

One week treatment for *Helicobacter pylori* infection

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Abstract

Helicobacter pylori is associated with primary antral gastritis, duodenal ulceration, and gastric cancer. Current regimens for treating infection in children using bismuth and antibiotics for two to six weeks are cumbersome. The aim of this study was to evaluate a one week course of treatment. All children undergoing endoscopy were assessed for the presence of *H pylori* by culture, histology, rapid urease test, and ¹³C urea breath test. Infected children received a one week course of colloidal bismuth subcitrate 480 mg/1.73 m²/day (maximum 120 mg four times a day), combined with metronidazole 20 mg/kg/day (maximum 200 mg three times a day), and clarithromycin 15 mg/kg/day (maximum 250 mg twice a day). To optimise compliance, drugs were dispensed in a 'Redidose' box containing a compartment for each day, and subcompartments marked 'breakfast', 'lunch', 'dinner', and 'bedtime'. Compliance and side effects were assessed immediately after treatment. A urea breath test was performed at least one month after treatment. Twenty two children infected with *H pylori* were entered into the study; 20 of these took all doses; two children suffered significant side effects (diarrhoea and vomiting). *H pylori* was eradicated in 21 of the 22 children (95.45%; 95% confidence interval 77% to 100%). This study shows that *H pylori* infection in children can be cleared by a one week course of treatment. (Arch Dis Child 1997;76:352-355)

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Helicobacter pylori is associated with primary antral gastritis in children and adults.¹⁻⁵ Eradication of *H pylori* from the gastric mucosa results in healing of gastritis.⁶⁻⁸ There is also a strong association between *H pylori* gastritis and duodenal ulceration in both adults and children.^{2 4 5 9 10} Duodenal ulcer disease does not relapse if *H pylori* is eradicated from the gastric mucosa.^{7 11-13} Infection with *H pylori* also appears to be associated with an increased risk of carcinoma of the stomach, especially in those infected as children.¹⁴⁻¹⁷

Current treatment regimens for *H pylori* infection in children using bismuth combined with one or two antibiotics for two to six weeks are cumbersome and compliance is difficult.^{6 11} Studies on adult patients suggest that one week courses of treatment are effective.¹⁸⁻²⁴

The aim of this study was to test the efficacy of a one week course of treatment combining colloidal bismuth subcitrate, metronidazole, and clarithromycin in eradicating *H pylori* in children.

Methods

Children undergoing upper endoscopy were routinely assessed for the presence of *H pylori*. Endoscopy was performed under general anaesthetic using Olympus paediatric gastroscopes QIF-P10 or XQ200. Three biopsy specimens were taken from the antral mucosa. One specimen was used for a rapid urease test (Clo, Delta West, Australia). A second specimen was fixed in 10% neutral formalin, embedded in paraffin wax, and cut at five micron thickness. The sections were then stained with haematoxylin and eosin for light microscopy. Further staining with cresyl violet allowed for easy identification of the spiral shaped organisms on the surface of the gastric mucosa. The third specimen was placed in RPMI 1640 (Gibco) tissue culture medium containing fetal calf serum. Culture was performed by inoculation of minced biopsy specimens onto Columbia blood agar (Gibco) plates containing 7% (vol/vol) defibrinated horse blood, and held for five to seven days at 37°C, in an atmosphere of 5% oxygen and 10% carbon dioxide (CO₂). Organisms were identified as *H pylori* if they were Gram negative, had a characteristic spiral shape on phase contrast microscopy, and showed urease, oxidase, and catalase activity.²⁵

Children were considered to be infected if *H pylori* was cultured from gastric biopsy specimens. If culture was negative, they were considered infected only if both the rapid urease test was positive and characteristic spiral shaped organisms were seen on histology.

