁺ strain have more severe gastritis and a higher prevalence of duodenal ulcer⁵ and need to be more carefully studied and followed up. Preliminary data suggest that saliva can be screened by western blotting, thus providing a non-invasive test to identify children infected by *cagA*⁺ *H pylori* strain,⁶ but more studies are needed to confirm these results.

On the other hand, if treatment is to be aimed at producing symptom remission, a better understanding of the whole symptom profile associated with the infection is needed, with endoscopic studies on mucosal lesions and their relation to symptoms. The problem of recurrent abdominal pain (RAP) in children is similar to non-ulcer dyspepsia in adults, and the causal role of *H pylori* is controversial.⁷ In a recent survey on German preschool children, no relation between RAP and infection was found.⁸ However, according to the classical criteria of Apley⁹ (pain for at least three months, with one or more episodes per month, impairing daily activity or sleep), RAP is a common problem, being reported by 10–15% of school-children, and requires more study. Possibly, Apley's criteria should be reconsidered to try to identify different symptom profiles, and duration, severity, frequency, location of pain, and associated symptoms such as diarrhoea, constipation, vomiting, nausea, and heartburn, should be taken into account, and all children should be evaluated with similar questionnaires, to ascertain whether there is more than one subgroup of children with RAP. Up until now, there have been no criteria by which to identify which children have symptoms that are due to the infection; the only option has been to treat them and follow them up, and in those in which eradication is followed by a sustained and complete remission of symptoms a causal relation is suspected, as in children with peptic ulcers.¹⁰ A high proportion of children with gastritis are still symptomatic after eradication; in these, RAP and *H pylori* infection may co-exist but are not related, and RAP may be due

Dipartimento di
Scienze Mediche,
Università di Torino
G Oderda

Correspondence to:
Dr G Oderda, Clinica
Pediatrica, Dipartimento di
Scienze Mediche, Università
di Torino, Via Solaroli 17,
28100 Novara, Italy.

to other more common causes such as irritable bowel or reflux oesophagitis.

NHI guidelines¹¹ are that all patients with peptic ulcer, which in children is infrequent, should be treated. However, in *H pylori* infected children, gastric or duodenal ulcers are found in up to 12–20% of those subjected to endoscopy for dyspeptic symptoms,^{12,13} and an even higher proportion in those infected with a *cagA*⁺ strain.⁵ Should we then perform an endoscopy in all children in which a non-invasive test such as serology or ¹³C-UBT is positive to distinguish and treat those with a peptic ulcer and not treat all the others? Maastricht guidelines¹⁴ suggest that all dyspeptic patients younger than 45 years could be tested with a non-invasive test when no alarming symptoms are present, and treated if positive for the infection, without the need to perform an endoscopy. Studies on symptoms associated with *H pylori* infection in children are scarce, but some report the presence of alarm symptoms, such as malabsorption with weight loss, delay in weight gain, short stature, iron deficiency anaemia, or recurrent diarrhoea and malnutrition in infected children. More studies are needed to confirm these data, but in the mean time children with these clinical manifestations should be studied more carefully. However, the Maastricht guidelines are not meant to be applicable to children. Therefore, with respect to children, the main questions about when and who to test for the infection and who to treat still need to be answered.

Little is known about what happens after the infection is acquired in children and for this reason in September 1997, immediately before the Xth International Workshop on Gastrointestinal Pathology and *Helicobacter pylori* held in Lisbon, the European *Helicobacter pylori* Study Group organised a Workshop in Estoril at which paediatricians from several European countries met to define how to design studies in the paediatric population to address some crucial questions (see box).

How to treat an *H pylori* infected child

While we await results from the studies designed in Estoril to answer the questions who and when to treat, data from the literature can help us to decide how to treat. However, even here we should be cautious when interpreting results, because most of the studies have been on small series of children and were not placebo controlled.

Questions to be tackled in future studies of *Helicobacter pylori* infection in children, defined at the Estoril Paediatric Workshop: focus on primary *H pylori* infection

- When and how does infection occur?
- When and how does infection reoccur?
- What is the natural history of *H pylori* infection?
- Why are there differences in pathological features between children and adults?
- Is there any correlation between infection and symptoms?
- How should a therapeutic scheme be evaluated in childhood?

Previous data, summarised in table 1, show that treatment with one antibiotic is not effective,^{15,16} dual therapy with or without bismuth salts is usually more effective than in adults,^{17–22} and triple therapy does not appear to produce any better eradication rates^{23,24}; however, the dual therapy was usually given for four weeks or longer. Shorter treatments have been tried with amoxycillin and tinidazole, and eradication has been achieved in 81% of children treated for two weeks, but only in 66 and 69% in those treated for one week.^{25,26} Short treatments have a low efficacy even in children colonised by nitroimidazole sensitive strains.²⁶ Antibiotic resistance is an important factor in impairing eradication rate, and frequency of resistant strains, principally those resistant to nitroimidazoles and macrolides, should be studied in any particular population before the antibiotics are used empirically.