A ¹³C urea breath test was performed on each infected child before treatment. A repeat test was carried out one and two months after the completion of treatment. After a two hour fast, a baseline breath sample was taken. Children were then given an oral dose of ¹³C labelled urea: 50 mg if the child was less than 50 kg body weight, or 75 mg if over 50 kg (99 atom%, Cambridge Isotopes, Cambridge, MA, USA). The labelled urea was given in a glucose polymer solution (50 mg Polycose in 7.5 ml water). Breath samples were repeated at 15 and 30 minutes after ingestion. ¹³C enrichment was determined by isotope ratio mass spectrometry. Isotope enrichment was expressed as corrected delta (δ) per thousand (0/00) relative to the international standard Pee Dee belemnite

Table 1 Schedule of seven day course of treatment for *H pylori* infection in children

Treatment	Total daily dose	Times per day	Maximum dosage
Colloidal bismuth subcitrate	480 mg/1.73 m ² body surface area	Four	120 mg four times daily
Clarithromycin	15 mg/kg	Two	250 mg twice daily
Metronidazole	20 mg/kg	Three	200 mg three times daily

limestone. $\delta 0/00 = \{^R\text{sample}/^R\text{PDB}-1\} \times 10$, where R is the isotope ratio (¹³C:¹²C) of the sample or standard. A positive result was defined as a $\delta^{13}\text{CO}_2$ excretion of > 3.5/ml.²⁶

TREATMENT

Infected children were started on a seven day course of treatment as outlined in table 1. Possible side effects were discussed with parents and informed consent was obtained. The parents of two children refused to consent to treatment. Parents received an instruction sheet detailing how and when to take the drugs. The importance of compliance was stressed. The tablets were dispensed in a 'Redidose' box, containing a compartment for each day, and subcompartments marked 'breakfast', 'lunch', 'dinner', and 'bedtime'. They were asked to return the box along with any unused tablets at their first review. Children who were unable to take tablets received the medication in liquid form (n = 4) and parents were asked to make a note of any doses missed. Patients were reviewed one day after the end of treatment. Returned medication was documented. Parents and children were asked about specific side effects, including taste disturbance, nausea, vomiting, diarrhoea, black stools, abdominal pain, or any other symptoms noted while taking the drugs.

All children were further reviewed at least four weeks after the end of treatment, and a urea breath test was done. This process was repeated at least eight weeks after the completion of treatment.

Results

During the 13 month study period, October 1994 to October 1995, 187 upper endoscopies were performed on 168 children. Indications for endoscopy were as outlined in table 2. Twenty eight (16.7%) were diagnosed as having *H pylori* infection. Twenty two children were entered into the study. Children were excluded if the parents did not wish to have their child participate in the study (n = 2), or if the child was suffering from a severe underlying medical condition, where *H pylori* infection was an incidental finding (n = 4).

The mean age of infected children was 12.1 years (range 14 months to 16 years). Twenty had a urea breath test before treatment. In the

other two children, there was insufficient CO₂ in the pretreatment breath test samples. Culture of a gastric biopsy was carried out in 20 of the children, and was positive in all cases. In two children, culture was not performed, but both the rapid urease test and histology confirmed infection.

Endoscopy findings included nodularity of the antral mucosa, which was present in 14 children, duodenitis in three, duodenal ulceration in one, oesophagitis in two, hiatus hernia in one, and a normal examination in eight children. Some children had more than one finding.

Twenty children took all doses of the regimen. One child omitted to take one tablet. A 17 month old child spat out or vomited many of the doses (elixir). All 22 children had a urea breath test performed at least one month after completion of treatment. *H pylori* was eradicated in 21 of 22 children treated. The eradication rate was therefore 95.45% (95% confidence interval 77% to 100%). Eighteen children have had a further urea breath test performed at least two months after completion of treatment. All children who were negative at one month remained negative on repeat testing. The one child who failed to clear the infection still had a positive urea breath test two months after treatment.

Fifteen children noted no side effects apart from black stools, which was expected due to the inclusion of a bismuth containing compound in the regimen. Two children (9%) had significant side effects. One of these children complained of multiple symptoms, including a burning sensation of the tongue, vomiting for one day, persistent diarrhoea, and nightmares. A second child vomited or spat out approximately 10 doses of elixir, and was noted to be irritable during the period of treatment. Milder side effects were observed by five children. Four (18%) complained of a bad taste or burning sensation on the tongue. The fifth child was nauseated for two days. None of the children withdrew from the study because of side effects.