In adults, one week treatments with two antibiotics and an antisecretory drug (triple therapy) are highly effective and can eradicate even antibiotic resistant strains.²⁷ Reducing gastric acidity has various advantages: at neutral pH most antimicrobials have a higher stability, gastric immunoglobulins are less denatured, and *H pylori* is less stable in an ammonia rich neutral environment. In children, triple therapy with antisecretory drugs has been seldom tried, but, when compliance is poor (as is common because they are given in capsules that are difficult to swallow), the eradication rate is similar to that produced by dual therapy.²⁸ In children with peptic ulcer, in whom gastric hyperacidity²⁹ is one of the factors contributing to the severity of the

Table 1 Eradication rate in children with *Helicobacter pylori* infection in some early studies performed before the use of antisecretory drugs became widespread in adults

Reference	No of children treated	Drug combinations used	Duration (weeks)	Eradication rate (%)
Drumm <i>et al</i> ¹⁷ (1988)	16	Bismuth + ampicillin	4 + 4	75
Oderda <i>et al</i> ¹⁵ (1989)	30	Amoxycillin	4	27
Oderda <i>et al</i> ¹⁸ (1989)	32	Amoxycillin + tinidazole	6 + 6	75
Yeung <i>et al</i> ¹⁶ (1990)	23	Amoxycillin + cimetidine	2 + 6	43
De Giacomo <i>et al</i> ¹⁹ (1990)	19	Bismuth + amoxycillin	4 + 2	68
Oderda <i>et al</i> ²⁰ (1992)	63	Amoxycillin + tinidazole	4 + 4	80
Mahony <i>et al</i> ²¹ (1992)	12	Bismuth + amoxycillin	8 + 2	75
Cucchiara <i>et al</i> ²³ (1992)	33	Bismuth + amoxycillin + tinidazole	8 + 2 + 2	78
Israel and Hassal ²⁴ (1993)	7	Bismuth + amoxycillin	6 + 6	71*
	3	Bismuth + amoxycillin + metronidazole	6 + 4 + 4	100*
Ashton <i>et al</i> ²² (1994)	21	Bismuth + tinidazole	4 + 2	67

*Only children with optimal compliance were considered out of 20 initial patients.

Table 2 Eradication rate in children with *Helicobacter pylori* infection in recent studies in which triple therapy was used

Reference	No of children treated	Drug combination used	Duration (weeks)	Eradication rate (%)
Oderda <i>et al</i> ²⁸ (1996)	45	Omeprazole + clarithromycin + amoxicillin	2	77
	34	Omeprazole + clarithromycin + metronidazole	1	68
Cucchiara <i>et al</i> ³¹ (1996)	30	Bismuth + amoxicillin + tinidazole	4	71
		Bismuth + amoxicillin + tinidazole	1	75
Walsh <i>et al</i> ³² (1997)	22	Bismuth + clarithromycin + metronidazole	1	95
Kato <i>et al</i> ³⁰ (1997)	10	Omeprazole + amoxicillin	2	70*
	12	Omeprazole + amoxicillin + clarithromycin	2	92*

*Of the total of 22 children, 12 had a duodenal and 3 a gastric ulcer.

symptoms, the addition of a proton pump inhibitor, which produces more rapid symptom remission, may increase compliance.³⁰ In relapsing symptomatic infection when patient motivation and compliance was good, eradication was achieved in 95% of 20 children treated with omeprazole, clarithromycin, and amoxicillin for two weeks (unpublished data). Bismuth based triple therapy seems to have similar problems of compliance: it was tried in Italian children, and had a similar effectiveness when given for one or four weeks, but, because of poor compliance, the overall eradication rate was low.³¹ When a "Redidose" box was used to optimise compliance, bismuth plus metronidazole and clarithromycin produced a better eradication rate in Irish children³² (table 2). Compliance is indeed a critical factor in treatment success, and short simple treatment regimens that produce rapid symptom remission with few side effects are needed to improve it.

After treatment, eradication must be proved. Serological tests can be used provided that pretreatment serum is available and three to six months have passed since the end of the treatment; pre- and post-treatment sera are tested in the same session, and a decrease of at least 20% in serum antibody level is found.^{18 20} However, these requirements can be seldom satisfied in a clinical practice. A ¹³C-UBT performed soon after treatment can give false negative results. In 59 Italian children, in whom endoscopy based tests were used to validate the accuracy of the ¹³C-UBT after treatment, false negative results were seen in 25% of cases after two weeks and in 14% after six weeks³³; a longer follow up may be necessary in children to obtain more accurate results. In 20 Irish children, ¹³C-UBT after treatment gave more accurate results when cut-off was adjusted.³⁴ Endoscopy based tests and culture should be performed in all patients in whom the infection is not eradicated to study antibiotic resistance in order to tailor a new treatment regimen.

Conclusion

Even though guidelines on the management of *H pylori* infection in children are still lacking, there may be some advantages to curing the infection in childhood. Although there are not enough data to justify eradication in all children with *H pylori* infection unless they have an ulcer, we should bear in mind that we still do not know the whole clinical picture of this chronic infection, and the longer the duration of the disease the worse seems to be the prognosis. Eradication in some children may promote symptom improvement, and in some

may prevent development of peptic ulcer or gastric cancer later in life, but the beneficial effect of treatment for prevention of complications later in life still needs to be demonstrated. To eradicate the infection early in life, at least in developed countries, could be worth while because of the low prevalence of infection in children and a satisfactory rate of eradication with the cheaper dual therapy. Moreover, if the new and intriguing hypothesis of "gastro-oral" transmission in children proves to be correct,³⁵ by eradicating the infection in children, limitation of the spread of the disease may be achieved. Infection is mainly acquired in childhood, when it can be readily transmitted; an acutely infected child may vomit and spread *H pylori* mixed with mucousy vomit throughout the house or classroom where siblings, parents, or schoolmates can easily pick it up and become infected.³⁶

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