Discussion

This study shows that a one week course of treatment can eradicate *H pylori* infection in children. Current regimens generally require two to six weeks of treatment and many people therefore fail to complete the full course. Compliance is even more difficult in young children, who may refuse to take the medicine. A recent study from Brazil has suggested that a one week course of treatment might be effective in eradicating *H pylori*.²⁷ We decided to formally assess the efficacy of a one week course of treatment while trying to ensure maximum compliance. The success rate for eradication of *H pylori* in this study was 95.45%. However, compliance

Table 2 Indications for endoscopy; values are number (%)

Symptoms	All children	Treatment group
Failure to thrive +/- diarrhoea	58 (31)	4 (18)
Abdominal pain	51 (27)	11 (50)
Oesophageal symptoms	20 (11)	4 (18)
Haematemesis	13 (7)	0 (0)
Inflammatory bowel disease	24 (13)	2 (9)
Liver disease/varices	11 (6)	0 (0)
Other	10 (5)	1 (5)
Total	187	22

was very closely monitored in this group. It is unlikely that this level of compliance would be achieved in routine practice. The one week course should, however, ensure much better compliance than previous treatment regimens. The 'Redidose' box used in 18 of the children in this study represents an attempt to improve compliance by presenting a visual reminder of what medications to take and when. Feedback from parents suggested that it was very effective in its purpose.

Studies in relation to treatment of *H pylori* have been hampered by the need to perform repeat endoscopies. The ¹³C urea breath test provides an ideal, non-invasive method for evaluating treatment. We have recently shown that the urea breath test is highly sensitive and specific in diagnosing *H pylori* infection in children. Furthermore, it is very accurate in determining the success of treatment when compared with endoscopy.²⁶

The development of antibiotic resistance by *H pylori* is a concern. Metronidazole is very effective in eradicating *H pylori* in vivo. However, resistance to metronidazole often develops in those who have previously been treated with this antibiotic.²⁸ Clarithromycin is a new macrolide antibiotic (6-methoxyerythromycin). It has a similar antimicrobial spectrum to erythromycin. It is, however, more acid stable and has higher bioavailability and fewer alimentary side effects. Its metabolite, 14-OH-clarithromycin, is more active than the parent compound in vitro against several pathogens. A longer half life allows for twice daily dosing.²⁹ Preliminary studies suggest that *H pylori* strains may develop resistance to clarithromycin. Subsequent studies should therefore focus on other antibiotic agents such as amoxicillin, where resistance appears to be very rare.

The question as to whether children infected with *H pylori* should be treated or not is still controversial. *H pylori* is very prevalent in developing countries, where up to 80% are infected by 20 years of age.³⁰ In children with chronic *H pylori* associated gastritis, there is no evidence of an association between *H pylori* infection and abdominal pain. In an earlier study, we, and our colleagues in Toronto, evaluated symptoms in children undergoing upper endoscopy before checking their *H pylori* status.³¹ It was not possible to distinguish between infected and non-infected children on the basis of symptoms. In a subsequent study, we evaluated children's symptoms following treatment of *H pylori* infection.³² Following eradication of *H pylori*, there was resolution of symptoms in those children who had *H pylori* gastritis associated with duodenal ulcer disease. However, there was no change in symptoms in children with *H pylori* gastritis alone. The presence or absence of symptoms failed to differentiate between those who had cleared the infection, and those who remained infected. In contrast, duodenal ulcer disease is an indication for the treatment of *H pylori* infection in adults and children. Almost 100% of children with duodenal ulcer disease will have *H pylori* associated gastritis.^{2 9 10} If *H pylori*

is eradicated from the gastric mucosa, duodenal ulcer disease will not relapse.^{7 11-13}

More recently, epidemiological studies suggest an association between *H pylori* infection and the subsequent development of gastric cancer.¹⁴⁻¹⁷ This has resulted in *H pylori* being considered a group 1 carcinogen.³³ If these studies are confirmed it may soon be necessary to consider treating all children with *H pylori* infection of the gastric mucosa. Short courses of therapy, which ensure maximum compliance, will be required if large numbers of children are to be treated.

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